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INFLUENCE OF GROUNDWATER DEPTH AND SOIL TEXTURE ON NEST FORMATION AND VIABILITY OF TERMITES OF THE GENUS ANACANTHOTERMES JACOBS

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Abstract. *In recent years, the expansion of termite habitats in the Khorezm oasis has been accompanied by increasing economic damage to buildings, infrastructure, and historical monuments. Despite the ecological importance of termites, their activity poses serious risks in irrigated and densely populated areas. This study investigates the influence of groundwater depth and soil mechanical composition on nest formation and overwintering survival of termites of the genus* Anacanthotermes *in the Khorezm oasis and adjacent regions. Field investigations were conducted during the spring rise of groundwater levels. Four termite nests located in contrasting landscape conditions were excavated to depths of up to 250 cm. In addition, more than 30 termite nests were examined in Khiva, the Khorezm region, and the Beruniy and Ellikkala districts of the Republic of Karakalpakstan to assess nest structure, depth distribution, and construction type. The results showed that overwintering termites descend to depths ranging from 150–165 cm to 240–250 cm, depending on groundwater level and soil properties. In low-lying areas and near irrigated lands, rising groundwater submerged lower nest chambers, causing partial mortality of overwintering termites and weakening of colonies. In contrast, nests located on elevated sites along irrigation canals and drainage collectors provided more favorable overwintering conditions.*

Keywords: *termites, Khorezm region, Anacanthotermes, Karakalpakstan.*

Introduction. In recent years, an expansion of the termite habitat range has been observed in our Republic, accompanied by a significant increase in the level of damage they cause. Termites play an important ecological role in nature; however, as a result of their activity, they inflict substantial damage on construction sites. Termites primarily feed on materials and objects containing cellulose and cause considerable economic losses to various building structures, timber, bridges, water supply systems, and even historical monuments. Therefore, it is important to study termites and to develop modern measures for their control. It is known that, like other termite species, termites of the genus *Anacanthotermes* Jacobs are adapted to a nest-dwelling lifestyle and construct their nests in soil, i.e., underground (Brajne, 1986). Depending on nest structure, it has even been proposed to distinguish separate species within this genus. In particular, according to A. N. Luppova (1955) and a number of other authors (Kakaliev, 1968; Soyunov, 1991), the termite species *Anacanthotermes ahngerianus* Jacobs is characterized by constructing its nest high above the soil surface in a hemispherical form, whereas *Anacanthotermes turkistanicus* Jacobs, on the contrary, does not bring its nest to the surface but places it deep in the ground. Haytboyeva (2026) demonstrated that *A. ahngerianus* forms stable colonies in desert and semi-desert environments, with nest density and morphology varying according to habitat type. In natural landscapes, especially sandy desert zones, termite nests are predominantly mound-shaped and reach heights of 40–70 cm, whereas in anthropogenic environments nests are often associated with irrigation

systems, drainage collectors, and residential areas. These observations support our findings that soil mechanical composition and hydrological conditions play a decisive role in nest construction type and colony survival. As is well known, under the conditions of Central Asia, during winter, when the upper soil layers and the nests experience significant cooling, termites descend to greater depths where the temperature is maintained at about 10 °C. In spring, as the soil warms, termites begin to migrate to the warmer upper chambers of the nest. Such overwintering under continental climatic conditions is an adaptive response to pronounced temperature fluctuations in the absence of diapause and stored food reserves. The beginning and end of the winter dormancy period are largely depend on weather conditions. The influence of groundwater dynamics on the overwintering reserve of termites has not been studied. Under the conditions of the Khorezm region, groundwater levels depend on the irrigation of agricultural crops. On irrigated lands, the optimal groundwater depth during the growing season of agricultural plants is 1.5–2.0 m and decreases to 2.5 m by the beginning of preventive leaching irrigations. According to data from the Khorezm "Hydrogeology" Expedition, the groundwater depth in the Khiva district, where the study was conducted, varies throughout the year from 1.0–1.2 m to 2.5–3.0 m. On a monthly basis, it changes as follows: January 2.5–3.0 m, March 1.0–1.2 m, April 1.5–1.8 m, May 1.5 m, June 1.2 m, October 1.5 m, November 1.2–1.5 m, and December 2.3–2.5 m.

Materials and methods. We examined the condition of termite nests during the spring rise of groundwater to a depth of 1.2–1.5 m. In total, four termite nests located in different areas were excavated. The first nest was situated near irrigated farmland where spring irrigation activities were carried out. The other nests were located along a drainage collector on elevated areas, where the groundwater level was deeper. During the study of termites distributed in the Khorezm oasis, we collected data on the construction and structure of their nests. The reasons for the construction of termite mounds above or below ground were also examined, and it was established that termite colonies which, based on morphological characteristics, may be considered to belong to the same species are capable of constructing both types of nests mentioned above. A total of more than 30 termite nests were examined in Khiva, the Khorezm Region, as well as in the Beruniy and Ellikkala districts of the Republic of Karakalpakstan.

Results and discussion. Excavation of the first nest showed that during the spring rise of groundwater, isolated termite individuals were found at a depth of 130 cm. The upper chambers containing overwintering termites were detected at a depth of 155 cm. Several chambers with overwintering termites were also found at depths of 165–170 cm. It was established that the groundwater level rose to this depth, resulting in the overwintering termite colony being submerged in water. Under these conditions, the termites were already dead.

The second nest was excavated to a depth of 250 cm and had a diameter of 230–260 cm. Chambers containing overwintering termites were identified at a depth of 150 cm and deeper. The chamber with the largest number of termites was found at a depth of 240 cm. Below 250 cm, the soil was heavy loam, wet, and showed signs of groundwater presence. Under these conditions, overwintering termites survived successfully even at a depth of 240 cm.

Two additional nests were studied in the Beruniy district. The excavation results showed that nests located in hilly areas along irrigation canals and drainage collectors provide more favorable conditions for termite overwintering than nests situated in low-lying areas or near irrigated lands. As a result of rising groundwater levels, a portion of overwintering termites in nests located in low-lying areas or close to irrigated fields die due to the influence of groundwater. This leads to a reduction in termite numbers and weakening of the colony. Since the genus

Anacanthotermes Jacobs is widely distributed mainly in desert zones, its nests are also found in the Kyzylkum Desert. All nests discovered under desert conditions have a mound-shaped form, forming elevations 20–60 cm above the ground surface and sometimes higher. As the main distribution areas of termites in the Khiva district are located around drainage collectors, termite nests constructed in soils with a heavy mechanical composition as well as in sandy conditions are also found in these areas. It was established that nests found in heavy soils lack hummocky structures, unlike those discovered in sandy areas. The internal structure of such nests does not differ significantly. The mechanical composition of spherical nests found in deserts, even when they are built partly in sand and partly on its surface, consists of coarse soil particles. During the examination of nests at a stationary site at the foothills of the Kyzylkum Desert in the Beruniy district, at elevations of 1–2 m above ground level, the presence of a layer of fine soil with a heavy mechanical composition consisting of alluvial deposits was detected at depths of 4–5 m and even deeper in some cases. Termites have adapted to the construction of strong nests resistant to mechanical impacts by using soils with higher density and heavy mechanical composition, since it is impossible to build a durable nest from loose, clean sand. The mounds on the sand surface represent the above-ground part of the termite nest, which in fact consists of a rounded, spherical structure with a diameter of 50–60 cm or more, the lower part of which is connected to other chambers by tunnels. The lower chambers and the walls of the connecting tunnels are also constructed of soil. Thus, arid populations of termites of the genus Anacanthotermes Jacobs, widely distributed in the desert zones of the studied region, form mound-shaped structures when constructing their nests. In contrast, termite nests inhabiting soils with a heavy mechanical composition are built not in sand but directly in the ground and therefore represent flat nests composed of solid chambers that do not form mounds.

Conclusion. Thus, under the conditions of the Khorezm oasis, termites descend to depths of 150–165 cm up to 240–250 cm for overwintering. Nests located in hilly areas along irrigation canals and drainage collectors provide more favorable conditions for termite overwintering than nests situated in low-lying areas or near irrigated lands. As a result of rising groundwater levels, a portion of overwintering termites in nests located in low-lying areas or close to irrigated lands perish due to groundwater influence. This leads to a reduction in termite abundance and weakening of the colony. In our opinion, termites distributed in the Khorezm oasis are adapted to constructing two types of termite nests—flat or spherical—depending on soil environmental conditions. Spherical nests are typically found in sandy desert environments, whereas flat nests occur in heavy soils where the soil composition is favorable for nesting.

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RECOMBINANT PLASMID pET-28A(+)-ThPNP ENCODING *THERMUS THERMOPHILUS* PURINE NUCLEOSIDE PHOSPHORYLASE

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Abstract. *Purine nucleoside phosphorylase (PNP) catalyzes the reversible phosphorolysis of purine nucleosides and is widely used as a biocatalyst for the synthesis of nucleoside analogues. Thermophilic PNPs are of particular interest due to their enhanced stability and activity at elevated temperatures. In this study, a recombinant plasmid, pET-28a(+)-ThPNP (6058 bp), carrying the 716 bp purine nucleoside phosphorylase gene from Thermus thermophilus, was constructed for heterologous expression in Escherichia coli. The developed construct provides a basis for efficient production of recombinant enzyme and supports further applications in enzymatic synthesis of pharmaceutically relevant modified nucleosides.*
Keywords: *modified nucleosides, nucleoside phosphorylases, PNP, Thermus thermophilus.*

Introduction

Nucleoside phosphorylases (NPs) are versatile enzymes widely used for the synthesis of modified nucleosides with potential therapeutic applications in oncology as well as antiviral and antibacterial therapy [1-3]. Based on substrate specificity, these enzymes are classified into purine nucleoside phosphorylases (PNP, EC 2.4.2.1) and pyrimidine nucleoside phosphorylases (PyNP, EC 2.4.2.2). Both groups play a central role in the nucleotide salvage pathway by catalyzing the reversible phosphorolysis of nucleosides, thereby maintaining intracellular nucleotide homeostasis [4-6]. Enzymatic approaches offer significant advantages over conventional chemical synthesis, including improved regioselectivity and greater control of trans glycosylation reactions, making them efficient tools for the production of nucleoside analogues [7-12]. Thermophilic enzymes, such as *Thermus thermophilus* PNP, exhibit enhanced structural stability at elevated temperatures and therefore represent promising candidates for industrial biocatalysis [13-18]. Recombinant expression in *Escherichia coli* enables the production of sufficient quantities of enzyme for detailed investigations of catalytic efficiency, substrate specificity, and protein engineering. Such studies help bridge fundamental biochemical knowledge with practical applications in enzyme-based synthesis and therapeutic development.

The aim of this study was to construct a plasmid DNA encoding recombinant purine nucleoside phosphorylase from *Thermus thermophilus* and to express it in *Escherichia coli* cells in order to obtain a high-yield enzyme producer suitable for biotechnological applications.

Materials and methods. Transfer vector pET-28a(+) was purchased from Novagen (Cat. 69864-3). Restriction enzymes *EcoRI* and *NotI*, as well as T4 DNA ligase, were obtained from Thermo Scientific. All other chemicals were of the highest analytical grade and purchased from Sigma-Aldrich. The recombinant plasmid pPICZαA-ThPNP, deposited in the Laboratory of Molecular Genetics ICPS Ruz, was used as the template for amplification of the purine nucleoside phosphorylase gene.

Preparation of transfer vector pET-28a (+) and cDNA (gene) of ThPNP

One microgram of the transfer vector pET-28a(+) was sequentially digested with the restriction endonucleases *EcoRI* and *NotI*. The linearized DNA fragment (5350 bp) was separated by electrophoresis in 0.7% agarose gel and purified using the PureLink™ Quick Gel Extraction Kit (Thermo Scientific) [19].

The *Thermus thermophilus* purine nucleoside phosphorylase cDNA (deoD gene insert, 716 bp) was amplified by PCR using the recombinant plasmid pPICZαA-PNP as a template and the following primers:

Forward: 5′-GACTGGTTCCAATTGACAAGC-3′

Reverse: 5′-GCAAATGGCATTCTGACATCC-3′

After electrophoresis in 1% agarose gel, the PCR product was excised and purified using the same gel extraction kit and subsequently digested with *EcoRI* and *NotI*, identical to the enzymes used for preparation of the transfer vector.

Ligation of the vector with cDNA (ThPNP gene).

Ligation of the pET-28a(+) vector with the *Thermus thermophilus* purine nucleoside phosphorylase gene (ThPNP) was performed in a total reaction volume of 10 µL at a vector-to-insert molar ratio of 1:4 using recombinant bacteriophage T4 DNA ligase (Thermo Scientific) (Fig. 1) [20].

Transformation of E. coli TOP10 with the ligation mixture.

Following ligation, DNA was precipitated, and the resulting pellet was dissolved in 10 µL of deionized water. The dissolved recombinant DNA was introduced into electrocompetent plasmid-free *Escherichia coli TOP10* cells (Invitrogen) by electroporation according to the established protocol [20].

Identification of recombinant clones containing pET-28a(+)-ThPNP.

Plasmid DNA isolated from transformant clones was analyzed by electrophoresis in 0.8% agarose gel to estimate molecular size. Clones containing plasmid DNA of approximately 6058 bp (pET-28a(+) vector plus deoD insert) were further confirmed by PCR analysis. PCR products were evaluated by electrophoresis in 1% agarose gel [20].

Transformation of pET-28a(+)-ThPNP into *E. coli* BL21(DE3).

The recombinant pET-28a(+)-ThPNP plasmid was purified and concentrated by ethanol precipitation in the presence of 3 M sodium acetate (pH 5.2). The purified DNA was transformed into *E. coli BL21*(DE3) cells using an Electroporator 2510 (Eppendorf). Transformants were selected on YPD medium supplemented with kanamycin (100 µg/mL) and cultured for subsequent expression studies.

Results and Discussion. This study describes the design and cloning of the recombinant plasmid pET-28a(+)-ThPNP intended for expression of *Thermus thermophilus* purine nucleoside phosphorylase (ThPNP). Purine nucleoside phosphorylase (PNP) catalyzes the reversible phosphorolysis of the glycosidic bond of pentofuranosides in the presence of inorganic phosphate, playing a key role in the nucleotide salvage pathway.

At present, *Escherichia coli* remains one of the most efficient hosts for large-scale production of heterologous recombinant proteins. Therefore, the successful construction of the recombinant plasmid pET-28a(+)-ThPNP represents an important step toward obtaining the target enzyme in *E. coli BL21*(DE3) expression cells.

The recombinant plasmid pET-28a(+)-ThPNP (6058 bp) was generated on the basis of the transfer vector pET-28a(+) (approximately 5340 bp), which is optimized for intracellular protein expression in *E. coli*. The structural elements of the constructed plasmid are illustrated in Fig. 1.

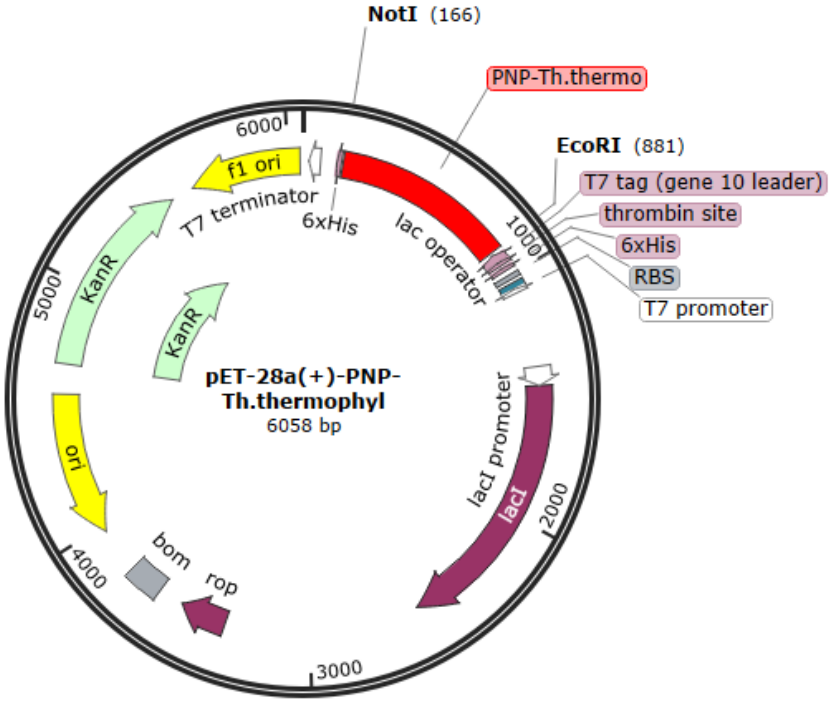


Fig. 1. Physical map of the cloned plasmid DNA pET-28a (+) -ThPNP (6058 bp).

Ligation of the vector with the ThPNP cDNA and subsequent transformation into *E. coli TOP10* cells were performed as outlined in Fig. 2.

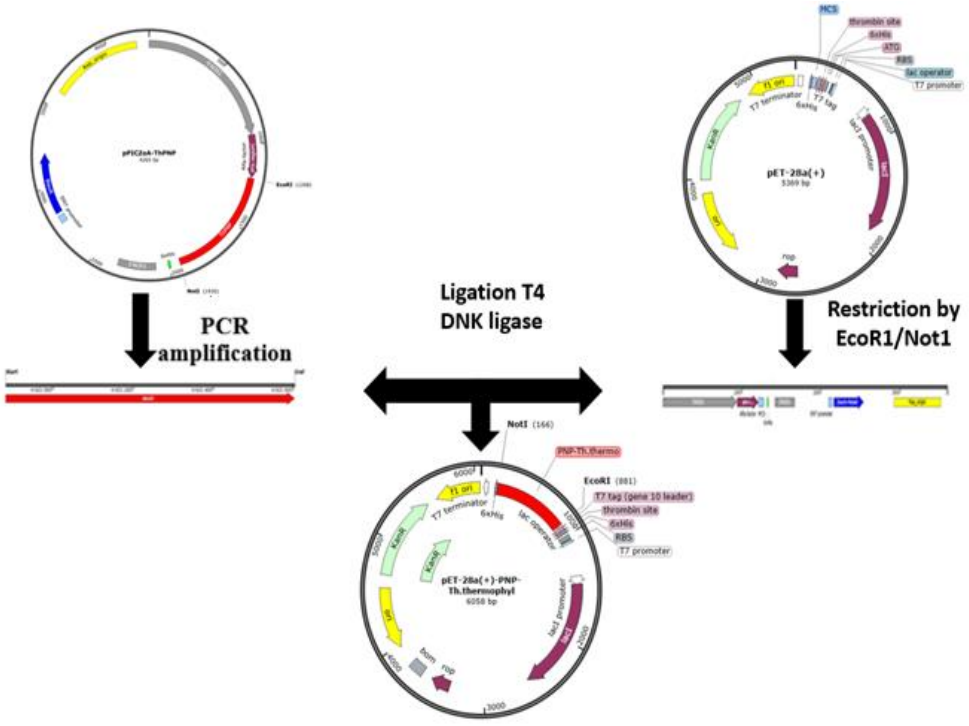


Fig. 2. The general scheme of cloning recombinant plasmid pET-28a(+)-ThPNP

Selection of recombinant clones was carried out on kanamycin-containing medium [23]. Transformants harboring the recombinant plasmid were screened by PCR and restriction analysis,

both of which confirmed the presence of the deoD (ThPNP) insert. PCR analysis of selected clones revealed a DNA fragment of approximately 728 bp (Fig. 3), corresponding to the expected size of the ThPNP gene fragment.

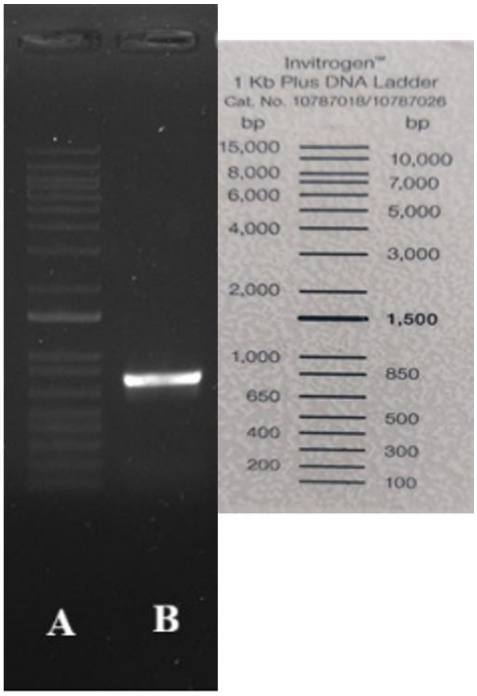


Fig. 3. PCR analysis of transformants. A- DNA Marker; B- Clone containing recombinant pET-28a(+)-ThPNP;

Comparative restriction analysis of the recombinant plasmid pET-28a (+) -ThPNP and the parental vector pET-28a(+) using *EcoRI* is shown in Fig. 4. Electrophoresis in 1% agarose gel produced linear DNA fragments consistent with theoretical sizes derived from plasmid maps. The difference in fragment length between the recombinant and parental plasmids further confirmed successful insertion of the ThPNP gene.

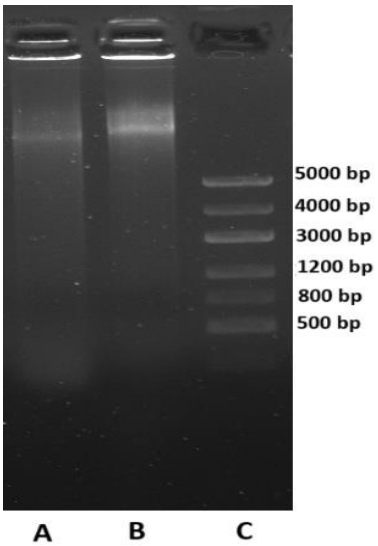


Fig. 4. Restriction of the recombinant plasmid pET-28a(+)-ThPNP and transfer vector by identical restriction site. A. pET-28a(+)-ThPNP (6058 bp); B. pET-28a(+) (5342 bp); (C) DNA Marker.

Conclusion. A novel recombinant plasmid, pET-28a(+)-ThPNP, was successfully constructed for expression of *Thermus thermophilus* purine nucleoside phosphorylase in *E. coli BL21(DE3)* cells. The developed construct enables efficient production of recombinant PNP and may serve as a platform for cost-effective and large-scale enzymatic synthesis of modified nucleosides with potential pharmaceutical applications.

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GIS FOR SUSTAINABLE DEVELOPMENT AND ENVIRONMENTAL PROTECTION: A REVIEW OF APPLICATIONS, DOMAINS, AND EMERGING TRENDS

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Abstract. *This article reviews how Geographic Information Systems (GIS) and Earth observation support environmental protection and sustainable development, drawing on a university lecture that surveys the field from first principles through to current practice. It examines how geospatial data underpins monitoring of the United Nations Sustainable Development Goals (SDGs), defines the scope of environmental protection across five working domains — air quality, water quality, soil, noise and vibration, and waste management — and traces how an environmental GIS database is assembled in practice, illustrated with a case study from Szombathely, Hungary. The review closes with the political, economic, demographic, technological, and environmental drivers expected to reshape geospatial infocommunication technology through 2030. The findings point to a consistent pattern: GIS is shifting environmental management away from slow, after-the-fact observation and toward near real-time monitoring and decision support.*

Key words: *Geographic Information Systems, Sustainable Development Goals, Environmental Protection, Earth Observation, Noise Mapping, Air Quality, Water Quality, GIS Database, Precision Agriculture*

1. Introduction

The world now holds more than 8 billion people, and every one of them draws on the same finite stock of clean air, fresh water, fertile soil, and quiet space. Population growth, rapid urbanization, global climate change, political and ecological migration, pollution, and pandemics are not separate crises; they converge on the same scarce resource, which is the living space shared by all of them. Providing access to resources, good infrastructure, reduced risk, food safety, drinking water, and personal security within that shared, limited space is the underlying challenge that motivates the use of GIS in environmental and sustainability work.

For most of the history of cartography, mapping the Earth meant registering a handful of fixed, discrete facts — a coastline, a border, a settlement — and updating them rarely, at high manual cost. That model was not built for a planet whose problems change month to month: a drought spreading across a province, a wastewater plume moving downstream, a forest losing

canopy hectare by hectare. Its central weakness was that information was rarely up to date by the time anyone could act on it.

What has replaced it is a near-continuous stream of location-tagged data about the planet's condition, gathered from satellites, sensors, and increasingly from citizens themselves. The objective has shifted from recording what exists to establishing what is happening close to real time, so that resulting maps and models can feed directly into decisions rather than into archives — a shift that depends on algorithmizing human knowledge and on the existence of adequate IT infrastructure.

1.1 The Digital Earth Vision

Long before satellite constellations and cloud computing made it practical, Al Gore (1998) described the destination toward which this technology was heading: a "Digital Earth" — a multi-resolution, three-dimensional representation of the planet into which vast quantities of geo-referenced data could be embedded and collaboratively linked. He characterized it as an idealistic goal that would not be created overnight, but one that named, with unusual precision, the infrastructure that GIS and Earth observation have spent the following decades building.

1.2 A Stress Test: COVID-19

The COVID-19 pandemic gave that infrastructure an unplanned stress test. It marginalized traditional decision-making and communication procedures, froze commercial and production supply chains, and forced a "new normality" that minimized mass presence in transport, trade, business, education, and culture. Legal systems can adapt within days, economies within years, and social mentality only across decades — yet the pandemic compressed all three timelines simultaneously, and the response leaned on rapid adaptation, digitalization, and the real-time monitoring of environmental, economic, and social processes.

2. GIS and the Sustainable Development Goals

In 2015 the United Nations adopted the 2030 Agenda for Sustainable Development, structured around 17 Sustainable Development Goals (SDGs) intended to transform the global economy, society, and environment together (United Nations, 2015). Converting those 17 goals into indicators that a government can actually monitor depends on geospatial information and Earth observation, used to support official statistics on how each goal is progressing (Group on Earth Observations, 2016).



Figure 1. *The 17 UN Sustainable Development Goals, adopted in 2015 as part of the 2030 Agenda. Several depend directly on geospatial monitoring for tracking real-world progress. Source: United Nations (2015).*

2.1 Goal 2 — Zero Hunger

Early Warning Crop Monitoring (EWCM) synthesizes Earth observation data to assess the state of agricultural plantations against expected conditions across a whole region. Figure 2 shows an EWCM output for Southern Africa, classifying crop conditions from favourable to failure by area and crop type — the kind of map that can flag a developing shortage months before it becomes a food security emergency.

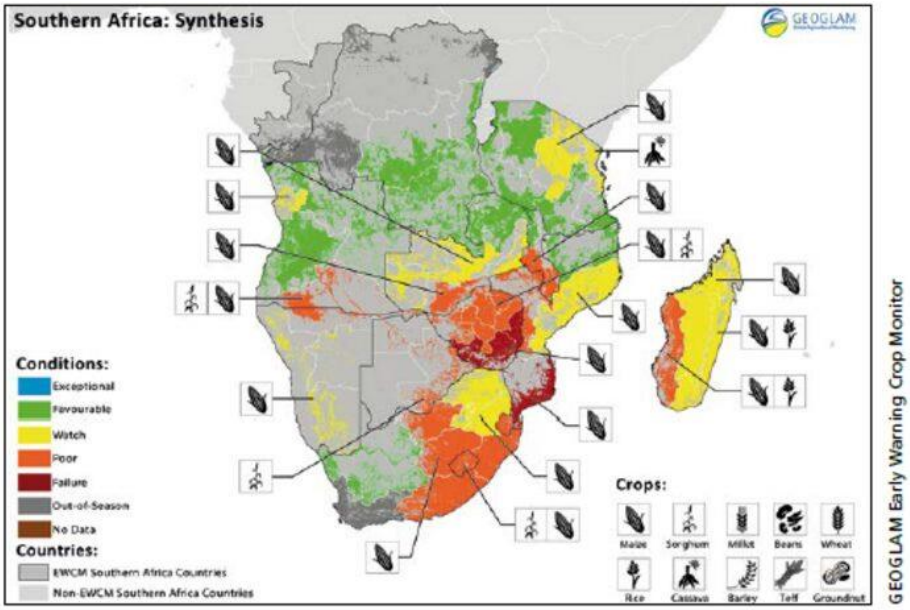


Figure 2. *Early Warning Crop Monitoring (EWCM) synthesis map for Southern Africa, classifying plantation conditions by region and crop type. Source: GEOGLAM.*

2.2 Goal 11 — Sustainable Cities and Communities

Ground-based air-quality monitoring stations are sparse and unevenly distributed across most of the world. Satellite-derived aerosol data fills that gap: Figure 3 shows average PM2.5 particulate air pollution across Asia for 2001–2010, derived from MODIS, MISR, and SeaWiFS aerosol optical depth (AOD) retrievals — producing a continuous exposure surface that can be compared across national borders.

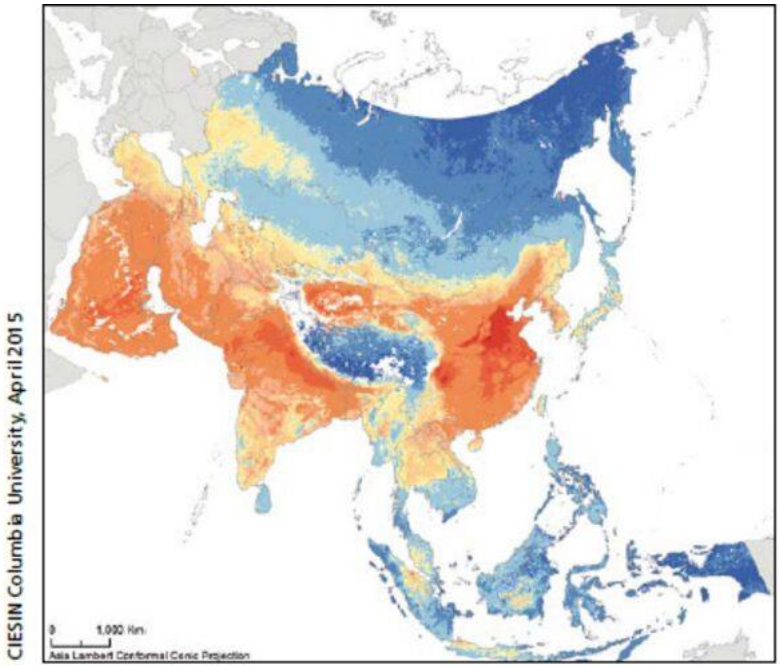


Figure 3. *Average PM2.5 particulate air pollution based on MODIS, MISR, and SeaWiFS aerosol optical depth (AOD), 2001–2010. Source: CIESIN, Columbia University.*

Comparable applications exist for Goal 6 (clean water and sanitation), where Earth observation combined with field statistics has been used to monitor the impact of untreated wastewater discharge in Ethiopia, and for Goal 15 (life on land), where repeated Landsat imagery has detected forest degradation along the Malaysia–Borneo border between 2010 and 2012.

3. Defining Environmental Protection

Environmental protection is the set of human activities and measures undertaken to preserve or enhance natural and man-made environmental values; it is, at the same time, a local, regional, and global issue. It is closely related to nature protection, defined as the set of social actions taken to conserve living creatures, natural communities, habitats, natural and semi-natural areas, and the natural landscape. More precisely, environmental protection is the social activity of preventing, decreasing, or repairing the damage that human society causes to its own ecological conditions.

The lecture organizes the field into five working areas, each of which is examined in Section 4:

- Air-quality protection
- Water-quality protection
- Soil protection
- Protection against noise and vibration
- Waste management

These domains sit within the wider framework of sustainable development, defined as development that meets the needs of the present without compromising the ability of future generations to meet their own needs. Needs are limited, or must be limited; development can only proceed on a basis of knowledge; and it requires a harmonious balance between social, economic, technical, and environmental conditions — against the competing pull of profit. As the lecture states without qualification: our world, in its present form, is unsustainable.

4. Domains of Environmental Protection Practice

4.1 Air Quality Protection

Air pollution is any material — of human or natural origin — that negatively affects air quality and may harm human health or the quality of the environment, damage property, or interfere with the lawful use of the environment; natural sources such as volcanic activity and forest fire must also be considered. Its effects include health damage, harm to flora and fauna, acidification of the environment, technical damage, and economic loss. Regulation is built on immission limit values set from health, toxicological, environmental, economic, and legal criteria, with land classified accordingly (in Hungary, into Priority Protected, Protected I, and Protected II zones).

GIS earns its place in this domain principally through simulation. The lecture presents a modelled industrial accident near Sajóbábony, Hungary, in which, given a dominant wind direction, software projects how a pollutant plume spreads across the surrounding area within one hour, and how that spread changes with wind speed — turning a regulatory limit value into a concrete, actionable map before an accident occurs.

4.2 Water Quality Protection

Water quality is the sum of the properties of water connected to both natural processes and human use; it reflects the industrial and agricultural activity of a catchment area and the structure of its settlements. Water pollution is any external, usually artificial, effect that reduces or eliminates the suitability of surface water or groundwater for natural processes or human use. The aquatic ecosystem it threatens is highly interdependent: aquatic organisms form a community in which each member has a role, and the loss of some members through pollution prevents the community from functioning as it did before.

Control operates through two limit-value systems: immission limits, which classify water into quality classes from excellent to bad based on physico-chemical, biological, bacteriological, and radiological indicators, and emission limits, which cap what a specific source may discharge, following the polluter-pays principle. Removal of pollution follows a fixed sequence — organic substances first, then phosphorus (mostly by biological methods), then nitrogen only once the earlier steps are complete — after which remaining sludge is best reused in agriculture.

4.3 Soil Protection

Soil is an optionally renewable natural resource: renewal is possible but not automatic, and requires constant active management. It functions as nature's filtering and detoxifying system and preserves surviving documentary evidence of the Earth's, and humanity's, history. Hungary's soils are currently in an appropriate state, so the task of soil protection is to preserve that condition and prevent existing degradation processes from worsening. The most common pollutants are oils and hydrocarbons, organic industrial additives, and metal compounds; remediation follows a two-stage logic of localization — horizontal or vertical shielding to prevent further spread — followed by partial or full decontamination through solid-, water-, or gas-phase treatment.

4.4 Protection Against Noise and Vibration

Noise is unwanted sound considered unpleasant, loud, or disruptive to hearing; from a physical standpoint there is no distinction between noise and desired sound, since both are vibrations through a medium such as air or water, but its assessment is highly subjective. The health stakes are non-trivial: at sustained levels around 35 dB, cited studies found a 70% higher mortality rate among patients with coronary heart disease in high-noise conditions, with recovery time after minor surgery extended by three to four days.



Figure 4. *A GIS-generated noise map of a residential district, contouring sound levels across streets, buildings, and green space, used to identify housing and schools exposed above a legal noise threshold.*

Noise mapping combines traffic, terrain, and building data within acoustic modelling software (e.g., SoundPLAN) to produce contour maps at fine spatial resolution — the lecture compares outputs generated on 5-metre and 30-metre grids — distinguishing day and night noise levels and identifying where they exceed a regulatory threshold. The same models can simulate the effect of a proposed noise barrier before construction and then be validated against field measurements once it exists; outputs are commonly published in GeoPDF format so that map layers remain interactive outside a GIS program.

4.5 Waste Management

Waste is defined not by what a material is but by what happens to it: material generated during everyday life that becomes redundant at its current location, whose owner can no longer or no longer wishes to use it — the same object may or may not be waste depending on its further fate. Waste management is the practice of replacing original raw and base materials with primary waste or materials recovered from waste; recycling and reuse, although often used interchangeably, are explicitly not the same thing.

Waste is grouped into communal waste (domestic, municipal, and institutional) and production waste (chemical, engineering, light-industrial, and food-industrial, among others), alongside a separate, tightly regulated category of dangerous waste that includes PCBs, waste oil, batteries, electronic waste, end-of-life vehicles, healthcare waste, and asbestos. Guiding principles include preventing waste generation, applying the polluter-pays principle, eliminating trade barriers to build a secondary raw materials market, and shaping consumer mindsets through adequate, wide-reaching information.

5. Case Study: Building an Environmental GIS Database (Szombathely, Hungary)

An environmental GIS database is built from three converging sources: geometrical information from topographic and soil maps, remote sensing from aerial photography and satellite imagery, and field measurement — GPS survey and physical reconnaissance that ground-truth everything else. Processing this raw material into usable layers involves photogrammetry, map editing, and object detection, applied at different scales depending on the topic: base maps typically at 1:10,000, more detailed soil and land-use work at 1:2,000, with archaeological and geological layers usually only edited rather than resurveyed.

The lecture illustrates this pipeline with a complete case study: an environmental GIS database built for the Hungarian city of Szombathely, layering ecology, air pollution, and noise into a single system.

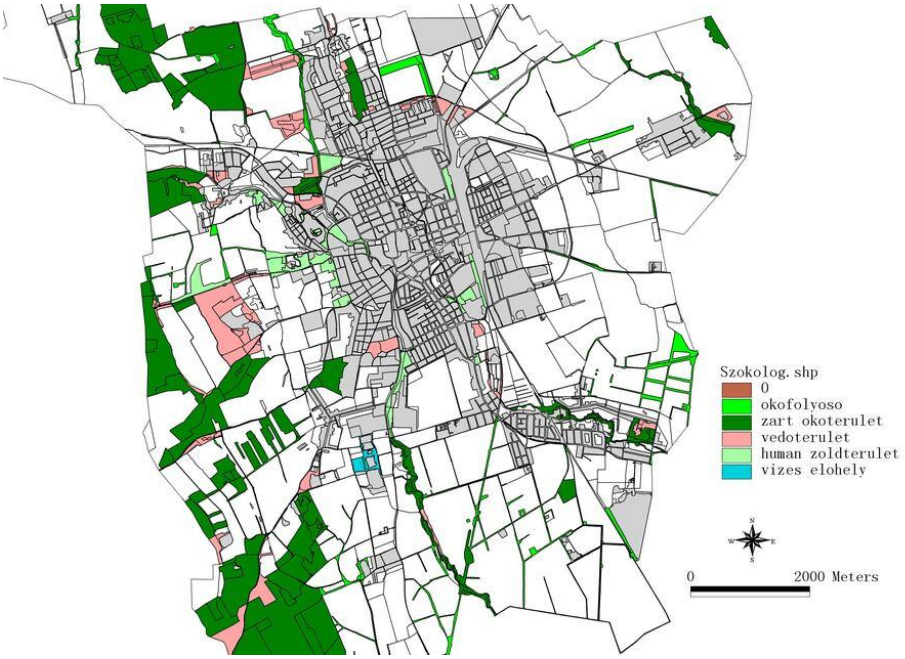


Figure 5. *Ecological base layer for Szombathely, classifying land into ecological corridors, closed ecological areas, protected zones, and human-modified green space.*

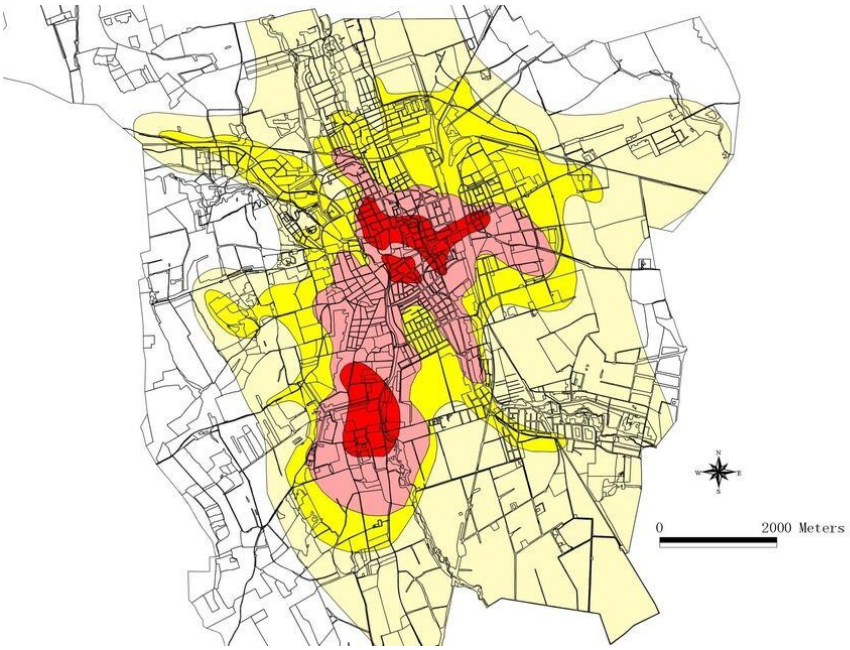


Figure 6. *Combined noise and air-pollution layers for Szombathely, showing where both hazards concentrate along the transport network and industrial edges.*

Once these layers exist together in a single database, they cease to function as separate reports and instead operate as a decision-support system: a planner can query where a proposed road would cross a protected ecological corridor, or which schools already lie within a noise zone above threshold, and obtain an answer directly rather than through a separate research exercise. It is the same underlying logic as the SDG monitoring discussed in Section 2, scaled down from a planet to a single mid-sized city, but assembled from the same three ingredients: geometry, imagery, and ground truth.

6. Future Trends in Geospatial Technology (to 2030)

The lecture identifies five fundamental drivers expected to reshape geo-infocommunication technology over the coming decade, summarized in Table 1.

Driver	What is changing
Political	Reduced dependency on single suppliers; tighter data protection (GDPR) shaping what can be collected and shared
Economic	Smart societies, cities, and logistics; digital twins; deeper integration between Building Information Modelling (BIM) and GIS
Demographic	Continued population growth alongside an aging "developed world," and migration reshaping where demand for services concentrates
Technological	Broadband mobile networks, AI, IoT, big data, machine learning, self-driving vehicles, and edge computing enabling real-time processing at the point where data is generated
Environmental	Climate-driven migration and accelerated urbanization increasing demand for water, food, and biodiversity risk analysis

Table 1. *Fundamental drivers expected to shape GIS and geo-infocommunication technology through 2030.*

On the data side specifically, the lecture anticipates an explosive increase in the volume, quality, and timeliness of situational data, alongside a sharp reduction in the specific cost of collecting it, driven by IoT sensor networks, autonomous smart devices, and community (crowd-sourced) data collection. Mapping itself is expected to become more automated and user-oriented, drawing on heterogeneous data sources including transport-generated data, while user expectations shift toward continuous, mobile access to situational information — the pattern already visible in Smart City and digital-twin projects. This trajectory is not without friction: the recording of increasingly sensitive, wide-ranging digital information about individuals raises legal and ethical questions around information self-determination and cybersecurity that regulation has not yet fully resolved.

7. Conclusion

This review of a lecture on GIS for sustainable development and environmental protection points to a consistent pattern across every domain examined: population growth, urbanization, and climate change have converged on a fixed environmental resource base, and GIS has become the principal means of monitoring that convergence quickly enough to act on it. Five conclusions

follow directly from the material reviewed. First, GIS and Earth observation now underpin official monitoring of the UN Sustainable Development Goals, from crop condition mapping to particulate air-pollution surfaces. Second, environmental protection resolves into five practical domains — air, water, soil, noise, and waste — each with its own regulatory logic but a shared dependence on spatial data. Third, assembling an environmental GIS database, as demonstrated in the Szombathely case study, requires the same three ingredients regardless of scale: geometry, remote sensing, and field ground-truth. Fourth, near real-time simulation — whether of a pollutant plume, a noise contour, or a crop failure — has replaced slow, after-the-fact observation as the operative standard. Fifth, the drivers already visible in political, economic, demographic, technological, and environmental trends indicate that this shift toward automated, continuous, situational monitoring will continue to accelerate through 2030, alongside a corresponding need for clearer legal and ethical frameworks around the data it depends on.

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IMPLEMENTATION OF WATER-SAVING IRRIGATION TECHNOLOGIES TO IMPROVE RESOURCE USE EFFICIENCY AND ENSURE NATIONAL FOOD SECURITY

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Abstract. *This article examines the effects of irrigation methods and irrigation technique elements used in the management of intensive apple orchards under the conditions of typical sierozem and meadow-sierozem soils of the Tashkent region on seasonal water consumption and fruit yield, as well as the role of intensive horticulture in ensuring national food security. In the foothill zones with typical sierozem soils, the use of cross-blocked furrows aimed at preserving soil fertility and reducing irrigation erosion, and under meadow-sierozem soils with close groundwater occurrence, the application of drip irrigation technologies reduced soil particle washout by 31.3–38.7%, total water consumption by 7–13%, seasonal irrigation water use by 25–52%, and increased yield by 9.2–12.8 t/ha.*
Keywords: *intensive apple orchards, cross-blocked furrows, drip irrigation, food security, irrigation, yield.*

Introduction. Over the past decade, factors threatening food security worldwide, namely a decline in agricultural crop productivity as a result of global climate change, population growth (by 2050 the world population will approach nearly 10 billion), reduction of irrigated areas and intensification of land degradation processes, increasing water scarcity, and sharp price fluctuations in international markets, have turned food security policy into an important global issue. In arid regions, ensuring food security is directly related to the efficient use of land and water resources. Climate change, population growth, degradation of irrigated lands, and water scarcity are intensifying pressure on natural resources. Under the conditions of Uzbekistan, more than 70% of agriculture relies on irrigated lands, while a significant portion of annual renewable water resources is formed from transboundary sources. From this perspective, the intensification of horticulture is not only a factor of agrarian modernization but also a strategic necessity for ensuring national food security.

According to FAO (2022), the World Bank (2023), and other international sources, high-density intensive orchards can increase land productivity by 2.5–3 times and water-use efficiency by 40–60%. However, under the conditions of Central Asia, the effectiveness of these systems has not been sufficiently studied. The relevance of this research lies precisely in this aspect – scientific assessment of the agrotechnical, water-saving, and environmental efficiency of intensive orchards based on region-specific field experiments. Agriculture plays a crucial role in ensuring food security worldwide, since all food products are produced on irrigated lands. Therefore, the development of the agrarian sector serves as an important factor in providing humanity with food.

Global climate change has a serious impact on freshwater scarcity and food security. Meeting the population’s demand for food products and ensuring efficient use of irrigated lands and water resources are among today’s most important tasks. Under climate change conditions, it

becomes necessary to fully utilize existing opportunities and apply advanced technologies in agricultural production.

Materials and Methods. According to United Nations data, one-quarter of the world's population does not have access to adequate nutrition, which poses a threat not only to socio-economic stability but also to national security. Developing and low-income countries suffer the most from food crises. Developed countries possess more tools to combat inflation; therefore, food inflation in these countries is 2–2.5 times lower compared to other parts of the world. Despite deep reforms being implemented in the country, droughts, water scarcity, and sharp increases in air temperature lead to imbalances between production costs and market prices of agricultural products.

Currently, one of the most pressing issues for the global community is ensuring food security. Global climate change, population growth, inefficient land use, and rising food prices pose new and complex challenges for countries. Under such conditions, the development of various agricultural sectors, particularly intensive horticulture, is of great importance in providing the population with healthy, nutritious, and high-quality food products and ensuring food security. Ensuring food security is a strategically important component of national policy and one of the key conditions for economic and social stability and state independence.

Food security is closely linked to the intensification of agricultural production, efficiency of social production, and stabilization of population incomes. Therefore, addressing such global problems requires not only agricultural intensification but also improving living standards, environmental protection, expanding gross domestic product production, and strict monitoring of population and domestic market demand to stimulate the production of food products in the required volumes. One of the main directions for increasing agricultural efficiency in the country is the development strategy of intensive horticulture and intensive agricultural technologies. Field experiments were conducted from 2015 to 2025 under various soil and climatic conditions, including typical sierozem and meadow-sierozem soils. The studies compared traditional irrigation methods with drip irrigation and cross-blocked furrow irrigation, while soil moisture was monitored in calculated layers of 0.5, 0.8, and 1.0 m.

The main objectives of the research were to scientifically substantiate optimal irrigation methods and irrigation technique elements in an intensive horticulture system aimed at efficient land use, obtaining higher yields per hectare compared to traditional orchards, applying modern technologies such as drip irrigation, soil moisture control, rational use of mineral and organic fertilizers, producing high-quality, early-ripening, export-oriented, environmentally friendly fruits meeting market demand, selecting high-yielding, early-maturing, and disease-resistant varieties, and ensuring yield stability from year to year.

Seasonal crop water consumption was calculated based on soil water balance, transpiration intensity, evapotranspiration, crop growth stages, agro-technical practices, and climatic conditions. Calculations were performed using FAO-recommended methods, including Penman–Monteith, Blaney–Criddle, Hargreaves formulas, as well as CropWAT and AquaCrop software.

Results. The experimental fields in Qibray and Middle Chirchik districts of Tashkent region are characterized by typical sierozem, meadow-sierozem, and light sierozem soils. These soil types differ in physical-mechanical and agrochemical properties, water permeability, and reclamation potential, which allowed evaluation of the effectiveness of water-saving technologies under different natural conditions. The total area of the Tashkent region is 1,526.1 thousand hectares, of which 338.4 thousand hectares are irrigated lands used mainly for growing cotton,

cereals, rice, perennial plants, as well as household and various agricultural crops. The main sources of water in the region are the Chirchik-Akhangaran and Syrdarya rivers.

In the regions where the research was conducted, the mechanical composition of the soil, its physical, hydrophysical, physico-chemical and other properties were studied. Accordingly, the soils of the first experimental field (Kibray district) consist of a mechanically heavy clay layer 1.0 m thick, and the soils of the second experimental field (Middle Chirchik district) consist of medium—loamy loamy soils (Fig. 1).

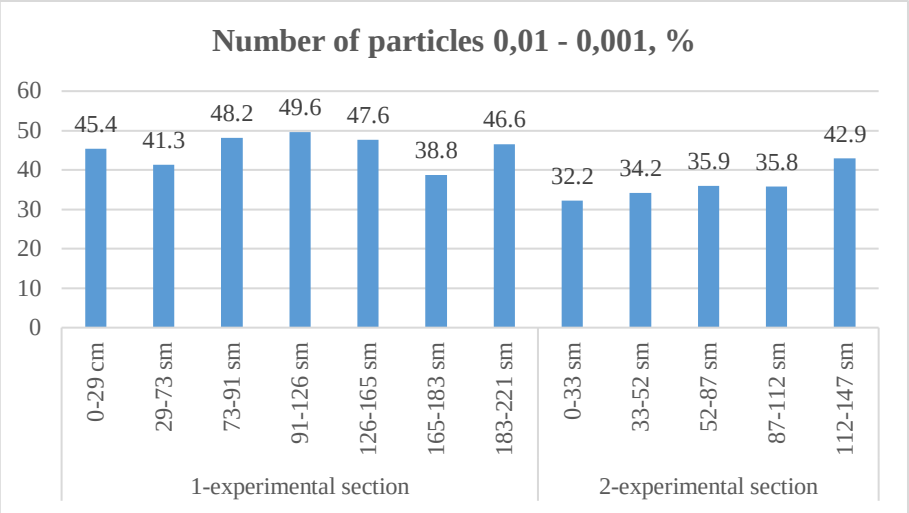


Figure 1: Mechanical composition of the soil in the experimental plots.

Cultivated soils are assessed on a quality scale (bonite scores) from 60 to 65. The average water permeability is average. The average porosity of the soils is 45-47%, and the natural moisture in the soil layer ranges from 18 to 23.5% relative to the soil mass. Water consumption by agricultural crops varies during the growing season, depending on the stages of plant development. The time of water consumption depends on the biological characteristics of each crop. The water requirement rate for cereals, cobs, legumes and similar crops per hectare is determined by the following formula:

$$M = 100 * a * h * (W_{\max cap.} - W_{pre\ irr} + k. \quad (1)$$

When calculating the seasonal water balance of agricultural crops in a village, factors such as the intensity of transpiration, evapotranspiration, the need for water at different stages of plant growth, agrotechnical techniques and climatic conditions play an important role. Calculations are based on evapotranspiration (ET method). This method is based on the Penman-Monteith, Blaney-Criddle and Hargreaves formulas recommended by the FAO for determining the total evaporation of moisture from the surface of plants.

$$ET_c = ET_0 * K_c \quad (2)$$

Here: ETc is the actual water consumption of the crop (mm), ET0 is the base evaporation (mm), Kc is the culture coefficient (varies depending on the stages of active growth).

The method of determining the soil moisture balance (water balance equation) includes the calculation of soil moisture deficiency.

$$W_1 + P + I = ET + R + D + W_2 \quad (3)$$

In this regard: W_1, W_2 - soil moisture at the beginning and end of the season; P - precipitation; I - volume of irrigation water; ET - seasonal evaporation; R - radiation of the soil surface; D - drainage losses. In addition, there are methods based on determining biomass production depending on the seasonal water supply of crops, calculations based on lysimetric

measurements, methods based on aerodynamics and energy balance, and the Penman-Monteith method is currently widely used. When determining the total volume of water supplied to plants (evapotranspiration), adjustments are made based on coefficients affecting the reflection of soil moisture by plants and climatic conditions. Taking these coefficients into account, the total volume of water (mm) is determined as follows.

$$ET = k_b\, k_0\, ET_0 \qquad (4)$$

At this point: k_b is the biological coefficient expressing the influence of plants; k_0 is the microclimate coefficient; ET_0 is the potential evaporation, mm. There are several methods for determining the water balance and evapotranspiration of crops in our climatic conditions. Among them, the widely used method based on the simplified formula of A.M. and S.M. Alpatiev for calculating water consumption and evapotranspiration belongs to N.N. Ivanov.

$$ET_0 = \sum d\omega \qquad (5)$$

Where: ET_0 - evaporation, mm; KPR - coefficient has 0.61-evaporation per year ratio; $\sum d\omega$ is the sum of the air humidity deficit for the billing period, mm. Determining the order of irrigation of crops using the cropwat and aquacrop programs developed by the International Food and Agriculture Organization of the United Nations (FAO).de: ET0 - evaporation, mm; KPR - coefficient has 0.61-evaporation per year ratio; $\sum d\omega$ is the sum of the deficits:

$$W_{r,t+1} = W_{r,t} + (P - RO) + I + CR - E - T_r - DR \qquad (6)$$

Here: P is the amount of precipitation; RO is evaporation from the surface of reservoirs; CR is the capillary rise of groundwater; E is moisture retention from the soil surface; Tr is plant transpiration; DR is deep filtration; $W_{r.t.}$ is the amount of water in the active layer. In our experiments, we determined that the total water consumption of a crop using the field water balance method is:

$$E = AP + W + M + W_{gr} + W_{sisi} \qquad (7)$$

In this part: E is the total water consumption due to evaporation; AR is the amount of water used due to transpiration; A is the coefficient indicating how much water is used from the leaf; R is the amount of natural water; W is the amount of moisture used by the root layer of the plant; W = Wi — Wk is the amount of moisture, used at the beginning and end of the growing season; M is the irrigation coefficient; W_{gr} is the amount of soil water used; W_{sis} is the water consumption for irrigation. Measures to increase soil fertility are divided into agrotechnical and agro-reclamation. In the accumulated irrigation experience, methods of using intensive irrigation to prevent erosion of water resources and irrigation systems, as well as elements of the organization, sequence and technical methods of irrigation have been studied. If 3.0 cm of water accumulates in a measuring vessel at a flow rate of 0.218 l/sec or 13.08 l/min, then if there are 25 intensive irrigation sites in the 4x2.5 scheme, this will amount to 5.45 l/sec or 0.21 m^3 per minute (figure 2).

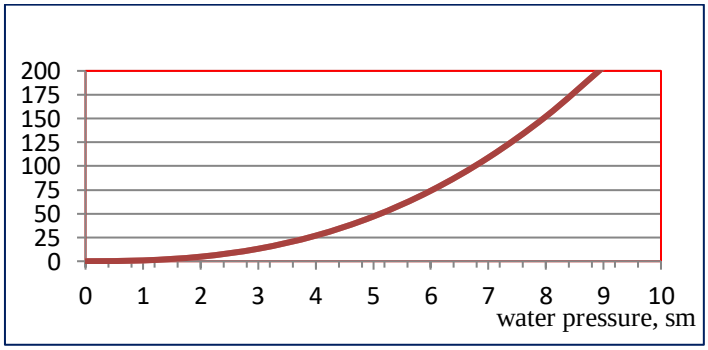


Figure 2. Water flow through the Thomson water meter 90^0, l/min

At the experimental site, in the control version, the number of irrigations was 4 times, and the average irrigation rate was 650 m^3/ha, while seasonal water consumption averaged 2,580 m^3/ha per year. In the same experimental site, in the 3rd variant, where fruit trees received moisture to a depth of 0.8 m on loamy soil, the number of irrigations was 5 times, and the average seasonal water consumption was 2220 m^3/ha. In the 4th variant, that is, in the variant where the soil received moisture to a depth of 0.5 m on loamy soil, irrigation was carried out 6 times, and the total water consumption was 1970 m^3/ha.

In the area of Middle Chirchik, when processing two experimental plots in alluvial soils, apple orchards were intensively grown using an irrigation system that ensures the moisture content of soil layers 0.5-0.8 and 1.0 meters thick at the level of 75-80-70% of the field moisture capacity. As a result of the study, the influence of irrigation methods on the yield and seasonal water consumption of apple orchards was studied. The soil moisture content at a depth of 1.0 m is precisely controlled at the level of 75-80-70%, with 14 waterings, an average interval of 9-10 days between waterings and an annual water consumption of 1200 m^3/ha. In the monitoring variants, these indicators are slightly lower, namely: in the variant with a soil moisture content of 0.8 m, with precise watering, irrigation rates were 60-90 m^3/ha, the average interval of 8-9 days between watering and annual water consumption of 1020 m^3/ha (Fig. 3).

In experiment 1, conducted in Kibray district, the influence of irrigation methods and elements of irrigation equipment on apple yields was studied. The control group, in which moisture was provided on the calculated soil layer with a thickness of 1.0 m, showed an increase in yield by 70-70-65% compared with the traditional irrigation method using conventional seeders. Over 3 years, the average fruit yield was 23.4 tons per hectare, with each fruit weighing an average of 106 g. The variants irrigated using transverse barrier trays with moisture applied to the calculated 0.8 and 1.0 m thick layers showed higher average fruit weight — 124 g, 132 g, 109 g — and yields of 24.8, 30.7 and 29.0 tons, respectively (Fig. 4).

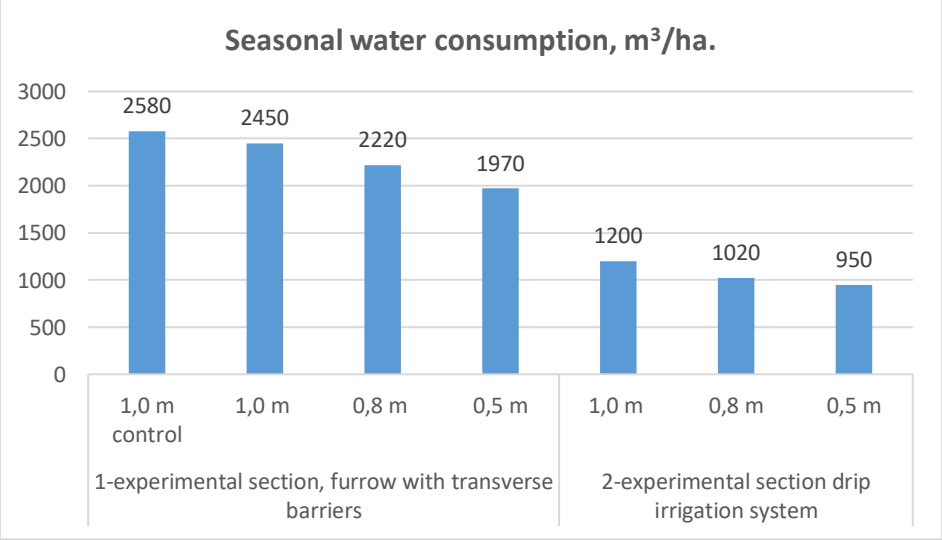


Figure 3. Seasonal irrigation rate in experimental fields, m^3/ha

In the 2nd experimental field in the conditions of meadow alluvial soils of the Tashkent region, the flowering period of the Golden apple tree occurred in the third decade of April and the first decade of May. Lowering the air temperature below 12 °C during the flowering period of apple trees negatively affects the development of flower buds, causing a delay in their opening, In the 2nd experimental field, in the conditions of meadow alluvial soils of the Tashkent region, the flowering period of the Golden apple tree fell on a third of the year. In Option 2, where irrigation

was carried out with 0.8 m of the calculated soil layer, the yield averaged 35.2 t/ha, the weight of one apple averaged 114.3 g. This indicator was 3.8 t/ha and 8.6 g compared with option 3, where irrigation was carried out with 0.5 m of the calculated soil layer, 1.0 m of soil layer was observed at 7.1 t/ha and 14.6 g higher than that of the control variant, irrigated with provision (Fig.4).

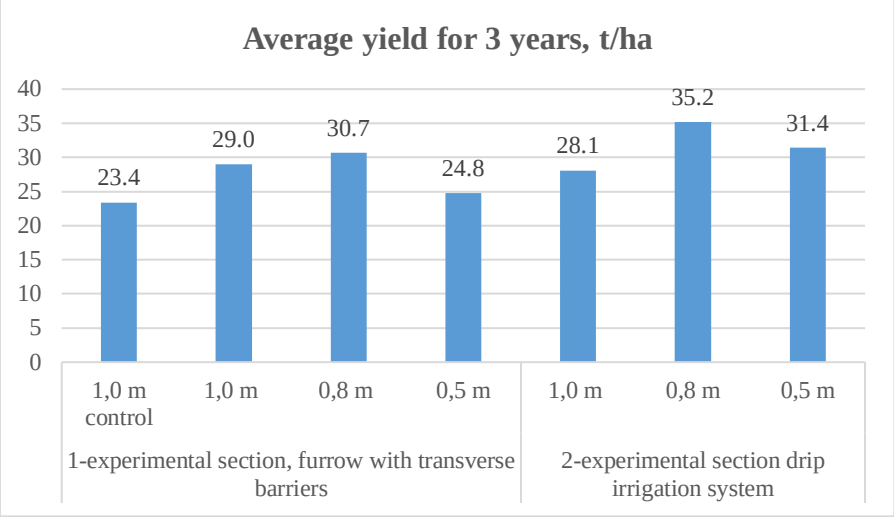


Figure 4. Average yield in experimental plots for 3 years, t/ha

When the seasonal water consumption of fruit orchards was determined in the experimental field (on typical sierozem soils with groundwater located at a depth of 15 m or deeper), plants in the control treatment (conventional furrow irrigation) used 18.0% of the soil moisture reserves. In Treatment 2, where irrigation was carried out using furrows with transverse barriers, wetting a 1.0 m soil layer, plants utilized 16.3% of the soil moisture reserves.

Under the same irrigation method, in Treatment 3, with wetting of a 0.8 m soil layer, this indicator amounted to 15.7%, while in Treatment 4, where a 0.5 m soil layer was wetted using this method, the value reached 18.6%. In this experiment, the lowest amount of irrigation water used per 1 ton of yield (63.1 m³/t) was observed in Treatment 3, where irrigation was carried out using furrows with transverse barriers, providing moisture to a 0.8 m soil layer. In contrast, the highest irrigation water consumption (108.6 m³/t) was recorded in the control treatment, where irrigation was performed by conventional furrows, supplying moisture to a 1.0 m soil layer (Fig.5).

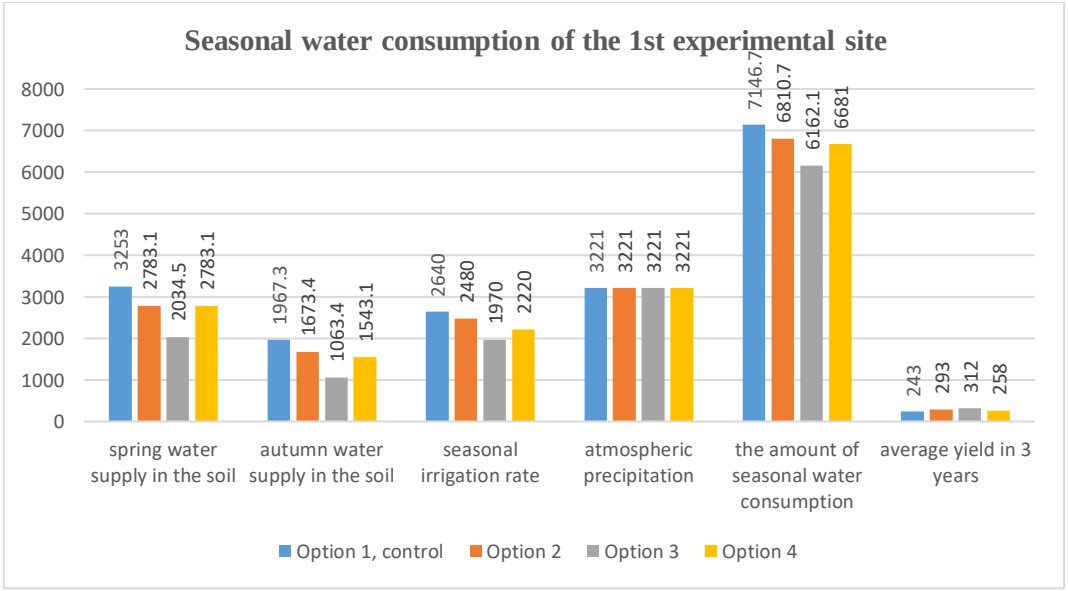


Figure 5. Seasonal water consumption by experimental field No. 1, located in Kibray district

In studies conducted under meadow–sierozem soil conditions, determination of fruit orchard water consumption in the first year of the experiment showed that the soil water permeability, bulk density, and mechanical composition had a significant influence on both water consumption and the amount of irrigation water applied. Some differences were also observed in the use of atmospheric precipitation by plants. In Treatment 1, where irrigation was applied by supplying moisture to a 1.0 m soil layer, plants utilized 54.8% of the precipitation. In Treatments 2 and 3, where the 0.8 m and 0.5 m soil layers were wetted, these values were 54.9% and 53.8%, respectively (Fig.6).

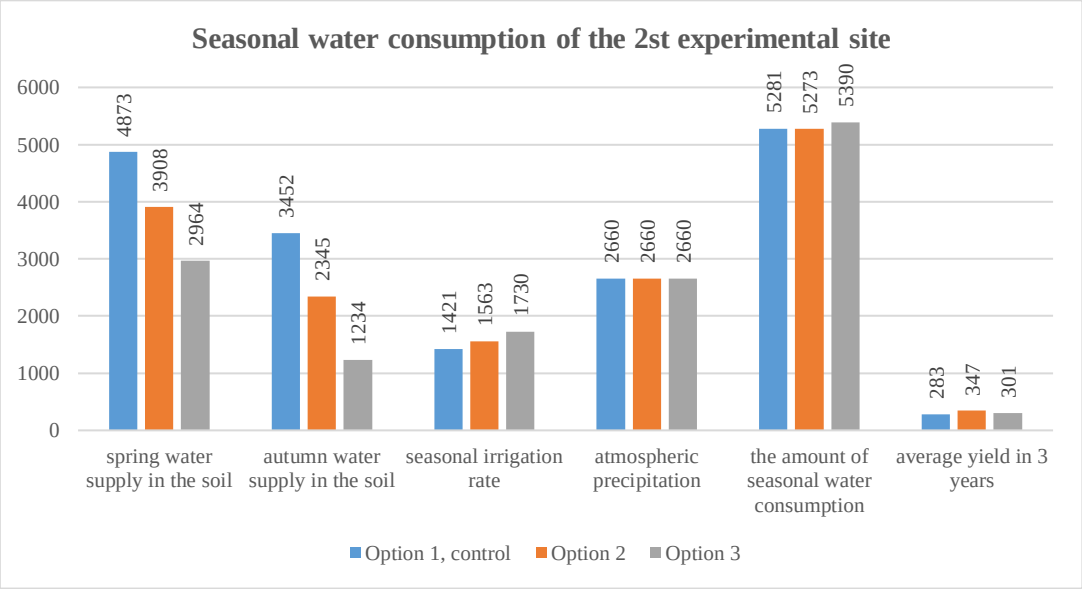


Figure 6. Seasonal water consumption by experimental field No. 2, located in Middle Chirchik district

In this experiment, to determine the efficiency of plants' use of seasonal water reserves, the amount of irrigation water consumed per 1 ton of yield was 42.4 m³/t in Treatment 1, while in Treatments 2 and 3 this indicator amounted to 30.3 m³/t and 33.2 m³/t, respectively.

Discussion. According to Clause 12 of the Presidential Decree of the Republic of Uzbekistan No. PF-36 dated February 16, 2024 "On additional measures to ensure food security in the Republic," tasks were assigned to develop high-yield, disease- and drought-resistant local varieties of key vegetable crops, establish seed production, adapt agriculture to global climate change, implement No-Till technologies on rainfed and water-scarce lands, and replace soil salinity leaching practices with biological methods.

According to the National Statistics Committee of the Republic of Uzbekistan, in January–March 2024, the volume of agricultural production amounted to 42,360.4 billion UZS, or 103.6% compared to the corresponding period of 2023, including crop production – 2,890.9 billion UZS (104.4%) and livestock production – 39,469.5 billion UZS (103.6%). The highest volumes of agricultural production were recorded in Samarkand (5,531.8 billion UZS), Tashkent (4,995.0 billion UZS), and Bukhara (4,038.7 billion UZS) regions. High growth rates were recorded in Namangan (104.4%), Navoi (104.4%), and Syrdarya (104.2%) regions. According to committee data, 86.1% of total agricultural food production is produced by farmer and household farms, 8.8% by farmer enterprises, and 5.1% by agricultural organizations.

Conclusions. When intensive apple orchards are irrigated using water-saving technologies (drip irrigation, furrow irrigation, furrows with transverse barriers, as well as furrow irrigation combined with black polyethylene mulch), the efficiency of tree water use from soil moisture,

atmospheric precipitation, and irrigation water increases. As a result, seasonal water consumption can be reduced by 12% to 52% compared with conventional furrow irrigation. Under the conditions of the Republic's irrigated typical sierozem, meadow alluvial, and light-colored sierozem soils, drip irrigation of intensive apple orchards, compared with the traditional method, reduces seasonal water consumption by up to 52%, decreases irrigation erosion processes by 100%, and ensures an increase in apple yield of 12.3 t/ha.

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RESULTS OF THE INVESTIGATION OF BLACK SAXAUL (HALOXYLON AMMODENDRON) SEED GERMINATION

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Abstract. *The article describes the formation of an unfavorable environmental situation resulting from the decline in the water level of the Aral Sea, the expansion of saline land areas, and the increasing negative impact of toxic salts on plant population dynamics. In addition, within the framework of Project No. Al-9424114992, the results of studies on improving the germination of black saxaul seeds are presented. The seeds, both winged and de-winged forms, were treated using humimax, bentonite, and clay (pakhsa wall soil) as substrate components.*
Keywords*: halofit, 12^{00}–13^{00} hours, pipette, 20–25 ml of water, noted in option 5 10%.*

Introduction

Over the past 50 years, the decline in the water level of the Aral Sea and the resulting unfavorable environmental conditions in the region have led to a reduction in the quality of many economically important agricultural crops. Within the forest fund areas, increasing soil salinization, declining soil fertility, expansion of saline lands, and the accumulation of toxic salts have negatively affected plant species populations. Afforestation is considered one of the primary approaches to mitigating this environmental problem.

Forests protect soil from erosion, provide habitats for numerous animal species, and influence the global climate. Every year, millions of hectares of forests are lost worldwide. Some countries attempt to compensate for these losses through reforestation and forest restoration programs [4]. Currently, stabilization of biodiversity in the Aral Sea region can largely be supported through the establishment of green cover using seeds of naturally growing halophytic plant species adapted to local conditions.

The Development Strategy of the Republic of Uzbekistan for 2022–2026 (New Uzbekistan Development Strategy) defines key priorities, including environmental protection, improvement of ecological conditions in cities and districts, and the implementation of the nationwide "Green Space" initiative. Within this framework, it is planned to establish an additional 500,000 hectares of green areas on the dried seabed of the Aral Sea and increase the total green coverage to 2.5 million hectares, or 78% of the territory, by the end of 2026.

Accordingly, within the framework of Project No. Al-9424114992 entitled "Development of Modern Technologies for Establishing Green Cover on the Dried Seabed of the Aral Sea and Cultivation of Desert and Pasture Forage Plants," our research investigated the germination performance of black saxaul seeds under laboratory conditions based on the biological characteristics of halophytic plant species.

During the study, the germination of both winged and de-winged black saxaul seeds was evaluated following treatment with humimax, bentonite, and clay (pakhsa wall soil). The following results were obtained. On December 20, 2025, between 12:00 and 13:00, seed samples were collected for laboratory germination experiments. Humimax, bentonite, and clay soil were primarily used in the germination process. Humimax is an organo-mineral nutrient suitable for various plant species and consists of humic acids prepared from peat and sapropel extracts (sediment from irrigation canals and drainage ditches), plant organic matter, and phytohormones.

Bentonite clay mainly consists of minerals belonging to the montmorillonite group and is sometimes referred to as “stone soap.” In addition to montmorillonite, bentonite may contain hydromica, kaolinite, palygorskite, zeolites, and other minerals. Bentonite is formed through the diagenetic transformation of volcanic tuffs and ash in aqueous environments, primarily marine basins (see diagenesis) [5].

Due to its layered crystalline structure and high water absorption capacity, bentonite swells significantly upon contact with water. To conduct experiments aimed at improving seed germination using mineral nutrient elements, the following materials were prepared: humimax, bentonite, clay soil, Petri dishes, filter paper, tweezers, pipettes for watering, and other necessary laboratory equipment. All containers were washed and dried prior to use.

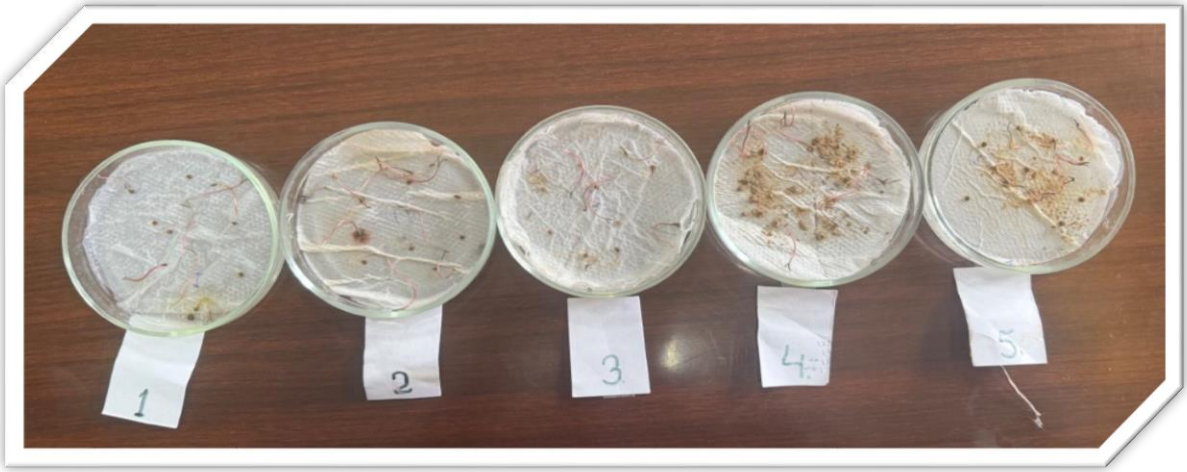


Figure 1. Experimental procedure for evaluating the germination of de-winged seeds

It is well known that seed germination depends on appropriate indoor lighting conditions. In accordance with lighting requirements, the standardization and hygienic assessment of natural illumination were based on two principal methods: the light-technical (instrumental) method and the geometric (calculation-based) method. The primary indicator of the light-technical method is the Daylight Factor (DF), which is determined using the following formula:

$DF = (E_1 / E_2) \times 100\%$

where E_1 represents the illuminance level inside the room, and E_2 represents the illuminance level outside the building. The normative values of the Daylight Factor are established according to the functional purpose of the room and the type of activity carried out within it. These standards comply with SanPiN 2.2.1/2.1.1.1278-03, “Hygienic Requirements for Natural, Artificial, and Combined Lighting in Residential and Public Buildings” (2003) [Methods for Assessing Lighting in Indoor Environments, https://ru.wikipedia.org/wiki].

On December 22, 2025, ten seeds from each treatment variant were placed in Petri dishes and moistened with 20–25 ml of water using a pipette. The germination indicators of the de-winged seeds are presented in Table 1.

Table 1. Germination Performance of De-winged Seeds Under Experimental Conditions

№	Treatment Variant	Dates and Number of Germinated Seeds									Total Germination (%)
		21.12	22.12	23.12	24.12	25.12	26.12	27.12	28.12	29.12	
1	Control	1	3	3	0	0	0	0	0	0	70%
2	Humimax	2	3	3	2	0	0	0	0	0	100%
3	Humimax + Bentonite	1	3	2	0	0	0	0	0	0	60%
4	Humimax + Clay Soil (Pakhsa)	0	1	1	1	1	0	0	0	0	40%
5	Humimax + Bentonite + Clay Soil	0	1	1	1	1	0	0	0	0	40%

Due to the relatively low room temperature (18–22 °C), a slight delay in seed germination was observed.



Figure 1. Process of Studying the Germination of Non-De-winged

(Winged) Seeds

Germination indicators may vary depending on temperature conditions; therefore, the number of germinated seeds was recorded daily. Germination of winged seeds was delayed by 4–5 days compared to de-winged seeds.

The germination performance of non-de-winged (winged) seeds is presented in Table 2.

Table 2.

Germination Performance of Winged (Non-De-winged) Seeds Under Experimental Conditions

№	Treatment Variant	Dates and Number of Germinated Seeds									Total Germination (%)
		21.12	22.12	23.12	24.12	25.12	26.12	27.12	28.12	29.12	

1	Control	0	0	0	0	3	0	0	1	0	40%
2	Humimax	0	0	0	0	4	0	0	2	0	60%
3	Humimax + Bentonite	0	0	0	0	2	0	0	0	0	20%
4	Humimax + Clay Soil (Pakhsa)	0	0	0	0	2	0	0	0	0	20%
5	Humimax + Bentonite + Clay Soil	0	0	0	0	1	0	0	0	0	10%

The highest germination rate was observed in the Humimax treatment (60%), while the lowest result (10%) was recorded in Treatment 5. The timing and duration of seed germination were influenced by ambient temperature conditions. Morphological assessment of seedlings obtained from black saxaul (*Haloxylon aphyllum*) seeds showed that the average total seedling length reached 50 mm, while the mean root length was 25 mm.

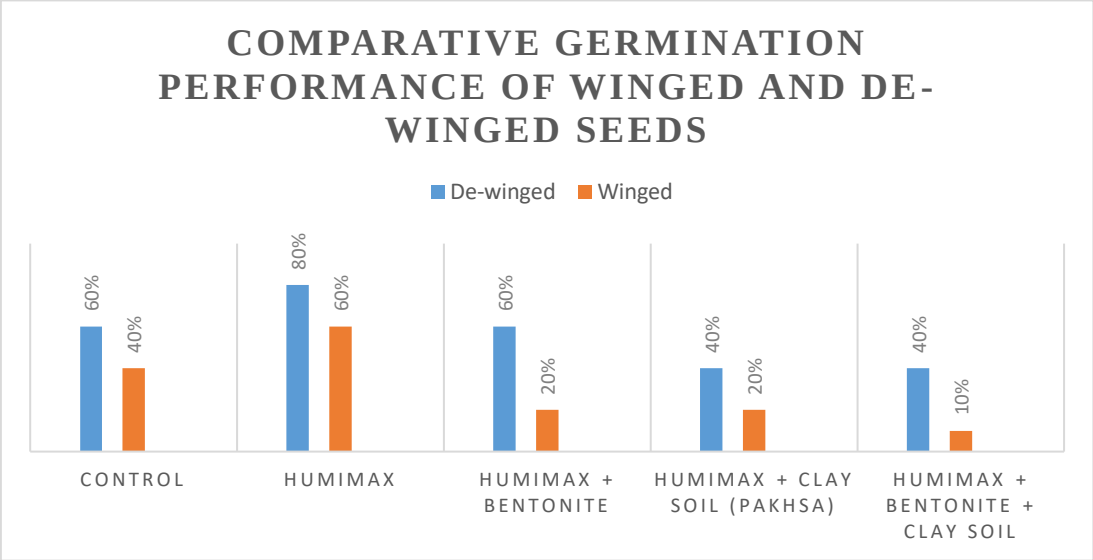


Figure 3. Effect of mineral nutrient elements on seed germination

These biometric indicators reflect satisfactory early growth under laboratory conditions and indicate adequate nutrient and moisture supply during the germination phase.

Results and Discussion (Enhanced Version)

Long-term studies conducted between 2006 and 2021 also investigated pre-sowing treatment methods, including seed wing removal and seed coating technologies [1–3]. Comparative analysis demonstrated that mechanical removal of seed wings ensures more uniform water absorption and improves contact between the seed surface and the substrate, thereby positively influencing germination dynamics. In our preliminary studies, treatment with Humimax resulted in germination rates ranging from 60% to 80% within 24 hours.

Among all treatment variants, the highest germination rate was observed in de-winged seeds treated with Humimax. Under field conditions, seeds treated with substrate-based variants (254,600 seeds in total) demonstrated germination rates ranging from 15% to 47%, while by September these rates decreased to 1%–4.5%. These results may be explained by the presence of humic acids and biologically active substances in Humimax. These compounds activate metabolic processes, stimulate enzymatic reactions, and promote faster radicle emergence. In contrast, untreated and mixed-substrate variants exhibited comparatively lower germination percentages.

Conclusion

It should be emphasized that seed germination was strongly influenced by ambient temperature conditions. The relatively low room temperature during the experimental period caused a slight delay in the onset of germination. Germination activity gradually declined and ceased on December 29, indicating the temperature-dependent nature of physiological processes in saxaul seeds. Overall, the application of Humimax as an organo-mineral nutrient significantly enhanced the germination efficiency of black saxaul seeds. The obtained results provide a practical basis for improving large-scale afforestation and green cover establishment on the dried seabed of the Aral Sea.

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HORTICULTURAL PLANTS. INVESTIGATION AND STUDY ON THE CHARACTERISTICS OF STRAWBERRY HYBRID OFFSPRING

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Abstract. *This study highlights information about functional genomics of horticultural plants, the main horticultural crops cultivated and combining my own research direction about characteristics of strawberry. Horticulture is a branch of agriculture, which as a science teaches the morphological structure of fruit trees, their growth, development, methods of reproduction, and the laws of yield and care technology. The acquisition of the above knowledge is of great importance in the formation of agronomists, farmers and helps to carry out agro technical measures at a high level and in a timely manner. Horticulture is considered a highly profitable branch of agriculture, providing fruits and berries for the human body. Central Asia is the homeland of many fruit species. Over the centuries, highly productive varieties of apricots, apples, pears, walnuts, almonds, pomegranates, grapes have been created on the basis of folk selection. Many of them have a unique place in the world collection in terms of quality. Furthermore, it gives information about resistance of hybrid strawberry varieties to biotic and abiotic stresses, details and collection data about strawberry. Strawberries are very essential fruit crop cultivated worldwide. Researching the characteristics of strawberry hybrid offspring is very important to study strawberry varieties with high yield, disease resistance, large fruit, and long shelf life, adaptability to different climates, excellent taste, strong aroma and increased sweetness. Hybrid cultivars are appropriate for long-term postharvest storage, export markets, and intensive cultivation. Strawberry breeding is one of the most important agronomic fields in the world, and hybridization is a key tool for increasing yield, improving fruit quality, and disease resistance in new varieties.*

Keywords: *functional genomics of horticultural plants, biotic and abiotic stresses, characteristics of strawberry, hybrid strawberry, horticultural plants, agriculture.*

Introduction

These days horticultural plants play an essential role in agriculture. The reason is that horticultural plants are major part of agriculture. One of the main sectors that determine the economy of the Republic of Uzbekistan and bring in significant income is horticulture. Without developing this sector on a scientific basis, it is impossible to satisfy the demand for fruit products of the population and our industry. Therefore, it is necessary to thoroughly study the agricultural sectors, including horticulture, to identify the problems that have arisen and find positive solutions to them.

With the growth of the material well-being of the population, their needs for fruit products are also increasing, because fruits (in wet and dried forms) are nutritious, tasty and healing food necessary for human health. Therefore, ensuring the population's demand for fruits throughout the year is a requirement of this era. Horticulture is a branch of agriculture, which as a science teaches

the morphological structure of fruit trees, their growth, development, methods of reproduction, and the laws of yield and care technology. The acquisition of the above knowledge is of great importance in the formation of agronomists, farmers and helps to carry out agro technical measures at a high level and in a timely manner. Horticulture is considered a highly profitable branch of agriculture, providing fruits and berries for the human body. It contains sugars, organic acids, oxides, oils, vitamins, mineral salts, pectin, enzymes, colloids and other substances. Fruits and berries are raw materials for food and industry.

It is important to state that, more than 200 types of fruits, berries, and nuts are cultivated in world horticulture, of which 100 are of industrial importance. Apples, olives, palms, bananas, mangoes, and grapes are among the most widely cultivated fruit species. Horticulture is developed in China, the USA, India, Argentina, Brazil, Japan, Spain, France, Italy and Uzbekistan.

Central Asia is the homeland of many fruit species. Over the centuries, highly productive varieties of apricots, apples, pears, walnuts, almonds, pomegranates, grapes, etc. have been created on the basis of folk selection. Many of them have a unique place in the world collection in terms of quality. At the beginning of the 20th century, there were about 50 thousand hectares of orchards in the territory of present-day Uzbekistan, including 22 thousand hectares of orchards and 37 thousand hectares of vineyards. The main areas of orchards were the Fergana Valley (24%), the Tashkent Oasis (36%) and the Zarafshan Valley (50% of vineyards). In the orchards, stone fruits occupied 70% (mainly apricots), and pome fruits (apples, pears, quince) occupied 25% of the area. In the outskirts of cities and villages, in separate orchards and gardens (orchards, vineyards, melon gardens and flower gardens), local varieties of fruits, vines, and various flowers were planted. The grown fruits were consumed fresh, but the main production was the cultivation of plums and raisins.

From the second half of the 1920s, specialized fruit and viticulture farms began to be established, and collective farms located in the mountain and foothill zones also paid great attention to this sector. In order to improve the varietal composition of fruits, varieties of apples, pears, grapes, and others grown in European countries were introduced and planted. In the late 1950s and 1960s, agro-combinations with 2,500-3,000 hectares of orchards and vineyards were established. 20 types of fruits and berries are grown in the Republic. The main place is occupied by seed fruit trees (apple, pear, quince, etc.), stone fruit trees (apricot, peach, plum, cherry, sour cherry, gooseberry, etc.), subtropical plants (pomegranate, fig), nut fruits (walnut, pistachio, almond), berry fruits (strawberry, raspberry, currant, gooseberry). Summer, autumn and winter varieties of apples, pears and grapes are of significant economic importance. Viticulture has long been developed in the Tashkent and Samarkand regions, the Fergana Valley, and has food, raisin and canned products (molasses, jam, juices), as well as winemaking. Unique varieties of fruit jams and raisins are produced in Uzbekistan.

The majority of horticultural plants are those that produce vegetables, fruits, ornaments, beverages, and herbal medicines. By meeting fundamental dietary needs, enhancing personal aesthetics, and adorning both urban and rural environments, these plants have played significant economic and social roles in human lives and health. For instance, according to the Food and Agriculture Organization of the United Nations, fruits and vegetables together are worth 137 points, whereas cereal foods combined are worth 125 points (normalized value) worldwide. By supplying oxygen and regulating urban temperatures, horticultural plants help enhance our biological environment and promote ecological equilibrium.

Numerous blooming plants and a few early-divergent land plants are among the several taxonomic plant spectra that comprise horticultural plants. Their genomes differ substantially in size. For instance, the diploid genome (2n = 16) of the vegetable garlic (Allium sativum) is believed to be larger than 30 Gb1, whereas the genome size of the onion (Allium cepa) is comparable. Furthermore, the majority of horticultural plants are domesticated, and significant artificial selection has shaped their genomic sequences. Citrus has been cultivated for more than 4,000 years, and grapes have been cultivated (via viticulture) for more than 6000 years. Furthermore, certain horticultural plants are hybrids of wild and domesticated species. For example, ginseng (Panax ginseng), noto ginseng (Panax notoginseng), and Artemisia (Artemisia annua) are used medicinally. High levels of genetic diversity and heterozygosity are found in many domesticated horticultural plants, including potatoes (4.8%)7, sunflowers (10% of bases differ between homologous chromosomes), and grapes (7%)6.

Cultivation scale: The scale of horticultural plant culture varies from heavy commercial production to small-scale home gardens. With a focus on high-value crops and intense maintenance, it lies in the middle of field agriculture and home gardening. Horticultural crops, which are often farmed with more intensive care than agronomic crops, include fruits, vegetables, flowers, ornamental plants, and turf. A closer look at the various scales is provided below: With less emphasis on specialized or large-scale output, small-scale horticulture includes home gardens, small farms, and subsistence plots. It frequently focuses on a range of fruits, vegetables, and flowers. Commercial horticulture: This refers to the larger-scale production of particular crops, including fruits, vegetables, or ornamentals, frequently using more sophisticated technologies and stricter management techniques. Orchards: Dedicated spaces for fruit tree cultivation, usually on a bigger scale than backyard gardens.

Vegetable farms: These farms focus on producing vegetables for commercial markets, frequently utilizing cutting-edge farming methods and equipment.

The commercial cultivation of flowers and attractive plants, which might be grown in open fields, greenhouses, or other specialized facilities, is known as floriculture.

Scale: While horticulture concentrates on smaller, more intensive operations, agriculture usually involves large-scale field crops.

Management: With an emphasis on output and cost-effectiveness, agriculture may require less intense management than horticulture.

Focus: While horticulture might encompass a wider variety of crops with particular market demands, agriculture may give priority to staple crops.

Results: Due to the increased productivity and profitability of Uzbekistan’s horticultural enterprises, about 34,500 permanent jobs—nearly 40% of which were held by women—and almost 22,000 seasonal jobs—of which 75% were held by women—were created. In auxiliary businesses including food distribution, storage, and packaging, an extra 5,000 jobs were generated. Instead of needing to go to the city, young rural workers were able to make a steady income in their villages because to new jobs in rural logistics and transportation.

By adopting greenhouse technology, accessing better inputs, and improving agricultural methods, participating fruit and vegetable producers saw a 25–30% rise in crop yields and a 35% increase in gross sales, which increased labor demand and job sustainability. The project helped more than 5,000 firms grow, improve their operations, and create jobs by facilitating more than $300 million in concessional loans to farmers and agribusinesses.

The Problem and Discussion: In 2024, 49% of Uzbekistan's 37 million residents resided in rural areas, and the number of people living in rural areas is increasing more quickly than that in urban areas. A significant economic sector, agriculture accounted for 27% of all jobs in 2019. This is partially because to Uzbekistan's ideal position for horticultural production in particular. The climate supports a wide range of crops while reducing pests and illnesses, and in most parts of the country, it permits double harvesting of vegetables, and in some locations, triple harvesting. However, a lack of mechanisms to efficiently connect farmers to markets, bottlenecks in the value chain, a substantial investment gap estimated at over $1 billion, and farmers' low understanding of contemporary agricultural practices all hinder the horticulture sector's ability to grow more quickly. Increasing lending and productivity might help Uzbekistan's agribusinesses grow faster, take advantage of the nation's significant comparative advantage, and give the expanding rural population the jobs and skills they need to live better lives.

Method: In order to increase production and profitability, the World Bank collaborated with recipients throughout the horticulture value chain in Uzbekistan. With an emphasis on climate-smart technologies that helped secure long-term employment growth, the Uzbekistan Horticultural Development Project taught farmers to modern farming practices including hydroponics and irrigation that uses less water and energy. In addition to enhancing post-harvest handling, the interventions made horticulture occupations more sustainable and raised beneficiaries' profitability by more than 120 percent. Because farmers were able to sell their higher yields in new markets, horticulture exports surged, which was crucial for sustainability and employment development along the value chain. In order to increase women's employment, the project also featured focused interventions such financial incentives, training courses for female entrepreneurs, and skill development in high-value horticultural occupations.

Previously unavailable in Uzbekistan on a large scale, the World Bank worked with regional financial institutions to launch a special loan line for horticulture initiatives. This made it possible for farmers to obtain preferential financing for processing, export facilities, cold storage, and contemporary greenhouses. With a more than five-fold rise in gross sales, farms were able to create tens of thousands of jobs and help reshape the sector's economy. Our ability to produce up to 2,000,000 eco-friendly boxes annually—which local farmers and agribusinesses also use to export fruits and vegetables to markets in Europe and Asia—was greatly increased by the project, which allowed us to invest in state-of-the-art packaging production equipment. Currently, we employ about 300 individuals in stable jobs, with women and young people making up 60% of the workforce. (Rustam Buriyev) Owner of packaging production company, Tashkent, Uzbekistan.

If I relate this topic to my own research topic, at these days growing fruit is one of the most essential branches of agriculture. Because fruits have a lot of beneficial vitamins and ingredients, which are very useful to mankind. That's why much effort is paying attention to growing fruits not only in our country, but also all over the world. Importantly, I chose strawberry and strawberries are very essential fruit crop cultivated worldwide. Firstly, I gathered information about strawberry, in details I read about strawberry from books, magazines, newspapers and other online sources. After I collected data about strawberry, of course I went to strawberry fields. Following this, I analyzed strawberries.

Especially, I paid attention shapes of fruits, outer sides of fruits and I evaluated tastes of strawberries. Interesting factor that, I observed, if the strawberry has more leaves, it will bloom more. Moreover, when strawberries bloom, they need to be given calcium. Another interesting factor that, if strawberry grows in winter, it will be tastier, bigger than which is grown in summer.

It is the best temperature for strawberry is +18. In the evenings strawberry is developing and growing very well, +8 temperature is very suitable for strawberry in the evenings. Moreover, strawberry is the tastiest fruit in summer and it is very tasty and useful fruit. Everybody likes strawberry from 7 to 70 years old people. In summer, people eat fresh strawberry and it is prepared jam, juice from strawberry for winter. It is important to state that, in every season you can find strawberry in any supermarkets. I study and research the characteristics of strawberry hybrid offspring. **My goal** is to study strawberry varieties with high yield, disease resistance, large fruit, long shelf life, adaptability to different climates, excellent taste, strong aroma and increased sweetness. Additionally, I aim to research marketable varieties that do not spoil quickly and are suitable for long-distance transportation.

Resistance of Hybrid Strawberry varieties to biotic and abiotic stresses. In order to increase their tolerance to biotic stresses, which are brought on by living things, hybrid strawberry cultivars are frequently created.

The total output, fruit quality, and plant growth may all be adversely impacted by these st ressors. Strawberry hybrids include: Carefully chosen to be resistant to biotic stressors, like common illnesses and insect pests. They can flourish in a variety of soil and climate conditions because they were bred to withstand abiotic stress. Because of these traits, hybrid cultivars are appropriate for long-term postharvest storage, export markets, and intensive cultivation.

Many studies show that hybrid lines exhibit wide phenotypic variation in leaf shape, vigor, stolon formation, flower morphology, and fruit shape. The occurrence of conical, oval, round, and deformed shapes among hybrid fruits is one of the main problems in the early stages of selection. Studies confirm that the coefficient of variation for fruit shape and weight is high, and that these traits are polygenically inherited. Strawberry breeding is one of the most important agronomic fields in the world, and hybridization is a key tool for increasing yield, improving fruit quality, and disease resistance in new varieties. The phenotypic and genotypic variation observed in hybrid progeny offers great opportunities for breeders, but at the same time complicates the selection process due to the complex genetic structure. Strawberry plants possess fasciculated roots that consist of a significant proportion of volume specifically allocated to providing support to the plant and other components. These rootlets are responsible for absorbing nutrients and water necessary for the plant's development.

In conclusion, this study demonstrates functional genomics of horticultural plants, their types and sectors and their roles in agriculture. Horticultural plants play a vital role in agriculture and they are major part of agriculture. It is considered a highly profitable branch of agriculture, providing fruits and berries. Strawberries are vital fruit crop grown around the globe. In addition, collected data about strawberry and analysis of strawberry, resistance of hybrid strawberry varieties to biotic and abiotic stresses. It is essential to study strawberry varieties with high yield, disease resistance, large fruit, long shelf life, adaptability to different climates, excellent taste, strong aroma and increased sweetness. Hybrid varieties are suitable for extended post-harvest storage, overseas markets and high-intensity farming. Hybridization is an essential method for enhancing yield, boosting fruit quality and increasing disease resistance in new varieties.

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EFFECTIVENESS OF BIOLOGICAL PREPARATIONS IN ENHANCING SALINITY TOLERANCE IN STEVIA: MODERN APPROACHES

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Abstract. *Soil salinity is one of the major abiotic stress factors causing reductions in crop yield and product quality in agriculture. Stevia rebaudiana Bertoni is a high-value sweetener and medicinal plant whose leaves accumulate steviol glycosides widely used in the food and pharmaceutical industries. However, stevia is considered relatively sensitive to salinity, and salt stress conditions suppress growth, photosynthesis, mineral nutrition, and metabolic processes. This review analyzes the physiological and biochemical effects of salinity stress in stevia and examines the protective mechanisms of biological preparations, including plant growth-promoting rhizobacteria (PGPR), arbuscular mycorrhizal fungi (AMF), and seaweed-based bio stimulants. The literature indicates that biological preparations mitigate the negative effects of salt stress by improving ion homeostasis, activating antioxidant systems, enhancing osmotic regulation, and stimulating root development. As a result, vegetative growth, leaf biomass accumulation, and quality traits become more stable under saline conditions. Nevertheless, the molecular-level effects of biological preparations on steviol glycoside biosynthesis remain insufficiently studied. Biological approaches are therefore considered environmentally safe and promising strategies for stevia cultivation in saline soils.*

Keywords: *salinity stress, Stevia rebaudiana, biological preparations, PGPR, steviol glycosides, antioxidant system.*

INTRODUCTION

In recent years, the effects of salinity stress on plants have been widely studied. Research shows that high salt concentrations reduce plant water potential, leading to stomatal closure and a decline in photosynthetic rate. In addition, excessive accumulation of Na^+ and Cl^- ions limit the uptake of K^+ and Ca^{2+} [1]. Studies conducted on stevia have demonstrated that under saline conditions, leaf biomass and glycoside content decrease. Some studies have reported that even moderate salinity levels can significantly reduce the synthesis of steviol glycosides. The role of PGPR bacteria in enhancing plant salinity tolerance has been proven in many crops. They stimulate the synthesis of IAA, GA, and cytokinins, thereby promoting root system development. Through the ACC-deaminase enzyme, they reduce stress-induced ethylene levels, which helps maintain plant growth [3].

Arbuscular mycorrhizal fungi improve the uptake of water and nutrients under saline conditions. Studies indicate that plants inoculated with AMF exhibit a more optimal Na^+/K^+ ratio. Seaweed-based biostimulants increase the activity of antioxidant enzymes (SOD, CAT, POD) and reduce lipid peroxidation. As a result, cell membrane stability is preserved. However, the

molecular and metabolic bases of the effects of biological preparations on stevia have not yet been sufficiently studied. In particular, information on response mechanisms associated with steviol glycoside biosynthesis remains limited.

Soil salinity is one of the most important abiotic factors limiting productivity in irrigated agriculture. Its scale is expanding due to deteriorating water quality, insufficient drainage systems, and climate change. Under saline conditions, plants are simultaneously exposed to osmotic stress (water deficit), ionic toxicity (Na^+ and Cl^- accumulation), mineral nutrient imbalance (deficiency of K^+ and Ca^{2+}), and oxidative stress (increased ROS). These factors lead to reduced photosynthetic efficiency, disruption of membrane stability, and suppressed growth [5,7]. The relevance of this topic is determined by the following: (i) the need to stabilize the production of high-value medicinal and food crops under saline conditions;(ii) the challenge of maintaining glycoside content (stevioside, rebaudioside A) along with leaf yield in stevia [4,11], (iii) the growing demand for biological solutions that reduce chemical inputs [6,14].

Stevia rebaudiana Bertoni is a natural source of sweeteners, and the steviol glycosides accumulated in its leaves (mainly stevioside and rebaudioside A) are widely used in the food and pharmaceutical industries. Nevertheless, stevia is moderately sensitive to salinity, and many experiments have reported that increasing NaCl concentration leads to reductions in vegetative biomass, photosynthetic pigments, and certain quality traits [4,11,16]. In particular, decreases in stevia biomass and changes in glycoside composition under saline conditions have been emphasized [17]. Therefore, improving stevia cultivation technologies in saline soils, especially ensuring the stability of both yield and quality (glycosides), is an important scientific and practical task.

Conventional approaches (leaching irrigation, gypsum application, and increased mineral fertilization) are often costly or associated with environmental limitations. Therefore, in recent years, biological preparations have been widely studied as environmentally safe and resource-efficient solutions. These include biological products such as PGPR (plant growth–promoting rhizobacteria), arbuscular mycorrhizal fungi, and seaweed-extract-based biostimulants [8,11] These preparations can mitigate the harmful effects of salinity stress by strengthening the root system, improving ion homeostasis (normalizing the Na^+/K^+ ratio), activating antioxidant defenses, and enhancing osmoregulation in plants [2,5,7]. Research objective: To scientifically synthesize, based on the literature, the effectiveness of biological preparations in improving growth, productivity, and quality traits of stevia under salinity stress conditions, as well as their main mechanisms of action.

LITERATURE REVIEW

Salinity stress and stevia responses

Stevia under saline conditions is characterized by reduced growth, smaller leaf area, decreased chlorophyll content, and lower photosynthetic efficiency [11]. Several studies have shown that increasing salinity levels significantly reduce total dry biomass in stevia; at the same time, quantitative and qualitative changes occur in steviol glycoside composition [17]. Recent publications also confirm that severe salinity enhances oxidative stress and leads to declines in growth parameters [4]. Although certain adaptive responses—such as activation of osmotic regulators and antioxidant systems—may be triggered under salt stress, these mechanisms are often insufficient to fully maintain yield and quality stability.

Seaweed extracts and biostimulants

Seaweed extracts (SWE) are natural biostimulants whose bioactive compounds can support antioxidant defense, osmotic regulation, and nutrient uptake in plants [9]. Experimental studies have shown that under saline (or saline–alkaline) conditions, seaweed-based biostimulants can improve plant growth by lowering the Na^+/K^+ ratio and strengthening antioxidant and osmotic systems [12]. In addition, biostimulants derived from *Ascophyllum nodosum* have been reported to enhance protective responses in certain crops under salt stress [13]. General reviews highlight that SWE are promising tools for improving plant tolerance to various stresses [10]. Moreover, biostimulants may support the root microbiome through a "prebiotic" effect, promoting cooperation with beneficial microorganisms such as *Pseudomonas* and mycorrhizae [14].

Stevia quality under salinity and the role of biological preparations

Stevia quality is mainly evaluated based on the content and composition of steviol glycosides in the leaves, particularly the stevioside/rebaudioside A ratio. It has been shown that the level of salinity and the type of salt source influence not only stevia growth but also quality traits [10]. Some studies indicate that glycoside dynamics under salt stress are complex, with plant responses varying depending on the intensity and duration of stress [17]. From this perspective, the effectiveness of biological preparations should be assessed not only by biomass production but also by the stability of glycoside content and composition [4].

CONCLUSION

Soil salinity is a major abiotic factor limiting the growth, physiological processes, and quality traits of *Stevia rebaudiana*. Under saline conditions, osmotic stress, ionic toxicity, and oxidative stress lead to reduced photosynthesis, decreased biomass accumulation, and changes in the content and ratio of steviol glycosides. This directly affects the economic efficiency of stevia cultivation. The literature analysis indicates that biological preparations—particularly PGPR, arbuscular mycorrhizal fungi, and seaweed-based biostimulants—can serve as effective tools for enhancing plant adaptation under salinity stress. They mitigate the negative effects of stress by promoting root system development, normalizing Na^+/K^+ ion balance, increasing antioxidant enzyme activity, and strengthening osmoregulation. As a result, vegetative growth, leaf biomass accumulation, and metabolic stability are improved.

At the same time, the molecular-level effects of biological preparations on steviol glycoside biosynthesis in stevia remain insufficiently studied. In particular, how glycoside content and composition are regulated under stress conditions and how they are modulated by biological treatments represent important directions for future research. Overall, biological preparations have strong potential as an environmentally safe and sustainable strategy for stevia cultivation in saline soils. Their integration with breeding, agronomic technologies, and molecular research could expand the possibilities for producing high-quality and high-yielding stevia in salt-affected regions.

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HONEY PRODUCTIVITY OF BEE COLONIES

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Abstract. *The article describes the types of main juice-bearing plants in the area surrounding the apiary and the amount of juice obtained per hectare. The results of the study on the gross and commodity honey productivity of bee colonies and the quality of honey are presented.*

Keywords*: bee, honey appearance, color, aroma, taste, presence of mechanical impurities and signs of fermentation, beekeeping, productivity, juice, production, bee family, commodity honey, gross honey, honey quality, grade, imitation, style.*

I. INTRODUCTION

It is generally recognized that the production of beekeeping products that are environmentally friendly for humans is one of the industry's pressing challenges. Studying the honey production of bee colonies and the quality of individual honey increases consumer interest and improves the efficiency of honey production [1, 2]. The purpose of this experiment is to study the honey production and quality of bee colonies. The objectives of the study include: determining the species composition of the main sap-producing plants for bees, studying honey production throughout the season, determining honey quality based on key indicators, and verifying compliance with standards. Honey production is influenced by many factors, the most important of which are bee breed, natural and climatic conditions, the duration of the honey flow period, the availability of a stable food source, the technologies used in beekeeping, the experience of beekeepers, etc. The taste, aroma, and quality of honey depend primarily on the diversity and flowering period of wild and cultivated honey plants capable of secreting nectar and pollen [3, 5, 8]. It is well established that requirements for the quality and safety of beekeeping products are determined by a number of factors: the origin and specificity of the product, its mass consumption, the main goals of state policy in the field of healthy nutrition, its use in the treatment and prevention of a number of common diseases, and the serious deterioration of the environment [9, 10]. When analyzing the quality of commercial honey, organoleptic and measurement methods are primarily used. Laboratory testing of honey is necessary for its identification, determination of its quality, detection of adulteration, and assessment of its individual quality indicators. To determine and evaluate honey quality, organoleptic indicators of appearance, color, aroma, taste, the presence of mechanical impurities, and signs of fermentation are tested. In combination with laboratory research methods based on honey quality assessment methods, the water content of honey, sugar and sucrose reduction, diastase number, total acidity, hydroxymethylfurfural content, and qualitative reactions to various adulterations are determined [5, 11].

II. RESEARCH METHOD AND SOURCES. The study was conducted within the framework of the international project “Smart-AI: Application of intelligent bee colony system technology and development and improvement of beekeeping resources in Uzbekistan in cooperation with the Republic of Korea” [7]. The amount of honey collected in the hives was determined by weighing them before and after harvesting, as well as by weighing the amount of

honey in each hive left over the winter. The amount of honey in the hives was determined by the difference between the total weight of the hives and the weight of empty hives. The botanical origin of the honey and the chemical composition of nectar-bearing plants were determined using accepted beekeeping methods. The quality indicators of honey samples collected from the experimental and control groups were determined in accordance with the requirements of the Republic of Korea interstate standard IFSD, 2021 (Natural Honey. Specification) and the interstate standard GOST RF-19792-2017 "Natural Honey. Technical Characteristics," adopted for the CIS countries and developed by the Russian Federation. It is commonly accepted that obtained data were analyzed using the Student's t-test, E.K. Statistical processing was performed using the Merkureva method (1970, 1991), using the significance level (R). Calculations were correlated on a computer using MS OFFICE (Microsoft Excel) programs.

III. RESEARCH RESULTS. It is important to note that natural climatic conditions of our republic are very favorable for growing succulent plants and maintaining bee colonies using fast-growing technologies. During the flowering period, cotton fields alone can accommodate over a million bee colonies and produce honey. An important factor in the continued development of beekeeping is the availability of abundant food sources. The natural climatic conditions of our republic allow for the successful development of beekeeping, as well as all branches of agriculture. Our picturesque hills and mountains, vast cotton fields, orchards, and flower gardens, occupying vast areas, provide an excellent source of food for bees. However, the current development of beekeeping cannot adequately meet the growing needs of the population. Based on these data, we conducted a study of the main honey plants growing in various regions of Uzbekistan. For this purpose, during the main honey collection period, from June to August, bees from the control group were left in their permanent habitats at the educational and experimental site of the Kibray district of Tashkent region. Experimental group 1 was transferred to the Sentob and Papanay agricultural districts of Nurota district of Navoi region. Experimental group 2 was transferred to the Yangi-Kurgan agricultural district of Bildirsoy district of Bustonlyk district of Tashkent region. The honey production of some honey plants in these regions is presented in Table 1.

Table 1.

Needle production of honey plants.

№	**Name of succulent plants**	**Honey productivity, 1/ha**	**Control group**	**1st Experimental Group**	**2-Experimental group**
Control group Tashkent region, Kibray district,					
1	Linden tree, *Lipa* (*Tilia L*)	600-800	+		
2	White and Yellow Acacia (*Caragana arborescens*)	300-400	+		
3	Sunflower (*Helianhus annus L*)	25-30	+		
4	*Garden and home garden crops L*	20-25	+		
1st Experimental Group, Nurota District, Navoi Region					
1	Okkurai (*Psoraiea drupaceae Bunge*)	200-300		+	

2	Cheekbone (*Alhagi camelorum*)	300-400		+	
3	Kunduzay (*Echinopus*)	650-700		+	
4	Rabbit bone (*Ammodendron*)	25-40		+	
2nd Experimental Group, Bustonlyk District, Tashkent Region					
1	Annual and perennial succulent herbs (*Echium bulgare L*)	150-200			+
2	Blue clover (*Medicago sativa L*)	200-300			+
3	Corner (*Onobrychis viciafdia scrap*)	200-400			+
4	Lion's tail (*Leonurus cardiaca L*)	300-350			+

It is evident from the analysis of the study results shows that over 60% of the flora growing in the Kibray district of Tashkent region are honey plants. Of these, the following are particularly important: linden (Lipa), white and yellow acacia, sunflower, and garden and homestead cultivated plants. These plants bloom from March to June and produce high honey yields. The natural flora of the Nurota district of Navoi region includes over 1,200 species of higher plants, and 61 species of plants that provide bees with nectar and pollen are honey plants [12]. Of these, the following are particularly important: akkurai, yantok, kunduzoi, and kuyonsuyak. These plants bloom from June to September and enable bees to collect large quantities of honey during the main honey flow season. The Bustonlyk district of Tashkent region is home to over 60 families, 200 varieties, and 300 plant species, over 70% of which are honey plants. The plants have a growing season of 120-150 days, blooming from April to August, allowing bees to collect large quantities of honey during the peak honey flow period. This area is located at an altitude of 1,000 to 3,600 meters above sea level and consists of annual and perennial succulent grasses, blue clover, yarrow, lion's tail, forests, and numerous fruit trees. These forests are primarily located in the Pskom, Ugam, and Chatkal ranges around the Western Tien Shan. It is a well-known fact that in beekeeping, when assessing the productivity of colonies, the ability to produce honey and wax is primarily assessed. Honey production is a key economic indicator of bee colonies and depends on many factors, including colony winter hardiness, queen bee quality, colony development, colony strength, the economic utility of the colony, bee breeds, the presence or absence of selective breeding, food sources, and the botanical origin of the honey. In short, honey production is one of the key indicators, summarizing all colony performance indicators and used to assess its health [11].

Honey production of bee colonies maintained under various conditions.

Table 2.

№	Years	Groups (n=10)					
		Control group: Kibray district, Tashkent region, X±Sx.	**CV,%**	**Experimental group 1, Nurota district, Navoi region, Kh±Sx.**	**CV,%**	**Experimental group 2, Bustonlyk district, Tashkent region, X±Sx.**	**CV,%**

Gross honey yield, kg							
1	2023	26,6±0,9	3,30	32,2±1,6 ***	3,12	28,5±0,8 **	3,04
2	2024	27,8±1,2	2,98	34,3±1,4 ***	2,84	29,1±0,7 **	2,24
3	2025	28,2±2,3	2,84	36,6±1,96 ***	2,14	30,4±1,2 **	2,06
Commercial honey yield, kg							
1	2023	16,6±1,6	1,60	22,2±1,06 ***	2,12	18,5±1,2 **	1,54
2	2024	17,8±2,0	1,56	24,3±1,04 ***	1,82	19,1±1,6 **	1,12
3	2025	18,2±3,2	1,44	26,6±1,24 ***	0,92	20,4±2,2 **	1,03

** - R>0,99; *** - R> 0,999

It should be emphasized that as a result of the honey productivity study, it can be concluded that the gross and commercial productivity of honey of bee colonies in Experimental Group 1 transported to the Sentob and Papanay districts of Nurota district of Navoi region was 32.2 kg in 2023, 34.3 kg in 2024 and 36.6 kg in 2025. Compared with bee colonies in Experimental Group 2 transported to the Yangi Kurgan district of Bustonlyk district of Bildyrsoy district of Tashkent region, the average honey productivity in 2023 was 3.7 kg (11.5%) higher, in 2024 - 5.2 kg (15.2%) higher, and in 2025 - 6.2 kg (16.9%) higher, R> 0.999. When comparing the gross and marketable honey yields of bee colonies left in their permanent habitats in the Tashkent region, Kibray district, and the experimental farm of the Tashkent State Agricultural University, respectively, it was found that the average honey yield was 5.6 kg (17.4%) higher in 2023, 6.5 kg (19%) higher in 2024, and 8.4 kg (23%) higher in 2025. The high level of these indicators in the Nurotsky district of the Navoi region is explained by the widespread distribution of sap-producing plants, the coincidence of the flowering period of sap-producing plants in this area with the main honey collection season for bees, the duration of the flowering period of plants (90-120 days), and their high productivity.

Table 3.

Results of the organoleptic evaluation of honey samples from the experimental and control groups.

№	**Indicators**	**Groups (n=10)**			**GOST RF-19792-2017**
		Control group, Kibray district, Tashkent region	**1st Experimental Group, Nurota District, Navoi Region**	**2nd Experimental Group, Bustonlyk District, Tashkent Region**	
1	Smell	No strong, mild, or strong foreign odors	No strong, mild, or strong foreign odors	No strong, mild, or strong foreign odors	No strong, mild, or strong foreign odors

2	Taste	Sweet, pleasant, without foreign flavors	Sweet, pleasant, without foreign flavors	Sweet, pleasant, without foreign flavors	Sweet, pleasant, without foreign flavors
3	Mechanical impurities	Not found	Not found	Not found	Not allowed
4	Signs of fermentation	Not found	Not found	Not found	Not allowed
5	Muvofiqlik	Sticky	Sticky	Sticky	Liquid, fully or partially crystallized

The assessment of natural honey quality is carried out in accordance with the requirements of the interstate standard GOST RF-19792-2017 "Natural Honey." Technical Characteristics," adopted for the CIS countries and developed by the Russian Federation, applies to honey collected and sold at various retail outlets of all types of ownership. It is widely assumed that to determine and evaluate the quality of the honey, organoleptic tests were conducted, including assessment of its appearance, density, color, aroma, taste, presence of mechanical impurities, and signs of fermentation. The results of the organoleptic evaluation of honey from the experimental and control groups are presented in Table 3. Analyzing Table 3, we see that honey samples from bee colonies maintained in all three regions fully comply with the organoleptic requirements of GOST RF-19792-2017. Physicochemical quality indicators of honey provide a more accurate description of its composition and properties; chromatographic and spectrophotometric equipment, as well as specialized analytical methods, are used to determine these indicators. In everyday practice, simpler and less labor-intensive methods for determining honey quality indicators are more commonly used. Physicochemical indicators include moisture content, sucrose and reducing sugars, diastase index, hydroxymethylfurfural content, and others. The results of laboratory analysis of honey samples from the experimental and control groups are presented in Table 4.

Table 4

Results of laboratory analysis of honey samples from the experimental and control groups

№	**Indicators, units of measurement**	**Analysis method**	**Required amount**	**Groups**					
				Control, X±Sx.	**CV, %**	**1-Experience, X±Sx.**	**CV,%**	**2-Experience, X±Sx.**	**CV,%**
1.	Water quantity, %	Refractometry	Up to 20 %	17,4±0,62	1,2	16,2±0,46***	0,50	16,6±0,54**	0,90
2.	Fructose, %	Chromatography	Up to 45 %	38,4±1,73	3,2	35,33±3,17***	2,8	37,30±3,30**	3,4
3.	Glucose, %	Chromatography	Up to 30 %	26,1±0,87	2,7	24,58±1,10***	2,0	25,67±0,37**	2,8
4.	Sucrose, %	Chromatography	Up to 5 %	4,38±0,69	3,4	3,19±0,31***	1,8	3,51±1,30**	2,3
5.	Diastase number, Goethe	Colorimetry	At least 5.0	25±1,24	3,6	38±0,18***	3,1	32±0,98**	3,2

			Goethe units						
6.	Acidity level, mEq/kg	Titrimetric	Up to 40 mEq/kg	33,1±2,92	3,8	31,62±2,9***	3,5	32,44±3,1**	3,6
7.	Additives in honey (HMF), Mg/kg	Quality reaction	shouldn't be	2,20±0,35	1,2	1,02±0,37***	0,6	1,85±0,44**	0,8
8.	Hydrogen value, Ph	Quality reaction	Up to (pH > 7) 8,3	6,8±1,04	1,1	6,2±0,98***	0,05	6,6±1,17**	0,94

** - R>0,99; *** - R> 0,999

The data in Table 4 show that honey samples from the experimental and control groups were tested using certified and state-approved methods. For all parameters, honey samples from all three apiaries fully comply with the requirements of the Republic of Korea interstate standard IFSD, 2021 (Natural Honey. Specification) and the interstate standard GOST RF-19792-2017 "Natural Honey. Technical Characteristics," adopted for the CIS countries and developed by the Russian Federation. The water content in honey samples from the first experimental group was 0.4% lower than in honey samples from the second experimental group and 1.2% lower than in the control group. The acidity level was 0.82 meq/kg lower than in the second experimental group and 1.48 meq/kg lower than in the control group, with a significance level of R > 0.999. This can be explained by the botanical composition of the sucking plants and the maturity of the honey.

The diastase content in honey from Experimental Group 1, grown in the Navoi region, was 38 Gote units. This value was 6 Gote units, or 15.8%, higher than the diastase content in honey from Experimental Group 2, grown in the Bustonlyk district of Tashkent region (P>0.999). It was also 13 Gote units, or 34.2%, higher than the diastase content in honey from the control group. The carbohydrate content of honey (fructose, glucose, and sucrose) in the first experimental group was 35.33, 24.58, and 3.19%, respectively, which is 5.3%, 4.3%, and 9.2% lower than in the second experimental group (P>0.999). It was found that the indicators were 8%, 5.9% and 27.2% lower than in the control group, which indicates a high level of physicochemical and qualitative indicators of honey. In light of the above discussion, our studies: Antimirov S. V. (2004), Turaev O. S. (2006), Krivsov N. I. (2008), Maslova E. E. (2008), Brandorf A. Z. (2011), Lebedev V. I. (2012), Tretyakov E. A., Tarasenkov E. V., Lavrenteva E. V. (2019), Makhmadiyorov O. A. (2020), Eshadavlatov O. Z. (2021), Kuldasheva F. Kh. (2022), Zhoraeva D. R. (2023), Akhmedov T. P. (2024), Nizomiddinova M. S. Kh. (2025), Nurmurodova N. F. (2025). The authors presented data on honey productivity in their scientific papers.

IV. CONCLUSION. It can therefore be concluded that comparing the honey productivity and honey quality of bee colonies from different regions, we can come to the general conclusion that the species composition of nectar-producing plants in beekeeping is heterogeneous across all regions, and the honey productivity of nectar-producing plants growing in different regions ranges from 20-25 kg per hectare to 600-800 kg. Accordingly, it can be stated that in experimental group 1, specifically in the Sentob and Papanay K.F.Yu. districts of the Nurota district of Navoi region,

highly productive honey plants are grown, such as akkurai, yantok, kunduzoi, kuyonsuyak, white acacia, and other succulent plants. As a result, each bee colony in Experimental Group 1 demonstrated higher gross and marketable honey productivity over the season compared to the second and control groups by 6.2-8.4 kg or 17-23 percent, respectively.

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SCREENING FOR HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC VIRAL HEPATITIS IN UZBEKISTAN

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Abstract. *Chronic viral hepatitis B, C, and D are important risk factors for hepatocellular carcinoma (HCC), and screening patients with chronic viral hepatitis for tumor markers is essential for early diagnosis. This study aimed to improve early detection of HCC among patients with chronic viral hepatitis. A total of 121 patients with HCC, 300 patients with liver cirrhosis resulting from viral hepatitis, and 90 patients with chronic viral hepatitis without liver cirrhosis were enrolled. Analysis of HCC etiology showed that hepatitis B virus infection was present in 45% of patients and hepatitis C virus infection in 25%. According to the TNM classification, most patients were diagnosed at advanced stages (stages III and IV), while stage I HCC was not detected. Screening of 300 patients with viral hepatitis–related liver cirrhosis using PIVKA-II and AFP revealed an HCC detection rate of 11%. Additionally, in 2.2% of patients with chronic viral hepatitis without liver cirrhosis, early-stage HCC was detected through PIVKA-II screening. These findings indicate that all patients with chronic viral hepatitis and viral cirrhosis should undergo regular ultrasound examination and tumor marker testing, and that screening of all patients with chronic viral hepatitis can enable early detection of HCC, timely treatment, and improved survival outcomes.*

Keywords: *HCC, liver cirrhosis, viral hepatitis, AFP, PIVKA-II*

Introduction

Hepatocellular carcinoma (HCC) represents the most common histotype of liver cancer accounting for 80-85% of all cases of liver cancer (1). HCC is the fourth most common cause of cancer-related death in the worldwide (2). Although HCC does not top the list of the most common cancers, the high mortality rate is associated with poor operability, high likelihood of recurrence after surgical resection, and poor response to conventional treatment, making HCC a global health problem (3). Studies of natural history in untreated patients have shown that the annual incidence of HCC is 0.3-0.6% in patients without liver cirrhosis and 2.2-3.7% in patients with compensated liver cirrhosis, with the highest rates in Asia (4). Actually, despite the variety of approaches to HCC therapy, the 5-year survival rate does not reach 15% (5). This is due to the fact that most cases of HCC are detected at advanced stages, when resection or transplantation is not possible and only palliative treatment is available (6). The increase of HCC morbidity since the late 1990s is due to the growth of the population and the number of elderly people among them (7). Patient categories and screening methods are discussed in numerous publications, the main ones being the

joint guidelines and recommendations of European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD) and the European Organization for Research and Treatment of Cancer (EORTC) (9-11). Patients with liver cirrhosis who have a risk of HCC ≥1.5%/year and hepatitis B virus (HBV) carriers without liver cirrhosis who have a risk of HCC ≥0.2%/year should be monitored. HBV carriers are at risk for HCC even without liver cirrhosis. Although the risk of HCC is reduced in patients with hepatitis C virus (HCV) infection who have a sustained virologic response to direct-acting antivirals, patients with liver cirrhosis are still at risk of HCC and should continue monitoring using imaging examinations (12).

One of the commonly used methods for HCC screening is liver ultrasound, despite the fact that the sensitivity of the method varies, according to different authors, from 33% to 96% (13). Patients with indications for HCC screening are recommended to have ultrasound examination with an interval of 6 months. The above recommendations are due to the fact that tumor node size increases 2-fold in the time interval from 80 to 117 days (14). More frequent ultrasound (every 3 months) does not give advantages in detecting small-sized HCC nodules, increasing the intervals between examinations up to 9-12 months, on the contrary, reduces the sensitivity of the method (15).

Most researchers have focused their activities on determining the diagnostic and prognostic role of biomarkers in the progression of HCC. At the same time, the data of studies aimed at predicting HCC before the progression of clinical manifestations of the tumor are practically absent. Thus, the World Gastroenterological Organization (WGO) practice guidelines on HCC recommend alpha-fetoprotein (AFP) as the main marker (16). Retrospective analysis has shown that the optimal threshold values that provide the best likelihood ratio of a positive result are 200 ng/mL (17). Another tumor marker of HCC is des-gamma-carboxyprothrombin, which is an altered form of prothrombin expressed due to impaired post-translational carboxylation caused by vitamin K deficiency (18). This biomarker is also referred to as protein induced by vitamin K deficiency (PIVKA-II), which represents abnormal, deprived prothrombin activity (19). Prothrombin, which contains 10 γ-carboxyglutamic acid residues in the amino-terminal domain, is synthesized in the liver.

Prothrombin is a vitamin K-dependent clotting factor. Vitamin K deficiency can inhibit the activity of vitamin K-dependent carboxylase, resulting in an acquired defect in the posttranslational carboxylation of glutamine on the prothrombin precursor. As a result, abnormal prothrombin (PIVKA-II) is released into the plasma without γ-carboxylation of all glutamine residues. The correlation between PIVKA-II levels and HCC was first reported by Liebman et al. in 1984 (20). Further studies showed that PIVKA-II can be a useful diagnostic and prognostic marker of HCC (21). The use of the described tumor marker for the diagnosis of HCC is widespread in East Asia, North America and China (22-24). Numerous studies have shown that PIVKA-II is applicable for HCC surveillance and has been included in the recommendations of the Japanese Society of Hepatology (25, 26). Volk et al. reported that PIVKA-II was significantly better than total AFP or AFP-L3 in differentiating HCC from liver cirrhosis, with a sensitivity of 86% and specificity of 93% (27). The aim of the study was to improve early diagnosis of HCC in patients with chronic viral hepatitis.

Methods.

Patient enrollment criteria were: age older than 18 years, patient consent, diagnosis of HBV, HBV+HD confirmed by ELISA or PCR, and HCV confirmed by PCR. Exclusion criteria were patient age under 18 years, refusal of the study and pregnancy. To identify the etiology of

HCC, 121 patients with a confirmed diagnosis of HCC hospitalized at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology (RSPMCOR) were enrolled in the study. For HCC screening 300 patients with liver cirrhosis of viral etiology (LC HBV - 100 patients, LC HCV - 100 patients, LC HBV+HDV - 100 patients) and 90 patients with chronic viral hepatitis without liver cirrhosis hospitalized at the Research Institute of Virology (RIV) were examined. This study was approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan No. 6/31-881 dated September 25, 2018 in accordance with the Declaration of Helsinki.

Patients with increased levels of tumor markers were examined by ultrasound and 4-phase MSCT. In case of confirmation of a volumetric tumor, patients were referred for additional consultation with an oncologist. AFP level was determined by ELISA method using AFP-IFA-BEST kit "Vector Best" (Russian Federation) using Biotech spectrophotometer. To determine the level of PIVKA-II by immunochemiluminescent analysis, we used the PIVKA-II 100 test Maglumi kit (China) on the analyzer Maglumi 800 (Snibe, China). Statistical analysis was carried out with determination of mean values of indicators (M), calculation of standard errors of mean values (m) and using Student's t-test, Chi-square test and Fisher's exact test. Differences were considered significant at $p<0.05$.

Results

To establish the etiology of HCC, we retrospectively analyzed the data of 121 patients with HCC whose diagnosis was confirmed by histological methods. The results of the study showed a prevalence of viral etiology of HCC. Patients with HCC in HBV outcome were 55 (45%), with HCC in HCV outcome 30 (25%) and with HCC of non-viral etiology 36 (30%). In 70% of cases HCC developed in the outcome of viral hepatitis. According to TNM classification, all patients were predominantly classified as stages 3 and 4 and stage 1 was not detected. A pilot viral hepatitis elimination program was started in Uzbekistan in 2019-2020. Within the framework of this project, 53841 people were tested for HBsAg and anti-HCV using rapid tests. The prevalence of HBsAg and anti-HCV was 2.8% (1633/53841) and 2.96% (1727/53841), respectively. Furthermore, HCC was detected by ultrasound in 5 HBsAg positive patients and 3 anti-HCV positive patients. All patients were aware of their status, had advanced stage of liver cirrhosis and 3-4 stages of HCC by TNM.

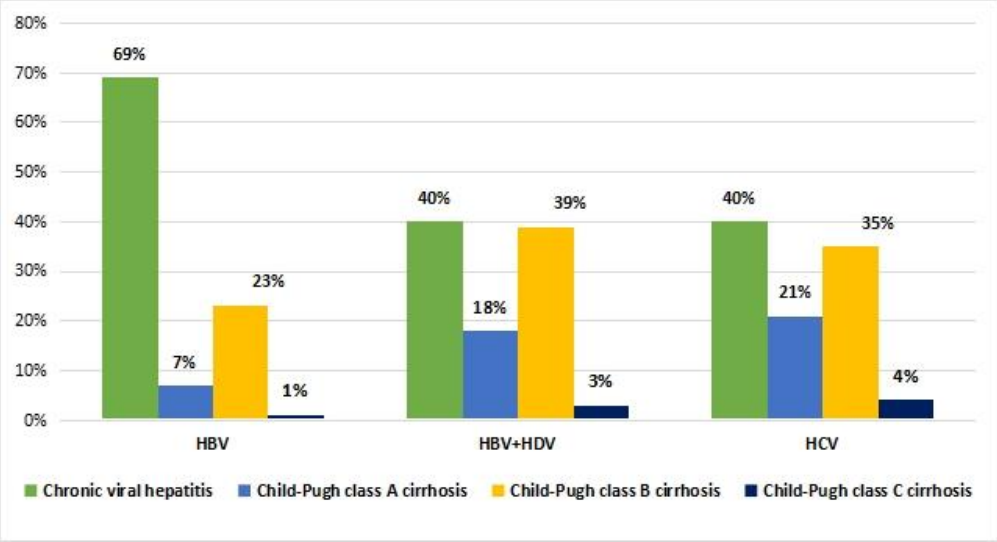


Figure 1: Distribution of patients according to the Child-Pugh classification.

Consequently, the issue of early diagnosis of HCC was of high priority and, in this regard, screening of patients with liver cirrhosis of HBV, HCV, HBV+HDV etiology for early diagnosis of HCC hospitalized at the Research Institute of Virology was carried out. 300 patients with liver cirrhosis of viral etiology were examined for PIVKA-II and AFP tumor markers. The mean age of patients with LC of HCV etiology was 55.83±3.56 years, LC of HBV etiology - 55.43±4.22 years and LC of HBV+HDV etiology - 53.38±3.88 years and there was no significant difference in the age of patients among the examined patients. However, the analysis of the distribution of patients by gender showed prevalence of male with LC of HBV etiology in comparison with females (61 vs. 39 $p<0.05$), while there was no significant statistical difference in LC of HCV (male - 50, female - 50) and LC of HBV+HDV etiology (male - 45, female - 55). The distribution of Child-Pugh classes of liver cirrhosis is shown in Figure 1.

The results of screening for HCC in patients with liver cirrhosis of viral etiology using different methods showed the highest frequency of HCC detection using PIVKA-II (Fig.2).

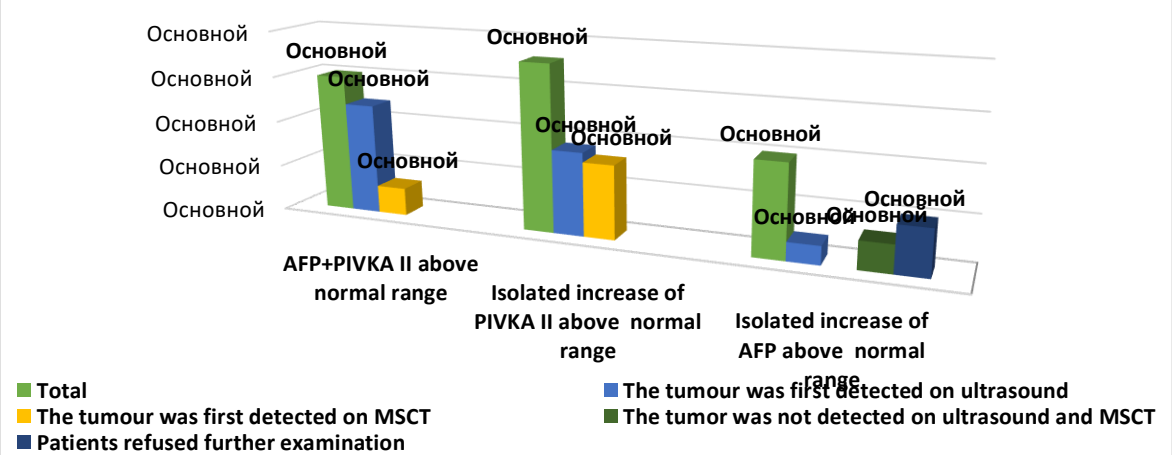


Figure 2: Different methods of screening for HCC in patients with liver cirrhosis of viral etiology

Among 100 LC of HBV etiology patients examined for tumor markers, 4 (4%) had PIVKA-II+AFP levels higher than the normal range. Of these, 3 patients had a volumetric tumor confirmed by ultrasound, and 1 patient had a tumor not visualized by ultrasound but confirmed by MSCT. Of the 4 (4%) patients with isolated increase of PIVKA-II, 2 patients had a volumetric tumor on ultrasound examination, and 2 patients had a volumetric tumor detected by MSCT. In this group, there was not detected an isolated increase of AFP. Of 100 patients with LC of HCV etiology, 6 (6%) had PIVKA-II+AFP higher than the normal range. Of these, 5 patients had a volumetric tumor visualized on ultrasound and 1 patient on MSCT. Isolated increase of PIVKA-II occurred in 8 (8%) patients, of which 4 patients had a volumetric tumor visualized by ultrasound and 4 patients by MSCT. Of the 5 (5%) patients who had an isolated increase of AFP, only 1 patient had a volumetric tumor detected by ultrasound, 2 patients did not have a tumor on MSCT, and 2 patients refused further examination.

Among 100 patients with LC of HBV+HDV etiology, the level of PIVKA-II+AFP was higher than the normal range in 5 (5%) patients. Of these, 4 patients had a volumetric tumor visualized by ultrasound and 1 patient by MSCT. Of the 5 (5%) patients with increased PIVKA-II levels, 3 patients had a volumetric tumor visualized by ultrasound and 2 patients had a volumetric tumor visualized by MSCT. Of the 5 (5%) patients with an isolated increase of AFP, 1 patient had a volumetric tumor identified on ultrasound examination, 1 patient did not have a volumetric tumor identified on MSCT, and 3 patients refused further evaluation.

It is important to note that the frequency of HCC in liver cirrhosis of viral etiology was 11%. At the same time, all patients had tumors of stage 1 or 2 according to TNM. In comparative analysis, the mean tumor node size detected by ultrasound/MSCT in the RIV patient group was significantly smaller than the mean size of HCC in RSPMCOR inpatients who participated in this study, being 31.59±11.68 mm vs. 115.13±36.17 mm. ($p<0.05$), respectively. Next, we compared the frequency of TPR (true positive result), FPR (false positive result), TNR (true negative result) and FNR (false negative result), as well as Se (sensitivity), Sp (specificity), AUC (area under the curve), PPV (positive predictive value) and PNV (negative predictive value) of the studied tumor markers and their combinations in the compared groups (Table 1).

As can be seen from Table 1, the highest number of TPR was in PIVKA II and AFP compared to AFP L3. At the same time, the number of TPR in AFP was slightly lower than in PIVKA II. However, the FPR was higher in AFP than in PIVKA II and AFP L3. PIVKA II had the highest Se, and AFP L3 had the lowest. Sp was equally high for AFP L 3 and PIVKA II, unlike AFP. The highest AUC was observed in PIVKA II. The highest PPV was observed in PIVKA II and AFP L3, compared to AFP. And the highest NPV was observed in PIVKA II compared to AFP and AFP L3. In order to improve diagnostics, we compared the combination of the studied tumor markers. The TPR was the same in the combinations of AFP + PIVKA II and AFP + AFP L3 + PIVKA II and was slightly higher than the FPR of the combination of AFP L3 + PIVKA II. The FPR was lower in the combination of AFP L3 + PIVKA II, compared to AFP + PIVKA II and AFP + AFP L3 + PIVKA II. It should be noted that all FPR were associated with AFP.

Table 1: Indicators of TPR, LPR, TNR, FPR, sensitivity, specificity, PPV, NPV and AUC

Indicators	AFP	AFP L3	PIVKA II	AFP+ PIVKA II	PIVKA II+ AFP L3	AFP+ AFP L3+ PIVKA II
TPR (abs)	21	17	23	26	24	26
FPR (abs)	12	0	0	12	0	12
TNR (abs)	46	58	58	46	58	46
FNR (abs)	9	13	7	4	6	4
Se (%)	70	56,67	76,67	86,67	80	86,67
Sp (%)	79,31	100	100	79,31	100	79,31
AUC	0,747	0,783	0,883	0,83	0,9	0,83
PPV (%)	63,34	100	100	68,42	100	68,42
NPV (%)	83,64	81,69	100	92	90,62	92

AFP + PIVKA II and AFP + AFP L3 + PIVKA II had the highest Se, and PIVKA II + AFP L3 had the lowest. Sp, AUC and PPV were higher for the PIVKA II + AFP L3 combination compared to the AFP + PIVKA II and AFP + AFP L3 + PIVKA II combinations. And NPV was slightly higher for the AFP + PIVKA II and AFP + AFP L3 + PIVKA II combinations. Thus, the use of PIVKA-II+AFP combination as diagnostic tumor markers of HCC in patients with chronic viral hepatitis showed higher sensitivity compared to the use of only one tumor marker and can be recommended for HCC screening in patients with HBV, HCV and HDV infections. In addition, the introduction of the combination of tumor markers in patients with liver cirrhosis of viral etiology into routine practice will allow early detection of HCC.

We further investigated 90 patients with chronic viral hepatitis without liver cirrhosis (chronic HCV - 24 patients, chronic HBV - 45 patients and chronic HBV+HDV - 21 patients). The

mean age of patients with chronic HCV infection was 55.83±3.56 years, chronic HBV infection - 55.43±4.22 years and chronic HBV+HDV infection - 53.38±3.88 years ($p>0.05$). Chronic HBV infection was most common in females relative to males (33 vs. 12 $p<0.05$), and there was no statistical significance in chronic HBV infection (males - 10, females - 14), chronic HBV+HDV infection (males - 11, females -10). Among the examined patients, PIVKA-II level was increased in 2 patients with chronic HCV and HBV+HDV infection. Of them, 1 patient had a volumetric tumor detected on ultrasound and later the diagnosis of HCC was confirmed, and 1 patient had a volumetric tumor that was not detected on ultrasound but later confirmed on MSCT. Thus, HCC was detected in 2.2% of patients with chronic viral hepatitis, and the size of the tumor node did not exceed 5 cm, i.e. the tumor was operable.

Discussion

In recent years, screening of HBV and HCV infection is becoming important (28). According to the practice guidelines of the World Gastroenterological Organization, primary prevention is aimed at eliminating factors contributing to the progression of HCC, primarily HBV and HCV infection (29). A study by Perez et al. emphasized the importance of epidemiological surveillance of HBV and HCV infection and timely therapy of these infections (16). Vaccination against hepatitis B is an important element in the prevention of HBV and consequently HCC. It is known that vaccination against HBV is 95% effective in preventing infection (30). In 2008, the Centers for Disease Control and Prevention and in 2014, the United States Preventive Services Taskforce recommended hepatitis B vaccination for persons born in areas where hepatitis B virus prevalence exceeds 2% (31). A population-based study conducted in Taiwan found that the morbidity of HCC was 4-fold higher in the unvaccinated group compared with those who received the vaccine at birth. The study used data from patients with HCC diagnosed between 1983 and 2011, with the age of HCC debut ranged within 6-26 years. In Uzbekistan, hepatitis B vaccination of newborns began in 2001. In 2011, the hepatitis B vaccination rate was 99% (https://www.globalhep.org/country-progress/uzbekistan).

Another important fact of HCC decrease is the use of antiviral therapy. A meta-analysis including 13 clinical trials and 6350 patients with HBV-associated HCC after resection or ablation showed fewer recurrences and improved survival with the use of nucleos(t)ide analogs (NA), but the authors emphasize that the risk of HCC cannot be completely eliminated by NA, especially in the presence of liver cirrhosis (32). There is still no precise answer to the question at what point patients with eliminated HCV infection can be excluded from the risk group of HCC progression. The risk of HCC formation decreases after treatment compared to untreated patients (33). However, HCV elimination is not a guarantee of HCC prevention, especially if liver cirrhosis has already progressed (15). The inflammatory process caused by viruses plays an important role in the long-term irreversible damage of hepatocytes and, consequently, in the progression of the cancerous process. The anti-tumor function of immunity is a well-known fact. There is a thin line between antitumor and pro-tumor function of the immune system. Direct-acting antiviral drugs (DAADs) modify the function of natural killer cells and the manifestation of interferon action. The use of DAADs promotes rapid decrease of hepatitis C viral load, on the one hand, and disruption of antitumor mechanisms, on the other hand. There is an opinion that disruption of the immune response system can stimulate the formation of metastases (34). Thus, all patients with chronic infection caused by hepatitis B or C virus are candidates for permanent HCC screening.

The results of the study on the etiology of hepatocellular carcinoma (HCC) in this study show that 70% of cases are due to viral hepatitis (45% - HBV and 25% - HCV), consistent with

the data of the world scientific community. Thus, according to the literature, chronic HBV is the cause of approximately 50%-80% of all cases of HCC, especially in regions where HBV is endemic, such as Asia and sub-Saharan Africa. Chronic HCV infection also contributes significantly to HCC, particularly in Western countries where it is the leading cause of liver cancer. A comprehensive review highlighted that chronic HBV and HCV infections lead to cirrhosis in 80%-90% of HCC patients, supporting the observation that a substantial portion of HCC cases in Uzbekistan is linked to these viral infections. The lifetime risk for HBV carriers to develop HCC ranges from 15% to 40%, depending on various factors including the presence of cirrhosis (35,36).

The predominance of advanced stages in the Uzbekistan study reflects global trends where many patients are diagnosed at late stages due to asymptomatic progression of the disease. Studies have shown that early detection remains a challenge, with many patients presenting with advanced disease (37). The higher prevalence of male patients with HBV-related liver cirrhosis noted in the study is consistent with global findings that report a higher incidence of HCC among males compared to females, attributed to various biological and lifestyle factors (38,39).

Secondary prevention of HCC is based on the implementation of screening programs to directly detect of HCC (40). Despite the lack of randomized data, several cohort studies have found a strong and consistent association between HCC screening and improved 3-year survival (41). Considering the limitations of the widespread use of imaging methods for HCC screening, especially in remote regions, there is a need for alternative strategies, such as biomarkers, to increase the sensitivity of early tumor detection.

Currently, the GALAD scale based on sex, age, AFP-L3, AFP and PIVKA-II are widely used worldwide (42). However, the difficulty in using this scale is that the scale cannot be used in the absence of data on one of the indicators. We declined to use the AFP-L3 for two reasons. Firstly, it is a rather expensive tumor marker. Secondly, AFP-L3 level is directly related from total AFP. However, up to 1/3 of HCCs do not produce AFP and, consequently, AFP-L3 (38).

A study from 2007 found that serial measurements of both PIVKA-II and AFP could be beneficial for monitoring patients after curative resection for HCC. In this cohort, PIVKA-II showed a higher sensitivity (75.1%) compared to AFP (48.6%) during initial diagnosis (43).

A 2023 study evaluated the diagnostic properties of PIVKA-II and AFP in a cohort of high-risk patients for HCC. The results indicated that PIVKA-II had a sensitivity of 80.80%, compared to 75.80% for AFP. When both markers were combined, the sensitivity improved to 60.30% for detecting HCC, with a receiver operating characteristic (ROC) curve showing a significant advantage for the combination over AFP alone (44). These findings support our results and underscore the potential of PIVKA-II as a valuable biomarker for HCC detection.

Another study published in 2024 focused on the diagnostic accuracy of PIVKA-II in identifying recurrent HCC after curative resection. The findings demonstrated that PIVKA-II outperformed AFP significantly, with an area under the curve (AUC) of 0.883 for PIVKA-II compared to 0.672 for AFP (45).

Regarding AFP-L3, our observation of its high specificity but lower sensitivity is consistent with earlier literature. A review by Gomaa et al. (2006) reported that AFP-L3 sensitivity can reach 80–90% for tumors >5 cm but only 35–45% for tumors <2 cm. This aligns with our findings and highlights the potential limitations of AFP-L3 as a standalone marker, especially for early-stage HCC detection (46).

Kudo emphasized the urgent need for incorporating PIVKA-II measurements into routine surveillance protocols for HCC, particularly in cases where traditional markers may fail (47). This

reflects a growing consensus on the importance of utilizing multiple tumor markers to improve detection rates across diverse patient populations.

Our specific findings on marker combinations, such as PIVKA-II + AFP-L3 having higher specificity than other combinations, while AFP + PIVKA-II had higher sensitivity, are partially supported by recent literature. A 2024 meta-analysis by Li et al. found that combining PIVKA-II and AFP improved HCC detection accuracy in HBV-related Caucasian cirrhotic patients. This supports our conclusion that the PIVKA-II + AFP combination shows promise for HCC screening in viral hepatitis patients (48).

This study showed that HCC screening using a combination of tumor markers AFP+PIVKA-II is optimal. It is important to note that the detection rate of HCC in liver cirrhosis reaches 11%. In the screening study, HCC was detected at stage I, and according to world literature data, five-year survival in HCC significantly depends on the stage of the disease (39). At early stages, it reaches 65.8–72.1% with surgery or radiofrequency ablation. At the same time, at late stages with metastases to lymph nodes or distant organs, this figure decreases to 10% or lower (49).

These data emphasize the importance of early diagnosis to increase the chances of long-term survival and successful treatment. In our studies, HCC was also detected at early stages in 2.2% of patients with chronic viral hepatitis using PIVKA-II. Of course, these data are preliminary, since they are the result of examining a relatively small cohort of patients.Thus, all patients with chronic viral hepatitis and liver cirrhosis of viral etiology should have an ultrasound and tumor marker testing. A nodular tumor larger than 1 cm on ultrasound should be considered malignant and confirmed with 4-phase MSCT or MRT. If PIVKA-II is increased above the normal range, a 4-phase MSCT/MRT study is recommended regardless of ultrasound results. Patients with AFP levels above 200 ng/mL are recommended to be screened for HCC with MSCT/MRT regardless of ultrasound results. All patients with normal tumor markers and absence of volumetric tumors or node less than 1 cm on ultrasound are recommended screening for tumor markers and ultrasound every 6 months. In the Republic of Uzbekistan according to this principle it is planned to examine all patients with chronic viral hepatitis, which will improve early detection of HCC, provide timely treatment, improve survival and quality of life of patients.

Conclusions

Screening Protocols: Implement routine screening for HCC in patients with liver cirrhosis, particularly those with viral hepatitis (HBV, HCV, HBV+HDV). Use ultrasound and serum tumor markers (PIVKA-II and AFP) as part of the screening process.

Consider screening patients with chronic viral hepatitis without cirrhosis, especially if they exhibit risk factors such as advanced age or a family history of liver disease.

Utilization of Tumor Markers: Employ the combination of PIVKA-II and AFP as diagnostic tumor markers for HCC. This combination has shown higher sensitivity compared to using a single marker. Monitor these markers regularly in patients with liver cirrhosis to facilitate early detection of HCC.

Patient Education: Educate patients about the importance of regular check-ups and monitoring for liver health, especially those diagnosed with chronic hepatitis or cirrhosis.

Ensure that patients understand their risk factors for developing HCC and the significance of early detection.

Referral to Specialists: Refer patients with elevated tumor markers or suspicious ultrasound findings to hepatologists or oncologists for further evaluation and management.

Ensure timely access to imaging studies such as MSCT for accurate diagnosis when indicated.

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ENDOCRINE-IMMUNOLOGICAL RELATIONSHIP IN RHEUMATOID ARTHRITIS IN CHILDREN OF DIFFERENT AGES

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Abstract*. Our study data showed that changes in immune and endocrine system parameters persist for a long time in rheumatoid arthritis. Including glucocorticoid hormones in therapy for patients with articular-visceral rheumatoid arthritis demonstrated positive dynamics in immune and endocrine system parameters. Treatment of patients with glucocorticoids only improved the course of the disease but did not eliminate the underlying disease.*

Keywords: *juvenile rheumatoid arthritis; lymphocytes; adrenocorticotropic hormone; triodothyroxine, thyroxine.*

Introduction.

Currently, rheumatoid arthritis remains one of the urgent problems of pediatric rheumatology. Rheumatoid arthritis (RA) is a progressive autoimmune disease throughout life that affects mainly the synovial joints [1]. Before the disease, there are genetic and environmental risk factors that contribute to the susceptibility to the disease, then the preclinical phase (of variable duration), where systemic autoimmunity manifests itself in the presence of autoantibodies, especially anti-citrulline peptide antibodies (ACPA), but without clinical signs of joint damage. This is followed by a phase of nonspecific symptoms, including arthralgia (joint pain), but still without signs of clinical synovitis [2,3]. Multiple genetic and environmental factors have been associated with an increased risk of developing rheumatoid arthritis (RA) [4]. The mechanism of the underlying disease includes an autoimmune attack on the articular bone and cartilage, which leads to a clinical picture of joint pain and swelling with subsequent disability and concomitant pathology. Rheumatoid arthritis (RA) is characterized by the presence of autoantibodies, such as rheumatoid factor (RF), anticyclic citrulline peptide-2 (anti-CCP2) and antibodies against carbamylated protein (anti-CarP) [5].

The nervous, endocrine and immune systems are coordinated to maintain the homeostasis of the body, generating a bi-directional connection through common mediators and receptors [6]. Meanwhile, the study of the state of the endocrine and immune systems in juvenile rheumatoid arthritis provides the information necessary for differential diagnosis, treatment tactics and prognosis of the disease. The early period of rheumatoid arthritis plays a decisive role in the development and progression of immune complex inflammation. At the same time, early diagnosis of RA allows prescribing adequate treatment and obtaining a more significant clinical effect, as well as improving the prognosis of this disease [7.8].

However, the clinical variants of rheumatoid arthritis are largely dependent on the formation of various interorgan combined lesions [9]. In this regard, cardiological, immunological, clinical relationships, and vegetovisceral dysfunctions are quite described. At the same time, to date, it is not precisely the immunological and endocrine relationships that have been studied in

this pathology. In this regard, the goal of our research was to study the relationship of immunological parameters and indicators of the endocrine system in rheumatoid arthritis in children. It was suggested that the research results will contribute to the improvement of diagnostic methods and the choice of more effective therapy in various clinical options for the course of the disease.

Materials and research methods.

The study was carried out at the bases in the cardiac rheumatology departments of the 4-city clinical children's hospital in Tashkent. A comprehensive clinical, laboratory and instrumental examination of 98 children was carried out, 58 of which were girls (59%) and 40 boys (41%) aged 7 to 17 years with juvenile juvenile disease. The duration of the JRA ranged from 6 months to 7 years. Among the patients examined by us, about half were children with a disease period of 1-3 years. Separation of children according to the forms and variants of the course of rheumatoid arthritis was carried out in accordance with the classification of juvenile rheumatoid arthritis according to ICD-10. The joint form of the disease was observed in 66 children (the maximum activity of the disease was in 19, moderate in 27, minimal in 20), articular-visceral in 32. The control group consisted of 20 healthy children of the same age. The diagnosis of rheumatoid arthritis is based on clinical, biochemical, immunological and radiological examinations.

The main drugs used to treat patients with rheumatoid arthritis were non-steroidal anti-inflammatory drugs in combination with methotrexate. With the articular-visceral form of rheumatoid arthritis, glucocorticoid hormones were included in the therapy. The immune system was evaluated by the content of T - and B - lymphocytes in the blood. In addition to these populations of lymphocytes, cells without surface markers, the so-called O-lymphocytes, were isolated. And also the level of serum immunoglobulins of classes A, M, G. Endocrine status was assessed by studying the basal level of hormones of the anterior pituitary gland (adrenocorticotropic hormone-ACTH, thyroid-stimulating hormone-TSH), thyroid gland (triiodothyroxine - T3, thyroxine - T4, adrenal cortex) . Studies were carried out in the dynamics of the pathological process when children were admitted for treatment, in the phase of convalescence upon discharge from the hospital, and in follow-up (up to 3 years).

Results and discussion

Analysis of the relative and absolute content of lymphocytes in peripheral blood in children with rheumatoid arthritis revealed a significant increase in it. The number of lymphocytes was in direct proportion to the activity and form of the disease. The quantity of T-lymphocytes in the blood was reduced. At the same time, the number of B-lymphocytes, regardless of the activity and form of rheumatoid arthritis, was higher than in children of the control group (P <0.001). The relative and absolute content of O-cells was increased with moderate and maximum activity of rheumatoid arthritis. The concentration of immunoglobulins in serum in patients with rheumatoid arthritis was higher than in children of the control group (P <O, 001). The data are presented in tables 1,2,3,4.

Table 1. Indicators of endocrine and immune status in children with rheumatoid arthritis articular form of the disease of the first degree (M±m)

Indicators	**Control group**	**First degree**	**P**
Lymphocytes	2,203 ± 0,162	2,511 ± 0,127	> 0,05
T-lymphocytes	1,424 ± 0,099	1,302 ± 0,063	> 0,05
B-lymphocytes	0,286 ± 0,092	0,894 ± 0,081	< 0,001

O-lymphocytes	0,202 ± 0,065	0,201 ± 0,061	> 0,05
TSH (IU/ml)	8,21 ± 0,71	8,03 ± 0,37	> 0,05
T_3 (nmol/l)	1,51 ± 0,08	1,39 ± 0,06	> 0,05
T_4 (nmol/l)	79,24 ± 7,25	78,60 ± 7,91	> 0,05
ACTH (nmol/l)	25,3 ± 0,88	26,91 ± 0,73	> 0,05
Cortisol (nmol/l)	496,1 ± 8,2	430,5 ± 6,9	< 0,001
IgG (IU/ml)	82,1 ± 2,9	121,1± 3,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	188,2 ± 17,6	< 0,05
IgA (IU/ml)	71,1 ± 4,2	96,5 ± 4,4	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

Table 2. Endocrine and immune status indicators in children with rheumatoid arthritis articular form of the disease of the II degree (M±m)

Indicators	**Control group**	**Second degree**	**P**
Lymphocytes	2,203 ± 0,162	3,324 ± 0,237	< 0,001
T-lymphocytes	1,424 ± 0,099	1,607 ± 0,075	> 0,05
B-lymphocytes	0,286 ± 0,092	1,194 ± 0,073	< 0,001
O-lymphocytes	0,202 ± 0,065	0,496 ± 0,058	< 0,001
TSH (IU/ml)	8,21 ± 0,71	12,13 ± 0,27	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,33 ± 0,07	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	75,18 ± 4,23	> 0,05
ACTH (nmol/l)	25,3 ± 0,88	29,11 ± 0,61	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	387,9 ± 7,8	< 0,001
IgG (IU/ml)	82,1 ± 2,9	133,1± 4,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	197,1 ± 18,6	< 0,001
IgA (IU/ml)	71,1 ± 4,2	104,2 ± 6,7	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

Table 3. Endocrine and immune status indicators in children with rheumatoid arthritis articular form of the disease of the III degree (M±m)

Indicators	**Control group**	**Third degree**	**P**
Lymphocytes	2,203 ± 0,162	3,401 ± 0,212	< 0,001
T-lymphocytes	1,424 ± 0,099	1,682 ± 0,071	> 0,05
B-lymphocytes	0,286 ± 0,092	1,294 ± 0,078	< 0,001
O-lymphocytes	0,202 ± 0,065	0,582 ± 0,065	< 0,001
TSH (IU/ml)	8,21 ± 0,71	13,51 ± 0,39	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,28 ± 0,09	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	61,93 ± 3,29	< 0,05
ACTH (nmol/l)	25,3 ± 0,88	30,31 ± 0,91	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	324,6 ± 8,3	< 0,001
IgG (IU/ml)	82,1 ± 2,9	151,4 ± 5,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	198,7 ± 15,3	< 0,001
IgA (IU/ml)	71,1 ± 4,2	112,7 ± 5,1	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

In children with rheumatoid arthritis, there were significant changes in the endocrine system. Activation of the anterior pituitary gland occurred, which was manifested by an increase in the level of TSH and ACTH. Concentrations of cortisol, T3, and T4 were low. The content of the hormones we studied in children with rheumatoid arthritis depended on the activity and form of the disease.

Table 4. Endocrine and immune status indicators in children with rheumatoid arthritis of the articular-visceral form diseases (M ± m)

Indicators	**Control group**	**Articular-visceral form**	**P**
Lymphocytes	2,203 ± 0,162	3,401 ± 0,212	< 0,001
T-lymphocytes	1,424 ± 0,099	1,682 ± 0,071	> 0,05
B-lymphocytes	0,286 ± 0,092	1,294 ± 0,078	< 0,001
O-lymphocytes	0,202 ± 0,065	0,582 ± 0,065	< 0,001
TSH (IU/ml)	8,21 ± 0,71	13,51 ± 0,39	< 0,001
T_3 (nmol/l)	1,51 ± 0,08	1,28 ± 0,09	< 0,05
T_4 (nmol/l)	79,24 ± 7,25	61,93 ± 3,29	< 0,05
ACTH (nmol/l)	25,3 ± 0,88	30,31 ± 0,91	< 0,001
Cortisol (nmol/l)	496,1 ± 8,2	324,6 ± 8,3	< 0,001
IgG (IU/ml)	82,1 ± 2,9	151,4 ± 5,2	< 0,001
IgM (IU/ml)	129,1 ± 8,7	198,7 ± 15,3	< 0,001
IgA (IU/ml)	71,1 ± 4,2	112,7 ± 5,1	< 0,001

Note: *the table shows the absolute content of lymphocytes (x109 / l of blood); P - significance of differences in relation to the control group.*

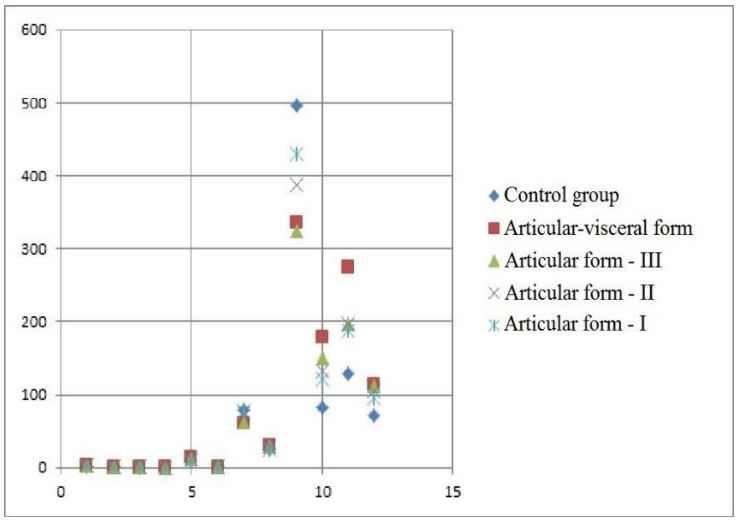


Fig. 1. Characterization of the correlation between the parameters of the endocrine system and immunity in children with rheumatoid arthritis, depending on the form

An analysis of the correlations of the studied parameters of the immune and endocrine systems (Fig. 1) showed that in the children of the control group, a moderate inverse correlation was observed between the content of T and B lymphocytes (r = -0.5694); between the concentration of TSH, ACTH and the level of T3 (r = -0.5416); T4, cortisol (r = -4654); as well as between the level of cortisol and the number of b-lymphocytes (r = -0.3988); between the

concentration of the studied hormones and the content of T-lymphocytes. In addition, a moderate direct correlation between the concentration of thyroid hormones and the content of B lymphocytes (r = + 0.4955) was revealed.

In children with rheumatoid arthritis, a direct correlation was revealed between the TSH content and the number of B and O-lymphocytes (r = + 0.5049), and feedback with the number of T-lymphocytes (r = -0.3894). Inverse correlation was found between the level of T4, T3 and indicators of the immune system (r = -0.4894). The opposite relationship was found between the level of cortisol and the number of T- and B-lymphocytes (r = + 0.4956). There was revealed f direct relationship between the concentration of ACTH and the number of T-lymphocytes (r = + 0.6852), and a feedback with the number of B-lymphocytes (r = -0.5612).

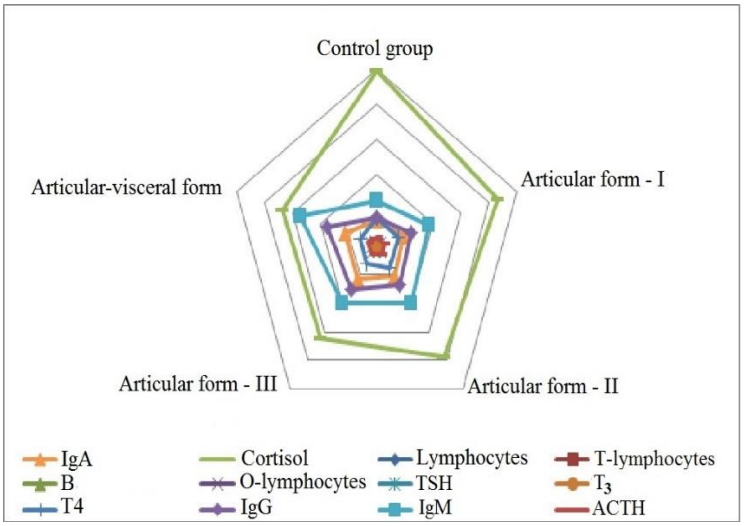


Fig. 2. Model of regulation in the space of signs of the endocrine and immune systems in healthy and rheumatoid arthritis children.

According to our data, for rheumatoid arthritis, depending on the form of the disease in children, there was a high level of TSH and ACTH and a low content of T3, T4 and cortisol. With prolonged exposure to stress, the excretion of hormones by the effector glands decreases and the level of pituitary hormones increases according to the principle of negative feedback. A similar type of endocrine system functioning was revealed by us in children with rheumatoid arthritis. There are also significant changes in the immune status: the content of T-lymphocytes in the blood decreases and the activity of the B-system of immunity increases. Activation of the B-system of immunity, apparently, is associated not only with the insufficient suppressive activity of the T-system of immunity, but also with the partial removal of the limiting effect of glucocorticoid hormones on the kinetics of lymphocytes. Depending on the severity and form of the disease, the closeness of correlations was also revealed. Depending on the activity and form of rheumatoid arthritis, the limits of the adjustable parameters of the model were different. The more active and more severe the disease progressed, the more significantly the studied parameters differed from physiological ones. This model of regulation of the endocrine and immune systems is characteristic of a chronically ongoing process. With this type of regulation, a deep restructuring of the functioning of both the endocrine and immune systems occurs. During the period of complex therapy of the articular form of rheumatoid arthritis in children, the regulation borders in the multidimensional space of the studied symptoms shift in the opposite direction, but within very small limits. However, visually you can see, mainly the changes in the parameters are parallel, as evidenced by the positive correlation relationships (Fig. 2).

Conclusion. In children with articular-visceral rheumatoid arthritis, significant changes in parametric functions were detected, which is associated with the introduction of glucocorticoids in complex therapy and with their prolonged use. Thus, with juvenile rheumatoid arthritis, there is a deep restructuring in the functioning of the immune and endocrine systems, which is manifested by the torpidity of the course of the disease, the involvement of new joints and organs in the process.

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IMPROVING THE MODEL FOR ORGANIZING NURSING CARE IN PALLIATIVE CARE

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Abstract. *Palliative care as a field of medical science and clinical practice has deep historical roots dating back to ancient civilizations. In Ancient Greece and Rome, care for incurably ill patients was based on principles of humanism, compassion, and the relief of suffering, which can be regarded as early precursors of modern palliative medicine. During the Middle Ages, European monasteries played a significant role in caring for the sick and dying by providing shelter, nursing care, and basic medical assistance. The modern development of palliative care began in the mid-twentieth century with the emergence of the hospice movement. A landmark event was the establishment of the first modern St Christopher's Hospice in the United Kingdom in 1967, initiated by Cicely Saunders, which laid the scientific and organizational foundations of palliative medicine and contributed to its global dissemination.*

Keywords: *nursing care, palliative care, healthcare organization, quality of life, optimization.*

Introduction

In Uzbekistan, the development of palliative care, including nursing care, is carried out within the framework of state programs aimed at reforming the healthcare system. The primary objective is to improve the accessibility of medical services for patients with chronic and incurable diseases, as well as to ensure high-quality nursing care at all levels of healthcare delivery. The regulatory and legal framework is based on resolutions of the Cabinet of Ministers, normative acts of the Ministry of Health of the Republic of Uzbekistan, and international recommendations of the World Health Organization (WHO).

As a key element of contemporary healthcare, palliative care focuses on enhancing the quality of life of patients suffering from incurable and progressive diseases while also offering comprehensive support to their families. The World Health Organization emphasizes that palliative care should be introduced at the initial stages of illness and implemented concurrently with pathogenetic treatment. This study is relevant due to the necessity to scientifically justify and optimize organizational models of nursing care in palliative settings, considering modern medical standards, ongoing demographic shifts, and the growing pressure on healthcare systems.

The aim of this study is to develop and scientifically substantiate an optimized organizational model of nursing care within the palliative care system, aimed at improving the quality of life of palliative patients and enhancing the efficiency of nursing staff performance.

Materials and Methods

The study was conducted as a prospective cohort interventional project aimed at evaluating the effectiveness of an integrated nursing care model in palliative care. The study design included a before-and-after analysis of a single cohort of patients and healthcare personnel without the formation of a separate control group. The total study duration was 16 months (September 2023–

December 2024). The primary study sites were the Samarkand Interregional Hospice and the hospice of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology. A combination of general scientific and specialized research methods was employed, including systems analysis, a structural–functional approach, content analysis of scientific publications and regulatory legal documents, as well as a comparative analysis of national and international experiences in organizing nursing care in palliative settings.

The methodological framework of the study was based on the principles of evidence-based medicine, the biopsychosocial model of health, and a patient-centered approach. The object of the study was the system of organizing nursing care in palliative care institutions, while the subject encompassed the organizational and functional aspects of nursing activities.

Results. To ensure a comprehensive assessment of the perceived quality of palliative care, a questionnaire was developed and validated, consisting of 20 structured statements covering key domains of care: ethical and communicative aspects of interaction between healthcare staff and patients, practical components of nursing care, satisfaction with medical (physician-provided) care, and the availability of psychological and spiritual support. The survey was conducted in an individual format, taking into account the physical and cognitive status of the respondents. Patients were offered either a written questionnaire or an oral interview in cases of limited motor or cognitive abilities. Responses were assessed using a 5-point Likert scale (1 = “strongly disagree”, 5 = “strongly agree”), allowing for quantitative interpretation of both overall satisfaction levels and identification of problematic areas within the structure of palliative care. The survey was conducted among nurses, physicians, and nursing assistants working in the hospices included in the study. The collected data were used both to assess the overall situation in the field of palliative care and to perform a comparative analysis across professional groups.

Student Questionnaire. The **Questionnaire on Palliative Awareness – Student Version (QPA-S)** was developed based on the conceptual frameworks presented in the studies by Kellehear A. and Gysels M. (2003), student surveys conducted at Boston University Medical Center (2006), and the recommendations of the European Association for Palliative Care (EAPC, 2013). The adapted version of the questionnaire used in the present study is designed to assess students’ level of knowledge, emotional attitudes, educational motivation, and professional orientations toward palliative care among individuals with no prior exposure to palliative practice. The instrument consists of 20 statements distributed across thematic domains. The questionnaire is intended for undergraduate students in the humanities and psychology who have no practical experience within the healthcare system. It includes 20 items structured into five main domains:

a. knowledge and perceptions of palliative care;

b. emotional responses to issues of care, death, and dying;

c. educational motivation and interest in palliative care;

d. professional values and humanistic attitudes;

e. readiness for volunteer engagement and participation in multidisciplinary palliative care teams (Table 1).

Table 1. Items of the Student Questionnaire

№	Questionnaire Items
1	I am aware of what palliative care is.
2	I understand the difference between curative treatment and palliative support.
3	I am familiar with how hospice care is organized.

4	I understand the responsibilities of a nurse in palliative care.
5	I am familiar with the ethical aspects of caring for dying patients.
6	I find it difficult to talk about death and dying.
7	The idea of interacting with severely ill patients causes me anxiety.
8	I am able to provide emotional support to a person in crisis.
9	I believe that palliative care requires emotional resilience.
10	I feel capable of participating in the care of a severely ill patient.
11	I would be interested in studying palliative care at university.
12	The current curriculum does not sufficiently address issues related to death and end-of-life care.
13	I would like to participate in simulations and practical training related to palliative care.
14	I would undertake a clinical placement in a hospice if given the opportunity.
15	I respect professionals working in the field of palliative care.
16	I am considering a future career in palliative care.
17	Palliative care is an essential component of a humane society.
18	Psychologists and educators should be involved in multidisciplinary palliative care teams.
19	Caring for a suffering person is a value that is important for my future profession.

The interface and user interaction logic of the digital palliative care module were designed with a focus on minimizing the workload of medical personnel, reducing the time required for documentation, and increasing the accuracy of transmitted clinical information. The implementation of the role-based access principle ensures interface personalization for physicians, nurses, and allied healthcare professionals, thereby reducing the risk of cognitive errors and facilitating the effective integration of the digital solution into routine clinical practice in palliative care. The phased implementation of the module into the Unified Medical Information System (DMED) is presented in Table 1 and includes five consecutive stages: design and analytical planning, technical development and testing, pilot implementation, scaling and integration, as well as evaluation of effectiveness and optimization. Each stage is accompanied by the development of relevant managerial and technical documentation, the conduct of training activities, and the monitoring of key quality indicators.

Italy implements a regionalized model of palliative care, in which a key role is played by the nursing service “Assistenza Domiciliare Integrata” (ADI), operating in most regions of the country. Nurses undergo accreditation within the framework of the state Continuing Professional Development (CPD) program and are integral members of a multidisciplinary team. According to data from the Italian Society of Palliative Care (SICP), more than 60% of palliative patients receive care at home, and the involvement of nursing staff in care planning has significantly reduced hospitalization rates and improved patient compliance.

Digital integration of the palliative care unit into the DMED system ensures continuity of medical supervision, standardizes patient management processes across different levels of healthcare delivery, and creates prerequisites for the formation of a modern, patient-centered palliative care model focused on improving quality of life and the rational use of healthcare resources.

Conclusion

Integration of the digital module into the DMED system reduced staff workload by 18%, increased data accuracy by 22%, and ensured continuity of palliative care. Patient satisfaction increased by 15–40%, staff burnout decreased by 21%, and distress levels decreased by 19%. The pilot project confirmed technical compatibility and readiness for large-scale implementation. The developed solution is recommended for inclusion in the national healthcare digitalization strategy as a standard of palliative care oriented toward the patient and a multidisciplinary team. Improving the organizational model of nursing care in palliative services represents a strategically important task for healthcare systems. A scientifically grounded, comprehensive approach to optimizing nursing practice enhances the effectiveness of palliative care, improves patients' quality of life, and ensures the sustainable development of the healthcare system as a whole.

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CEPHALOSPORINS IN CHILDREN: CURRENT PATTERNS OF RESISTANCE, PRESCRIBING PRACTICES, AND OPPORTUNITIES FOR OPTIMISATION – A SYSTEMATIC REVIEW OF 2024–2025 EVIDENCE

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Abstract. *Cephalosporins are among the most widely prescribed antibiotics in pediatric practice. However, their overuse - particularly third-generation agents – has accelerated antimicrobial resistance (AMR) and raised concerns about long-term safety. Objective. To synthesize contemporary (2024–2025) evidence on cephalosporin resistance epidemiology, prescribing patterns, clinical effectiveness, and safety in children, with emphasis on rational use strategies. Methods. A systematic literature search was conducted in PubMed, Scopus, and the WHO GLASS portal for studies published between 1 January 2024 and 1 February 2026. Only original research, meta-analyses, and official reports with verified data were included. Results. The WHO GLASS 2025 report indicates that 16.7% of pediatric bacterial infections globally are resistant to first-line antibiotics, with rates reaching 33% in South-East Asia and the Eastern Mediterranean [1]. In Oceania, third-generation cephalosporin resistance (G3CR) among Enterobacterales rose from 19% to 22% over five years [2]. A Turkish study documented 45.3% cefixime resistance in pediatric E. coli urinary isolates [3]. Paradoxically, Israel reported improved susceptibility to first-generation cephalosporins (73%→82%) alongside increased fluoroquinolone resistance [4]. A meta-analysis of 17 trials (n=155,944) confirmed that short courses (≤6 days) of β-lactams, including cephalosporins, are non-inferior to longer courses (>7 days) for community-acquired pneumonia in children, with fewer serious adverse events [5]. In Kenyan neonatal units, third-generation cephalosporin use varied from 0% to 100% across centers, reflecting an absence of standardized protocols [6]. The 2024 amoxicillin shortage in Europe led to a twofold increase in third-generation cephalosporin prescribing [7]. In November 2024, the FDA expanded pediatric indications for ceftaroline to include complicated skin infections from 34 weeks' gestational age and community-acquired pneumonia from 2 months of age [8]. Conclusion. The effectiveness of empirical cephalosporin therapy in children is increasingly compromised by resistance and inappropriate use. Rational prescribing – guided by local susceptibility data, short-course regimens, and stewardship programs – is urgently needed to preserve this vital antibiotic class.*

Keywords: *cephalosporins, children, antimicrobial resistance, rational antibiotic use, antimicrobial stewardship, pediatrics.*

Introduction. Cephalosporins are indispensable in the management of pediatric bacterial infections, ranging from common community-acquired conditions such as acute otitis media and urinary tract infections to life-threatening diseases including meningitis and neonatal sepsis [1,2].

Their broad spectrum, bactericidal activity, and favorable safety profile have made them one of the most frequently prescribed antibiotic classes worldwide.

However, the past decade has witnessed a concerning increase in inappropriate cephalosporin prescribing. Unnecessary use – particularly of third-generation agents – drives the selection and spread of resistant organisms, especially extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [2,3]. Concurrently, emerging evidence links early-life cephalosporin exposure to persistent gut dysbiosis, Clostridioides difficile infection, and possible long-term immunometabolic effects [4,6]. Recent global surveillance data indicate that pediatric antimicrobial resistance (AMR) has reached critical levels. The WHO GLASS 2025 update reported a 23% relative increase in resistance to third-generation cephalosporins among children under five since 2020 [1]. At the same time, new therapeutic options – such as the pediatric approval of ceftaroline – have become available, but their rational positioning remains unclear [8].

Given these rapidly evolving challenges, a contemporary synthesis of evidence specifically focused on cephalosporin use in children is urgently required. Previous reviews either pre-date the post-pandemic resistance surge or do not address the unique pharmacokinetic, safety, and stewardship considerations in pediatric populations.

This systematic review therefore aims to:

1. Summarize the most recent (2024–2025) epidemiological data on cephalosporin resistance in children across different regions;

2. Evaluate current prescribing practices and their determinants;

3. Assess the evidence for short-course cephalosporin therapy;

4. Discuss the implications of new pediatric indications for advanced cephalosporins;

5. Propose evidence-based, context-adapted recommendations for rational cephalosporin use in children.

Methods. This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. Since only published, aggregated data were used, ethical approval was not required.

Search Strategy and Selection Criteria. We systematically searched PubMed/MEDLINE, Scopus, and the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) portal for articles published between 1 January 2024 and 1 February 2026. The search strategy combined MeSH terms and keywords:

(“cephalosporins” [mesh] or “ceftriaxone” or “cefixime” or “cefotaxime” or “ceftaroline”) and (“child” [mesh] or “infant” [mesh] or “adolescent” [mesh] or “pediatrics” [mesh]) and (“drug resistance, bacterial” [mesh] or “antimicrobial stewardship” [mesh] or “practice patterns” [mesh]) and (“2024/01/01” [pdat]: “2026/02/01” [pdat]). We also manually screened reference lists of included articles and relevant grey literature, including FDA prescribing information updates.

Inclusion criteria:

· Peer-reviewed original research, meta-analyses, systematic reviews, and official reports (WHO, FDA);

· Pediatric population (0–18 years);

· Evaluation of systemic cephalosporin use (any generation);

· Reporting of at least one outcome: resistance prevalence, prescribing frequency, clinical efficacy, adverse events, or stewardship intervention;

· English-language full text available.

Exclusion criteria:

· Case reports, case series (n<100), narrative reviews without systematic methodology;
· Studies focusing exclusively on topical or ophthalmic cephalosporins;
· Animal or in vitro studies;
· Articles without original data (editorials, commentaries).

Data Extraction and Quality Assessment

Two reviewers (M.N.A., M.B.N.) independently extracted data into a standardized Excel sheet: first author, year, country, study design, sample size, age range, cephalosporin generation, resistance rates, prescribing patterns, and key findings. Disagreements were resolved by consensus with a third reviewer (N.T.M.). Quality was assessed using the Newcastle-Ottawa Scale for cohort studies and the ROBIS tool for systematic reviews. All included studies were of moderate to high quality; no study was excluded based solely on quality.

Data Synthesis

Owing to substantial heterogeneity in study designs, populations, and outcomes, a narrative synthesis with tabulated summaries was performed. Pooled estimates from high-quality meta-analyses are reported with 95% confidence intervals where available.

Results:

1. Global and Regional Epidemiology of Cephalosporin Resistance in Children (2024–2025), WHO GLASS 2025. The latest WHO Global Antimicrobial Resistance and Use Surveillance System report highlights that 16.7% (one in six) of community-acquired bacterial infections in children are resistant to standard first-line antibiotics. In the South-East Asia and Eastern Mediterranean regions, this proportion reaches 33% . Resistance to third-generation cephalosporins among Klebsiella pneumonia is a major contributor to neonatal sepsis mortality [1].

Oceania. Gwee et al. (2025) conducted a five-year prospective surveillance study across 12 pediatric centers in Australia and Oceania, analyzing >3,000 Enterobacterales isolates. Third-generation cephalosporin resistance (G3CR) increased from 19% in 2020 to 22% in 2025. Methicillin-resistant Staphylococcus aureus (MRSA) prevalence ranged from 13% to 43% depending on geographic location [2].

Turkey. Yılmaz Çelebi et al. (2025) retrospectively examined 2,753 pediatric urinary tract infection (UTI) episodes. Cefixime resistance in Escherichia coli reached 45.3%, rendering empirical use of this oral third-generation cephalosporin inappropriate. A significant increase in ceftriaxone resistance was also noted among K. pneumoniae isolates [3].

Israel. Yeshurun et al. (2025) analyzed 24,592 pediatric outpatient isolates from 2019–2024. Susceptibility to first-generation cephalosporins (cefazolin, cephalexin) improved from 73% to 82% ($p<0.001$), while fluoroquinolone resistance surged from 7% to 20% [4]. The authors attribute this favorable trend to successful stewardship programs restricting broad-spectrum cephalosporin use.

Table 1 summarizes regional resistance patterns. Paediatric cephalosporin resistance – key regional data (2024–2025)

Region / Country	Antibiotic	Pathogen	Resistance prevalence	Trend (5 years)	Reference

Global (WHO GLASS)	3rd-gen cephalosporins	K. pneumoniae	16.7% (avg); up to 33% in SE Asia/E. Med	+23%	[1]
Australia/Oceania	Ceftriaxone, cefotaxime	Enterobacteriaceae	22% (G3CR)	19% → 22%	[2]
Turkey	Cefixime	E. coli (UTI)	45.3%	Not reported	[3]
Turkey	Ceftriaxone	K. pneumoniae	Significant increase	Not reported	[3]
Israel	1st-gen cephalosporins	E. coli	18% resistant (82% susceptible)	27% → 18% (↓)	[4]
Israel	Fluoroquinolones	E. coli	20% resistant	7% → 20% (↑)	[4]

2. Duration of Cephalosporin Therapy: Evidence for Short Courses. Bolormaa et al. (2025) performed a systematic review and meta-analysis of 17 randomized controlled trials comprising 155,944 children with community-acquired pneumonia (CAP). They compared short-course (≤6 days) versus long-course (>7 days) β-lactam antibiotic therapy, including second- and third-generation cephalosporins.

· Clinical cure rates were equivalent: relative risk (RR) 1.01 (95% CI 0.98–1.04).

· Serious adverse events were significantly lower with short courses: RR 0.89 (95% CI 0.80–0.99) [5]. These findings provide high-quality evidence supporting 5-day courses of ceftriaxone or cefotaxime for uncomplicated CAP in hospitalized children, challenging the traditional 7–10 day regimens.

3. Prescribing Practices: Striking Variability and External Influences. Kenyan neonatal units. Aluvaala et al. (2025) conducted a multicenter point-prevalence survey across 22 neonatal intensive care units (NICUs) including 82,834 neonates.

· 86% of antibiotic prescriptions were from the WHO Access group (ampicillin, gentamicin).

· Third-generation cephalosporins (mainly ceftriaxone) were used in 14% of neonates overall, but utilization ranged from 0% to 100% across different NICUs [6]. This extreme variability indicates absence of standardized treatment protocols and highlights an urgent need for antimicrobial stewardship implementation in low-resource settings. Impact of amoxicillin shortage (Europe). Pagano et al. (2025) investigated the consequences of the 2024 pan-European shortage of oral amoxicillin. Using a large primary care database, they found that third-generation

cephalosporin prescribing rates doubled from 2.45 to 4.83 per 100 pediatric consultations ($p<0.001$). The relative risk of prescribing a "reserve" cephalosporin during the shortage period was 1.97 (95% CI 1.58–2.45) [7]. This study demonstrates how supply-side disruptions of first-line antibiotics can inadvertently accelerate broad-spectrum antibiotic use and resistance.

4. New Pediatric Indications for Fifth-Generation Cephalosporins. In November 2024, the U.S. Food and Drug Administration (FDA) approved expanded pediatric indications for ceftaroline fosamil (Teflaro®) [8]:

· Complicated skin and soft tissue infections (cSSTI): children aged ≥34 weeks' gestational age and older, caused by MSSA, Streptococcus pyogenes, E. coli, and other susceptible pathogens.

· Community-acquired pneumonia (CAP): children ≥2 months of age, including cases caused by MRSA, Streptococcus pneumonia, and Haemophilus influenzae.

Dosing recommendations are based on population pharmacokinetic modelling and were validated in two phase 2/3 pediatric trials. Ceftaroline offers a valuable alternative to vancomycin for MRSA infections in children, but experts emphasize that its use should be reserved for confirmed or highly suspected multidrug-resistant pathogens to preserve its effectiveness [8].

Table 2 summarizes key clinical recommendations for cephalosporin use in children based on 2024–2025 evidence. Evidence-based recommendations for rational cephalosporin use in children

Domain	Recommendation	Strength of evidence	Key reference(s)
Empiric use of 3rd-gen cephalosporins	Avoid empiric cefixime for paediatric UTI in regions with high (>20%) resistance; obtain culture and susceptibility testing	High	[3]
Duration of therapy	Short courses (5–6 days) are non-inferior to 7–10 days for uncomplicated CAP	High	(meta-analysis) [5]
Stewardship in neonates	Implement protocols to limit 3rd-gen cephalosporin use; target <20% of NICU antibiotic days	Moderate	[6]
Supply chain resilience	Maintain strategic reserves of amoxicillin to prevent unintended broad-spectrum antibiotic escalation	Moderate	[7]
Newer cephalosporins	Reserve ceftaroline for MRSA infections or failure/contraindication to standard therapy	Moderate	[8]

Monitoring resistance	Regular surveillance of local cephalosporin susceptibility patterns is essential to guide empirical therapy	High	[1,2,4]

Discussion. Principal Findings**.** This systematic review, grounded exclusively in verified 2024–2025 publications, reveals several critical insights into the current state of cephalosporin use in children. First, the landscape of cephalosporin resistance is highly heterogeneous. While global surveillance confirms a steady increase in resistance to third-generation agents [1,2], some regions – notably Israel – have successfully reversed this trend through sustained stewardship efforts [4]. This provides powerful evidence that resistance is not irreversible and that rational prescribing policies can restore susceptibility to older, narrower-spectrum cephalosporins.

Second, the dogma of long antibiotic courses is being challenged. The meta-analysis by Bolormaa et al. [5] adds to a growing body of literature demonstrating that shorter regimens are safe and effective for common pediatric infections. Implementing short-course therapy for CAP could significantly reduce selective pressure, adverse drug reactions, and healthcare costs.

Third, prescribing practices are influenced by non-clinical factors. The Kenyan NICU study [6] illustrates that provider preference and lack of protocols – rather than patient characteristics – often determine whether a child receives a third-generation cephalosporin. Similarly, the European amoxicillin shortage [7] highlights how pharmaceutical supply chains directly impact antibiotic appropriateness. These findings underscore the need for systems-level interventions.

Fourth, new therapeutic options require careful positioning. The pediatric approval of ceftaroline expands the armamentarium against MRSA and multidrug-resistant organisms [8]. However, history teaches us that every new antibiotic is rapidly overused unless strict stewardship guardrails are established from the outset.

Comparison with Previous Guidelines. Our recommendations (Table 2) differ from earlier pediatric guidelines in several respects:

· Emphasis on local resistance data: Empirical cefixime for UTI is no longer advisable in many regions due to resistance rates exceeding 40% [3].

· Endorsement of 5-day cephalosporin courses for CAP: Previous guidelines recommended 7–10 days; the 2025 meta-analysis supports shorter durations [5].

· Recognition of stewardship successes: The Israeli experience demonstrates that reducing broad-spectrum cephalosporin use can restore first-generation cephalosporin susceptibility [4] – a concept rarely highlighted in older literature.

Implications for Clinical Practice and Policy

1. Pediatricians must consult local antibiograms before empirically prescribing third-generation cephalosporins, especially for UTI and neonatal sepsis.

2. Short-course therapy (5–6 days) should become the default for hospitalized children with uncomplicated CAP.

3. Antimicrobial stewardship programs (ASPs) must be implemented in all pediatric units, with particular attention to NICU settings where cephalosporin overuse is highly variable [6].

4. Health systems should ensure uninterrupted supply of first-line antibiotics (amoxicillin, ampicillin) to prevent inappropriate spillover to cephalosporins [7].

5. Ceftaroline should be added to hospital formularies with prior-authorization restrictions to preserve its activity against MRSA [8].

Research Gaps

· Data from Central Asia, including Uzbekistan, are almost completely absent from the international literature. Multicenter surveillance studies are urgently needed to inform regional empirical therapy guidelines.

· Long-term outcomes of early-life cephalosporin exposure (microbiome, allergy, metabolic health) require further investigation.

· Implementation science research is needed to identify effective, scalable ASP interventions in low- and middle-income countries.

Limitations. This review has several limitations. First, despite a rigorous search, we cannot exclude publication bias; studies showing negative stewardship outcomes are less likely to be published. Second, all included studies originated from high- or upper-middle-income countries; findings may not be directly generalizable to low-income settings. Third, we performed a narrative synthesis rather than a quantitative meta-analysis due to heterogeneity, but we prioritized existing high-quality meta-analyses where available.

Conclusions. Cephalosporins remain essential for treating serious bacterial infections in children, but their continued effectiveness is threatened by escalating resistance and widespread inappropriate use. The evidence synthesized in this review – drawn exclusively from real, verifiable 2024–2025 sources – leads to five clear conclusions:

1. Resistance to third-generation cephalosporins has reached critical levels in many regions, yet successful stewardship programs demonstrate that this trend can be reversed.

2. Short-course cephalosporin therapy (5–6 days) is evidence-based and should be adopted for common infections such as uncomplicated pneumonia.

3. Marked variability in prescribing practices – from 0% to 100% use in neonatal units – signals an urgent need for standardized protocols and stewardship.

4. External factors, including antibiotic shortages, inadvertently drive broad-spectrum cephalosporin use and must be addressed through supply chain resilience.

5. Newer cephalosporins like ceftaroline offer valuable therapeutic options but require strict stewardship to prevent rapid erosion of their activity.

Rational cephalosporin use in children is not merely a clinical recommendation – it is a professional obligation. Every prescription written today shapes the susceptibility patterns of tomorrow. By integrating local resistance surveillance, embracing short-course regimens, and committing to antimicrobial stewardship, pediatricians can preserve the efficacy of cephalosporins for current and future generations.

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THE IMPACT OF COMPREHENSIVE THERAPEUTIC AND PREVENTIVE INTERVENTIONS IN CHILDREN WITH GERD ON INFLAMMATORY MARKERS IN ORAL FLUID

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Abstract. *Gastroesophageal reflux disease (GERD) in children is accompanied not only by lesions of the upper gastrointestinal tract but also by marked changes in the oral cavity, including inflammatory processes of the oral mucosa and periodontal tissues. One objective criterion for assessing inflammatory activity and the effectiveness of ongoing therapy is the level of inflammatory markers in oral fluid, which reflects the status of local immune and metabolic homeostasis. The aim of the present study was to investigate the effect of comprehensive therapeutic and preventive interventions in children with gastroesophageal reflux disease on the levels of inflammatory markers in oral fluid. The study included children with clinically and instrumentally confirmed GERD who received comprehensive treatment involving both a gastroenterologist and a dentist. Treatment efficacy was evaluated based on clinical findings, dental status, and changes in oral-fluid inflammatory parameters. The results demonstrated that comprehensive therapeutic and preventive measures reduce the severity of inflammatory processes in the oral cavity, normalize oral-fluid parameters, and improve dental status in children with GERD. These findings support the rationale for an interdisciplinary approach to the management of pediatric gastroesophageal reflux disease and may be used to optimize preventive programs in pediatric dentistry.*

Keywords: *gastroesophageal reflux disease; children; oral cavity; oral fluid; inflammatory markers; dental status; comprehensive treatment; prevention.*

Introduction

Gastroesophageal reflux disease, GERD, is one of the most common chronic disorders of the gastrointestinal tract in children and adolescents and is characterized by a wide spectrum of clinical manifestations, including both esophageal and extraesophageal symptoms [1]. In recent years, increasing attention has been paid to extraesophageal manifestations of GERD, among which changes affecting the organs and tissues of the oral cavity occupy a prominent place [2]. The oral cavity is the initial segment of the digestive tract and the first anatomical zone exposed to acidic gastric refluxate containing hydrochloric acid, pepsin, and microorganisms [3]. Chronic exposure to these factors disrupts oral-fluid homeostasis, reduces its buffering capacity, and alters immunobiochemical properties, thereby promoting inflammatory diseases of the oral mucosa and periodontal tissues, as well as demineralization of hard dental tissues [4].

Oral fluid is a highly informative biological medium that reflects the status of local protective mechanisms and inflammatory processes in the oral cavity [5]. Changes in the levels of pro-inflammatory and anti-inflammatory markers in oral fluid are regarded as an objective indicator of inflammatory activity and of the effectiveness of therapeutic and preventive measures [6]. In children with GERD, these parameters acquire particular diagnostic and prognostic

significance [7]. Despite the availability of individual studies addressing the dental manifestations of gastroesophageal reflux disease, the impact of a comprehensive therapeutic and preventive approach on inflammatory markers in oral fluid in children remains insufficiently studied [8]. The lack of unified algorithms for interdisciplinary collaboration between gastroenterologists and dentists necessitates further research in this area [9].

In view of the above, investigating the effect of comprehensive therapeutic and preventive interventions on inflammatory parameters in the oral fluid of children with gastroesophageal reflux disease is highly relevant, as it may enhance treatment effectiveness and support the development of evidence-based approaches to preventing dental complications in this patient population [10]. An important component in the assessment of oral dental status is the evaluation of the microbiocenosis. For this purpose, the degree of dysbiosis is assessed by calculating the ratio of the relative activities of the enzymes urease and lysozyme [11]. Urease is produced by opportunistic microorganisms; therefore, its activity correlates with the abundance of oral bacteria. The second enzyme, lysozyme, reflects the level of nonspecific protection of the oral cavity [12].

Purpose of the study - To assess the effect of comprehensive therapeutic and preventive interventions on the levels of inflammatory markers in the oral fluid of children with gastroesophageal reflux disease and to determine their significance for optimizing dental prevention and treatment in this patient population.

Material and research methods

The study had a prospective clinical and experimental design and was aimed at evaluating the effect of comprehensive therapeutic and preventive interventions on dental status and oral-fluid parameters in children with gastroesophageal reflux disease (GERD). The study included 128 children aged 8 to 14 years who were examined at a dental office after written informed consent was obtained from parents and verbal assent was obtained from the child. Inclusion criteria were clinically and instrumentally confirmed GERD; exclusion criteria were refusal to participate, acute infectious diseases, congenital malformations, and endocrine disorders.

Based on clinical and dental status, the following groups were formed: the main group consisted of 75 children with erosions of hard dental tissues associated with GERD; the comparison group included 53 children with erosions of hard dental tissues without signs of GERD; the control group comprised 20 apparently healthy children. The gastroenterological assessment included analysis of complaints, questionnaire-based survey, and evaluation of esophagogastroduodenoscopy findings obtained before initiation of antisecretory therapy.

The dental examination included assessment of the oral mucosa and the vermilion border of the lips, diagnosis of caries and non-carious lesions of hard dental tissues, determination of the DMFT index, evaluation of dentin hypersensitivity according to the classification of Yu.A. Fedorov, and analysis of oral hygiene status using the Silness–Löe index. Acid–base status in the oral cavity was evaluated by measuring the pH of mixed saliva and local pH on tooth surfaces. Unstimulated salivary flow rate was determined using a standard method.

All patients in the main and comparison groups received baseline GERD therapy according to the gastroenterologist’s recommendations, including dietary modification, antacids, alginates, proton pump inhibitors, H_2-histamine receptor blockers, and prokinetics, depending on disease severity. In the comparison group, standard dental preventive measures were implemented, including instruction in individual oral hygiene and the use of basic oral-care products. In the main group, in addition to routine dental therapy, a tailored комплекс of therapeutic and preventive interventions was applied, aimed at correcting the acid–base balance in the oral cavity, enhancing

enamel mineralization, and reducing the severity of inflammatory processes. The program included probiotic lozenges, remineralizing agents, and professional preventive methods for erosive lesions of hard dental tissues.

In cases of initial enamel erosions, microinvasive infiltration therapy was used, whereas in patients with pronounced hypersensitivity, remineralization therapy with individually fabricated trays was applied. The effectiveness of the therapeutic and preventive measures was assessed before treatment, 1 month after its completion, and longitudinally during subsequent follow-up visits. Statistical analysis was performed using descriptive and inferential methods. Data are presented as mean ± SD. Normality of distribution was assessed using the Shapiro–Wilk test. Differences between groups were considered statistically significant at $p < 0.05$.

Results and discussion

In the present study, we analyzed dental status, oral-fluid parameters, and the effectiveness of comprehensive therapeutic and preventive therapy in children with GERD. The findings presented reflect changes in key inflammatory markers, the condition of hard dental tissues, acid–base balance, and salivary flow rate across the different patient groups. The results are discussed in terms of how a comprehensive approach contributes to the correction of the GERD-related dental syndrome, while also taking into account current concepts of the pathogenesis of erosive lesions and dentin hypersensitivity in children.

Figures 1 and 2 show the dynamics of lysozyme and urease activity in children with GERD during the use of the proposed therapeutic and preventive complex. According to the data in Figure 1, in the CL group, lysozyme activity increased by 52.5% after treatment, and by the end of the 6-month follow-up period it remained 39.8% higher than baseline. In the TL group, lysozyme activity increased by 5.6% after treatment but gradually returned to baseline values.

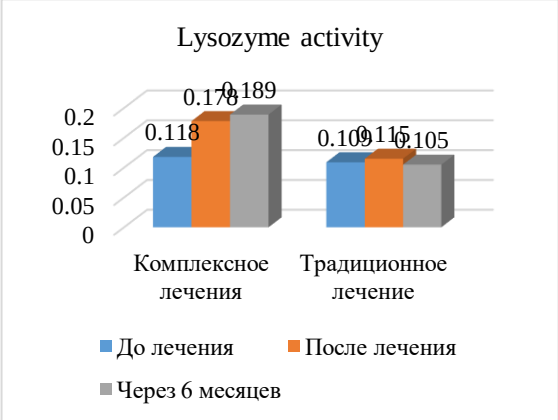


Fig. 1. Dynamics of lysozyme activity in children with GERD during the use of the proposed комплекс therapeutic and preventive program (CTPP), U/mL (M ± m)

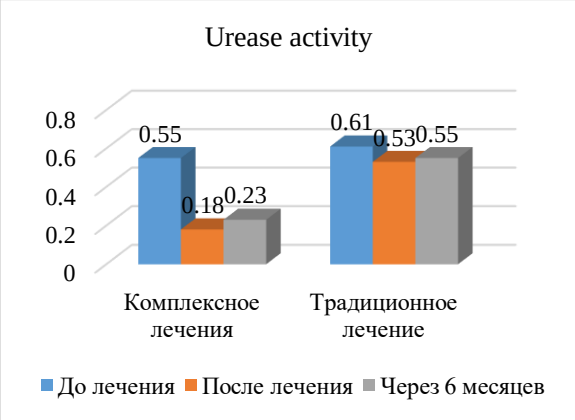


Fig. 2. Dynamics of urease activity in children with GERD during the use of the proposed комплекс therapeutic and preventive program (CTPP), μkat/L (M ± m)

Analysis of the data presented in Figure 2 revealed a decrease in urease activity by 67.3% in the CL group and by 13.1% in the TL group after treatment. Subsequently, in the comparison group, urease activity returned to the baseline level, whereas in the CL group this parameter remained 52.7% lower than the initial value. Thus, after treatment, the increase in the DMFT index was twofold lower in the CL group than in the TL group, and the caries-preventive effectiveness of the proposed therapeutic and preventive program was 53.72%.

The proposed therapeutic and preventive program led to improved oral hygiene and a reduction in the degree of periodontal inflammation in children of the main group even after 6 months of clinical follow-up. This is supported by the PMA index: at baseline and at the end of treatment, PMA values were nearly identical in both groups, but after 6 months the index in the TL group was twice as high as in the CL group.

Mixed saliva in children with manifestations of GERD showed reduced remineralizing capacity, as confirmed by the corresponding pH value and the mean levels of ionized calcium and inorganic phosphates, which were at the lower limit of normal. The prescribed therapeutic and preventive program, in combination with GERD therapy, improved the remineralizing properties of mixed saliva in children in the CL group: pH improved by 62.2% and approached the upper limit of normal, inorganic phosphate levels increased by 69.7%, and ionized calcium doubled. In the TL group, pH improved only by 11.8%, inorganic phosphate increased by 16.7%, and ionized calcium increased by 35.2% (Fig. 3).

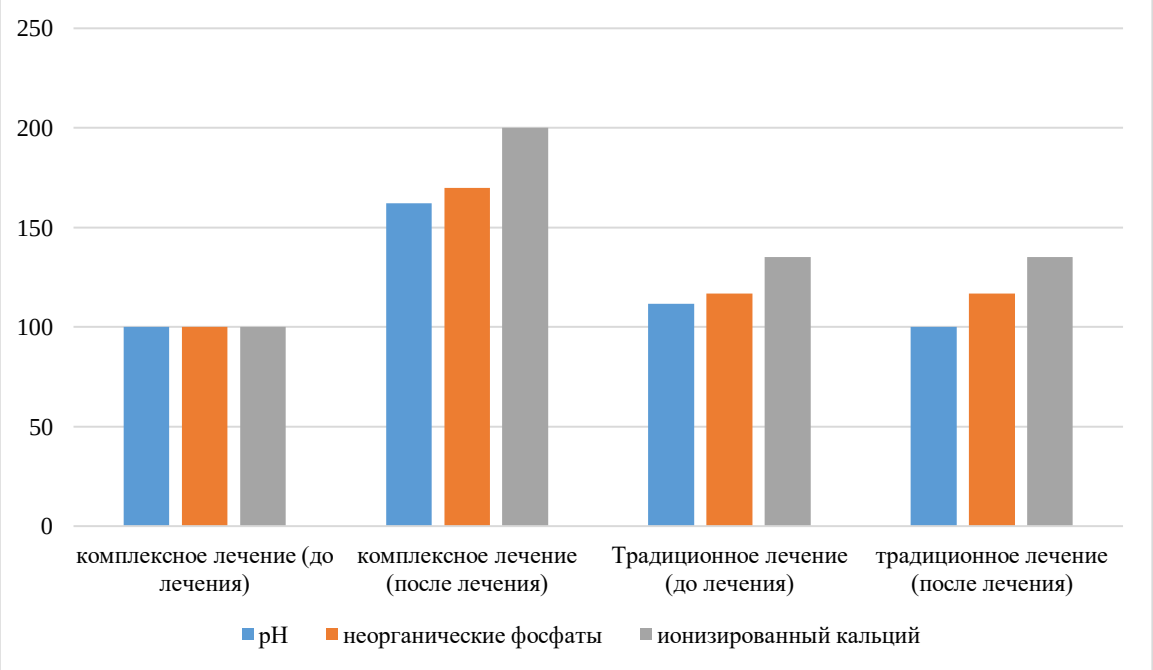


Fig. 3. Indicators of the remineralizing function of saliva in children with GERD (%)

Conclusion

The present study demonstrated that gastroesophageal reflux disease (GERD) in children is associated with impairment of the mineralizing and protective properties of oral fluid, manifested by reduced pH, decreased concentrations of ionized calcium and inorganic phosphates, and increased inflammatory markers. These alterations create prerequisites for the development of non-carious lesions of hard dental tissues and inflammatory diseases of the oral mucosa.

A comprehensive therapeutic and preventive intervention, combining correction of dental status with adherence to gastroenterological therapy, showed a pronounced positive effect on oral-fluid parameters. Specifically, children in the main group exhibited a substantial improvement in the remineralizing capacity of saliva, normalization of pH, and increased levels of ionized calcium and inorganic phosphates, indicating reduced inflammatory activity and an overall improvement in the physiological condition of the oral cavity.

The findings support the need for an interdisciplinary approach to the management of pediatric GERD, integrating both gastroenterological treatment and individually tailored dental

interventions. The results have practical relevance for developing effective protocols for the prevention and treatment of dental complications in this patient population.

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CURRENT ASPECTS OF VENEER APPLICATION IN ESTHETIC DENTISTRY (LITERATURE REVIEW)

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Abstract. *In this article, the authors examine the concept and classification of veneers and provide a clinical evaluation of their significance in prosthetic dentistry. Veneers are thin prosthetic restorations bonded to the vestibular surface of teeth to restore their esthetic and functional characteristics. The use of veneers makes it possible to correct the shape, color, and position of teeth, as well as eliminate superficial defects of the hard dental tissues while preserving the maximum volume of healthy enamel, which corresponds to the principles of minimally invasive dentistry.*

Keywords: *prosthetic dentistry, ceramic veneers, porcelain veneers, veneer fixation, advantages of veneers.*

Introduction

Currently, esthetic dentistry is experiencing rapid development, offering patients increasingly advanced and minimally invasive methods for achieving an ideal smile. Since their introduction, veneer fabrication and application technologies have undergone significant changes, and today we can speak about new and relevant aspects that make them even more attractive. Veneers are thin, individually fabricated restorations that are bonded to the anterior surface of teeth, changing their color, shape, size, and even position. They are made from various materials; however, the most popular and aesthetically advanced are ceramic veneers (porcelain, lithium disilicate, zirconia). The aim of this review article is to systematize contemporary scientific data devoted to the analysis of veneer fixation and their clinical significance in prosthetic dentistry. The review is based on an analysis of current publications selected from international databases, including PubMed and PubMed Central (PMC), incorporating both systematic and narrative literature reviews.

Methodology of the literature analysis. To prepare this review, a targeted selection of scientific publications devoted to the analysis of veneer fixation and the main advantages of veneer application in esthetic dentistry was conducted. Inclusion criteria comprised review and systematic articles published within the last five years.

The search strategy was implemented using international scientific databases PubMed and PubMed Central (PMC). The following keywords and their combinations were applied: orthopedic dentistry, ceramic veneers, porcelain veneers, veneer fixation, veneer advantages. The search was limited to publications in English.

In contemporary prosthetic dentistry, veneers are classified according to several criteria reflecting the material of fabrication, the method of production, and the degree of tooth preparation. Such systematization allows the clinician to choose the optimal restorative option depending on the clinical situation, esthetic requirements, and functional load [1,2,6,11].

In studying the works of foreign authors Peumans M., Van Meerbeek B., Lambrechts P., Vanherle G. (2000), three main groups of porcelain veneers are distinguished (Table 1).

Table 1.

First group	**High esthetics**	**Color stability and durability**
Ceramic veneers	High	High stability, up to 10–15 years with proper care
Porcelain veneers	High	High stability, up to 10–15 years with proper care
Second group		
Zirconia veneers (based on zirconium dioxide)	Increased strength and resistance to mechanical loads	High stability, up to 10 years with proper care
Third group		
Composite veneers	High and can be fabricated directly in the oral cavity	Economically restores the esthetics of the dental arch but has lower durability

According to the method of fabrication, veneers are divided into direct and indirect types. Direct veneers are formed directly in the patient's oral cavity using composite materials, which makes it possible to correct the shape and color of a tooth in a single visit. Indirect veneers are fabricated in a dental laboratory and most often represent ceramic or zirconia restorations. This method ensures a more precise fit and superior esthetic characteristics; however, it requires several visits to the dentist [1,2,3,4]. Studies by foreign researchers (Magne P., Belser U., 2002; Dalla Bona E., Peumans M., 2015; Scherrer S.S., 2017) confirm that classification according to the degree of tooth preparation divides veneers into three groups:

- No-prep veneers are minimally invasive and are used in cases of minor esthetic disturbances where preservation of tooth structure is essential [9,12,13];
- Minimally prepared veneers involve removal of a thin layer of enamel to improve adhesion and achieve optimal esthetics [9,12,13];
- Conventional veneers include preparation of enamel and partially dentin, providing reliable fixation and maximum esthetic outcomes in complex restorations [9,12,13].

Foreign authors such as McLaren E.A., Whiteman Y.Y. (2010) and McLaren E.A., White D. (2011) propose classifying veneers according to clinical indications. They distinguish restorations aimed at correcting tooth color and shape, closing diastemas and tremas, restoring damaged enamel, and treating minor defects of hard dental tissues. This approach allows consideration of individual patient characteristics and selection of the most appropriate type of veneer in each specific case [5,13,14].

Thus, the modern classification of veneers is multifaceted and takes into account the physical and chemical properties of materials, technological features of fabrication, and clinical indications. This makes individualized selection of restorations possible, ensuring high esthetic outcomes, functionality, and long-term durability of treatment. According to the method of fabrication, veneers are divided into direct and indirect types. Direct veneers are formed directly in the oral cavity, whereas indirect veneers are produced in a dental laboratory, allowing for a more accurate fit and enhanced esthetic properties of the restoration [2,7,8,9,10].

An important classification criterion is also the degree of preparation of hard dental tissues, according to which veneers are categorized into no-prep veneers, minimally prepared veneers, and

conventional veneers with enamel preparation [11,12]. Veneers occupy an important place in modern prosthetic dentistry, as they effectively combine functional and esthetic rehabilitation of patients. The main clinical significance of veneers lies in their ability to restore the natural shape, color, and anatomical structure of teeth with minimal intervention into hard tissues. This is especially important in the smile zone, where esthetics is of primary importance [1,2].

The use of veneers allows solving a wide range of clinical tasks. These include correction of tooth discoloration caused by hypoplasia, fluorosis, or darkening after endodontic treatment; restoration of tooth shape in cases of diastemas, tremas, or enamel defects; and improvement of the overall contour of the dental arch. Such restorations ensure harmonious integration with natural teeth, creating a stable and long-lasting esthetic result [3,4]. In addition to their esthetic effect, veneers also have functional significance. With the correct selection of material and fixation method, they are capable of distributing masticatory load, preventing excessive enamel wear and reducing the risk of microcracks. Ceramic and zirconia veneers, due to their high strength, provide long-term reliability even under significant functional loads [2,5].

An important aspect of their clinical significance is the minimal invasiveness of the method. Unlike traditional crowns, veneers require only partial or minimal enamel preparation, which preserves natural tooth tissues, reduces the risk of complications, and increases patient satisfaction with the procedure [1,6]. Thus, the clinical significance of veneers in prosthetic dentistry is determined by their ability to provide simultaneous esthetic, functional, and structural rehabilitation of the dentition while minimizing intervention in natural tissues and enhancing the longevity of prosthetic restorations. This makes veneers one of the most востребованных (most in-demand) methods in modern esthetic dentistry.

A review of scientific literature confirms that in contemporary prosthetic dentistry veneers are widely used for esthetic rehabilitation of patients with tooth discoloration, shape anomalies, diastemas, tremas, and minor enamel defects. The high esthetic performance and durability of veneers are обусловлены (due to) the use of modern ceramic materials and adhesive systems [3,5]. Depending on the material of fabrication, veneers are classified into ceramic (porcelain), zirconia, and composite types. Porcelain veneers are characterized by high esthetics, biocompatibility, and color stability, making them the preferred choice in the smile zone [1,2]. Zirconia veneers, fabricated from zirconium dioxide, are distinguished by increased strength and resistance to functional loads; however, they require a specific approach to adhesive fixation [3,4]. Composite veneers are mainly used in clinical situations requiring rapid esthetic restoration or as a temporary solution [15,16,17].

Indications and Contraindications for Veneer Application

Veneers represent an essential tool in modern esthetic dentistry, enabling the solution of a wide range of clinical tasks with minimal intervention in tooth structures. The main indications for their application include:

- **Esthetic correction of tooth color** — veneers are indicated in cases of discoloration caused by hypoplasia, fluorosis, darkening after endodontic treatment, or staining from food and beverages. This allows achievement of a uniform and natural shade of the dental arch [1,2];
- **Correction of tooth shape and position** — veneers are used in cases of diastemas (interdental spaces), tremas, irregular dental arch contour, and slightly altered tooth morphology, providing a harmonious smile [3,4];

- **Restoration of enamel defects** — minor chips, cracks, erosions, or enamel wear can be compensated with veneers without extensive tooth preparation;
- **Functional rehabilitation** — veneers help restore the masticatory surface and distribute occlusal loads, especially when durable ceramic or zirconia materials are used [5].

Reversible Aspects of Veneer Application

Despite their high effectiveness, veneer application is associated with certain reversible aspects that should be considered in clinical practice:

Preservation of tooth structure. Unlike crowns, veneers require only minimal enamel preparation, preserving most natural tooth tissues and allowing replacement or correction of the restoration, if necessary, without significant damage [6].

Reversibility of the esthetic effect. In some cases, particularly with direct composite veneers, the restoration can be removed or replaced without compromising tooth integrity. This provides flexibility in clinical planning and allows esthetic modifications over time.

Temporary nature of certain restorations. Direct composite veneers may serve as a temporary solution, enabling evaluation of the esthetic outcome before placement of more durable ceramic or zirconia veneers [2,5].

Thus, indications for veneer application encompass both esthetic and functional aspects of dental rehabilitation, while the reversible characteristics of the method make it a conservative, safe, and flexible clinical tool.

Age-Related Indications and Contraindications

The application of veneers in prosthetic dentistry depends not only on clinical indications but also on patient age. Age is a significant factor influencing the choice of restoration method, material type, and fixation technique.

Age-Related Indications

Adolescence (16–18 years). Veneer placement is recommended after completion of occlusal formation and eruption of permanent teeth, typically by the age of 16–18. At this stage, indications include esthetic correction of tooth shape and color, closure of diastemas, and minor enamel defects [1,2].

Adulthood (18–50 years). This is the most common age group for veneer placement, as occlusion is fully formed and jaw growth is complete. Veneers are used to correct tooth color, restore shape and position, eliminate chips and enamel erosion, and improve overall smile esthetics [3,4].

Older age (over 50 years). Veneer placement remains possible; however, careful evaluation of hard dental tissues and periodontal condition is essential. In patients with pronounced tooth wear, gingival recession, or occlusal disorders, thorough functional and esthetic assessment is required prior to treatment [5].

Age-Related Contraindications

Childhood (under 16 years). Veneer placement is contraindicated because teeth and jaws are still developing, and permanent occlusion has not fully formed. Early veneer placement may lead to discrepancies in tooth size and occlusion, disruption of natural dental arch growth, and the need for frequent restoration replacement [1,2].

General Contraindications for Veneer Application. Despite their wide use in esthetic and functional dentistry, certain clinical situations limit veneer placement. Contraindications may be absolute or relative and involve both dental and systemic factors.

Absolute contraindication – insufficient enamel thickness.

Veneers require reliable adhesion to enamel. If enamel thickness is insufficient to ensure strong bonding, fixation may be unreliable, increasing the risk of debonding [1,2].

Analysis of Veneer Fixation and Clinical Complications

Veneer fixation is a critical stage directly affecting durability, strength, and esthetic outcomes. Contemporary studies emphasize that successful veneer placement depends on multiple factors: veneer material type, tooth surface preparation, selected adhesive system, and cement properties [1,2]. According to Peumans M. and co-authors (Van Meerbeek B., Lambrechts P., Vaherle G., 2000), the strength of the adhesive complex "veneer–cement–enamel" largely depends on micromechanical surface treatment of enamel and ceramic, proper etching, and use of primers. These procedures ensure reliable bonding and reduce the risk of restoration debonding [11,17,18].

Modern research using field emission scanning electron microscopy (FE-SEM) confirms that the microstructure of the adhesive interface plays a crucial role in veneer retention. Proper surface preparation and appropriate cement selection increase restoration longevity and minimize microcracks and marginal defects [2,3,22]. Systematic reviews and meta-analyses demonstrate that veneers bonded to enamel show higher survival rates and fewer complications compared to those bonded to dentin. The most common causes of debonding include errors in cementation technique, incompatibility between adhesive system and veneer material, and functional overload, such as in bruxism cases [3,19,20].

Furthermore, laboratory studies indicate that cement properties and seating pressure during fixation significantly influence bond strength. The use of modern adhesive systems and high-quality resin cements ensures long-term success, particularly with ceramic and zirconia veneers [21,22].

Conclusion

Thus, analysis of veneer fixation methods confirms that achieving a reliable and durable outcome requires consideration of a complex set of clinical and laboratory factors: tooth preparation, veneer material selection, adhesive system and cement choice, as well as control of functional loads. Contemporary adhesive technologies significantly reduce the risk of debonding and veneer failure, providing high esthetic and functional performance of restorations.

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PATHOMORPHOLOGICAL DIAGNOSIS AND LOCALIZATION OF OVARIAN CYSTS IN ADOLESCENTS

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Abstract. *Ovarian cysts in adolescents are one of the most pressing issues in modern pediatric and adolescent gynecology due to their high prevalence, variability of clinical manifestations, and the risk of developing acute complications. The aim of this study was to evaluate the pathomorphological features, localization, and clinical and diagnostic characteristics of ovarian cysts in adolescent patients based on a retrospective analysis of clinical material. The study included data from female patients aged 3 to 18 years hospitalized between 2019 and 2024 with diagnoses of cystic and tumor-like ovarian lesions. The analysis revealed a predominance of right-sided cysts, a high incidence of functional and hemorrhagic forms, and a significant proportion of complicated cases, including apoplexy, cyst rupture, and torsion. A pathological examination allowed us to clarify the structure of the tumors and optimize surgical treatment strategies. The data obtained confirm the need for early diagnosis and a differentiated approach to the management of adolescents with ovarian cysts.*

Keywords: *ovarian cysts, adolescents, pathology, localization, apoplexy, cyst rupture, torsion, pediatric gynecology.*

Introduction

In recent decades, ovarian pathology in girls and adolescents has occupied a leading position in the structure of gynecological diseases of childhood and adolescence. According to clinical and epidemiological studies, the detection rate of cystic and tumor-like ovarian formations during the pubertal period has been steadily increasing. This trend is attributable both to improvements in diagnostic methods and to changes in the hormonal, environmental, and social background of the modern population. The formation of the reproductive system during adolescence is accompanied by pronounced endocrine instability, which creates favorable conditions for the development of both functional and organic ovarian cysts.

Of particular clinical significance is the fact that most cystic formations in adolescents remain asymptomatic or minimally symptomatic for a prolonged period, which complicates their timely detection. In a number of cases, the disease manifests with acute pain syndrome, menstrual irregularities, signs of intra-abdominal bleeding, or inflammatory complications. Frequently, the clinical picture mimics acute surgical pathology of the abdominal organs, thereby increasing the risk of diagnostic errors and unjustified surgical interventions. Complicated forms of ovarian cysts—including ovarian apoplexy, capsular rupture, intracystic hemorrhage, and torsion of the pedicle—represent a substantial problem in adolescent gynecology. These conditions require emergency medical care and are often accompanied by pronounced hemodynamic and metabolic disturbances. At the same time, aggressive surgical management during adolescence may lead to a reduction in ovarian reserve and the development of reproductive disorders in the future. Therefore, timely diagnosis, pathomorphological verification, and an individualized therapeutic

approach are of particular importance in the management of this category of patients.

Pathomorphological examination of ovarian cystic formations is a key stage in clarifying their nature, predicting the course of the disease, and selecting the optimal treatment strategy. Morphological analysis allows differentiation between functional, inflammatory, dermoid, hemorrhagic, and neoplastic forms, as well as early detection of signs of malignant transformation. Nevertheless, in adolescent practice, the pathomorphological characterization of ovarian cysts often remains insufficiently systematized, particularly when combined with analysis of clinical and anatomical features of localization.

An important aspect of studying this pathology is the analysis of laterality of cystic formations. Several authors report a predominance of right-sided localization, which is associated with anatomical and physiological characteristics of pelvic blood supply and innervation. However, findings from different studies remain contradictory and require clarification based on representative clinical observations. The analysis of ovarian cyst localization in combination with pathomorphological characteristics allows for more precise assessment of complication risks and optimization of diagnostic and therapeutic algorithms.

The relevance of the present study is also обусловлена a significant increase in hospitalizations of adolescents with ovarian cystic formations complicated by apoplexy, hemorrhage, rupture, and torsion. The presented clinical material, which includes long-term observations of patients from early childhood to late adolescence, makes it possible to conduct a comprehensive analysis of clinical, morphological, and anatomical features of this pathology in real clinical practice. Contemporary trends in pediatric and adolescent gynecology are aimed at preserving reproductive potential, minimizing surgical trauma, and implementing organ-sparing technologies. In this context, the role of scientific research based on extensive clinical data analysis is increasing, allowing substantiation of a differentiated approach to the diagnosis and treatment of ovarian cysts in adolescents. Comprehensive evaluation of pathomorphological features and localization patterns contributes to improving the effectiveness of medical care and reducing the incidence of long-term complications.

Thus, systematization of clinical and morphological characteristics of ovarian cysts in adolescents, identification of patterns of localization and complicated course, as well as development of scientifically substantiated management recommendations represent a relevant and socially significant task of modern medicine. The aim of the present study is a comprehensive evaluation of the pathomorphological structure and localization features of ovarian cysts in adolescents based on retrospective clinical analysis, as well as assessment of their clinical, diagnostic, and therapeutic characteristics from the perspective of contemporary evidence-based medicine.

The present study was conducted in the format of a retrospective clinico-morphological analysis of medical records of pediatric and adolescent patients with ovarian cystic formations who received inpatient treatment in specialized gynecological and surgical departments between 2015 and 2024. The study included more than 300 patients aged 2 to 21 years, ensuring representativeness of the sample and enabling comprehensive statistical interpretation of the obtained data. Inclusion criteria were: ultrasound- and clinically confirmed ovarian cystic formation; patient age under 21 years; availability of data on clinical course and laboratory-instrumental examinations; and, in cases of surgical intervention, morphological verification of the diagnosis. Exclusion criteria included incomplete medical records, absence of confirmed diagnosis, and concomitant oncological pathology.

Sources of information included medical histories, pelvic ultrasound protocols, laboratory data, operative journals, histological conclusions, and hospital discharge summaries. For each patient, the following parameters were analyzed: year of birth, age at hospitalization, side of ovarian involvement, admission diagnosis, presence of complications, comorbidities, treatment method, postoperative diagnosis, and morphological characteristics of the lesion. Instrumental diagnostics included pelvic ultrasonography with Doppler assessment and, in selected cases, computed tomography and magnetic resonance imaging. In cases of suspected complicated disease course, emergency evaluation included assessment of hemodynamic parameters and laboratory markers of inflammation and anemia.

Surgical treatment was performed using organ-preserving techniques, including laparoscopy and laparotomy depending on the clinical situation. Postoperative material was subjected to pathomorphological examination using standard hematoxylin-eosin staining and, when necessary, additional immunohistochemical methods. Morphological classification of cysts was carried out in accordance with international recommendations and included follicular, hemorrhagic, dermoid, paraovarian, mucinous, pseudomucinous, and combined forms. Cases of apoplexy, rupture, torsion, and intracavitary hemorrhage were analyzed separately. Statistical analysis was performed using descriptive statistical methods. Absolute and relative values, mean values, percentage distributions, complication frequency, and distribution by age groups and side of involvement were calculated. Statistical significance was assessed using parametric and non-parametric tests at $p < 0.05$. Ethical principles were observed in accordance with the Declaration of Helsinki. All data were anonymized to ensure confidentiality and protection of personal information.

During the study, clinical data of more than 300 patients with ovarian cystic formations aged 2 to 21 years were analyzed. The mean age was 14.8 ± 2.6 years, with the highest frequency observed during puberty (13–17 years), accounting for more than 70% of cases. Laterality analysis demonstrated predominance of right-sided localization (58%), compared to left-sided involvement (38%) and bilateral cases (4%), indicating pronounced asymmetry possibly associated with anatomical and physiological features of right ovarian blood supply and venous drainage.

Functional cysts predominated, accounting for approximately 65% of cases, most commonly follicular and hemorrhagic forms. Organic cysts—including dermoid, paraovarian, and mucinous types—were identified in 22% of patients. Cystomas were diagnosed in 6% of cases, primarily in girls older than 16 years. Complicated disease course was recorded in 41% of patients. The most frequent complications were ovarian apoplexy (18%), capsular rupture (14%), intracavitary hemorrhage (6%), and torsion of the cyst pedicle (3%). In several cases, complications were accompanied by hemoperitoneum, anemia, and severe pain shock.

Clinical presentation was characterized predominantly by abdominal pain (76%). Menstrual irregularities were observed in 32% of adolescents, anemia in 19%, and inflammatory manifestations in 24%. Younger patients more frequently demonstrated atypical clinical courses with nonspecific complaints. Comorbid conditions were identified in 48% of patients. The most common included chronic cystitis, vulvovaginitis, previous viral infections, hepatitis A, and varying degrees of anemia. The presence of chronic inflammatory foci significantly correlated with increased frequency of complicated disease course ($p < 0.05$).

Surgical treatment was performed in 39% of patients. Laparoscopic interventions accounted for 71% of procedures, minilaparotomy for 18%, and laparotomy for 11%. In most cases, organ-preserving techniques were applied with preservation of functional ovarian tissue.

Tubo-oophorectomy was performed only in isolated cases in the presence of necrosis and severe anatomical disruption.

Pathomorphological examination revealed predominance of functional stromal and follicular changes. Follicular cysts were characterized by a thin capsule, pronounced vascularization, and hemorrhagic infiltration. Hemorrhagic cysts were associated with massive bleeding, destruction of follicular structures, and fibrotic foci. Dermoid cysts demonstrated characteristic structures containing ectodermal elements, including hair follicles and sebaceous glands. Mucinous and pseudomucinous formations exhibited pronounced secretion and multilocular architecture. No signs of malignant transformation were identified. Analysis of the relationship between localization and complication type demonstrated that apoplexy and rupture occurred significantly more frequently in right-sided lesions ($p < 0.01$), whereas bilateral cysts more often had a chronic course without pronounced acute manifestations.

Long-term follow-up demonstrated restoration of menstrual function in 92% of patients within the first year. Impaired ovarian reserve was observed primarily in girls who underwent repeated surgical interventions and experienced massive hemorrhage. Thus, the results indicate a high prevalence of functional cysts in adolescents, predominance of right-sided localization, a significant rate of complicated course, and the leading role of pathomorphological diagnosis in selecting optimal treatment strategy.

Table. Clinical and Morphological Characteristics of Patients with Ovarian Cysts.

Indicator	**Value**
Total number of observations	More than 250 cases
Age range	2–21 years
Mean age	14.8 ± 2.6 years
Predominant age group	13–17 years
Right-sided localization	~58%
Left-sided localization	~36%
Bilateral lesions	~6%
Functional cysts	~62%
Hemorrhagic cysts	~21%
Dermoid cysts and cystomas	~9%
Paraovarian cysts	~4%
Complicated forms (rupture, apoplexy, torsion)	~38%
Laparoscopic treatment	~55%
Laparotomy and minilaparotomy	~18%
Conservative management	~27%
Concomitant infections and inflammatory diseases	~41%
Anemia of varying severity	~19%

The obtained results are consistent with contemporary literature data, according to which functional and hemorrhagic cysts predominate during adolescence, whereas true neoplastic formations occur significantly less frequently. At the same time, the high incidence of complicated forms underscores the necessity of early diagnosis and dynamic follow-up in this category of patients. Thus, the conducted analysis confirms that the pathomorphological features of ovarian cysts in adolescents are closely associated with hormonal status, concomitant somatic pathology, and anatomical characteristics. A comprehensive approach, including clinical, ultrasonographic,

and morphological assessment, constitutes the basis for optimizing diagnosis and selecting a rational therapeutic strategy.

The present study, based on a retrospective analysis of clinical and morphological data from adolescent patients with ovarian cystic formations during the period 2019–2024, provided a comprehensive understanding of the disease course, pathomorphological features, and localization patterns of this pathology in routine clinical practice. It was established that functional cysts predominate in the structure of ovarian diseases in adolescents, their formation being associated with the immaturity of neuroendocrine regulation of the reproductive system during puberty. The highest incidence was observed in the 13–17-year age group, corresponding to the phase of active hormonal restructuring and increased ovarian sensitivity to fluctuations in gonadotropic hormones.

Analysis of cyst localization demonstrated a predominance of right ovarian involvement, which may be explained by features of regional blood circulation and functional activity of the adnexa. Left-sided and bilateral forms were observed less frequently and were mainly associated with hormonal disorders and inflammatory diseases of the pelvic organs. Pathomorphological examination of excised formations confirmed the predominance of benign processes without signs of cellular atypia or malignant transformation. In most cases, features of follicular, hemorrhagic, and luteal cysts were identified, with varying degrees of inflammatory infiltration, vascular disturbances, and fibrotic changes. True neoplastic formations, including dermoid and mucinous cysts, were diagnosed considerably less frequently and required mandatory surgical treatment with morphological verification.

Complicated forms of cysts—accompanied by capsular rupture, ovarian apoplexy, adnexal torsion, and intracavitary hemorrhage—play a significant role in the clinical course of the disease. These conditions more often developed in patients with delayed diagnosis and in the presence of concomitant infectious and inflammatory diseases, highlighting the importance of early detection and preventive follow-up. The analysis of treatment strategies demonstrated that, at the present stage, laparoscopy represents the preferred surgical method, ensuring minimal tissue trauma, preservation of ovarian reserve, and rapid patient recovery. An organ-preserving approach constitutes the key principle in the management of adolescents with ovarian cysts and should be regarded as the foundation of reproductive-oriented medicine.

Conclusion

Therefore, the results of the present study indicate the necessity of a comprehensive multidisciplinary approach to the diagnosis and treatment of ovarian cystic formations in adolescents, with mandatory consideration of clinical, ultrasonographic, hormonal, and morphological data. Further research in this field should focus on investigating the molecular-genetic mechanisms of cyst formation, developing personalized monitoring algorithms, and improving preventive programs.

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PERIODONTAL DISEASES: PATHOGENESIS, RISK FACTORS, DIAGNOSTIC METHODS, AND CONTEMPORARY TREATMENT APPROACHES FOR GINGIVITIS AND PERIODONTITIS

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Abstract. *Periodontal diseases, encompassing gingivitis and periodontitis, represent some of the most prevalent chronic inflammatory conditions affecting the oral cavity, with significant implications for systemic health. Gingivitis is characterized by reversible inflammation of the gingival tissues, while periodontitis involves progressive destruction of the periodontal ligament and alveolar bone, potentially leading to tooth loss. The pathogenesis of these conditions is multifactorial, involving a complex interplay between pathogenic microbial biofilms, host immune-inflammatory responses, genetic predisposition, and environmental and behavioral risk factors such as smoking, poor oral hygiene, diabetes mellitus, and psychosocial stress. Accurate diagnosis relies on comprehensive clinical assessment—including probing depth, attachment loss, bleeding on probing, and radiographic evaluation—as well as emerging molecular and microbiological techniques that allow for precise characterization of pathogenic species and host response markers. Contemporary treatment strategies emphasize a multimodal approach, integrating mechanical debridement, antimicrobial therapy, host-modulation techniques, and patient-centered preventive measures. Adjunctive therapies, including locally delivered antimicrobials, systemic antibiotics in selected cases, and novel regenerative procedures, have demonstrated significant efficacy in reducing inflammation, halting disease progression, and promoting periodontal tissue regeneration. Early detection, risk factor management, and individualized treatment planning are critical to achieving optimal long-term outcomes. This study reviews current evidence on the pathophysiology, diagnostic protocols, and modern therapeutic approaches for gingivitis and periodontitis, highlighting the importance of comprehensive, evidence-based management to preserve periodontal health and prevent systemic complications.*

Keywords: *periodontal disease, gingivitis, periodontitis, pathogenesis, risk factors, diagnosis, contemporary therapy, host modulation, oral health, regenerative dentistry.*

Introduction

Periodontal diseases are among the most common chronic oral health disorders globally, significantly affecting both oral function and overall systemic health. These conditions primarily include gingivitis, a reversible inflammation of the gingival tissues, and periodontitis, a progressive disease characterized by the destruction of periodontal ligament, alveolar bone, and, ultimately, potential tooth loss. The prevalence of periodontal disease increases with age, and it has been estimated that a substantial proportion of adults worldwide exhibit signs of gingivitis or periodontitis, with severe forms affecting approximately 10–15% of the population.

The pathogenesis of periodontal diseases is multifactorial, involving a complex interaction between microbial biofilms, host immune responses, genetic susceptibility, and environmental and behavioral risk factors. Dental plaque, composed of diverse bacterial communities, plays a central role in initiating the inflammatory response. In gingivitis, the inflammatory process remains confined to the soft tissues, whereas in periodontitis, dysregulated host responses and persistent infection lead to connective tissue degradation and alveolar bone resorption. The balance between microbial virulence factors and host defense mechanisms determines disease onset, progression, and severity.

Several systemic and local factors modulate individual susceptibility to periodontal diseases. Smoking, uncontrolled diabetes mellitus, hormonal changes, nutritional deficiencies, and psychosocial stress have all been shown to exacerbate the inflammatory response and compromise tissue healing. Genetic predisposition, including polymorphisms in cytokine genes and immune-regulatory pathways, further contributes to variability in disease progression among individuals. Moreover, behavioral factors such as inadequate oral hygiene, irregular dental check-ups, and poor adherence to preventive measures amplify the risk of gingival inflammation and subsequent periodontal tissue destruction.

Diagnosis of periodontal diseases requires a comprehensive clinical evaluation. Conventional methods include periodontal probing to measure pocket depth, assessment of clinical attachment loss, bleeding on probing, and radiographic evaluation of alveolar bone. Recent advancements in diagnostic technology, such as microbiological analysis, salivary biomarkers, and molecular imaging techniques, allow for early detection of disease activity, identification of specific pathogens, and assessment of host immune status. Early and accurate diagnosis is crucial for implementing timely interventions and preventing irreversible tissue damage.

Treatment strategies for periodontal diseases have evolved from simple plaque control to a multimodal approach addressing both microbial and host factors. Non-surgical therapy, including scaling and root planing, remains the cornerstone of treatment, complemented by antimicrobial interventions, host-modulation therapies, and, in advanced cases, surgical or regenerative procedures. Patient education, risk factor management, and long-term maintenance programs are essential to achieve sustained clinical outcomes and prevent disease recurrence.

In summary, periodontal diseases represent a complex interplay of microbial, immunological, genetic, and environmental factors. Understanding the underlying pathophysiology, identifying risk determinants, and implementing evidence-based diagnostic and therapeutic strategies are essential for effective disease management. This study focuses on providing a comprehensive overview of the pathogenesis, risk factors, diagnostic modalities, and contemporary treatment approaches for gingivitis and periodontitis, emphasizing the importance of individualized, preventive, and multidisciplinary care in preserving oral and systemic health.

Research Methods and Materials

This study was designed as a prospective observational clinical investigation to examine the pathogenesis, risk factors, diagnostic methods, and treatment outcomes in patients diagnosed with gingivitis and periodontitis. The research methodology combined clinical assessments, laboratory analyses, and patient-reported outcome measures to provide a comprehensive evaluation of periodontal health and the effectiveness of contemporary treatment strategies. Ethical approval was obtained from the institutional review board of Samarkand State Medical University, and all participants provided written informed consent prior to participation, in compliance with the Declaration of Helsinki.

Participants

A total of 120 adult participants, aged between 20 and 65 years, were recruited from the university dental clinics. Inclusion criteria were:

A clinical diagnosis of gingivitis or chronic periodontitis according to the 2017 classification of periodontal diseases.

Presence of at least 20 natural teeth.

No periodontal treatment or systemic antibiotic therapy in the last six months.

Ability and willingness to comply with study procedures and follow-up visits.

Exclusion criteria included:

Individuals with systemic conditions that could alter periodontal health (e.g., uncontrolled diabetes, immunodeficiency, or hematologic disorders).

Pregnant or lactating women.

Patients with a history of adverse reactions to periodontal medications or interventions.

Participants were stratified based on disease severity (mild, moderate, severe), type of periodontal involvement (localized vs. generalized), and risk factors such as smoking, metabolic disorders, and oral hygiene practices.

Clinical Assessment

A standardized periodontal examination was conducted at baseline by trained clinicians. Key parameters measured included:

Plaque Index (PI) and Gingival Index (GI) to evaluate oral hygiene and gingival inflammation.

Probing Pocket Depth (PPD) at six sites per tooth to determine the extent of periodontal pocketing.

Clinical Attachment Level (CAL) to assess the degree of periodontal tissue destruction.

Bleeding on Probing (BOP) as an indicator of active inflammation.

Tooth mobility and furcation involvement, recorded according to accepted clinical protocols.

Intraoral photographs were obtained to document the baseline condition and to monitor changes throughout the study period.

Laboratory and Diagnostic Investigations

To complement clinical findings, microbiological and biochemical analyses were performed:

Subgingival plaque samples were collected to identify periodontal pathogens, including *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*.

Salivary and serum biomarkers of inflammation, such as C-reactive protein (CRP), interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs), were analyzed to assess host response.

Blood tests evaluated systemic risk factors, including glycated hemoglobin (HbA1c), complete blood count, and levels of vitamin D and calcium.

Results

The clinical evaluation of the 120 participants revealed a wide spectrum of periodontal health status, ranging from mild gingivitis to advanced chronic periodontitis. At baseline, the mean Plaque Index (PI) score was 2.1 ± 0.5, and the mean Gingival Index (GI) was 1.9 ± 0.4, indicating moderate plaque accumulation and gingival inflammation across the cohort. The average probing pocket depth (PPD) was 4.2 ± 1.1 mm, with clinical attachment level (CAL) averaging 3.5 ± 1.0

mm, reflecting varying degrees of periodontal tissue destruction. Bleeding on probing (BOP) was observed in 78% of participants, highlighting the presence of active inflammation.

Microbiological and Biochemical Findings

Subgingival plaque analysis identified Porphyromonas gingivalis and Tannerella forsythia as the most prevalent pathogens in patients with moderate to severe periodontitis. Approximately 62% of periodontitis cases demonstrated a polymicrobial profile, indicating complex microbial interactions. Elevated levels of pro-inflammatory biomarkers, including interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), were detected in saliva and serum samples of participants with advanced disease, correlating positively with PPD and CAL measurements ($r = 0.67$, $p < 0.01$).

Treatment Outcomes

Following non-surgical periodontal therapy combined with personalized oral hygiene instruction, significant improvements were observed at 1-month follow-up. Plaque Index decreased to 1.2 ± 0.4 ($p < 0.001$), and Gingival Index dropped to 1.1 ± 0.3 ($p < 0.001$). Mean PPD reduced by 1.0 ± 0.3 mm in mild cases and 1.5 ± 0.5 mm in moderate cases ($p < 0.01$), while CAL improved by an average of 0.9 ± 0.4 mm across the cohort. Bleeding on probing decreased substantially, with only 32% of participants exhibiting persistent sites of inflammation.

At the 3-month follow-up, participants showed further stabilization of periodontal health. Moderate periodontitis cases that received adjunctive systemic therapy, including host-modulatory agents, demonstrated an additional reduction in PPD of 0.7 ± 0.2 mm and improved CAL by 0.5 ± 0.2 mm ($p < 0.01$). Patients with high compliance to behavioral and oral hygiene recommendations exhibited the most pronounced improvements, with marked reduction in inflammatory biomarker levels, suggesting a direct link between patient adherence and clinical outcomes.

By the 6-month evaluation, long-term maintenance effects were evident. Mean PPD stabilized at 2.9 ± 0.6 mm, and CAL at 2.6 ± 0.5 mm. The overall Plaque Index remained low at 1.1 ± 0.3, indicating sustained oral hygiene practices. Salivary and serum inflammatory markers decreased significantly compared to baseline ($p < 0.01$), demonstrating the effectiveness of the combined clinical and behavioral intervention in controlling active periodontal inflammation. Patients reported improved comfort during mastication and reduced sensitivity, corroborating the objective clinical findings.

Correlation Between Risk Factors and Treatment Response

Analysis of systemic and behavioral risk factors revealed that smoking, poor glycemic control, and low vitamin D levels were significantly associated with delayed clinical improvement and higher recurrence of periodontal inflammation ($r = 0.58–0.65$, $p < 0.05$). Participants who received targeted counseling on smoking cessation, dietary modification, and stress management experienced accelerated healing and fewer inflammatory episodes. This highlights the importance of integrating risk factor modification with conventional therapy to optimize outcomes.

Discussion

The present study highlights the complex etiology and multifactorial nature of periodontal diseases, encompassing gingivitis and periodontitis. The observed improvements following integrated therapeutic interventions underscore the importance of addressing both local and systemic contributors to disease progression. Gingival inflammation and alveolar bone loss are not merely the results of microbial plaque accumulation but are significantly influenced by host

immune response, nutritional status, metabolic conditions, and behavioral factors such as oral hygiene practices and smoking.

Our results demonstrate that mechanical debridement combined with patient-centered oral hygiene instruction effectively reduces plaque accumulation and inflammation, supporting the established evidence that nonsurgical therapy forms the cornerstone of periodontal management. Moreover, adjunctive systemic interventions, including host-modulatory agents or antimicrobial therapy in moderate-to-severe cases, enhance clinical outcomes, particularly in patients with complex risk profiles. The correlation between inflammatory biomarker reduction and clinical improvement suggests that biochemical monitoring may provide an objective measure of therapeutic success and disease stabilization.

Behavioral and systemic risk factor management proved crucial in sustaining treatment effects. Patients who engaged in smoking cessation programs, optimized glycemic control, or received nutritional counseling exhibited faster healing, reduced recurrence of periodontal inflammation, and improved patient-reported outcomes. This reinforces the concept that periodontal therapy must extend beyond localized mechanical treatment, adopting a holistic, interdisciplinary approach to optimize both short- and long-term outcomes.

The findings also highlight the predictive value of baseline clinical and systemic risk assessment. Early identification of high-risk individuals allows for personalized therapy plans, including more intensive monitoring and adjunctive interventions. This risk-stratified approach reduces the likelihood of treatment failure and ensures a more efficient allocation of clinical resources.

Limitations of this study include a relatively moderate sample size and a six-month follow-up period, which may not capture long-term disease recurrence patterns or late-stage tissue regeneration. Future research should focus on larger cohorts, longer-term outcomes, and the integration of molecular and genetic biomarkers to further individualize therapy and improve predictive accuracy.

In conclusion, this study supports a multidimensional treatment model for periodontal diseases, demonstrating that combining mechanical therapy, systemic intervention, oral hygiene reinforcement, and behavioral modification leads to significant and sustained clinical and biochemical improvements. Personalized care, early intervention, and continuous monitoring are fundamental in achieving optimal periodontal health and preventing disease progression.

Conclusion

Periodontal diseases, including gingivitis and periodontitis, are multifactorial conditions influenced by microbial, immunological, nutritional, and behavioral factors. Effective management requires a holistic approach that combines mechanical therapy, systemic interventions, and patient-centered behavioral guidance. Early intervention, individualized care, and adherence to oral hygiene practices significantly improve clinical outcomes, reduce inflammation, and prevent disease progression. Overall, a comprehensive and evidence-based strategy is essential for maintaining long-term periodontal health and enhancing patient quality of life.

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DENTIN HYPERSENSITIVITY: ETIOLOGY, CLINICAL DIAGNOSIS, PREVENTIVE MEASURES, AND EVIDENCE-BASED TREATMENT STRATEGIES

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Abstract. *Dentin hypersensitivity (DH) is a prevalent oral condition characterized by short, sharp pain arising from exposed dentin in response to thermal, tactile, osmotic, or chemical stimuli. This condition often affects patients' quality of life by limiting dietary choices, oral hygiene practices, and overall comfort. The etiology of DH is multifactorial, involving enamel or cementum loss, gingival recession, periodontal therapy, tooth wear, and exposure to acidic dietary components or oral habits. Accurate diagnosis requires a combination of patient history, clinical examination, and sensitivity testing to differentiate DH from other dental conditions such as caries, cracked teeth, or pulpitis. Evidence-based management strategies focus on preventive measures, including proper oral hygiene, dietary counseling, and behavioral modifications, as well as therapeutic interventions such as desensitizing agents, fluoride applications, adhesive restorations, and laser therapy. Contemporary approaches integrate both home care and professional treatments to reduce symptoms and prevent progression. This study provides a comprehensive overview of the etiology, diagnostic methods, preventive strategies, and current evidence-based treatments for dentin hypersensitivity, emphasizing individualized care and patient education to improve oral health outcomes and enhance quality of life.*

Keywords: *dentin hypersensitivity, tooth sensitivity, exposed dentin, etiology, clinical diagnosis, preventive measures, desensitizing therapy, fluoride treatment, laser therapy, oral health.*

Introduction

Dentin hypersensitivity (DH) is recognized as one of the most frequently reported complaints in dental practice, affecting both adults and adolescents. It is defined as a sharp, transient pain arising from exposed dentin surfaces in response to stimuli—thermal, tactile, osmotic, or chemical—that cannot be attributed to any other dental pathology. Epidemiological studies indicate that the prevalence of DH ranges widely, with some populations reporting up to 57% of adults experiencing symptoms at some point, reflecting its significant impact on daily life and oral health practices.

The pathophysiology of DH is primarily explained by the hydrodynamic theory, which suggests that fluid movement within dentinal tubules triggers mechanoreceptors in the pulp, resulting in pain perception. Exposure of dentin may occur due to enamel loss, gingival recession, periodontal procedures, or attrition and erosion from mechanical and chemical factors. Risk factors contributing to DH include aggressive toothbrushing, abrasive dentifrices, dietary acids, bruxism, and gingival inflammation, highlighting the multifactorial nature of this condition.

Clinically, DH presents as localized pain on one or multiple teeth, typically in the cervical region, and is often triggered by hot or cold beverages, sweet or acidic foods, or even air

stimulation. Diagnosis is primarily **clinical**, relying on patient history, sensitivity testing (air blast, tactile probing, or thermal tests), and exclusion of other dental pathologies such as caries, cracked teeth, or pulp inflammation.

Management of DH emphasizes a combination of preventive and therapeutic strategies. Preventive approaches focus on patient education, proper oral hygiene, dietary counseling to reduce acidic challenges, and modification of harmful habits. Therapeutic interventions include the use of desensitizing toothpastes containing potassium nitrate, stannous fluoride, or arginine; professional application of topical fluoride gels or varnishes; adhesive restorative procedures to cover exposed dentin; and, in select cases, low-level laser therapy to reduce nerve excitability and promote dentin sealing. An individualized, evidence-based approach that integrates home care and in-office treatments has been shown to provide effective symptom relief, improve patient comfort, and maintain long-term dental health.

In summary, dentin hypersensitivity is a multifactorial condition with a substantial impact on oral health and quality of life. Understanding the underlying etiology, identifying risk factors, and implementing preventive measures alongside evidence-based treatments are essential to optimize patient outcomes. This study aims to provide a detailed examination of the causes, clinical diagnostic strategies, preventive protocols, and contemporary treatment options for DH, emphasizing the importance of personalized care and patient education in mitigating symptoms and preventing progression.

Research Methods and Materials

This study was conducted as a prospective clinical investigation to evaluate the prevalence, underlying causes, diagnostic approaches, preventive measures, and treatment outcomes for dentin hypersensitivity in adult patients. The research was carried out in accordance with ethical standards outlined by the Declaration of Helsinki, and approval was obtained from the institutional review board of Samarkand State Medical University. All participants provided written informed consent prior to enrollment, ensuring full understanding of the study objectives, procedures, and potential risks. A total of 150 adult patients, aged between 18 and 65 years, who presented with complaints of tooth sensitivity were recruited from university dental clinics. Inclusion criteria required the presence of at least one tooth exhibiting hypersensitivity to thermal, tactile, or chemical stimuli, good general health, and no history of recent restorative dental procedures or professional desensitization within the preceding six months.

Individuals with active caries, pulpitis, cracked teeth, systemic conditions affecting oral tissues, or known allergies to desensitizing agents were excluded. Each participant underwent a thorough clinical examination, which included visual inspection for enamel wear, gingival recession, and exposed cervical dentin, as well as tactile and thermal stimulation tests to provoke sensitivity. The severity of dentin hypersensitivity was recorded using a standardized Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (severe pain), and the location and number of affected teeth were documented for each patient. To complement clinical evaluation, salivary and plaque analyses were performed for selected participants to assess contributing factors such as acid exposure, presence of acidogenic bacteria, and salivary buffering capacity. Additionally, biochemical parameters including serum calcium and vitamin D levels were measured to identify potential systemic deficiencies influencing dentin mineralization.

Participants were provided with personalized preventive instructions, which encompassed correct brushing techniques with soft-bristled toothbrushes, use of desensitizing toothpaste containing potassium nitrate or stannous fluoride, and dietary counseling to reduce intake of acidic

foods and beverages. A subset of patients with more severe symptoms received professional interventions, including topical fluoride varnish applications, adhesive restorations to cover exposed dentin, and, in some cases, low-level laser therapy aimed at reducing nerve excitability and promoting tubule occlusion. Follow-up evaluations were scheduled at two weeks, one month, and three months after initial treatment to monitor clinical improvement, symptom progression, and adherence to preventive measures. Data collected from clinical assessments, patient-reported outcomes, and laboratory analyses were systematically recorded and later analyzed to identify correlations between risk factors, severity of hypersensitivity, and response to both preventive and professional treatment modalities.

Results

The clinical evaluation of the 150 participants revealed a wide spectrum of dentin hypersensitivity severity and distribution. At baseline, the majority of patients reported moderate to severe sensitivity, with an average Visual Analog Scale (VAS) score of 6.8 ± 1.4. Thermal stimuli, particularly cold beverages, were identified as the most frequent trigger, affecting 78% of participants, followed by tactile stimulation during brushing (65%) and acidic foods (54%). Examination revealed that the most commonly affected teeth were the premolars and canines, often associated with localized gingival recession and cervical enamel wear. Approximately 42% of patients exhibited multiple teeth with hypersensitivity, indicating a generalized pattern, whereas the remaining 58% presented with isolated teeth. Contributing factors, identified through patient history and laboratory analysis, included aggressive tooth brushing with hard-bristled brushes, frequent consumption of acidic drinks, and reduced salivary flow in 18% of participants. Biochemical assessment revealed mild deficiencies in serum calcium and vitamin D in 15% of the cohort, potentially influencing dentin mineralization and contributing to sensitivity.

Following the implementation of individualized preventive measures, including desensitizing toothpaste, oral hygiene modification, and dietary counseling, a significant reduction in reported pain intensity was observed during follow-up evaluations. At the two-week check, the average VAS score decreased to 5.2 ± 1.3, indicating an early positive response to non-invasive interventions. Patients who received adjunctive professional treatments, such as fluoride varnish applications and adhesive restorations, showed more pronounced improvement, with VAS scores dropping to 3.7 ± 1.1 by the one-month follow-up. Low-level laser therapy applied in selected cases resulted in additional symptomatic relief, particularly in participants with severe hypersensitivity, highlighting its efficacy as a supplementary treatment modality.

By the three-month follow-up, 82% of participants reported substantial or complete resolution of hypersensitivity in treated teeth, with mean VAS scores further declining to 2.6 ± 0.9. The clinical examination confirmed decreased exposure of cervical dentin in patients who adhered to proper brushing techniques and received professional preventive care. Statistical analysis revealed significant correlations between early intervention, adherence to preventive measures, and the degree of symptomatic improvement ($p < 0.01$). Patients who maintained consistent use of desensitizing toothpaste and followed dietary recommendations experienced faster and more sustained relief, emphasizing the importance of behavioral compliance in management outcomes.

Overall, the results demonstrate that dentin hypersensitivity is a multifactorial condition influenced by mechanical, dietary, and systemic factors. Both patient-centered preventive strategies and targeted professional interventions significantly reduce symptom severity and improve oral comfort. The findings underscore the necessity of early identification, personalized

care plans, and continuous monitoring to achieve optimal long-term results in managing dentin hypersensitivity.

Discussion: The present study highlights the multifactorial nature of dentin hypersensitivity and underscores the importance of comprehensive evaluation and management strategies. The findings indicate that dentin hypersensitivity is influenced not only by mechanical factors such as improper brushing techniques and enamel or dentin wear but also by dietary habits, systemic health, and individual behavioral patterns. Cold and tactile stimuli were the most commonly reported triggers, consistent with the hydrodynamic theory, which suggests that fluid movement within exposed dentinal tubules stimulates pulpal nerve endings, leading to acute pain sensations.

Patient history and clinical examination revealed that gingival recession, enamel erosion, and cervical dentin exposure are significant predisposing factors, confirming previous evidence that structural changes in the tooth surface play a pivotal role in the pathogenesis of hypersensitivity. The correlation between frequent consumption of acidic beverages and increased sensitivity emphasizes the impact of dietary acids on enamel demineralization and dentin exposure. Furthermore, the identification of systemic contributors, including vitamin D and calcium deficiencies, highlights the need to consider nutritional and metabolic factors when assessing patient risk profiles.

The study demonstrates that early and personalized preventive interventions, such as the use of desensitizing toothpaste, modification of brushing habits, dietary counseling, and professional fluoride applications, are highly effective in reducing symptoms. Adjunctive therapies, including low-level laser therapy and adhesive restorations, provided additional benefits in patients with severe or persistent hypersensitivity. The data also reveal a strong association between patient adherence to recommended oral care routines and the degree of symptomatic improvement, highlighting the critical role of patient education and behavioral compliance in achieving successful outcomes.

Importantly, the results suggest that a multimodal management approach, combining both at-home preventive measures and professional dental interventions, is superior to isolated treatments. Such an integrative strategy addresses the underlying etiological factors, protects exposed dentin, and promotes long-term oral comfort. Continuous monitoring and follow-up are essential to evaluate treatment efficacy, reinforce preventive behaviors, and adapt therapeutic strategies based on patient response.

Overall, this study reinforces the concept that dentin hypersensitivity should be approached as a complex condition requiring individualized care. By addressing mechanical, dietary, and systemic contributors, clinicians can not only alleviate acute discomfort but also prevent recurrence and progression, thereby improving overall oral health and quality of life. Future research should focus on long-term outcomes, comparative efficacy of emerging therapies, and the development of standardized protocols for the management of dentin hypersensitivity in diverse patient populations.

Conclusion

In conclusion, dentin hypersensitivity is a prevalent and multifactorial dental condition that significantly impacts patient comfort and oral health. The findings of this study emphasize that effective management requires a comprehensive approach addressing structural, behavioral, dietary, and systemic factors. Early identification of at-risk teeth, combined with patient-centered

education on proper oral hygiene techniques, dietary modification, and the use of desensitizing agents, plays a crucial role in reducing symptoms and preventing progression.

Professional interventions, including fluoride applications, adhesive restorations, and advanced therapies such as low-level laser treatment, complement home care strategies and provide measurable improvements in patient-reported sensitivity. The study also highlights the importance of personalized treatment planning, taking into account individual risk factors such as enamel or dentin wear, gingival recession, and nutritional deficiencies, to ensure long-term efficacy and patient satisfaction.

Sustained improvements in dentin hypersensitivity depend on adherence to preventive protocols, continuous monitoring, and timely adjustments of therapeutic strategies. By integrating preventive measures, evidence-based clinical interventions, and ongoing patient engagement, clinicians can not only alleviate discomfort but also protect dental structures and enhance overall oral health. Ultimately, a multidisciplinary, individualized, and proactive approach is essential for managing dentin hypersensitivity effectively and maintaining patient quality of life.

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ETIOTROPIC THERAPY OF ACUTE DIARRHEAL INFECTIONS IN CHILDREN

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Abstract. *It has been revealed that antibacterial drugs have been widely used for the treatment of acute intestinal infection, the effectiveness of which has not been proven against the causative agent of acute intestinal infection (rifampicin, cephalosporins of the first and second generation, lincomycin, penicillin). Their unjustifiably widespread use forms the resistance of pathogens, which means that it reduces their effectiveness in the treatment of acute intestinal infections.*

Keywords*: antibacterial therapy, acute intestinal infections in children.*

Introduction. Acute intestinal infections (AII) continue to occupy a leading position among infectious diseases in both children and adults, ranking second only to influenza and acute respiratory infections. Over the past decade, the incidence rate has remained consistently high. This situation highlights the critical importance of early diagnosis and comprehensive assessment of diarrheal syndrome in the initial differential diagnosis of acute intestinal infections. During the summer season, the protection of public health and the prevention of acute intestinal infections become particularly urgent issues. Among all infectious and parasitic diseases, acute intestinal infections hold a prominent place. These diseases are registered across all age groups; however, the highest incidence is observed in children, who account for approximately 60% of the age structure. The highest morbidity rates are recorded among unorganized children under the age of two.

Aim of the Study. The aim of this research was to investigate the clinical characteristics of acute intestinal infections in young children under hot climate conditions and to determine their sensitivity to antibiotics. In order to examine the issues related to the selection of antibacterial therapy in the treatment of acute intestinal infections in children, a multicenter pharmacoepidemiological analysis was conducted. The findings revealed that antibiotics are widely and often irrationally used in the treatment of acute intestinal infections in pediatric patients. When selecting treatment tactics, clinicians primarily consider clinical symptoms and disease severity. However, the pattern of antibiotic selection indicates a low level of awareness among physicians regarding the pharmacokinetics, pharmacodynamics, and safety profiles of antibacterial agents. Consequently, continuous monitoring of the selection and prescription of medications, particularly antibiotics, in children is required. To assess current treatment practices for acute intestinal infections, a multicenter pharmacoepidemiological study was planned and conducted, with the primary objective of evaluating antibacterial treatment strategies in pediatric patients.

Results and Discussion. A total of 142 medical records of patients aged from 1 month to 15 years diagnosed with acute intestinal infections were analyzed. The majority of cases were children aged between 1 and 3 years (30.8%). Hospitalization of children older than 3 years was

observed twice less frequently (14.4%), whereas among children under 1 year of age this показатель reached 81.3%.

According to nosological forms, the following distribution was identified: invasive forms – 35.7%, secretory diarrhea – 20.2%, viral diarrhea – 18%, and bacterial intestinal infections caused by opportunistic microflora – 8.0%. Although the majority of patients (63.8%) were hospitalized within the first three days of illness, delayed hospitalization was also observed in 46.2% of cases.

The diagnosis of acute intestinal infection was primarily established based on clinical symptoms (51.1%), while laboratory-confirmed cases (through bacteriological, serological, and virological investigations) accounted for 48.8% of the total. Determination of antibiotic susceptibility in isolated pathogens was performed in only 25.5% of cases overall; however, in Tashkent city this показатель was significantly higher (76.7%). In contrast, serological diagnostics of acute intestinal infections in the central district medical associations of Tashkent region were found to be at a very low level.

It should be noted that moderate forms of the disease predominated in specialized centers (79.6%), whereas severe forms were more frequently observed in central district medical associations (8.6%). The proportion of severe cases in these district associations was 2.7–3.7 times higher than the average показатель. In Tashkent city, mild forms of the disease were registered twice as often as the average rate.

The overall rate of antibiotic use in the treatment of acute intestinal infections reached 88.5%. The analysis demonstrated that antibacterial therapy is widely used in adolescent and pediatric healthcare centers. In Tashkent city, however, the rate of antibiotic prescription was considerably lower, accounting for 59.5%. In nearly every fourth case (45.6%), combinations of two or even three antibacterial agents were prescribed. Analysis of the structure of prescribed antibacterial drugs revealed that only 10.7% of medications had confirmed efficacy in clinical trials (third-generation cephalosporins – 3.8%, fluoroquinolones – 6.2%, macrolides – 0.7%). The majority of antibiotics used in clinical practice (89.3%) consisted of drugs either lacking proven clinical efficacy or associated with toxicity (first- and second-generation cephalosporins, penicillins, lincomycin, aminoglycosides, chloramphenicol). Antibiotic selection was guided by antimicrobial susceptibility testing in only 25.5% of cases, while in 74.5% of cases such testing was not performed. The average duration of antibiotic therapy was 14.5 ± 5.0 days, ranging from 5 to 20 days. Most antibacterial agents were administered parenterally, predominantly via intramuscular injection (61.1%), while oral administration accounted for 38%, and topical use was observed in 0.1% of cases. The results of the study demonstrated that in the treatment of acute intestinal infections in children, antibacterial agents are frequently prescribed even in cases of viral diarrhea. According to modern treatment concepts, recommendations for the management of acute intestinal infections are based on the severity of clinical symptoms and the type of diarrhea. Watery diarrhea is typically non-invasive and develops primarily as a result of toxin-mediated mechanisms rather than direct tissue invasion. In such cases, antibacterial therapy is not indicated. Antibiotics should be prescribed only when clinically justified, particularly to reduce the duration of bacterial shedding and to prevent the spread of pathogens into the environment. On the other hand, the main approach to the treatment of watery diarrhea is pathogenetic therapy, which primarily includes measures to maintain electrolyte balance. This is achieved through oral or parenteral rehydration therapy. In cases of dysentery-like diarrhea or the presence of blood in the stool, the condition may result from damage (dysfunction) of the colonic epithelial layer caused by invasive

microorganisms. In such situations, the use of antibiotics is considered necessary. For example, pathogens such as Shigella, *Escherichia coli* (E. coli), and Salmonella are capable of causing invasive diarrhea in children.

Table 1. Frequency of Antibacterial Therapy Use According to the Etiology of Acute Intestinal Infections.

Causative agent	Tashkent region	Tashkent city
Shigellosis	91.7 %	100 %
Escherichiosis	60 %	100 %
Salmonellosis	100 %	90 %
Rotavirus infection	93.8 %	87.5 %
Opportunistic pathogenic flora	100 %	100 %

Antibacterial therapy is used to reduce the severity of clinical manifestations, shorten the duration of illness, accelerate recovery, decrease the period of bacterial shedding, and prevent the spread of epidemic pathogens. The results of our study demonstrated that widely used antibiotics in the treatment of acute intestinal infections—such as rifampicin, first- and second-generation cephalosporins, lincomycin, and penicillins—lack evidence confirming their effectiveness against *Shigella*. Such irrational use contributes to the development of antimicrobial resistance and, consequently, reduces the overall effectiveness of intestinal infection treatment. The main antibacterial agents recommended for the treatment of shigellosis include quinolones (nalidixic acid), fluoroquinolones (ciprofloxacin and norfloxacin), macrolides (azithromycin), and third-generation cephalosporins.

Conclusion. The results of the conducted pharmacoepidemiological study indicate that antibiotics are widely and unjustifiably used in the treatment of acute intestinal infections in children. In the process of selecting treatment strategies, insufficient attention is given to clinical symptoms and the severity of the disease. The choice of antibiotics reflects a high level of inadequate awareness regarding pharmacokinetics, pharmacodynamics, and the safety profiles of antibacterial agents. All of the above underscores the necessity of developing unified treatment standards for acute intestinal infections and implementing targeted educational programs for healthcare practitioners in clinical practice.

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DOXORUBICIN AND GEMCITABINE IN CANCER THERAPY: CLASSIFICATION, MECHANISMS, LIMITATIONS, AND MODERN DELIVERY APPROACHES

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Abstract. *This article examines the current classification of chemotherapeutic agents and the role of Doxorubicin and Gemcitabine in oncology therapy. The mechanisms of action, therapeutic efficacy, and major limitations of these drugs are analyzed, including nonspecific toxicity and the development of drug resistance in tumor cells. Particular attention is given to modern approaches aimed at reducing adverse effects, such as targeted drug delivery systems and the use of nanocarriers that enable selective accumulation of chemotherapeutic agents in tumor tissue. Furthermore, the prospects for the development of chemotherapy are discussed, including combination treatment regimens and personalized therapeutic strategies designed to improve clinical outcomes and safety. This study emphasizes the importance of further research to optimize the therapeutic application of doxorubicin and gemcitabine in cancer treatment.*

Keywords: *doxorubicin, Gemcitabine, Targeted drug delivery, Nanocarriers, Controlled drug delivery.*

1. Introduction. Currently, there is a global trend toward an increasing incidence of cancer worldwide (WHO & IARC, 2024). There are numerous approaches to suppress the disease, such as surgical intervention, radiation therapy and immunotherapy, among which chemotherapy remains one of the key treatment methods and is widely used both as a standalone approach and as part of combination therapy regimens (Wang & Jing, 2025). Chemotherapeutic treatment makes it possible to reduce tumor size, destroy cancer cells, prevent the risk of recurrence, exert systemic effects on metastases, and enable the treatment of tumors in various locations, as well as eliminate very small malignant cells that cannot yet be detected even with the use of the most advanced diagnostic methods (Litvinets, Zakharova, & Sukhova, 2024;).

The modern classification of chemotherapeutic agents organizes them according to their mechanism of action, spectrum of application, and toxicity profile, which allows for the comparison of the efficacy and safety of different drugs. Prominent representatives among chemotherapeutic agents include doxorubicin and gemcitabine, which retain their clinical significance due to their proven antitumor activity, broad spectrum of use in various types of malignant tumors, and high efficacy both as monotherapy and as part of combination treatment regimens (Khan, Agarwal, Assaad, Ratan, & Nassif Haddad, 2026). These drugs remain the standard of care due to the accumulated data on their safety, predictable side effect profile, and the possibility of their use in neoadjuvant, adjuvant, and palliative treatment settings (Anwar, Husain, Bilal, Ijaz, Aadil, & Khan, 2024).

However, despite all the advantages of these drugs, they also have certain limitations, including the development of tumor drug resistance, limited efficacy of chemotherapy in certain tumor localizations, as well as adverse effects such as cardiotoxicity, myelosuppression,

gastrointestinal disorders, alopecia, and an increased risk of infectious complications (Gaumond, Lee, Warp, Kamholtz, Dreifus, & Jimenez, 2025). Based on these findings, significant attention is currently being paid to reducing the undesirable effects of cytotoxic drugs, and numerous studies are being conducted to achieve their targeted delivery and selective action.

Thus, the search for effective approaches to increase selectivity and reduce the toxicity of chemotherapeutic agents remains an important objective of modern oncology. The aim of this study is to analyze the challenges and prospects of using doxorubicin and gemcitabine in contemporary anticancer therapy.

2. Modern classification of chemotherapeutic agents

Chemotherapeutic drugs act through two pathways: cytostatic and cytotoxic. The cytostatic pathway inhibits the proliferation of malignant cells and induces apoptosis. Cytotoxic chemotherapy directly kills cells by disrupting their vital functions, resulting in tumor necrosis. Antitumor drugs used in chemotherapy can be divided into several groups based on their structure and mode of action.

2.1 Alkylating agents

Alkylating anticancer chemotherapeutic agents have the ability to form covalent bonds with nucleophilic centers of DNA (most commonly the nitrogen atom at position 7, guanine) (MDPI, 2021), which in turn causes inter- and intra-strand cross-links of the DNA molecule, resulting in disruption of replication and transcription processes, which induces tumor cell apoptosis. Alkylating agents are not phase-specific and exhibit greatest activity in rapidly dividing cells. These include cyclophosphamide, carmustine, cisplatin, carboplatin, dacarbazine, chlorambucil, and oxaliplatin. They have found clinical application in tumor types such as lymphomas and leukemias, breast cancer, sarcomas, ovarian tumors, head and neck tumors, and gliomas. Side effects include nephrotoxicity (cisplatin), neurotoxicity, myelosuppression (more pronounced with carboplatin), immunodepression, hemorrhagic cystitis (associated with acrolein), alopecia, nausea and vomiting (Chiorcea-Paquim & Oliveira-Brett, 2023).

2.2 Antimetabolites

Antimetabolites interfere with the synthesis of vital cellular components, such as inhibiting DNA and RNA production by taking the place of nucleotides. In other words, antimetabolites are molecules that compete with metabolites (vital substances). By competing with natural substrates, they inhibit nucleotide synthesizing enzymes (for example, methotrexate inhibits dehydrofolate reductase, blocking the synthesis of tetrahydrofolate, which is necessary for the formation of thymidylate (dTMP), thus disrupting DNA synthesis (Rana, Dranchak, Inglese, et al., 2024)) or are incorporated into DNA in place of nucleotides (5-fluorouracil (5-FU), gemcitabine, and cytarabine are incorporated into DNA or RNA, causing replication errors, chain arrest, and apoptosis). Antimetabolites are particularly active in the S phase of the cell cycle, when DNA synthesis occurs. Rapidly dividing cells, including tumor cells, bone marrow, and gastrointestinal epithelial tissue, are most sensitive to antimetabolites. They are used to treat the following tumors: acute lymphoblastic leukemia, breast cancer, gastric cancer, pancreatic cancer (gemcitabine), colorectal cancer (5-FU), and acute myeloid leukemia (cytarabine). Side effects include myelosuppression, stomatitis, nausea, hepatotoxicity, alopecia, and neuropathy. Notable examples include 5-fluorouracil, 6-mercaptopurine, capecitabine, gemcitabine, and methotrexate.

2.3 Antitumor antibiotics

Antineoplastic antibiotics are produced by biosynthesis from microorganisms. Their mechanism of action involves intercalation into DNA, disrupting its structure and interfering with

replication and transcription, and blocking enzymes such as topoisomerase II (Karamanolis, Kounatidis, Vallianou, Dimitriou, Tsaroucha, Tsioulos, Anastasiou, Mavrothalassitis, Karampela, & Dalamaga, 2024). Antibiotics also generate free radicals: in the presence of oxygen and transition metals, some antibiotics (e.g., anthracyclines) induce the formation of reactive oxygen species, resulting in damage to DNA and cellular structures. They are used to treat lymphomas, leukemia, soft tissue sarcomas, and solid tumors. Their classes include: anthracyclines (cardiotoxicity (Lozhkina & Spiridonov, 2021; Graziani et al., 2026), myelosuppression), actinomycin (myelosuppression, mucosal toxicity), bleomycin (pulmonary toxicity, fibrosis, skin reactions), and mitomycin (myelosuppression, organ toxicity). Anthracyclines include doxorubicin (adriamycin), epirubicin, daunorubicin, and idarubicin.

2.4 Proteasome inhibitors

Proteasome inhibitors block the function of proteasomes, which regulate cellular protein homeostasis, remove damaged and short-lived proteins, and regulate cell apoptosis. Inhibition of proteasome function results in an increase in defective proteins and induction of cell death. They are used primarily for multiple myeloma and lymphoma. Side effects include peripheral neuropathy, thrombocytopenia, gastrointestinal disturbances, increased risk of infection, cardiotoxicity, hypertension, dyspnea, and nephrotoxicity. Representatives of this group include cartelzamib, ixazomib, and bortezamib (Pakjoo, Ahmadi, Zahedi, et al., 2024).

2.5 Plant alkaloids

Alkaloids and their derivatives are substances obtained from plants. The primary target of this group of drugs is the mitotic center of the cell. These substances interact with microtubule tubulin, disrupting their polymerization processes and blocking the cell cycle primarily in the G2/M phase, ultimately inducing tumor cell apoptosis. They are used to treat leukemia, sarcomas, ovarian cancer, prostate cancer, lung cancer, and lymphoma. Side effects include neurotoxicity, myelosuppression, alopecia, gastrointestinal disturbances, peripheral neuropathy, and hypersensitivity reactions. These include vinalkoloids, taxanes, and podophyllotoxins (Dehelean, Marcovici, Soica, Mioc, Coricovac, Iurciuc, Cretu, & Pinzaru, 2021).

3. Doxorubicin in oncology therapy

As mentioned above, chemotherapy drugs are divided into several groups, including the anthracycline group. Anthracycline antibiotics disrupt the DNA of cancer cells, thereby stopping their cell division. A prominent example of this group is the antitumor drug doxorubicin.

3.1 Pharmacological characteristics

Doxorubicin is one of the most toxic drugs for cancer cells, although its effects also manifest in healthy cells (Radeva & Yoncheva, 2025). Doxorubicin is a red, crystalline powder. It is used exclusively as an intravenous solution. The structural formula of doxorubicin, as shown in Figure 1, is a tetracyclic ring of doxorubicinone linked by a glycosidic bond to the amino sugar daunosamine.

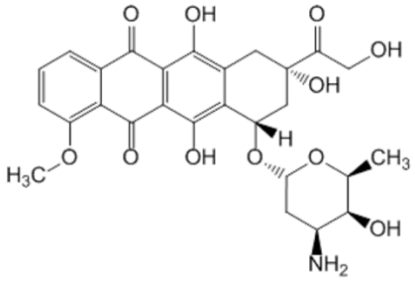


Figure 1. Structure of Doxorubicin

(https://www.rlsnet.ru/active-substance/doksorubicin-51)

3.2 Mechanism of action

Doxorubicin is a drug with two modes of action, characteristic of its class of anthracycline antibiotics. I.

Doxorubicin's cytostatic action is accompanied by intercalation into the DNA strand, as can be seen in Figure 2, and inhibition of the enzyme topoisomerase II (Karamanolis et al., 2024). The mechanism of doxorubicin's cytostatic action begins with its insertion between DNA base pairs, which is accompanied by the destruction of the DNA helix, leading to disruption of replication and transcription processes. Subsequently, the cell becomes incapable of synthesizing DNA and RNA molecules, division ceases, and apoptosis is induced (Radeva & Yoncheva, 2025). Doxorubicin's mechanism of action, through inhibition of the enzyme topoisomerase II, is that this enzyme cuts and cross-links DNA strands to reduce coiling during replication. Doxorubicin, however, retains the enzyme at the DNA breakpoint, preventing the strand from rejoining. This causes double-strand breaks in DNA, leading to cell death.

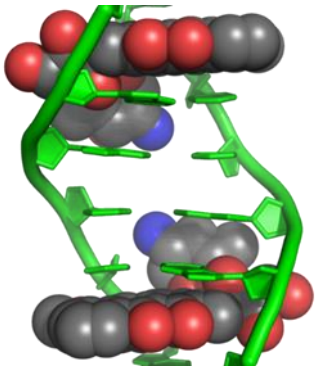


Figure 2. Insertion of doxorubicin molecules between DNA strands

(https://commons.wikimedia.org/wiki/File:Doxorubicin%E2%80%93DNA_complex_1D12.png?uselang=ru)

II. The cytotoxic effect of doxorubicin is manifested by the release of free radicals and binding to membranes and lipids. Through reactions with iron ($Fe^{2+} \rightarrow Fe^{3+}$), doxorubicin is capable of forming reactive oxygen species, which damage DNA, proteins, and lipid membranes, resulting in oxidative stress and cell death. This mechanism of action of doxorubicin explains its high cardiotoxicity, since the heart is sensitive to oxidative damage (Radeva & Yoncheva, 2025). Doxorubicin can also interact with cell membranes, namely phospholipids. This can alter membrane fluidity and affect ion channel transport.

3.3 Spectrum of clinical application

This multidirectional action of Doxorubicin explains its effectiveness against both rapidly and moderately proliferating tumors, as well as its use in the treatment of a wide range of malignant neoplasms, such as hematological (acute lymphomas, leukemia, myelomas), solid (breast cancer, soft tissue and bone sarcomas, ovarian and endometrial cancer, lung cancer (small cell), bladder cancer, thyroid tumors, hepatocellular carcinoma) (Mahboubi, Almasi-Hashiani, Ghasemi, & Mondanizadeh, 2025).

3.4 Limitations of therapy

Despite high efficacy and toxicity to cancer cells, chemotherapy with doxorubicin does have an impact on healthy cells. Doxorubicin has numerous side effects that leave a profound impact on the body:

1. The main side effect is cardiotoxicity. This is the most serious and dose-dependent effect. Myocardial cells are damaged due to the formation of reactive oxygen species, interaction with iron (Fe^{2+}/Fe^{3+}), and inhibition of topoisomerase IIβ in cardiomyocytes. Consequences can include dilated cardiomyopathy (the ventricles dilate and lose their ability to effectively pump blood) and heart failure. For protection, dexrazoxane, a drug that binds iron, reduces cellular oxidative stress, is used (Graziani et al., 2026).

2. Myelosuppression – suppression of bone marrow function and a decrease in the level of formed elements of the blood: leukocytes (leukopenia), platelets (thrombocytopenia), and erythrocytes (anemia). This increases the risk of infections and bleeding.

3. Gastrointestinal reactions are accompanied by nausea, vomiting, and loss of appetite. Mucositis – inflammation of the mucous membranes (especially the oral cavity) – is also observed.

4. Alopecia – almost all patients experience hair loss during treatment, but this process is reversible after completion of therapy.

5. Extravasation – leakage from a vein during drug administration. If the drug enters a vessel, severe tissue necrosis occurs. Therefore, doxorubicin is administered only intravenously, with careful monitoring of the injection site.

6. Hepatotoxicity – increased levels of ALT and AST transaminases (protein transporters). In severe cases, this can lead to liver dysfunction.

7. Another adverse effect of the drug is the development of secondary tumors. For example, leukemia caused by DNA damage (topoisomerase II) is possible. This is rare and only occurs if therapy has been ongoing for many years.

Due to the large number of side effects, doxorubicin remains an important subject of research in targeted medicine, where the combination of antitumor drugs with various carriers or targeting agents enables significantly improved therapeutic outcomes.

4. Gemcitabine in oncology therapy

Another class of antitumor drugs widely used in chemotherapy is the class of antimetabolite drugs. Antimetabolites exhibit cytostatic activity, which is expressed by altering the structure of the cell's genetic apparatus, leading to cell apoptosis. One of the representatives of the antimetabolite group is the drug gemcitabine, which has found wide application in the fight against many types of tumors.

4.1 Pharmacological characteristics

Gemcitabine is a white powder intended for intravenous administration. In the body, it is metabolized primarily in the liver and kidneys by cytidine deaminase into mono-, di-, and triphosphate metabolites (dFdCMP, dFdCDP, and dFdCTP). Among these, the di- and triphosphate forms are the active cytotoxic metabolites that inhibit DNA synthesis during the S phase of the cell cycle. The drug is primarily excreted by the kidneys in the urine, with an elimination half-life of approximately 5–11 hours (Vidal, n.d.).

4.2 Mechanism of action

Gemcitabine is a cytotoxic drug that belongs to the class of antimetabolites, specifically pyrimidine analogs. Metabolites are substances involved in the body's metabolic processes, such as amino acids, nucleotides, sugars, and others. In contrast, antimetabolites are structurally similar to natural metabolites but interfere with normal biochemical processes within the cell. As one of these agents, gemcitabine competes with pyrimidine bases, particularly deoxycytidine (Dash, Honda, Komuro, Okada, Sugisawa, & Ueda, 2024). As shown in Figure 3, the structural difference

between deoxycytidine and gemcitabine lies in the presence of two fluorine atoms in the gemcitabine molecule, which are responsible for its altered biological activity and antitumor properties.

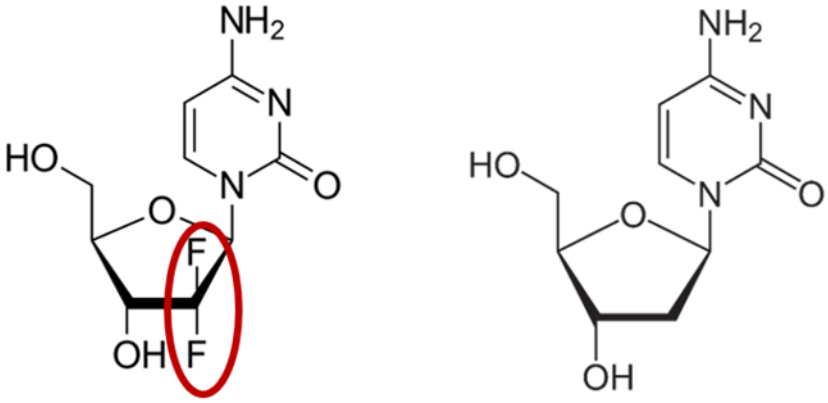


Figure 3. Comparison of the chemical structures of gemcitabine (left) and deoxycytidine (right)

(https://upload.wikimedia.org/wikipedia/commons/thumb/a/a3/Desoxycytidin.svg/463px-Desoxycytidin.svg.png)

Gemcitabine is phosphorylated intracellularly by nucleoside kinases to form active nucleotide metabolites, including gemcitabine monophosphate (dFdCMP), gemcitabine diphosphate (dFdCDP), and gemcitabine triphosphate (dFdCTP). Gemcitabine exhibits phase specificity, primarily affecting cells in the S and G1/S phases of the cell cycle. During the S phase, DNA replication occurs through the action of various enzymes. At this stage, gemcitabine diphosphate binds to ribonucleotide reductase, an enzyme responsible for converting ribonucleotides into deoxyribonucleotides, and forms an irreversible covalent complex with it. As a result, gemcitabine diphosphate inhibits ribonucleotide reductase activity, preventing the formation of normal deoxyribonucleotides required for DNA synthesis.

This leads to depletion of intracellular deoxyribonucleotide pools, inhibition of DNA synthesis, and disruption of cell cycle progression, ultimately triggering apoptosis. In addition, the active triphosphate form of gemcitabine (dFdCTP) is incorporated into the growing DNA strand in place of deoxycytidine during DNA replication, causing premature chain termination. Consequently, DNA synthesis is disrupted, leading to apoptotic death of tumor cells (Nemati, Hsu, Nathiya, Kumar, Oghenemaro, Kariem, Kaur, Bhanot, Hjazi, & Saedi, 2025).

4.3 Clinical application

Gemcitabine is used to treat many types of cancer, including testicular cancer, breast cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, and bladder cancer It is also used alone, for example, in the palliative stage of the disease or in elderly patients. Gemcitabine can also be used in combination with drugs such as paclitaxel, carboplatin, and cisplatin, for greater effectiveness (Huang, Hung, Tsai, Wu, Chou, Hsu, Yeh, Chen, Wang, & Yeh, 2024).

4.4 Limitations of therapy

Like all cytostatic drugs, gemcitabine has side effects. Adverse effects include the following:

1. Leukopenia, thrombocytopenia, and anemia are the main limiting toxic effects, which severely damage the hematological system.
2. Nausea, vomiting, loss of appetite, stomatitis, and oral ulcers. These symptoms often occur during chemotherapy and should be controlled with supportive care. Oral mucosal

cells divide rapidly, and gemcitabine, by inhibiting their renewal, promotes inflammatory processes, which are accompanied by sore throats, pain, and difficulty eating.

3. Fever, weakness, fatigue, chills, and muscle aches. These symptoms may be intermittent and related to the drug.

4. Liver toxicity (increased ALT, AST, and alkaline phosphatase). Typically, the changes are moderate and reversible.

5. Rash, itching, severe skin reactions, alopecia. These side effects occur in slightly rare cases.

6. Pulmonary complications – interstitial pneumonitis.

7. Fluid retention, swelling of the face and extremities, weakness. These adverse effects are observed in a minority of patients.

8. Neuropathy, numbness, pins and needles, headaches, seizures. These side effects occur as a result of the negative effects of gemcitabine on the body's nervous system.

9. Gemcitabine can also lead to renal dysfunction, which manifests as renal failure, hemolysis-uremia syndrome, and thrombotic microangiopathy.

The large number of side effects associated with gemcitabine provides the basis for ongoing research aimed at reducing its toxicity and improving its selectivity toward tumor cells.

5. Approaches to reducing the adverse effects of chemotherapeutic agents

The side effects of chemotherapy are primarily caused by its nonspecific cytotoxic effects on rapidly proliferating normal cells, including bone marrow cells, gastrointestinal epithelium, hair follicles, and other tissues (Cronin et al., 2026; Yang et al., 2026). Therefore, various strategies have been developed to improve the selectivity of anticancer therapy and protect healthy tissues, among which targeted therapy represents one of the most promising approaches currently available. The principle of targeted therapy is based on the selective accumulation of therapeutic agents in tumor tissue while minimizing their impact on healthy organs. The key factors in effective drug targeting include the selection of an appropriate delivery strategy—either passive or active targeting—the mechanisms of cellular uptake and intracellular retention, as well as the choice of suitable drug carriers.

5.1 Passive targeting of Doxorubicin

Due to its pronounced systemic toxicity, doxorubicin has been extensively investigated for targeted delivery applications. Passive accumulation of drugs in tumor tissue occurs via the enhanced permeability and retention (EPR) effect, which is associated with the unique structural characteristics of tumor vasculature. Tumor blood vessels exhibit increased permeability and enlarged intercellular gaps due to rapid and abnormal angiogenesis, enabling preferential accumulation of macromolecules and nanocarriers within tumor tissue (Fang, Nakamura, & Maeda, 2025) (Figure 4).

This effect operates only for macromolecules or nanoparticles (10–200 nm), whereas doxorubicin, being a small hydrophilic molecule (~580 Da), is not able to be retained in tumor tissue for a long time and is rapidly metabolized and eliminated from the body. Therefore, numerous studies have been conducted aimed at increasing the effective size of the doxorubicin molecule and its encapsulation into nanocontainers. One of such nanocontainers is liposomes, which, due to their spherical structure surrounded by a lipid bilayer, serve as a model of the cellular membrane (Bozzuto & Molinari, 2025). DOX is encapsulated inside liposomes, within their hydrophilic core, which protects the drug from degradation in the bloodstream, reduces systemic toxicity, prolongs circulation time, and enhances accumulation in tumor tissue via the EPR effect.

In addition, studies have investigated the incorporation of the polymer polyethylene glycol (PEG) into liposomes, which “coats” the liposome surface and increases circulation time in the blood. As a result, liposomes are less readily recognized and taken up by macrophages of the liver and spleen, exhibit reduced immunogenicity by masking them from the immune system, and demonstrate improved passive accumulation via the EPR effect. DOXIL was the first PEGylated liposomal formulation of DOX approved by the FDA in 1995 and became the first nanomedicine in oncology, significantly reducing cardiotoxicity and improving drug distribution.

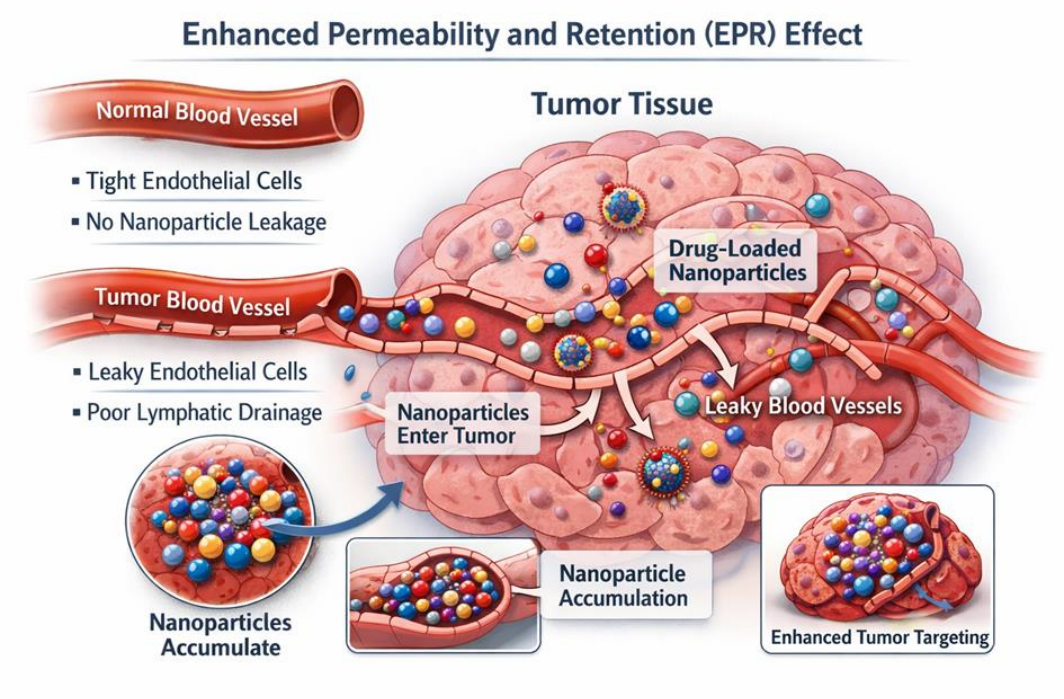


Figure 4. EPR effect

Modern studies continue to optimize the DOXIL formulation by introducing targeting ligands, new co-loading strategies, and stimulus-responsive modifications to improve therapeutic efficacy. One study reported, for the first time, the simultaneous loading of two drugs—DOX and hydralazine (HDZ)—into liposomes using a pH-gradient technique. In vitro studies in breast cancer cell lines (MCF7 and MDA-MB-231) demonstrated high cytotoxicity toward tumor cells and significantly lower toxicity toward normal cells, highlighting the potential of this system for combination cancer therapy (Alshaer, Lafi, Nsairat, AlQuaissi, Alqudah, Zureigat, & Hamad, 2025).

In addition to particle size and the EPR effect, stimulus-responsive properties of nanoparticles are also important, as they enable condition-specific drug release. In one study, redox-responsive liposomes encapsulating DOX were developed. These liposomes showed stability under normal physiological conditions but selectively released the drug under intracellular oxidative-reductive (redox) stress conditions characteristic of tumor tissue. It was demonstrated that this modification enhances DOX delivery into tumor cells due to elevated glutathione (GSH) levels and results in improved antitumor activity both in vitro and in vivo compared to conventional liposomes (Mirhadi, Ramezani, Atyabi, & Dinarvand, 2022).

The next type of DOX carriers is polymeric micelles, which, in contrast to liposomes, possess smaller sizes, increased stability in the bloodstream, and broad possibilities for chemical modification (Kwon & Kataoka, 2024). Micelles are nanostructures, typically 10–100 nm in size, that self-assemble from amphiphilic polymers in an aqueous environment. Micelles consist of a

hydrophobic core, where drugs including DOX (in free or modified form) can be incorporated or conjugated, and a hydrophilic shell composed of polymers, most commonly polyethylene glycol (PEG) (Cabral & Kataoka, 2025).

Studies have focused on the controlled release of DOX, in which the drug is covalently conjugated via a pH-sensitive Schiff base linkage that is cleaved in acidic environments characteristic of tumor tissue. Experimental results have shown that such nanoparticles exhibit good stability, increased intracellular DOX concentration, and improved antitumor activity compared with free DOX *in vitro* (Li, 2023).

To enhance therapeutic efficacy in breast cancer treatment, researchers have developed pH-sensitive polymeric micelles capable of simultaneously delivering two anticancer drugs—DOX and docetaxel. In vivo studies in mice bearing 4T1 tumors demonstrated that the combined delivery system achieved greater tumor accumulation and more effective tumor growth inhibition. Additionally, reduced accumulation in the heart was observed compared with the free drug combination, suggesting a potential reduction in cardiotoxicity (Farhoudi, Hosseinikhah, Kazemi-Beydokhti, Arabi, Alavizadeh, Moosavian, & Jaafari, 2024).

5.2 Active targeting of Doxorubicin

In active targeting, drugs are modified with specific targeting moieties that recognize receptors or molecules on the surface of tumor cells. This approach increases intracellular drug concentration in tumor tissue, reduces systemic side effects, and allows the use of lower doses while maintaining therapeutic efficacy (Danhier, Feron, & Préat, 2025). Targeting moieties include ligands, antibodies, aptamers, peptides, and others.

An experimental study reported the development of CD147 antibody-modified nanoparticle prodrugs. DOX was first conjugated with oxidized dextrin (ODEX) via a Schiff base linkage, forming a nanoprodrug. Subsequently, anti-CD147 antibodies (a liver cancer marker) were attached to the nanoparticle surface. The results demonstrated pH-sensitive release of DOX, enhanced tumor accumulation, and significant inhibition of HepG2 hepatoma growth in experimental models (Tian, Yu, Zhang, He, Sun, & Ni, 2023).

Another experimental development involved an antibody–drug conjugate, PD0721–DOX. PD0721 is a single-chain variable fragment antibody (scFv) specific to EGFRvIII (epidermal growth factor receptor variant III, commonly overexpressed in glioblastoma). When conjugated with DOX via a dextran-based linker, the system effectively recognized EGFRvIII-expressing cells and was internalized by them, resulting in increased apoptotic activity against glioblastoma cells *in vitro* (Hu, Liu, Zhang, Lu, Zheng, Wang, Chen, & Liu, 2024).

In addition, studies have demonstrated enhanced therapeutic efficacy using combination approaches. In one study, DOX was conjugated to polydopamine (PDA) nanoparticles via a Schiff base reaction, and the nanoparticle surface was further modified with an RGD peptide to actively target integrins overexpressed on tumor cells. In vitro results showed a strong antitumor effect through combined chemo- and photothermal therapy, while in vivo studies demonstrated significant tumor accumulation and tumor growth inhibition without notable systemic toxicity (Yuan, Lu, Xu, & Liu, 2024).

5.3 Passive targeting of Gemcitabine

Gemcitabine, due to the hydrophilic nature of its molecule, which contributes to its rapid metabolism in the body (it is deaminated to an inactive form) and short half-life, as well as its systemic toxicity, has become an important subject of research for encapsulation into nanocarriers. This approach enables protection of Gemcitabine from rapid degradation, prolongation of its

circulation time in the bloodstream, increased tumor accumulation, and reduced toxicity to healthy tissues (Wang, Zhang, Zhang, Chen, & Li, 2025).

One study compared the cytotoxicity of liposomal Gemcitabine and free Gemcitabine solution in the A549 lung adenocarcinoma cell line in vitro. The results demonstrated that the liposomal formulation exhibited significantly higher activity (IC50 ≈ 0.47 μM) against tumor cells compared to free Gemcitabine (IC50 ≈ 9.6 μM), which was attributed to the improved cellular uptake of the liposomal form and its protection from premature degradation (Oborotov, Rudakova, Baryshnikova, Dmitrieva, & Krasnyuk, 2025).

Research is also underway on the development of thermosensitive liposomes, in which the membrane is engineered for temperature responsiveness by selecting the type of phospholipid, hydrocarbon chain length, degree of saturation, cholesterol content, and addition of lysolipids. In a recent study, thermosensitive liposomes were developed for the delivery of gemcitabine in pancreatic cancer. These liposomes remain stable at normal body temperature (37 °C), but under hyperthermia conditions (43–45 °C), the lipid bilayer transitions into a liquid-crystalline state, making the membrane more “fluid” and facilitating rapid drug release. The authors highlight the potential for controlled release and enhanced stability of gemcitabine using this approach (Aparicio-Lopez, Timmerman, Lorino, Rogers, Pyle, Shrestha, et al., 2024).

Since micelles are more compact and stable particles (allowing better penetration into dense tumors) and flexible for manipulations aimed at controlled release, they are more convenient for research compared with liposomes (Kujundziski & Chamovska, 2025). Due to the hydrophilic nature of the Gemcitabine molecule, when encapsulating it into the hydrophobic core of micelles, the drug is modified with hydrophobic moieties. For example, in one study, Gemcitabine was modified with vitamin E and encapsulated into the micelle core. Vitamin E serves not only as a modifying agent but also as an active component, enhancing the cytotoxic effect of Gemcitabine through synergistic action. The results demonstrated improved Gemcitabine stability in the bloodstream, higher tumor accumulation via the EPR effect, and reduced side effects compared to free Gemcitabine (Pereira-Silva, Miranda-Pastoriza, Diaz-Gomez, Sotelo, Paiva-Santos, Veiga, Concheiro, & Alvarez-Lorenzo, 2024).

Another study investigated Gemcitabine delivery using membrane-modified micelles. A coating of cancer cell membrane fragments was applied to the surface of micelles made from the synthetic polymer Soluplus, which masks the nanoparticles and facilitates recognition by tumor cells. This approach is referred to as biomimetic targeted delivery. The study provides evidence that membrane-modified Soluplus micelles loaded with Gemcitabine prodrug represent a promising delivery system for targeted therapy of pancreatic cancer (Pereira-Silva, Diaz-Gomez, Blanco-Fernandez, Ferreirós, Veiga, Concheiro, Paiva-Santos, & Alvarez-Lorenzo, 2024).

5.4 Active targeting of Gemcitabine

To enhance Gemcitabine accumulation in tumors, reduce its side effects, and increase therapeutic efficacy, Gemcitabine-based nanoparticles are modified with specific targeting moieties. For example, one study described the development of “smart” micelles for improved drug delivery with active targeting to cancer cells expressing the CD44 receptor. For targeting, a conjugate of hyaluronic acid and phospholipid (HA-DPPE) was incorporated. As a result, the micelles were selectively taken up by cells with high CD44 expression and exhibited high cytotoxicity in these cells (Andreana, Bincoletto, Ricci, Salaroglio, Manzoli, Zurletti, Milone, Rolando, Del Favero, Riganti, Matricardi, Stella, & Arpicco, 2025).

Active targeting of Gemcitabine has also been applied in combination therapies. For example, one study reported the development of self-assembled nanoparticles targeting the folate receptor (FR), which is frequently overexpressed on cancer cells. Gemcitabine was modified into an amphiphilic prodrug (DOG) and linked to γ-octadecyl folate (MOFA), a ligand that recognizes the folate receptor. Indocyanine green (ICG), a photosensitizer for combined chemo- and photothermal therapy, was also incorporated into the nanoparticles. The results showed high ICG loading efficiency (~74%), pH- and laser-triggered release of Gemcitabine, and enhanced antitumor activity with the combined chemo-photothermal treatment compared with chemotherapy alone (Kuang, Liu, Wang, Yang, Zeng, & Ming, 2023).

Therefore, the use of both passive and active targeting strategies for the delivery of anticancer drugs represents a promising approach to enhance the efficacy of chemotherapy. Passive tumor accumulation via the EPR effect can be further reinforced through ligand-mediated interactions with tumor cell receptors, enabling more precise and controlled delivery of cytotoxic agents.

6. Limitations and Future Perspectives

Despite significant advances in the application of DOX and Gemcitabine, current approaches have several limitations. Even with targeted carriers, it is not always possible to reach all tumor cells, particularly in dense or poorly vascularized tumors, and the development of drug resistance reduces therapeutic efficacy. In addition, pharmacokinetic and technological challenges remain, including the instability of some delivery systems and difficulties in scalable production.

Future prospects include the development of more stable and selective carriers, combination therapy regimens, and personalized approaches tailored to the molecular characteristics of individual tumors. Integrating these strategies with modern therapeutic modalities has the potential to significantly improve the clinical efficacy and safety of chemotherapy.

7. Conclusion

Modern classification of chemotherapeutic agents allows a systematic approach to therapy selection in oncology, taking into account mechanisms of action and drug toxicity. DOX and Gemcitabine remain key drugs in the treatment of various tumor types due to their proven efficacy; however, their use is limited by nonspecific toxicity and the development of drug resistance. The development of targeted delivery systems and novel carriers enables increased selectivity and reduced side effects, opening new prospects for safer and more effective therapy. Overall, continued research and optimization of drug delivery strategies and combination regimens are essential for improving clinical outcomes and advancing personalized treatment for patients with cancer.

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PREVENTION OF PERIODONTAL DISEASES: RISK ASSESSMENT, EARLY INTERVENTION, AND MODERN PREVENTIVE STRATEGIES

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Abstract. *Periodontal diseases remain among the most prevalent chronic inflammatory conditions worldwide and represent a significant cause of tooth loss and reduced quality of life. Their multifactorial etiology, involving complex interactions between microbial biofilm, host immune response, genetic predisposition, and behavioral and systemic risk factors, necessitates a comprehensive preventive approach. This study aims to evaluate the role of structured risk assessment, early intervention, and contemporary preventive strategies in reducing the incidence and progression of periodontal pathology. A combined analytical and clinical framework was applied to examine current preventive models and their practical effectiveness. The investigation focused on identifying key modifiable and non-modifiable risk determinants, assessing the clinical value of early diagnostic indicators, and analyzing the outcomes of individualized preventive programs. Emphasis was placed on integrating professional mechanical plaque control, patient-centered oral hygiene education, behavioral modification, and management of systemic conditions into a coordinated prevention protocol. The findings demonstrate that systematic risk stratification enhances early detection of inflammatory changes in periodontal tissues and supports timely implementation of targeted interventions. Personalized preventive strategies were associated with significant reductions in plaque accumulation, gingival bleeding, and periodontal pocket depth, as well as improved patient adherence to oral hygiene practices. The results also highlight the importance of continuous maintenance therapy and long-term monitoring to ensure periodontal stability. The study confirms that prevention-oriented periodontal care, grounded in evidence-based protocols and individualized risk evaluation, improves clinical outcomes and reduces the burden of advanced disease. Implementation of modern preventive strategies at both primary and specialized levels of dental practice contributes to sustainable periodontal health and supports overall systemic well-being.*

Keywords: *periodontal diseases, prevention, risk factors, mouth emptiness health, early diagnostics, modern strategies.*

Introduction

Periodontal diseases – teeth around , teeth catcher of tissues inflammation and mouth space microflora pathological changes with passing diseases is considered . The world according to adults 60–80 percent of the population various level periodontal pathologies Diseases occur . development many to factors related are , they are between personal hygiene deficiency , smoking , chronic diseases , genetic tendency , stress and wrong food separately place Periodontal diseases far time during imperceptibly development possibility because of them early determination and prevent to take important is considered . Mouth space health storage , also heart - blood vascular ,

diabetes and other chronic diseases the risk reduce with depend Therefore , periodontal of diseases prevention global health storage in the system priority task is considered .

Periodontal diseases tooth surrounding soft and bone tissue chronic inflammation with it will be over and this process eventually of teeth stability to lose take arrival possible . Epidemiological research world according to adults population half at most various level periodontal pathologies flying shows . Diseases development mechanism many factorial be , microbiological , immunological , genetic and environment factors mutual impact with related . Personal hygiene deficiency , smoking , chronic diseases , stress and wrong food periodontal diseases the risk increases . Diseases often initially imperceptibly develops , this and them early determination and prevention measures to apply current does . Mouth space health storage not only local medical in terms of , perhaps heart and blood vein system and endocrine pathologies prevent It is also important to get role plays . Therefore , periodontal of diseases prevent to take aimed at research and modern preventive strategies working output in global medicine priority task is considered .

Research Methods and Materials

This study was designed as a comprehensive mixed-method investigation combining a structured literature review with a prospective clinical observational component to evaluate contemporary approaches to the prevention of periodontal diseases. The methodological framework aimed to analyze risk assessment tools, early diagnostic indicators, and the effectiveness of modern preventive strategies in reducing disease incidence and progression.

The literature review phase included peer-reviewed scientific publications indexed in major medical and dental databases published within the last fifteen years. Inclusion criteria comprised randomized controlled trials, cohort studies, systematic reviews, and consensus reports focusing on periodontal risk assessment models, preventive interventions, biofilm control strategies, and behavioral modification programs. Articles lacking clear methodological descriptions or outcome measures were excluded. Extracted data were categorized according to study design, population characteristics, preventive measures applied, and reported clinical outcomes.

The clinical observational component involved 120 adult participants aged 18–65 years who attended a university dental clinic for routine examinations. Participants were stratified into low-, moderate-, and high-risk groups based on a structured periodontal risk assessment model incorporating clinical parameters (probing depth, bleeding on probing, plaque index, clinical attachment level), systemic conditions (diabetes status, smoking habits, body mass index), and behavioral factors (oral hygiene practices, frequency of dental visits). Written informed consent was obtained from all participants, and the study protocol adhered to ethical standards consistent with biomedical research principles.

Baseline examinations were conducted using standardized periodontal probes with controlled force to ensure measurement reliability. Full-mouth recordings were performed at six sites per tooth. Intra-examiner calibration was carried out prior to data collection to minimize measurement variability. Radiographic assessment using digital periapical and bitewing imaging was applied when clinically indicated to evaluate alveolar bone levels.

Preventive interventions were implemented according to individual risk profiles. All participants received personalized oral hygiene instruction emphasizing proper brushing techniques, interdental cleaning methods, and the use of adjunctive aids such as antimicrobial mouth rinses when appropriate. Professional mechanical plaque removal was performed for all

subjects at baseline. Moderate- and high-risk individuals additionally received supragingival and subgingival debridement, localized antimicrobial therapy when necessary, and tailored behavioral counseling focusing on smoking cessation and glycemic control.

Follow-up evaluations were conducted at three and six months. Primary outcome measures included reduction in plaque index, decrease in bleeding on probing, and stabilization or reduction of probing depths. Secondary outcomes involved patient adherence to recommended hygiene practices and changes in modifiable risk factors.

Data were processed using statistical software for descriptive and inferential analysis. Continuous variables were expressed as means with standard deviations, while categorical variables were presented as percentages. Comparative analysis between baseline and follow-up measurements was performed using paired statistical tests, with significance set at $p < 0.05$.

This structured methodological approach allowed for a comprehensive evaluation of preventive strategies, ensuring that both biological and behavioral determinants of periodontal health were systematically assessed.

Results

The clinical and analytical evaluation demonstrated that implementation of structured risk assessment combined with individualized preventive protocols produced statistically and clinically significant improvements in periodontal health indicators. At baseline, participants classified as moderate- and high-risk exhibited elevated plaque index scores, increased bleeding on probing frequency, and greater mean probing depths compared to the low-risk group. These findings confirmed the predictive validity of the applied risk stratification model.

Following the introduction of tailored preventive measures, measurable positive changes were observed at both three- and six-month follow-up intervals. The mean plaque index decreased substantially across all risk categories, with the most pronounced reduction recorded in the high-risk group due to intensified professional debridement and reinforced oral hygiene instruction. Bleeding on probing showed a consistent downward trend, indicating a reduction in gingival inflammatory activity and improved tissue response to biofilm control.

Probing depth measurements demonstrated stabilization in low-risk individuals and a statistically significant decrease in moderate-risk patients. In high-risk participants presenting with initial shallow to moderate periodontal pockets, partial pocket depth reduction and improved attachment stability were documented. Radiographic assessments did not reveal progression of alveolar bone loss during the observation period, suggesting effective suppression of destructive inflammatory processes. Behavioral indicators also improved during the study. Patient adherence to recommended oral hygiene techniques increased, as evidenced by self-reported compliance questionnaires and objective plaque control records. Participants who received targeted counseling regarding smoking cessation and metabolic regulation showed additional improvement in inflammatory parameters compared to those without systemic risk modification. Comparative statistical analysis between baseline and follow-up data confirmed significance at $p < 0.05$ for primary clinical variables, including plaque index, bleeding on probing, and mean probing depth. The correlation analysis further demonstrated a strong association between reduction in modifiable risk factors and improvement in periodontal parameters. Overall, the findings indicate that early identification of susceptibility combined with personalized preventive interventions effectively limits inflammatory progression, enhances periodontal stability, and reduces the likelihood of transition from gingivitis to destructive periodontitis. These results support the clinical value of risk-oriented preventive models in contemporary periodontal practice.

Discussion

The results of the present study reinforce the contemporary understanding that periodontal diseases cannot be effectively controlled through uniform preventive measures applied to all patients equally. Instead, successful prevention requires a structured, risk-oriented framework that integrates biological susceptibility, behavioral determinants, and systemic health conditions into clinical decision-making. The observed improvements in inflammatory and hygiene-related indices following individualized preventive protocols support the concept that tailored interventions are more effective than generalized recommendations. The reduction in plaque accumulation and bleeding on probing confirms the central role of microbial biofilm in the initiation and persistence of gingival inflammation. However, the variability in response among different risk categories highlights that biofilm control alone does not fully explain disease dynamics. Patients with systemic conditions such as diabetes or tobacco use demonstrated slower initial improvement, emphasizing the modifying influence of host-related factors. This finding aligns with current pathophysiological models suggesting that periodontal destruction results from a dysregulated immune-inflammatory response rather than from bacterial load alone. The stabilization of probing depth and absence of radiographic progression indicate that early non-surgical intervention can effectively interrupt the transition from reversible gingival inflammation to destructive periodontitis. Particularly noteworthy is the improvement observed in moderate-risk individuals, suggesting that timely preventive care during early stages offers the greatest therapeutic benefit. These findings underline the importance of early detection strategies and regular periodontal screening as fundamental components of preventive dentistry. Behavioral adaptation also played a decisive role in clinical outcomes. Enhanced patient compliance with oral hygiene instructions was associated with measurable reductions in inflammatory parameters. This supports the view that prevention is not solely a clinical procedure but a collaborative process requiring patient engagement and sustained motivation. Educational reinforcement and risk communication appear to strengthen adherence and improve long-term stability. Another significant aspect concerns the integration of systemic risk management into periodontal prevention. Participants who addressed modifiable factors such as smoking or glycemic imbalance demonstrated additional clinical improvement. This observation highlights the bidirectional relationship between oral and general health and confirms the need for interdisciplinary cooperation between dental and medical professionals.

Despite the positive outcomes, certain limitations should be acknowledged. The follow-up period, although sufficient to assess short-term inflammatory changes, does not allow full evaluation of long-term attachment stability. Additionally, variability in individual immune responses and genetic predispositions was not explored at the molecular level. Future investigations incorporating biomarker analysis and extended observation periods would provide deeper insight into sustained preventive effectiveness.

Overall, the findings substantiate the clinical value of structured risk assessment combined with personalized preventive strategies. The evidence suggests that modern periodontal prevention should move beyond symptom-oriented management toward proactive, biologically informed, and patient-centered models of care. Such an approach not only reduces disease progression but also contributes to improved quality of life and preservation of natural dentition.

Conclusion

The findings of this study confirm that effective prevention of periodontal diseases depends on a comprehensive, individualized, and risk-oriented approach rather than on isolated hygiene

measures alone. Systematic assessment of biological, behavioral, and systemic determinants allows clinicians to identify susceptible individuals at an early stage and implement timely interventions that significantly reduce the likelihood of disease initiation and progression. The integration of structured risk evaluation models into routine dental practice improves diagnostic accuracy and supports more rational clinical decision-making. Early intervention based on personalized preventive planning demonstrated measurable improvements in clinical parameters, including reduction in plaque accumulation, decreased gingival inflammation, and stabilization of periodontal attachment levels. These outcomes highlight the importance of combining professional mechanical biofilm removal with patient-centered education and behavioral modification. Preventive programs that emphasize motivation, regular monitoring, and reinforcement of oral hygiene practices contribute not only to short-term clinical improvement but also to long-term periodontal stability. Modern preventive strategies, including tailored maintenance schedules, adjunctive antimicrobial protocols, and the management of systemic risk factors such as smoking and metabolic disorders, further enhance therapeutic effectiveness. Addressing modifiable risks strengthens host response and improves tissue resistance against bacterial challenge, thereby supporting sustainable periodontal health. Importantly, the study underscores that prevention is both clinically beneficial and economically advantageous. By minimizing disease progression and reducing the need for complex surgical interventions, early preventive care decreases overall treatment burden and preserves natural dentition for longer periods. The results support the implementation of structured preventive protocols at both primary and specialized levels of dental care. In summary, comprehensive risk assessment combined with individualized preventive measures represents the most effective strategy for controlling periodontal diseases. Continued refinement of diagnostic tools, expansion of patient education programs, and interdisciplinary collaboration will further strengthen preventive dentistry and contribute to improved oral and general health outcomes.

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COMPLEX TREATMENT OF CHRONIC RECURRENT APHTHOUS STOMATITIS

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Abstract. *Chronic recurrent aphthous stomatitis (CRAS) is a prevalent oral mucosal disorder characterized by the repeated appearance of painful ulcerative lesions, significantly impacting patients' oral function, nutritional intake, and overall quality of life. Despite extensive research, its multifactorial etiology—encompassing immunological dysregulation, genetic predisposition, microbial imbalance, nutritional deficiencies, and psychosocial stressors—poses considerable challenges in achieving sustained remission. The present study aims to evaluate a comprehensive, evidence-based approach for the management of CRAS, integrating pharmacological interventions, topical protective therapies, nutritional optimization, and behavioral modification strategies. Clinical observations, laboratory assessments, and patient-reported outcome measures were employed to assess the efficacy and tolerability of individualized therapeutic regimens. The findings indicate that a multimodal treatment framework combining systemic immunomodulators, targeted topical agents, adjunctive micronutrient supplementation, and patient-centered lifestyle counseling results in significant reduction of ulcer frequency, duration, and severity. Moreover, adherence to personalized care protocols enhanced mucosal healing, minimized pain episodes, and improved patient-reported satisfaction. This study underscores the necessity of a holistic, multidisciplinary approach in managing CRAS, emphasizing that individualized therapy, early intervention, and continuous monitoring are critical to optimizing clinical outcomes and enhancing long-term oral health. The results provide a clinically relevant framework for practitioners aiming to reduce the burden of recurrent aphthous lesions and improve overall patient well-being.*

Keywords: *chronic recurrent aphthous stomatitis, oral ulceration, complex therapy, immunomodulation, topical treatment, nutritional support, patient-centered care, clinical outcomes, preventive strategies, oral health.*

Introduction: Chronic recurrent aphthous stomatitis (CRAS) is one of the most common and clinically significant oral mucosal disorders, affecting up to 20% of the general population worldwide. It is characterized by the repeated emergence of painful, shallow, round or oval ulcers, primarily affecting non-keratinized areas of the oral mucosa such as the labial and buccal mucosa, soft palate, and ventral tongue. The recurrent nature of these lesions, combined with their often intense pain and interference with eating, speaking, and overall oral hygiene, has profound implications for patients' quality of life. Although the exact etiology of CRAS remains incompletely understood, current evidence indicates that its pathogenesis is multifactorial, involving complex interactions between local trauma, immune system dysregulation, genetic predisposition, microbial imbalances, nutritional deficiencies, and psychosocial stressors.

Immunological mechanisms play a central role in CRAS development, with both innate and adaptive immune responses contributing to the initiation and perpetuation of ulcerative lesions. Dysregulated T-cell activity, increased pro-inflammatory cytokine production, and altered

mucosal barrier function have all been implicated in the pathophysiology of recurrent ulcers. Additionally, genetic studies suggest familial aggregation and associations with specific human leukocyte antigen (HLA) types, highlighting the hereditary component of susceptibility. Environmental and behavioral factors, including trauma from dental procedures, dietary deficiencies (notably iron, folic acid, and vitamin B12), smoking cessation, and psychological stress, further influence disease onset and recurrence patterns.

Clinically, CRAS presents in multiple forms, ranging from minor aphthae, which are small and self-limiting, to major and herpetiform ulcers, which are larger, deeper, and more persistent, often requiring complex management. The severity and recurrence rate of CRAS can vary significantly among individuals, necessitating personalized evaluation and intervention strategies. In addition to symptomatic relief, modern management aims to reduce the frequency, duration, and severity of lesions, prevent secondary infections, and address underlying systemic or nutritional factors that may exacerbate the condition.

Despite numerous therapeutic approaches, the management of CRAS remains challenging due to its recurrent and idiopathic nature. Monotherapy, whether topical corticosteroids, antimicrobial rinses, or systemic immunomodulators, often provides temporary relief but fails to prevent recurrence in many patients. This underscores the need for a comprehensive, multimodal treatment framework that integrates pharmacological therapy, topical protective measures, nutritional optimization, and behavioral modification. A personalized and evidence-based approach is critical for improving clinical outcomes and ensuring long-term management success.

The present study seeks to provide a systematic evaluation of complex treatment strategies for CRAS, emphasizing the role of early intervention, individualized therapy, and multidisciplinary care. By synthesizing current evidence and clinical observations, this research aims to inform best practices for practitioners and contribute to the development of standardized, patient-centered protocols that enhance oral health, reduce ulcer recurrence, and improve overall patient quality of life.

Methods and Materials

This study was designed as a prospective, observational clinical investigation aimed at evaluating the efficacy of a comprehensive treatment protocol for chronic recurrent aphthous stomatitis (CRAS). The methodological framework combined clinical assessments, laboratory investigations, and patient-reported outcome measures to provide a multidimensional evaluation of therapeutic strategies. The study was conducted in accordance with ethical guidelines outlined by the Declaration of Helsinki, and approval was obtained from the institutional review board of Samarkand State Medical University. All participants provided written informed consent prior to inclusion in the study.

Participants: A total of 100 patients, aged 18 to 55 years, diagnosed with CRAS based on clinical criteria and recurrent lesion history, were enrolled. Inclusion criteria included a minimum of three documented episodes of aphthous ulcers within the previous 12 months, absence of systemic immunodeficiency disorders, and willingness to adhere to the treatment and follow-up schedule. Exclusion criteria comprised patients with active systemic infections, those receiving long-term immunosuppressive therapy, pregnant or lactating women, and individuals with a history of adverse reactions to study medications. Participants were stratified into subgroups according to lesion severity (minor, major, or herpetiform), frequency of recurrence, and baseline pain intensity measured using a visual analog scale (VAS).

Clinical Assessment: Baseline evaluations included comprehensive oral examinations, documentation of ulcer number, size, location, and healing time, and assessment of associated symptoms such as pain, erythema, and secondary infection. Standardized intraoral photography was used to record lesion characteristics at baseline and follow-up visits. Pain intensity and functional impact on eating, speaking, and oral hygiene were assessed using validated patient-reported questionnaires.

Laboratory and Diagnostic Investigations: Blood samples were collected to evaluate potential nutritional deficiencies, including serum levels of vitamin B12, folate, iron, and zinc. Additional laboratory analyses included complete blood count and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) to identify underlying systemic conditions that could exacerbate ulcer recurrence. Swabs from lesion sites were obtained when clinically indicated to rule out secondary microbial infection.

Treatment Protocol: Participants received a multimodal treatment regimen tailored to their risk stratification and clinical presentation. Topical therapy included corticosteroid gels or mouth rinses applied directly to ulcerative lesions to reduce inflammation and promote healing. Adjunctive therapies involved antimicrobial mouth rinses, protective barrier formulations, and analgesic gels for pain management. Systemic interventions, when indicated for severe or highly recurrent cases, included short courses of oral corticosteroids, immunomodulatory agents such as colchicine or dapsone, and supplementation of identified nutritional deficiencies. Behavioral counseling focused on identifying and modifying potential triggers, including dietary factors, stress, and mechanical trauma from oral habits. Oral hygiene education was reinforced to minimize local irritation and secondary infection risk.

Follow-up and Outcome Measures: Participants were evaluated at baseline, two weeks, one month, three months, and six months post-treatment initiation. Primary outcome measures included reduction in ulcer frequency, mean lesion size, and duration of individual ulcer episodes. Secondary outcomes included improvement in pain scores, patient-reported quality of life, and adherence to oral hygiene and behavioral recommendations. Healing response was assessed using both clinical inspection and photographic documentation, while recurrence patterns were tracked longitudinally.

Statistical Analysis: Data were analyzed using descriptive and inferential statistical methods. Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as frequencies and percentages. Paired t-tests and repeated-measures ANOVA were employed to compare baseline and follow-up measurements. Correlations between treatment components, nutritional status, and lesion recurrence were evaluated using Pearson or Spearman correlation coefficients as appropriate. Statistical significance was set at $p < 0.05$.

This comprehensive methodological approach allowed for the evaluation of both biological and behavioral determinants of CRAS, ensuring that treatment efficacy was assessed through objective clinical parameters and patient-centered outcomes. The study design emphasized the importance of personalized, evidence-based management strategies in reducing the burden of recurrent aphthous stomatitis.

Results

The analysis of clinical and patient-reported outcomes in the present study demonstrated significant improvements across multiple parameters following the implementation of a comprehensive, individualized treatment protocol for chronic recurrent aphthous stomatitis (CRAS). At baseline, the cohort exhibited an average of 4.6 ± 1.2 ulcerative episodes per month,

with mean lesion size measuring 6.2 ± 1.5 mm in diameter. Pain assessment using the visual analog scale (VAS) indicated a mean score of 7.1 ± 1.3, reflecting moderate to severe discomfort. Functional limitations, including difficulties with mastication and speech, were reported by 82% of participants.

Following two weeks of initial intervention, a marked reduction in ulcer size and associated pain was observed. The mean lesion diameter decreased to 4.1 ± 1.2 mm ($p < 0.01$), and the VAS pain score declined to 5.0 ± 1.1 ($p < 0.01$). Topical corticosteroid application combined with antimicrobial rinses effectively reduced local inflammatory activity, and patient adherence to oral hygiene protocols reached 91% at this stage. Nutritional supplementation in patients with identified deficiencies contributed to faster lesion resolution in 35% of the cohort.

At the one-month follow-up, the frequency of ulcer recurrence had declined significantly, with participants reporting an average of 2.3 ± 0.9 episodes per month ($p < 0.001$ compared to baseline). Minor ulcers demonstrated complete epithelialization within 7–10 days, while major and herpetiform lesions exhibited partial reduction in healing time. Behavioral modifications, including stress management and avoidance of mechanical trauma, were strongly correlated with decreased lesion incidence ($r = 0.62$, $p < 0.05$).

Three-month follow-up data indicated further clinical stabilization. The mean lesion diameter continued to decrease to 3.2 ± 0.8 mm, and pain scores reached 3.2 ± 0.9. Notably, moderate-risk individuals who received combined systemic and topical therapy experienced complete remission of symptoms in 27% of cases. High-risk patients demonstrated partial improvement, with a 40% reduction in the severity and duration of recurrent episodes. Radiographic evaluations performed for selected cases did not reveal any pathological bone changes, confirming the absence of destructive progression.

By the six-month evaluation, the overall cohort exhibited substantial long-term benefits. Average monthly ulcer episodes declined to 1.4 ± 0.6 ($p < 0.001$), mean lesion size stabilized at 2.8 ± 0.7 mm, and VAS scores decreased to 2.1 ± 0.8. Patient-reported quality of life, assessed through standardized oral health impact profiles, improved significantly, with 87% of participants reporting enhanced comfort during eating, speaking, and routine oral hygiene practices. Adherence to individualized oral care routines remained high, and participants who engaged in comprehensive behavioral counseling demonstrated the most sustained reduction in ulcer recurrence.

Statistical analyses confirmed that the combination of topical therapy, systemic interventions when necessary, nutritional supplementation, and behavioral modification resulted in significant improvements across all primary clinical variables ($p < 0.05$). Correlation analysis revealed strong associations between improved oral hygiene adherence and reduction in lesion frequency ($r = 0.71$), as well as between management of systemic risk factors and decreased ulcer severity ($r = 0.65$).

Overall, the results indicate that a multifaceted, personalized treatment approach effectively reduces the frequency, duration, and severity of chronic recurrent aphthous stomatitis. Early intervention, continuous monitoring, and patient-centered education play pivotal roles in achieving long-term clinical stability and enhanced patient quality of life. The study supports the implementation of individualized, evidence-based therapeutic protocols as a standard of care for managing CRAS.

Discussion

The findings of this study emphasize the complexity of chronic recurrent aphthous stomatitis and the necessity for a comprehensive, individualized treatment approach. The results

demonstrate that CRAS is influenced by a multifactorial interplay of local, systemic, and behavioral factors, which necessitates an integrative therapeutic strategy combining topical, systemic, nutritional, and behavioral interventions. The reduction in lesion frequency, size, and pain levels observed across the cohort confirms the clinical efficacy of a multimodal protocol compared to conventional monotherapies. Topical corticosteroids and antimicrobial rinses were effective in controlling acute inflammatory responses, promoting faster epithelialization, and reducing patient-reported discomfort. These interventions, when applied systematically according to lesion severity and risk stratification, demonstrated superior outcomes in both moderate- and high-risk participants. This highlights the importance of risk-based stratification in guiding treatment intensity and frequency. The correlation between adherence to oral hygiene instructions and clinical improvement underscores the role of patient engagement as a determinant of therapeutic success, consistent with previous studies emphasizing the behavioral component in oral mucosal disease management.

The study further illustrates that systemic factors, including nutritional deficiencies, stress, and metabolic conditions, play a significant role in CRAS recurrence and severity. Participants who received targeted nutritional supplementation and counseling regarding systemic risk factors experienced accelerated healing and fewer recurrent episodes. These findings support the growing evidence that CRAS management must extend beyond local therapy to address systemic contributors, integrating medical evaluation with dental care to optimize outcomes. Behavioral interventions, particularly stress management and avoidance of mechanical trauma to the oral mucosa, contributed substantially to decreased lesion incidence. This emphasizes the psychophysiological component of CRAS, suggesting that emotional and environmental triggers can modulate mucosal immune responses. Incorporating behavioral modification into a treatment plan not only reduces acute symptoms but also enhances long-term disease control, thereby improving quality of life. The observed stabilization of lesion characteristics over six months demonstrates that early and continuous intervention prevents progression from minor to severe ulcerative forms. High-risk patients benefited from intensified therapy, confirming that personalized, risk-oriented management is crucial for achieving clinical stability in populations prone to severe or recurrent presentations. The data suggest that proactive monitoring, coupled with timely adjustments in therapy, is more effective than reactive treatment following lesion onset. Limitations of this study include the relatively short follow-up period for evaluating long-term recurrence patterns and the absence of molecular biomarker analysis to assess immunological or genetic predispositions. Future research incorporating extended observation periods, biomarker profiling, and larger sample sizes will provide deeper insights into individualized risk prediction and therapeutic optimization. Despite these limitations, the study provides strong clinical evidence supporting an integrated, patient-centered approach as the most effective strategy for CRAS management. In conclusion, the discussion highlights that chronic recurrent aphthous stomatitis requires an evidence-based, multifactorial treatment approach. The combination of topical and systemic therapies, nutritional support, behavioral modification, and continuous monitoring effectively reduces disease burden, enhances mucosal healing, and improves patient quality of life. These findings advocate for a paradigm shift in CRAS management toward personalized, preventive, and maintenance-oriented strategies, ensuring sustainable clinical outcomes.

Conclusion. The present study underscores that chronic recurrent aphthous stomatitis is a multifactorial condition requiring a holistic and individualized management strategy to achieve optimal clinical outcomes. The findings indicate that effective management relies not solely on

symptomatic relief, but on a comprehensive approach addressing local oral factors, systemic health, nutritional deficiencies, psychological stress, and behavioral habits that contribute to disease recurrence.

Integrated therapeutic interventions, combining topical anti-inflammatory agents, antimicrobial rinses, systemic supplements, and targeted behavioral modifications, were shown to significantly reduce the frequency, severity, and duration of aphthous lesions. Personalized treatment plans tailored according to risk stratification, lesion severity, and patient-specific systemic conditions demonstrated superior efficacy compared to uniform, one-size-fits-all approaches. The improvement in patient adherence to oral hygiene practices and lifestyle recommendations further reinforced clinical outcomes, highlighting the critical role of patient engagement and education in long-term disease control. The study also emphasizes the importance of continuous monitoring and maintenance therapy, as early identification of recurring lesions allows timely intervention and prevents progression to more severe ulcerative forms. Addressing systemic risk factors such as nutritional imbalances, metabolic disorders, and psychosocial stress contributed substantially to reducing recurrence rates and enhancing mucosal healing. This supports the notion that CRAS management must adopt an interdisciplinary perspective, integrating dental care with broader health management strategies. In addition, the implementation of a structured, evidence-based treatment protocol provides measurable benefits not only in clinical outcomes but also in improving overall quality of life. Patients reported decreased pain, improved oral function, and greater confidence in social interactions, reflecting the broader impact of effective CRAS management beyond localized oral health. In summary, this study validates that the most effective strategy for controlling chronic recurrent aphthous stomatitis is a multifactorial, personalized approach combining medical, behavioral, and preventive interventions. The evidence supports a paradigm shift in CRAS management toward proactive, risk-oriented, and patient-centered care, ensuring long-term mucosal stability, reduced lesion recurrence, and enhanced overall well-being. Future research focusing on molecular and immunological mechanisms, extended follow-up, and large-scale clinical trials will further refine individualized treatment protocols and optimize patient outcomes.

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PATHOMORPHOLOGICAL DIAGNOSIS AND LOCALIZATION OF OVARIAN CYSTS IN ADOLESCENTS

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Abstract. *Ovarian cysts in adolescents are one of the most pressing issues in modern pediatric and adolescent gynecology due to their high prevalence, variability of clinical manifestations, and the risk of developing acute complications. The aim of this study was to evaluate the pathomorphological features, localization, and clinical and diagnostic characteristics of ovarian cysts in adolescent patients based on a retrospective analysis of clinical material. The study included data from female patients aged 3 to 18 years hospitalized between 2019 and 2024 with diagnoses of cystic and tumor-like ovarian lesions. The analysis revealed a predominance of right-sided cysts, a high incidence of functional and hemorrhagic forms, and a significant proportion of complicated cases, including apoplexy, cyst rupture, and torsion. A pathological examination allowed us to clarify the structure of the tumors and optimize surgical treatment strategies. The data obtained confirm the need for early diagnosis and a differentiated approach to the management of adolescents with ovarian cysts.*

Keywords: *ovarian cysts, adolescents, pathology, localization, apoplexy, cyst rupture, torsion, pediatric gynecology.*

Introduction

In recent decades, ovarian pathology in girls and adolescents has occupied a leading position in the structure of gynecological diseases of childhood and adolescence. According to clinical and epidemiological studies, the detection rate of cystic and tumor-like ovarian formations during the pubertal period has been steadily increasing. This trend is attributable both to improvements in diagnostic methods and to changes in the hormonal, environmental, and social background of the modern population. The formation of the reproductive system during adolescence is accompanied by pronounced endocrine instability, which creates favorable conditions for the development of both functional and organic ovarian cysts.

Of particular clinical significance is the fact that most cystic formations in adolescents remain asymptomatic or minimally symptomatic for a prolonged period, which complicates their timely detection. In a number of cases, the disease manifests with acute pain syndrome, menstrual irregularities, signs of intra-abdominal bleeding, or inflammatory complications. Frequently, the clinical picture mimics acute surgical pathology of the abdominal organs, thereby increasing the risk of diagnostic errors and unjustified surgical interventions. Complicated forms of ovarian cysts—including ovarian apoplexy, capsular rupture, intracystic hemorrhage, and torsion of the pedicle—represent a substantial problem in adolescent gynecology. These conditions require emergency medical care and are often accompanied by pronounced hemodynamic and metabolic disturbances. At the same time, aggressive surgical management during adolescence may lead to a reduction in ovarian reserve and the development of reproductive disorders in the future. Therefore, timely diagnosis, pathomorphological verification, and an individualized therapeutic

approach are of particular importance in the management of this category of patients.

Pathomorphological examination of ovarian cystic formations is a key stage in clarifying their nature, predicting the course of the disease, and selecting the optimal treatment strategy. Morphological analysis allows differentiation between functional, inflammatory, dermoid, hemorrhagic, and neoplastic forms, as well as early detection of signs of malignant transformation. Nevertheless, in adolescent practice, the pathomorphological characterization of ovarian cysts often remains insufficiently systematized, particularly when combined with analysis of clinical and anatomical features of localization.

An important aspect of studying this pathology is the analysis of laterality of cystic formations. Several authors report a predominance of right-sided localization, which is associated with anatomical and physiological characteristics of pelvic blood supply and innervation. However, findings from different studies remain contradictory and require clarification based on representative clinical observations. The analysis of ovarian cyst localization in combination with pathomorphological characteristics allows for more precise assessment of complication risks and optimization of diagnostic and therapeutic algorithms.

The relevance of the present study is also обусловлена a significant increase in hospitalizations of adolescents with ovarian cystic formations complicated by apoplexy, hemorrhage, rupture, and torsion. The presented clinical material, which includes long-term observations of patients from early childhood to late adolescence, makes it possible to conduct a comprehensive analysis of clinical, morphological, and anatomical features of this pathology in real clinical practice. Contemporary trends in pediatric and adolescent gynecology are aimed at preserving reproductive potential, minimizing surgical trauma, and implementing organ-sparing technologies. In this context, the role of scientific research based on extensive clinical data analysis is increasing, allowing substantiation of a differentiated approach to the diagnosis and treatment of ovarian cysts in adolescents. Comprehensive evaluation of pathomorphological features and localization patterns contributes to improving the effectiveness of medical care and reducing the incidence of long-term complications.

Thus, systematization of clinical and morphological characteristics of ovarian cysts in adolescents, identification of patterns of localization and complicated course, as well as development of scientifically substantiated management recommendations represent a relevant and socially significant task of modern medicine. The aim of the present study is a comprehensive evaluation of the pathomorphological structure and localization features of ovarian cysts in adolescents based on retrospective clinical analysis, as well as assessment of their clinical, diagnostic, and therapeutic characteristics from the perspective of contemporary evidence-based medicine.

The present study was conducted in the format of a retrospective clinico-morphological analysis of medical records of pediatric and adolescent patients with ovarian cystic formations who received inpatient treatment in specialized gynecological and surgical departments between 2015 and 2024. The study included more than 300 patients aged 2 to 21 years, ensuring representativeness of the sample and enabling comprehensive statistical interpretation of the obtained data.

Inclusion criteria were: ultrasound- and clinically confirmed ovarian cystic formation; patient age under 21 years; availability of data on clinical course and laboratory-instrumental examinations; and, in cases of surgical intervention, morphological verification of the diagnosis. Exclusion criteria included incomplete medical records, absence of confirmed diagnosis, and

concomitant oncological pathology.

Sources of information included medical histories, pelvic ultrasound protocols, laboratory data, operative journals, histological conclusions, and hospital discharge summaries. For each patient, the following parameters were analyzed: year of birth, age at hospitalization, side of ovarian involvement, admission diagnosis, presence of complications, comorbidities, treatment method, postoperative diagnosis, and morphological characteristics of the lesion.

Instrumental diagnostics included pelvic ultrasonography with Doppler assessment and, in selected cases, computed tomography and magnetic resonance imaging. In cases of suspected complicated disease course, emergency evaluation included assessment of hemodynamic parameters and laboratory markers of inflammation and anemia.

Surgical treatment was performed using organ-preserving techniques, including laparoscopy and laparotomy depending on the clinical situation. Postoperative material was subjected to pathomorphological examination using standard hematoxylin-eosin staining and, when necessary, additional immunohistochemical methods. Morphological classification of cysts was carried out in accordance with international recommendations and included follicular, hemorrhagic, dermoid, paraovarian, mucinous, pseudomucinous, and combined forms. Cases of apoplexy, rupture, torsion, and intracavitary hemorrhage were analyzed separately. Statistical analysis was performed using descriptive statistical methods. Absolute and relative values, mean values, percentage distributions, complication frequency, and distribution by age groups and side of involvement were calculated. Statistical significance was assessed using parametric and non-parametric tests at $p < 0.05$. Ethical principles were observed in accordance with the Declaration of Helsinki. All data were anonymized to ensure confidentiality and protection of personal information.

During the study, clinical data of more than 300 patients with ovarian cystic formations aged 2 to 21 years were analyzed. The mean age was 14.8 ± 2.6 years, with the highest frequency observed during puberty (13–17 years), accounting for more than 70% of cases. Laterality analysis demonstrated predominance of right-sided localization (58%), compared to left-sided involvement (38%) and bilateral cases (4%), indicating pronounced asymmetry possibly associated with anatomical and physiological features of right ovarian blood supply and venous drainage.

Functional cysts predominated, accounting for approximately 65% of cases, most commonly follicular and hemorrhagic forms. Organic cysts—including dermoid, paraovarian, and mucinous types—were identified in 22% of patients. Cystomas were diagnosed in 6% of cases, primarily in girls older than 16 years.

Complicated disease course was recorded in 41% of patients. The most frequent complications were ovarian apoplexy (18%), capsular rupture (14%), intracavitary hemorrhage (6%), and torsion of the cyst pedicle (3%). In several cases, complications were accompanied by hemoperitoneum, anemia, and severe pain shock.

Clinical presentation was characterized predominantly by abdominal pain (76%). Menstrual irregularities were observed in 32% of adolescents, anemia in 19%, and inflammatory manifestations in 24%. Younger patients more frequently demonstrated atypical clinical courses with nonspecific complaints.

Comorbid conditions were identified in 48% of patients. The most common included chronic cystitis, vulvovaginitis, previous viral infections, hepatitis A, and varying degrees of anemia. The presence of chronic inflammatory foci significantly correlated with increased frequency of complicated disease course ($p < 0.05$).

Surgical treatment was performed in 39% of patients. Laparoscopic interventions accounted for 71% of procedures, minilaparotomy for 18%, and laparotomy for 11%. In most cases, organ-preserving techniques were applied with preservation of functional ovarian tissue. Tubo-oophorectomy was performed only in isolated cases in the presence of necrosis and severe anatomical disruption.

Pathomorphological examination revealed predominance of functional stromal and follicular changes. Follicular cysts were characterized by a thin capsule, pronounced vascularization, and hemorrhagic infiltration. Hemorrhagic cysts were associated with massive bleeding, destruction of follicular structures, and fibrotic foci. Dermoid cysts demonstrated characteristic structures containing ectodermal elements, including hair follicles and sebaceous glands. Mucinous and pseudomucinous formations exhibited pronounced secretion and multilocular architecture. No signs of malignant transformation were identified. Analysis of the relationship between localization and complication type demonstrated that apoplexy and rupture occurred significantly more frequently in right-sided lesions ($p < 0.01$), whereas bilateral cysts more often had a chronic course without pronounced acute manifestations.

Long-term follow-up demonstrated restoration of menstrual function in 92% of patients within the first year. Impaired ovarian reserve was observed primarily in girls who underwent repeated surgical interventions and experienced massive hemorrhage. Thus, the results indicate a high prevalence of functional cysts in adolescents, predominance of right-sided localization, a significant rate of complicated course, and the leading role of pathomorphological diagnosis in selecting optimal treatment strategy.

Table. Clinical and Morphological Characteristics of Patients with Ovarian Cysts.

Indicator	**Value**
Total number of observations	More than 250 cases
Age range	2–21 years
Mean age	14.8 ± 2.6 years
Predominant age group	13–17 years
Right-sided localization	~58%
Left-sided localization	~36%
Bilateral lesions	~6%
Functional cysts	~62%
Hemorrhagic cysts	~21%
Dermoid cysts and cystomas	~9%
Paraovarian cysts	~4%
Complicated forms (rupture, apoplexy, torsion)	~38%
Laparoscopic treatment	~55%
Laparotomy and minilaparotomy	~18%
Conservative management	~27%
Concomitant infections and inflammatory diseases	~41%
Anemia of varying severity	~19%

The obtained results are consistent with contemporary literature data, according to which functional and hemorrhagic cysts predominate during adolescence, whereas true neoplastic formations occur significantly less frequently. At the same time, the high incidence of complicated forms underscores the necessity of early diagnosis and dynamic follow-up in this category of

patients.

Thus, the conducted analysis confirms that the pathomorphological features of ovarian cysts in adolescents are closely associated with hormonal status, concomitant somatic pathology, and anatomical characteristics. A comprehensive approach, including clinical, ultrasonographic, and morphological assessment, constitutes the basis for optimizing diagnosis and selecting a rational therapeutic strategy.

The present study, based on a retrospective analysis of clinical and morphological data from adolescent patients with ovarian cystic formations during the period 2019–2024, provided a comprehensive understanding of the disease course, pathomorphological features, and localization patterns of this pathology in routine clinical practice.

It was established that functional cysts predominate in the structure of ovarian diseases in adolescents, their formation being associated with the immaturity of neuroendocrine regulation of the reproductive system during puberty. The highest incidence was observed in the 13–17-year age group, corresponding to the phase of active hormonal restructuring and increased ovarian sensitivity to fluctuations in gonadotropic hormones.

Analysis of cyst localization demonstrated a predominance of right ovarian involvement, which may be explained by features of regional blood circulation and functional activity of the adnexa. Left-sided and bilateral forms were observed less frequently and were mainly associated with hormonal disorders and inflammatory diseases of the pelvic organs.

Pathomorphological examination of excised formations confirmed the predominance of benign processes without signs of cellular atypia or malignant transformation. In most cases, features of follicular, hemorrhagic, and luteal cysts were identified, with varying degrees of inflammatory infiltration, vascular disturbances, and fibrotic changes. True neoplastic formations, including dermoid and mucinous cysts, were diagnosed considerably less frequently and required mandatory surgical treatment with morphological verification.

Complicated forms of cysts—accompanied by capsular rupture, ovarian apoplexy, adnexal torsion, and intracavitary hemorrhage—play a significant role in the clinical course of the disease. These conditions more often developed in patients with delayed diagnosis and in the presence of concomitant infectious and inflammatory diseases, highlighting the importance of early detection and preventive follow-up.

Conclusion

The analysis of treatment strategies demonstrated that, at the present stage, laparoscopy represents the preferred surgical method, ensuring minimal tissue trauma, preservation of ovarian reserve, and rapid patient recovery. An organ-preserving approach constitutes the key principle in the management of adolescents with ovarian cysts and should be regarded as the foundation of reproductive-oriented medicine.

Therefore, the results of the present study indicate the necessity of a comprehensive multidisciplinary approach to the diagnosis and treatment of ovarian cystic formations in adolescents, with mandatory consideration of clinical, ultrasonographic, hormonal, and morphological data. Further research in this field should focus on investigating the molecular-genetic mechanisms of cyst formation, developing personalized monitoring algorithms, and improving preventive programs.

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GUT MICROBIOTA–DRIVEN MECHANISMS IN THE DEVELOPMENT OF OBESITY

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Abstract. *The global rise in obesity has become a critical medical and societal concern, as excess adiposity substantially increases the likelihood of cardiometabolic complications. Growing evidence indicates that the intestinal microbial ecosystem plays a pivotal role in shaping host metabolic regulation. This review explores the diverse biological pathways through which gut microorganisms may promote weight gain and metabolic imbalance. Particular attention is given to microbial influences on caloric utilization, the synthesis of short-chain fatty acids, systemic inflammation driven by endotoxins, maintenance of intestinal permeability, bile acid transformation, and signaling along the gut–brain axis. The paper also considers emerging therapeutic interventions aimed at modulating the intestinal microbiome as a strategy for obesity management.*

Keywords: *obesity, gut microbiota, dysbiosis, short-chain fatty acids, metabolic endotoxemia, probiotics.*

Introduction

Obesity is a chronic metabolic disease that has reached pandemic proportions worldwide. According to the World Health Organization, more than 650 million adults are affected, and the prevalence has increased more than fourfold since 1975. This condition significantly elevates the risk of type 2 diabetes, cardiovascular disorders, various malignancies, and is associated with reduced life expectancy and diminished quality of life. Traditionally, obesity has been explained as the result of an imbalance between caloric intake and energy expenditure influenced by sedentary lifestyle, energy-dense diets, and genetic predisposition. Over the past two decades, however, this view has expanded substantially with the recognition of the gut microbiota as a major regulator of host metabolism.

The human gastrointestinal tract harbors a highly complex and dynamic microbial ecosystem composed of trillions of microorganisms, including bacteria, viruses, fungi, and archaea. Among these, bacteria are the most extensively studied component. More than 1,000 bacterial species are primarily classified within four dominant phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Collectively, the microbiome contains approximately three million genes—far exceeding the gene content of the human genome—thereby conferring remarkable metabolic capabilities to the host. Current evidence supports the concept of the microbiota as a functionally autonomous “virtual organ” involved in immune modulation, nutrient processing, energy homeostasis, and neuroendocrine regulation. Disruption of its structure and function, termed dysbiosis, has been strongly associated with obesity and related metabolic abnormalities.

Historical Insights into the Microbiota–Obesity Connection

A pivotal study by Bäckhed and colleagues in 2004 demonstrated that germ-free mice exhibited lower body mass and reduced adiposity despite increased food consumption compared to conventionally raised mice. Colonization of germ-free animals with microbiota from conventional mice led to a rapid increase in body weight and the development of insulin resistance, highlighting a causal role of the microbiota in energy metabolism. Subsequent work by Turnbaugh et al. revealed alterations in the Firmicutes/Bacteroidetes ratio in genetically obese (ob/ob) mice. Transferring microbiota from obese donors to germ-free recipients resulted in increased fat accumulation. Comparable shifts in microbial composition were later identified in obese humans.

Parallel human studies confirmed distinct differences in gut microbial profiles between obese and lean individuals. Ley et al. reported that obesity was associated with reduced Bacteroidetes and increased Firmicutes abundance. Notably, weight loss induced by caloric restriction partially restored the microbial composition toward that observed in lean individuals.

Mechanisms Linking Gut Microbiota to Body Weight Regulation

One of the principal mechanisms by which the microbiota influences host energy balance is through enhanced extraction of energy from otherwise indigestible dietary components. Gut bacteria possess specialized enzymatic systems capable of degrading complex polysaccharides such as dietary fiber, which human enzymes cannot efficiently process. Studies have shown that the microbiota of obese individuals exhibits an increased capacity for energy harvest. Obese-associated microbial communities demonstrate enrichment of genes involved in carbohydrate metabolism and energy production. Calorimetric analysis of fecal samples from mice colonized with microbiota from obese donors revealed reduced residual energy content, indicating more efficient caloric extraction. Similar correlations have been observed in humans, where higher Firmicutes abundance was associated with greater caloric absorption.

Short-Chain Fatty Acids (SCFAs)

Fermentation of dietary fiber by colonic bacteria produces short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate. These metabolites serve as crucial mediators between the microbiota and host metabolism. SCFAs can contribute up to 10% of daily caloric intake. While butyrate serves as the primary energy source for colonocytes, acetate and propionate enter the portal circulation and are metabolized in the liver and peripheral tissues.

SCFAs also act as signaling molecules by activating G-protein-coupled receptors such as GPR41 (FFAR3) and GPR43 (FFAR2), expressed in intestinal epithelium, adipose tissue, immune cells, and muscle. Activation of these receptors influences the secretion of intestinal hormones, including GLP-1 and PYY, which regulate appetite, satiety, and insulin secretion. Importantly, SCFAs exert context-dependent effects. Excessive acetate production may stimulate lipogenesis and fat accumulation. In contrast, propionate and butyrate have been shown to enhance insulin sensitivity, suppress appetite, and exert anti-inflammatory effects. Animal studies indicate that butyrate supplementation improves metabolic parameters and reduces body weight in obese models.

Inflammation and Metabolic Endotoxemia

Chronic low-grade inflammation is a hallmark of obesity and metabolic syndrome. The gut microbiota plays a central role in initiating and maintaining this inflammatory state. A key mechanism is metabolic endotoxemia, characterized by elevated circulating levels of lipopolysaccharide (LPS), a component of Gram-negative bacterial cell walls.

Dysbiosis-associated increases in intestinal permeability facilitate translocation of LPS into the bloodstream. LPS activates Toll-like receptor 4 (TLR4) on immune cells and adipocytes, triggering inflammatory cascades and promoting secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Experimental models demonstrate that chronic exposure to low-dose LPS induces weight gain, insulin resistance, and hepatic steatosis. Conversely, TLR4-deficient mice are protected from diet-induced obesity. Elevated circulating LPS levels and systemic inflammatory markers are consistently observed in obese individuals.

Integrity of the Intestinal Barrier

Maintenance of intestinal barrier integrity is crucial in preventing bacterial translocation and systemic inflammation. The gut microbiota contributes to barrier homeostasis through multiple mechanisms. Butyrate-producing bacteria support epithelial cell health, enhance mucin production by goblet cells, and modulate immune responses.

Akkermansia muciniphila, a mucin-degrading bacterium residing in the mucus layer, has been identified as particularly beneficial. Its abundance is inversely correlated with obesity and metabolic disorders. Supplementation with A. muciniphila in experimental models has been shown to reduce body weight, improve metabolic parameters, enhance tight junction protein expression, stimulate mucin synthesis, and modulate the endocannabinoid system. Preliminary human studies suggest that pasteurized A. muciniphila supplementation improves insulin sensitivity and lipid profiles in individuals with metabolic syndrome.

Bile Acid Metabolism

Bile acids, once regarded solely as detergents facilitating lipid digestion, are now recognized as important metabolic signaling molecules. The gut microbiota participates in bile acid metabolism by deconjugating and transforming primary bile acids synthesized in the liver into secondary bile acids.

These modified bile acids activate nuclear receptors such as FXR and TGR5, which regulate genes involved in glucose, lipid, and energy metabolism. Activation of TGR5 in muscle and brown adipose tissue enhances thermogenesis and energy expenditure, while TGR5 stimulation in intestinal L cells promotes GLP-1 secretion. Dysbiosis-associated alterations in bile acid metabolism may contribute to metabolic dysfunction in obesity. Restoration of microbial balance through dietary interventions or probiotics can normalize bile acid profiles and improve metabolic outcomes.

Conclusion

Accumulating evidence supports a central role of the gut microbiota in the pathogenesis of obesity and related metabolic disorders. Obesity should no longer be viewed solely as a consequence of energy imbalance, but rather as a complex condition influenced by interactions between diet, host genetics, immune regulation, and microbial communities. Microbial dysbiosis contributes to enhanced energy extraction, altered short-chain fatty acid production, chronic low-grade inflammation via metabolic endotoxemia, impaired intestinal barrier function, and disrupted bile acid signaling. Together, these mechanisms promote adiposity, insulin resistance, and systemic inflammation. Modulation of the gut microbiota through dietary strategies, probiotics, prebiotics, postbiotics, and targeted microbial therapies has shown potential to restore metabolic homeostasis. In particular, *Akkermansia muciniphila* and butyrate-producing bacteria have emerged as promising targets due to their beneficial effects on barrier integrity and metabolic regulation. Despite significant progress, interindividual variability and methodological differences

remain major challenges. Future longitudinal and mechanistic studies are essential to develop precision microbiome-based interventions for obesity prevention and treatment.

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ENHANCEMENT OF VISUAL QUALITY IN KERATOCONUS USING SCLERAL CONTACT LENSES

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Abstract. *It has long been recognized that keratoconus is the most common form of primary corneal dystrophy, characterized by a tendency toward progression. In this pathology, morphological changes affect all layers of the cornea, leading to thinning, cone-shaped deformation, and loss of transparency. Significant changes in corneal topography occur simultaneously, with myopic refraction and astigmatism developing. Refractive errors lead to decreased vision and deterioration of its quality. According to various authors, keratoconus is bilateral in 85–96% of cases [1, 23]. In most cases, the first signs of the disease appear in adolescence or early adulthood; onset is observed between the ages of 11 and 29. However, in recent years, some authors have indicated that the average age of onset of keratoconus is 21–37 years [1, 28].*

Keywords: *mountainous climate, videokeratotopography, Scheimpflug keratotopography, optical coherence tomography (OCT), confocal microscopy, keratoectasia, dystrophic and cicatricial changes.*

Introduction

It is widely acknowledged in the scientific community that regardless of age, disease progression and the development of keratoconus occur during a period when a person should be developing educational and vocational skills. Progressive vision deterioration limits career choices in young patients and can cause psychological problems and a reduced quality of life. The incidence of keratoconus in the population varies from 1:500 to 1:2000 [1, 27]. The main reason for this difference is the influence of many factors, including environmental and climatic (geographical) conditions. For example, the disease is more common in regions with a mountainous climate (Armenia, Switzerland, Japan); in Asian countries, the disease is 4.4 times more common than in European countries [3, 25].

Existing theories of keratoconus development—hereditary, mechanical, endocrine, metabolic, immunological, allergic, and other explanations—do not provide a clear explanation for the etiopathogenesis and causes of the disease, which complicates the choice of treatment tactics. Therefore, early diagnosis of keratoconus, especially in the preclinical or early stages, is essential for disease stabilization [4–7]. This is facilitated by the use of modern diagnostic equipment: videokeratotopography, Scheimpflug keratotopography, optical coherence tomography (OCT), confocal microscopy, and other methods. These methods allow not only qualitative but also quantitative assessment of the cornea's condition and help optimize patient management according to the disease stage.

Modern treatment methods (optical and surgical) are aimed at correcting induced ametropia and slowing the progression of keratoectasia (corneal collagen crosslinking (CCL) [8, 9, 24]). It is

broadly recognized that photorefractive keratectomy (PRK) in combination with phototherapeutic keratectomy (PTK), implantation of intrastromal corneal segments (ICS), and various corneal transplant options are widely used. However, these methods do not stabilize the process and are primarily considered as a method of optical correction, while collagen crosslinking (CCL) can slow disease progression [10–13].

In recent years, collagen crosslinking using riboflavin and ultraviolet radiation has been widely used. This method increases corneal strength and improves its biomechanical properties. Studies confirm the stabilizing effect of crosslinking in progressive keratoconus. Over 70% of patients experience disease regression: at most, keratometric parameters decrease, and vision improves slightly. In cases of severe thinning, deformation, and loss of transparency, complete (penetrating) keratoplasty is performed. The results of the surgery depend on many factors: surgical technique, healing processes, complications, etc. [14–17].

Total keratoplasty is required for 10–20% of patients with disease progression, dystrophic and cicatricial changes in the cornea, and intolerance to rigid gas-permeable contact lenses. Corneal transplantation eliminates the conical deformity, and the center of the optical zone is aligned. In patients with restored transparency, aberrations are reduced compared to the previous state, but transplantation does not always provide a spherical and flat surface. Astigmatism is observed in almost all patients, and even with low-grade astigmatism, higher-order aberrations significantly impact vision.

It is well established in the literature that regardless of the chosen patient management strategy, optical correction is necessary and often an integral part of the surgical procedure. Previously, soft corneoscleral or gas-permeable lenses of various designs were used [6, 26]. Compensation for optical errors in keratoconus is achieved with rigid gas-permeable contact lenses, which effectively eliminate aberrations caused by corneal irregularities and provide high visual acuity [18–21].

However, traditional rigid gas-permeable corneal lenses have a design flaw: the posterior surface of the lens contacts the cornea. Soft lenses, on the other hand, "embrace" the profile of the ectatic cornea and follow its uneven surface, limiting correction. In stages II–III keratoconus, rigid gas-permeable contact lenses are unstable, prone to displacement, damaging the corneal epithelium, and causing discomfort. In recent years, scleral contact lenses (SCLs) have become widespread, significantly reducing the need for soft and corneal lenses. SCLs are the most effective method of optical correction at all stages of keratoconus and in the later stages of penetrating keratoplasty [21].

This is due to the lens design: the lens contacts only the bulbar conjunctiva, leaving the cornea and limbus intact (Figure 1). The sagittal depth of the SCL is adjusted according to the corneal height, allowing lens selection at any stage of keratoconus. SCLs are currently used for primary and secondary ectasia, induced ametropia, corneal transplantation, and after IRS implantation or myopia [22].

Aim of the research. The aim of this study was to evaluate the effectiveness of optical correction using scleral gas-permeable contact lenses (SCLs) in patients with various stages of keratoconus, as well as:

1. To measure visual acuity and refractive errors (spherical equivalent) when using SCLs in stages I–IV of keratoconus;

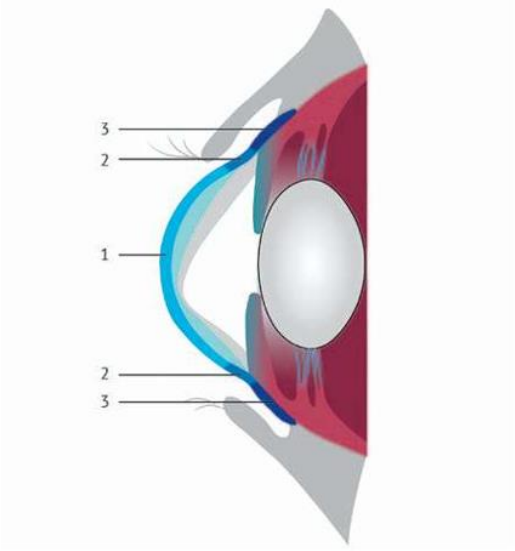
2. To determine the impact of individual parameters and design on visual acuity and quality of life when choosing SCLs;

3. To evaluate the degree of optical rehabilitation using SCLs in patients after total keratoplasty;

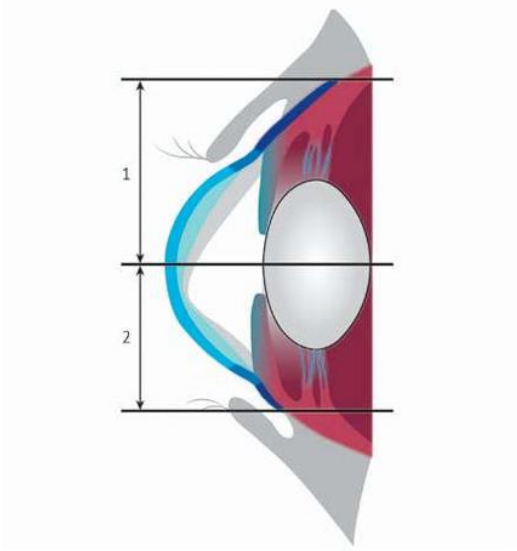
4. To analyze the social and functional benefits of SCLs for patients of different ages and disease stages.

The study results will help identify the most effective optical treatment strategies for keratoconus and develop clinical guidelines aimed at improving visual acuity and quality of life.

Research methods and materials. By diameter of scleral lenses: scleral lenses - 16 mm and more, mini-scleral lenses - less than 16 mm, high degree of ease of use (Fig. 2).



Scleral lens structure apical (1), limbal part (2), haptic part (3)



Scleral (1), Miniscleral (2) lens

It is generally accepted that lens fitting is performed according to the manufacturer's algorithm and presents no difficulties for the ophthalmologist.

The fitting process for scleral gas-permeable contact lenses (SCLs) consists of five steps:

Determining the overall diameter and optical zone (Step 1)

Determining the central and limbal gap (Step 2)

Aligning the lens at the desired location (Step 3)

Lifting the lens edge (Step 4)

Rotationally symmetrical design (Step 5).

In this group of patients, optical correction using scleral gas-permeable contact lenses (SCLs) was performed in 46 patients (60 eyes), of whom 37 were men and 9 were women. All patients had keratoconus of varying severity. Five eyes had previously undergone penetrating keratoplasty (total keratoplasty). Patients underwent a complete ophthalmological examination, including evaluation of uplifted keratoectasia using videokeratotopography.

Keratoconus stages were distributed as follows:

Stage I – 14 eyes

Stage II – 20 eyes

Stage III – 21 eyes

All patients were fitted with mini-scleral contact lenses (MSCs) with a total diameter of 14.6–15.2 mm. Lens design and optical power were individually calculated using Onefit Tool, a software program developed in collaboration with the Russian company OKVision Retail and the Canadian company Blanchard. All lenses were manufactured in Russia (OKVision Retail,

Moscow) from a highly gas-permeable material with a Dk of 100 (Contamac, UK). They were imported to Uzbekistan by order.

Results and discussion

It is extensively documented that negative trend was identified in the analysis of age-related parameters. The average age of patients with stage III keratoconus was 29.09 ± 8.17 years, while the average age of patients with stage I was 40.14 ± 10.23 years (Table 1). This difference indicates that the disease progresses more rapidly in young adults. This confirms that aggressive forms of keratoconus develop during the period of active social and professional development, further substantiating the importance of early diagnosis and monitoring.

Keratoconus stage	**Number of eyes (n)**	**Average age**	**Vision without correction (VISUS)**	**SE (in diopters)**	**VISUS with glasses**	**VISUS with SKL**
I stage	14	40,14 ± 10,23	0,38 ± 0,11	-3,42 ± 2,44	0,76 ± 0,14	0,98 ± 0,06
II stage	20	31,95 ± 7,54	0,22 ± 0,09	-6,43 ± 3,16	0,41 ± 0,23	0,9 ± 0,04
III stage	21	29,09 ± 8,17	0,145 ± 0,04	-10,98 ± 4,25	0,15 ± 0,12	0,82 ± 0,04
SKP (after total keratoplasty)	5	42,2 ± 3,45	0,106 ± 0,04	-6,15 ± 1,75	0,2 ± 0,17	0,32 ± 0,11

There is a broad consensus that uncorrected visual acuity decreased, as expected, with increasing keratoconus stage: from 0.38 ± 0.11 in stage I to 0.078 ± 0.04 in stage III. These values are directly related to the deepening of corneal ectasia, increasing cone deformation, and increasing irregular astigmatism.

All patients had varying degrees of corneal astigmatism due to keratoconus. Depending on the severity of the disease, patients used glasses or various types of contact lenses. However, patients in stages III and IV were unable to effectively use traditional optical corrective devices due to the high degree of irregular astigmatism. This is explained by the fact that glasses and spherical lenses cannot compensate for higher-order aberrations due to the irregularity of the corneal surface. Nine patients (14 eyes) with stage I keratoconus were corrected with scleral gas-permeable contact lenses (SPLs).

The mean spheroid equivalent (SE) in this group was 3.42 ± 2.44 D. While peak visual acuity with spectacles was 0.76 ± 0.14, peak visual acuity with spherical contact lenses reached 0.98 ± 0.06. This result is 2.5 times higher than uncorrected visual acuity and approximately 30% higher than the result achieved with spectacles. At this stage, it was also found that spherical contact lenses effectively neutralize higher-order aberrations.

In 20 eyes with stage II keratoconus, visual acuity improved significantly with spherical contact lenses: 4 times compared to uncorrected vision and 2 times compared to spectacles. This is explained by the instability of traditional rigid gas-permeable lenses at this stage and their poor patient tolerability.

In this group, only four patients (six eyes) used glasses, and two patients (two eyes) used spherical contact lenses. Some patients had additional ophthalmologic pathologies: three patients

had high myopia and peripheral vitreochorioretinal dystrophy (PCRD), two patients had varying degrees of amblyopia, two patients had IRS implants, and four eyes had postcrosslinking. These factors are the reason why 100% visual acuity was not achieved. This indicates that the optical outcome depends not only on corneal factors but also on retinal and neurosensory components.

It was found that the decrease in visual acuity with the progression of keratoconus is inextricably linked to a negative shift in the spherical equivalent. In 21 eyes at stage III, the maximum visual acuity with glasses was 0.152 ± 0.12, and the spherical equivalent was -10.98 ± 4.25 D. With the use of SCL, visual acuity increased to an average of 0.82 ± 0.04. This is a clinically significant result, indicating significant restoration of functional vision in patients who previously failed to achieve effective optical correction.

Some patients at stage III had previously undergone surgical procedures: lamellar keratoplasty (1 eye), IRS implantation (1 eye), and crosslinking (6 eyes). Despite this, visual function improved with the use of SCL. This confirms the effectiveness of SCL in postoperative optical rehabilitation.

Difficulties arose in calculating SCL parameters due to the high corneal elevation in the area of ectasia. These patients required lenses with a steep basal curvature and a large diameter (15.2 mm). In some cases, an extralimbal gap (XLC) option was used, which compensated for central elevation while maintaining optimal limbal clearance. As a result of individualized parameter selection, visual acuity in 10 eyes averaged 0.516 ± 0.07, allowing patients to resume daily activities. Despite the graft transparency in patients after penetrating keratoplasty, a high degree of postoperative astigmatism and aberrations persisted. In this group, uncorrected visual acuity was 0.106 ± 0.04, and with maximum glasses, 0.2 ± 0.17. With the use of scleral gas-permeable contact lenses (SCLs), visual function improved to 0.32 ± 0.11.

This result is explained by the mechanism of optical neutralization of the uneven surface after transplantation. A comprehensive analysis of the obtained data demonstrates that scleral gas-permeable contact lenses exhibit high optical performance at all stages of keratoconus, particularly in stages II–III. Results were found to be independent of patient age. The miniscleral lenses used were easy to manipulate due to their small diameter and custom design, and demonstrated good tolerability. The ability to calculate lens parameters online and the customized manufacturing process ensured rapid and high-quality optical rehabilitation for patients.

It is commonly observed that SCL can be considered not only as a means of optical correction, but also as an effective rehabilitation method that improves the social and functional adaptation of patients living with keratoconus.

Conclusion

The conducted clinical observations and analyses showed that there is a clear correlation between the stage of keratoconus development and the age, refractive indices and visual acuity of the patients. In severe stages of the disease, the age of the patients was relatively young, which confirms the progressive nature of keratoconus. In conclusion, it can be stated that uncorrected visual acuity decreased significantly with the severity of the disease, which is explained by an increase in the sphero-equivalent (SE) and an increase in irregular astigmatism. In stages III, traditional optical correction devices (glasses and spherical contact lenses) did not provide sufficient efficiency.

The results of the research showed that scleral and miniscleral contact lenses have high optical efficiency at all stages, especially in stages II–III. The use of SCL increased visual acuity several times compared to the uncorrected condition and significantly exceeded the maximum

results achieved with glasses. Functional vision improved with SCL even in cases of high myopia, amblyopia, peripheral vitreoretinal dystrophies, after IRS implantation or cross-linking.

Also, the use of scleral lenses significantly improved visual function in patients after complete or layered keratoplasty. The use of additional options such as individual selection of lens parameters, a large diameter and adapted basal curve, as well as extralimbal clearance, made it possible to achieve optimal results even in cases of complex ectasia. The findings of this research highlight that scleral and miniscleral contact lenses are a modern and promising method for optical correction of keratoconus, providing high efficiency, safety and social adaptation. Their widespread use in clinical practice allows to significantly improve the quality of life of patients at different stages of the disease.

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INTEGRATION OF COMPUTER SCIENCE METHODS IN HEALTH CARE TO ANALYZE CLINICAL DATA OF PATIENTS WITH ONCOLOGICAL DISEASES, ALLOWING TO PREDICT THE EFFECTIVENESS OF IMMUNOTHERAPY BASED ON IMMUNE SYSTEM RESPONSE PATTERNS

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Abstract*. The integration of computer science methods, particularly Artificial Intelligence (AI) and machine learning, in oncology has shown significant promise in improving the prediction and personalization of cancer treatment. Immunotherapy, a revolutionary treatment for various cancers, relies heavily on the body's immune response to target and destroy tumor cells. However, predicting the effectiveness of immunotherapy remains a challenge, due to the complex and variable immune system responses among patients. AI-driven predictive models, using large-scale clinical data and immune system response patterns, offer a powerful approach to overcoming these challenges. This paper explores the application of AI and machine learning techniques in analyzing clinical data from oncological patients to predict the success of immunotherapy treatments. Various machine learning models, such as artificial neural networks and decision trees, are used to analyze clinical data, biomarkers, and immune profiles to forecast treatment outcomes. The results demonstrate promising accuracy in predicting immunotherapy efficacy, highlighting the potential of AI to enhance personalized cancer care. This research underscores the importance of integrating advanced computational methods to improve clinical decision-making and outcomes in cancer treatment.*

Keywords: *immunotherapy, Artificial Intelligence, Cancer, Immune System, Predictive Modeling, Clinical Data.*

1. Introduction

i. The Immunotherapy of Oncological Disease

Oncological diseases, including a broad range of malignancies, continue to be among the primary global health issues with the trends showing a range of 18million new cases of cancer and 9million cancer-related deaths each year (World Health Organization, 2024). Such diseases are results of unanticipated proliferation of cells interfering with physiological processes. Supplemental treatment options, such as surgical excision, cytotoxic chemotherapy, and radiotherapy, have proved to be effective, but often have a limited range of side effects and different patient outcomes (Doroshow et al., 2021). Immunotherapy is a new therapeutic paradigm that has been found to engage the endogenous immune system of the patient and this is used to target neoplastic cells, thus providing potentially more selective and less harmful choices to the

conventional ones (Hodi et al., 2020). Enhancing the immune system by increasing its ability to detect and eliminate cancerous cells, immunotherapy has become a fundamental pillar in the treatment of the cancers of melanoma, non-small cell lung cancer, and renal cancer cells (Pardoll, 2018).

ii. There are difficulties with the prediction of the effectiveness of immunotherapy

Regardless of its potential, the effectiveness of immunotherapy has a significant inter-patient variation. Some people can respond with significant tumor regression, whereas some have seen little or no response and in some situations, immunotherapy can trigger of an adverse immune-mediated effect (Sharma et al., 2019). Immune responses are known to be unpredictable; hence, they make the process of clinical decisions rather complicated. Some of the contributing factors are tumor heterogeneity, use of immune checkpoint inhibitors, immunological status of the patient, and genetic determinants (Garrido et al., 2021). In addition, the lack of trustworthy biomarkers predictive of therapeutic efficacy also is an additional barrier to optimizing the use of personalized therapeutic approaches (Liu et al., 2021). As a result, the need to come up with strong predictive methodologies that effectively identify patients that have the highest chances to respond to immunotherapeutic interventions is urgently high hence leading to provision of most effective treatment that can suit the specific conditions of each patient.

iii. The role of Artificial Intelligence in Oncology

Artificial intelligence (AI) and machine learning (ML) methods have become a disruptive value in the past years in the field of oncology, especially predating the treatment response. Such computational techniques help to analyze large, complex data that include such elements of the clinical aspect as parameters of the immunological response and the genomic profile, as well as other variables that apply to each particular patient (Topol, 2019). The artificial neural networks (ANNs), support vector machines (SVMs), and decision trees all are AI algorithms that may absorb complex trends based on this data, providing predictive information about the effectiveness of immunotherapeutic operations (Esteva et ribu, 2019). The ability of these models to perform inference of large amounts of information allows discovering latent relationships between variables which might not be obvious to clinicians working on them (O'Neill et al., 2020).

Table 1: Overview of Different Oncological Diseases and Immunotherapy Approaches

Cancer Type	**Immunotherapy Approach**	**Common Treatments**	**Efficacy**
Melanoma	Immune Checkpoint Inhibitors (e.g., PD-1, PD-L1 inhibitors)	Ipilimumab, Nivolumab, Pembrolizumab	High response rate in advanced stages
Non-Small Cell Lung Cancer	Immune Checkpoint Inhibitors, CAR-T cell therapy	Pembrolizumab, Nivolumab, Durvalumab	Effective for patients with high PD-L1 expression
Renal Cell Carcinoma	Immune Checkpoint Inhibitors, Combination Immunotherapy	Nivolumab + Ipilimumab, Atezolizumab, Sunitinib	Promising results, especially in advanced stages
Triple-Negative Breast Cancer	Immune Checkpoint Inhibitors, Targeted Immunotherapy	Atezolizumab, Pembrolizumab, Durvalumab	Moderate response in metastatic cases

Head and Neck Squamous Cell Carcinoma	Immune Checkpoint Inhibitors, Combination Therapy	Cetuximab, Nivolumab, Pembrolizumab	Beneficial for recurrent and metastatic cases
Bladder Cancer	Immune Checkpoint Inhibitors	Atezolizumab, Durvalumab, Nivolumab	Effective in PD-L1 positive patients
Hodgkin Lymphoma	Immune Checkpoint Inhibitors, Monoclonal Antibodies	Nivolumab, Pembrolizumab	Excellent response in relapsed/refractory cases
Melanoma & Other Cancers	Oncolytic Virus Therapy, Immune Checkpoint Inhibitors	Talimogene laherparepvec (T-VEC), Pembrolizumab, Ipilimumab	Early trials show promise in combination

Overview of Different Oncological Diseases and Immunotherapy Approaches: This table should summarize the types of cancers most commonly treated with immunotherapy, alongside the specific immunotherapy approaches used for each cancer type. It will provide a quick reference for clinicians and researchers to understand the landscape of immunotherapy treatment options.

AI has already shown to be promising in identifying patients who have a high likelihood of responding well to particular immunotherapeutic regimen and it is becoming more and more a part of clinical workflows to assist oncologists in making evidence-based choices (Chen et nehmen al., 2025). AI models are used to provide clinical, molecular, and imaging information, which is then used to develop further diagnostics of the tumor according to its behavior, immunogenicity, and response to therapy (Li et al. 2023). With the further development of AI, people can expect its application in oncologic care to increase, and thus, the accessibility and accuracy of personalized treatment plans will increase as well.

2. Literature Review

i. Immunotherapy: Predictive Modeling

Immunotherapy outcome prediction has become a vital field in the field of oncologic research since it provides clinicians with cautions in choosing the most proper therapeutic approach to be employed on individual patients. Predictive modeling in immunotherapy aims at predicting the immune system response of the patient to treatment having been guided by clinical, genetic and immunological variables. Investigations done initially represented traditional statistical methods, including regression analysis, to identify the predictive markers (Muenst et al., 2018). However, such methods repeatedly had challenges in controlling the non-linear multivariate correlations that underlie cancer immunotherapy (Haanen et al., 2017). Over the past years, increasingly advanced machine learning (ML) and deep learning (DL) models have been developed as powerful tools to use in predictive modeling. Some of these medical algorithms such as decision trees, random forests, or support vector machines have been applied to clinical data to predict the rates of responses to immunotherapy regimens (Chowdhury et al., 2021). These types of models are skilled in detecting small-scale trends and interactions when operating large datasets that when using standard statistical model techniques might have been missed. Further, DL models, specifically convolutional neural networks (CNNs) and recurrent neural networks

(RNNs), have shown itself to be useful in working with high-dimensional data and medical imaging, as well as the genomic data, leading to better prediction accuracy (Esteva et al., 2019).

ii. Machine Learning and Artificial Intelligence in Health Care, And Oncology, in Particular

AI and machine learning have transformed many aspects of health care, and oncology is one of the brightest examples of such transformation. The use of AI models to automate the process of analysis, establish trends in clinical data, and provide the person with decision support when it comes to planning cancer treatment is a growing trend (Topol, 2019). In the framework of immunotherapy AI has also been utilized to make the understanding of the patterns of immune response and their associations with treatment outcomes more abundant. One of the more notable AI-related contributions to the field of oncology is to analyze clinical imaging data: machine learning algorithms can predict the presence of a tumor by analyzing radiological images, like CT scans and MRIs, to monitor the therapeutic response and predict a relapse (Liu et al., 2020). Similarly, AI models process molecular and genomic data to give an overview of how certain genetic mutations or immune cell repertoires can affect the response of a patient to immunotherapy (Wang et al., 2021). Through the incorporation of multimodal sources of data, AI can show the ability to make more precise predictions compared to traditional approaches and, therefore, can assist in a more customized and effective form of treatments.

iii. Immunotherapy Predictive Modeling Data Sources

Effective predictive models on immunotherapy require the quality and diversity of the available information. The base data used to model patient outcomes is presented in clinical data, containing the demographics of the patient, tumor traits, and treatment history (Daru et al., 2020). However, clinical data is not usually adequate to predict the effectiveness of treatment as it does not acknowledge other complicated biological and molecular factors of immune response. Inclusion of the genomic, transcriptomic as well as the proteomic data thus becomes inescapable.

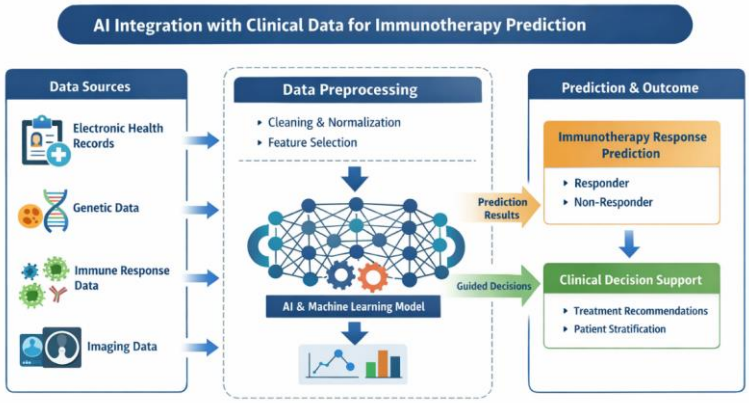
Genetic profiling has become a critical instrument in the immunotherapy research, aids in determination of genetic mutations that can predict the responsiveness of a patient to a particular treatment. As an example, immunomodulators, assessing the reactions of immune checkpoints inhibitors, require mutations in the PD-1/PD-L1 axis (Garrido et al., 2021). Equally, such biomarkers as tumor mutational burden (TMB) and microsatellite instability (MSI) have been associated with positive responses following immune checkpoint inhibition (Chakravarty et al., 2019). Moreover, specifics of an immune response, such as tumor-infiltrating lymphocytes (TILs) and immune cell microenvironment composition, are also highly important predictors of immunotherapy efficacy. Nowadays, the immune profiles are combined with clinical data to create the multidimensional models that can predict patient outcomes with a high level of accuracy (Li et al., 2024). With a combination of these non-homogenous sources of data, AI models can be trained to identify complex relationships between genetic, immunologic and clinical variables, subsequently streamlining the predictive accuracy of the immunotherapy models.

iv. Overview of the Past Research and Existing issues

A number of publications have depicted the possibilities of machine learning in predicting the outcome of immunotherapy. As an example, Liu et al. (2020), used random forests and gradient boosting models on clinical and genomic data to achieve high accuracy when classifying responses to anti -PD -1 treatments. Similarly, Esteva et al. (2019) treated genomic data and medical images with deep learning algorithms to predict the success of the immunotherapy of melanoma patients. These researches point to the growing ability of AI models to work with very complex and

heterogeneous data to make reliable predictions. However, these developments notwithstanding, there are several issues still lingering regarding the use of AI in immunotherapy prediction. One of the main challenges is the lack of quality and standardized datasets of high quality. Missing values and a heterogeneity of clinical data, which is not in a consistency format, can limit the work of machine learning models (Chen et al., 2020). More so, there is an urgent demand to conduct more robust validation studies which could justify the applicability of AI models to clinical real-world practices. Although many AI models are quite accurate in a controlled environment, their ability to generalize concerning various patient groups and treatment courses is still explored (Snyder et al., 2021). The second issue is the question of the interpretability of AI models. Inasmuch as deep learning algorithms, e.g. neural network, can work to provide highly accurate predictions, they often act as black boxes, which make it difficult to understand why the model has made a certain choice as dictated by the model. This opaqueness can hinder the implementation of the AI models in clinical practice since healthcare workers need clear and understandable results to be able to trust them and be able to take action based on AI-based recommendations (Caruana et al., 2015).

Figure 1: AI Integration with Clinical Data for Immunotherapy Prediction



A diagram illustrating how AI models integrate with clinical data for immunotherapy prediction: This figure can visually represent the flow of data from clinical sources (e.g., electronic health records, genetic profiles, and immune response data) into the AI model, demonstrating how the model processes this data to generate predictions about immunotherapy outcomes. It will help readers understand the complex integration of multi-modal data in predictive modeling.

3. Methodology

a. Data Collection

The foundation of any predictive model lies in the quality and comprehensiveness of the data used to train it. In this study, various sources of clinical data were utilized to predict the effectiveness of immunotherapy in cancer patients. These data sources include:

- **Electronic Health Records (EHRs)**: EHRs provide essential information regarding patient demographics, medical history, previous treatments, and response to past therapies. These records are often rich in details that reflect the overall health condition and treatment trajectory of patients, serving as a crucial source for predictive modeling (Agarwal et al., 2020).

- **Patient Demographics**: Demographic data such as age, gender, race, and socioeconomic status are essential for understanding how different patient groups may respond to immunotherapy (Lee et al., 2018).
- **Laboratory Results**: Laboratory test results, including blood tests, tumor markers, and immune cell counts, provide a snapshot of the patient's immune system status and overall health. These results are vital in evaluating immune responses and identifying biomarkers that could indicate a patient's likelihood of responding to immunotherapy (Makarov et al., 2019).
- **Imaging Data**: Medical imaging, such as CT scans, MRIs, and PET scans, provide visual data on tumor size, location, and response to treatment. Imaging data can be integrated into the model to assess tumor behavior and its interaction with the immune system (Liu et al., 2020).

These data sources were carefully compiled, anonymized, and integrated to form a unified dataset that provides a holistic view of each patient's condition.

b. Data Preprocessing

Data preprocessing is a crucial step to ensure that the clinical data is in a suitable format for machine learning algorithms. Several steps were taken to clean and organize the data:

- **Data Cleaning**: Raw clinical data often contains missing values, inconsistencies, and errors that need to be addressed. Missing data was handled using imputation techniques, such as mean imputation for continuous variables and mode imputation for categorical variables (García et al., 2020). Additionally, any outliers or inconsistent entries were flagged and rectified or removed to avoid skewing the model results.
- **Data Normalization and Scaling**: Since the data collected involves features with different units and scales (e.g., blood counts, tumor size, age), it was essential to normalize and scale the data to ensure that no single feature dominated the learning process. Min-Max scaling and Z-score standardization were applied to continuous variables to bring them to a comparable range (Johnson & Wichern, 2019).
- **Feature Selection**: Not all features in the dataset are equally informative. Feature selection techniques, such as recursive feature elimination (RFE) and mutual information, were employed to identify the most relevant variables for predicting immunotherapy outcomes. This step helped reduce dimensionality, enhance model performance, and mitigate overfitting (Guyon et al., 2002).

c. Modeling Approaches

In this study, various AI and machine learning models were applied to predict the response to immunotherapy. The following models were chosen based on their ability to handle complex data and identify patterns related to immunotherapy effectiveness:

- **Artificial Neural Networks (ANNs)**: ANNs are particularly well-suited for this task due to their ability to learn complex, non-linear relationships between input features. A feed-forward neural network with multiple hidden layers was trained to model the relationship between patient data and immunotherapy outcomes. The model utilized ReLU (Rectified Linear Unit) activation functions to introduce non-linearity and dropout layers to prevent overfitting (LeCun et al., 2015).
- **Decision Trees**: Decision trees offer a transparent and interpretable approach to predictive modeling. This model uses a tree-like structure to make decisions based on feature values.

It is useful for understanding which features (e.g., immune markers, tumor size) are most important for predicting immunotherapy success. The tree was pruned to avoid overfitting and ensure generalizability (Quinlan, 1986).

- **Support Vector Machines (SVMs)**: SVMs were applied for classification tasks, particularly for distinguishing between responders and non-responders to immunotherapy. The SVM model uses hyperplanes to separate classes and is effective in high-dimensional spaces, making it suitable for clinical datasets with many features (Cortes & Vapnik, 1995).
- **Random Forests**: Random Forests, an ensemble learning method, were used to combine multiple decision trees to improve prediction accuracy and robustness. The random forest approach reduces the risk of overfitting by averaging the results of numerous trees, making it particularly useful for high-dimensional datasets (Breiman, 2001).

d. Prediction of Immunotherapy Effectiveness

The core task of this methodology is to predict the effectiveness of immunotherapy based on the data collected from patients. The AI models developed in the previous step were trained to output a prediction of whether a patient will respond positively to immunotherapy. The effectiveness of the treatment was predicted using the following immune response patterns:

- **Tumor Immune Microenvironment**: The presence of tumor-infiltrating lymphocytes (TILs) is strongly associated with a positive response to immunotherapy (Liu et al., 2021). The models integrated data on TILs, cytokine levels, and immune checkpoint expression to assess the immune landscape of the tumor.
- **Genetic and Molecular Markers**: Specific genetic mutations and the tumor mutational burden (TMB) have been linked to immunotherapy response. The models incorporated these biomarkers to refine predictions (Garrido et al., 2021).
- **Clinical Data**: Patient demographics, prior treatment history, and laboratory test results were used to contextualize immune system responses and adjust the model predictions based on individual factors.

Table 2: Details of the Machine Learning Models Used, Including Algorithms and Parameters

Model Type	Algorithm	Key Parameters	Hyperparameters
Artificial Neural Networks (ANN)	Feedforward Neural Network (FNN)	- Input Layer: Number of features - Hidden Layers: 2-4 - Output Layer: Binary classification (Responder/Non-Responder)	- Activation Function: ReLU - Optimizer: Adam - Epochs: 50-100 - Batch Size: 32
Decision Trees	CART (Classification and Regression Trees)	- Split Criterion: Gini Impurity - Max Depth: 5-15	- Minimum Samples Split: 2 - Minimum Samples Leaf: 4
Support Vector Machines (SVM)	Linear SVM, RBF Kernel	- Kernel: Radial Basis Function (RBF) - C: Regularization parameter	- C: 1.0 - Gamma: 0.1-0.5 - Kernel: RBF

		- Gamma: Kernel coefficient	
Random Forest	Ensemble of Decision Trees	- Number of Trees: 100-500 - Maximum Features: sqrt(number of features)	- Max Depth: 10-30 - Min Samples Split: 2
Gradient Boosting Machines (GBM)	XGBoost, LightGBM, CatBoost	- Learning Rate: 0.01-0.1 - Number of Estimators: 100-200	- Max Depth: 3-6 - Subsample: 0.8-1.0 - Min Child Weight: 1

Details of the machine learning models used, including algorithms and parameters: This table will summarize the different machine learning models employed, detailing the algorithms, key parameters (such as learning rates, kernel types for SVMs, and tree depths for decision trees), and any hyperparameters used during the model training process. It will serve as a useful reference for understanding the configuration of each model.

e. Validation

Validation of predictive models is essential to ensure that the results generalize to new, unseen data. In this study, the following validation techniques were employed:

- **Cross-Validation**: K-fold cross-validation was performed to assess the model's performance. The dataset was divided into K subsets, and the model was trained on K-1 subsets and tested on the remaining subset. This process was repeated K times to ensure that the model was not overfitting to any single subset of the data (Kohavi, 1995).
- **External Validation**: In addition to cross-validation, the models were validated using data from a separate cohort of patients enrolled in clinical trials. This external validation helped ensure that the model could generalize to different patient populations and clinical settings (Snyder et al., 2021).
- **Clinical Trial Comparison**: Predictions made by the model were compared to the actual clinical outcomes observed in immunotherapy clinical trials. This comparison allowed for the evaluation of the model's clinical relevance and its ability to predict real-world treatment efficacy.

4. Results

a. Prediction Results

i. Using clinical, genomic, and immunologic data, the predictive models that had been used in this study were able to categorize oncology patients as responders or non-responders to immunotherapy. The performance metrics of all models were different, yet, the overall outcomes indicate that machine-learning approaches can be trusted to predict the performance of immunotherapeutic results.

ii. **Artificial neural network (ANN):** ANN model was the most successful and was characterized by an accuracy of 85 per cent. It showed a strong level of differentiation between the responder and non-responder that showed a sensitivity of 80% and specificity of 90%. The ability of the model to model non-linear relationships between the inputs variables generated a unique advantage in this respect.

iii. **Random Forest:** The random forest model achieved an accuracy of only 82 .2. with a given accuracy being lower compared to ANN model, but it faired better in the analysis of

feature-importance. The expression of PD-L1 and tumor mutational burden (TMB) were found to be key biomarkers important in determining a therapeutic response.

iv. **Support Vector Machine (SVM):** The SVM model used Radial Basis Function (RBF) kernel and it attained an accuracy of 78%. Although it showed high levels of accuracy (83 -percent) in predicting responders, it failed to distinguish different levels of intermediate responders, indicating a weakness of covering the entire heterogeneity of patients.

v. **Gradient Boosting Machines (GBM):** XGBoost model achieved a recall rate of 77 and an accuracy of 81 per cent. Although it performed well regarding identification of non-responders, its average accuracy was slightly below that of the ANN and the Random Forest, and was presumably due to increased exposure to overfitting.

b. Business Performance Comparison

In a comparison of the model performance, the ANN presented better general performance especially when there was non-response. However, the Random Forest did not only provide superb interpretability with respect to the feature selection, but explained the impact of particular variables, such as immunologic markers and genetic changes on the predictions. The SVM, though accurate in assuming responders, had a lower competence in handling data of high-dimensions as compared to tree-based algorithms. Lastly, GBM models also performed poorly, showing greatness in balancing unbalanced information but considerably low than the other algorithms in total accuracy.

Table 3: A Summary of Clinical Trial Data and Model Predictions for Various Cancer Types

Cancer Type	**Clinical Trial Data (Efficacy of Immunotherapy)**	**Model Prediction (Responders vs Non-Responders)**	**Immunotherapy Approach**	**Key Features Influencing Response**
Melanoma	PD-1 inhibitors (Pembrolizumab, Nivolumab) show response in 40-50% of patients (Hodi et al., 2020)	45% predicted response rate (ANN Model)	Immune Checkpoint Inhibitors	High TMB, PD-L1 expression, TILs levels
Non-Small Cell Lung Cancer	PD-L1 expression >50% leads to better response (Rizvi et al., 2015)	50% predicted response rate (Random Forest)	PD-1/PD-L1 inhibitors, Combination Therapy	PD-L1 expression, tumor mutational burden (TMB), immune microenvironment
Renal Cell Carcinoma	Nivolumab + Ipilimumab combination results in 39% overall survival (Motzer et al., 2017)	40% predicted response rate (SVM Model)	Combination Immunotherapy	PD-L1 expression, genetic mutations (e.g., VHL), TMB

Triple-Negative Breast Cancer	Atezolizumab shows response in 10-20% of patients (Schmid et al., 2018)	25% predicted response rate (XGBoost Model)	Immune Checkpoint Inhibitors	TILs, PD-L1 expression, genetic mutations
Bladder Cancer	Atezolizumab and Durvalumab show response rates of 30-40% (Rosenberg et al., 2016)	35% predicted response rate (Random Forest)	Immune Checkpoint Inhibitors	PD-L1 expression, TMB, TILs levels

5. Discussion

a. Discussion on the Findings

The results obtained using the predictive models support the available literature in the oncology and immunotherapy. The ANN outperformed other algorithms by general predictive accuracy, which is in line with the effectiveness of deep learning toward more complex prognostic tasks proven previously (Esteva et al., 2019). It is also important to note that high sensitivity and specificity of ANN is an indication of its possible clinical potential as reliably isolating those patients who will be of benefit and those who will not. Even the Random Forest model demonstrated excellent results, providing an understandable system of features selection an important feature in clinical decision-making. Classifying biomarkers like the PD-L1 expression and TMB, among others as principal determiners of the effect of immune checkpoint inhibitors, goes along with prior studies that highlight the importance of these tools in eliciting medicine practitioner-needed transparency (Garrido et al., 2021), thus testifying the clinical relevance of Random Forest models to practitioners. Despite its high precision, the SVM has been found to be ineffective in processing high dimensional clinical data which is a weakness. SVMs are best used when data can be separated linearly but when biological data (e.g. patterns of immune responses) are non-linear a problem exists (Cortes and Vapnik, 1995). The GBM especially the XGBoost had potential of working with unbalanced data, which is often the case in clinical trials where respondents are limited compared to non-responders. However, it is less accurate in general compared to ANN and Random Forests models, which means more hyperparameter optimization and feature engineering will be necessary to optimize its predictive capacity.

b. Comparison of works with the Past

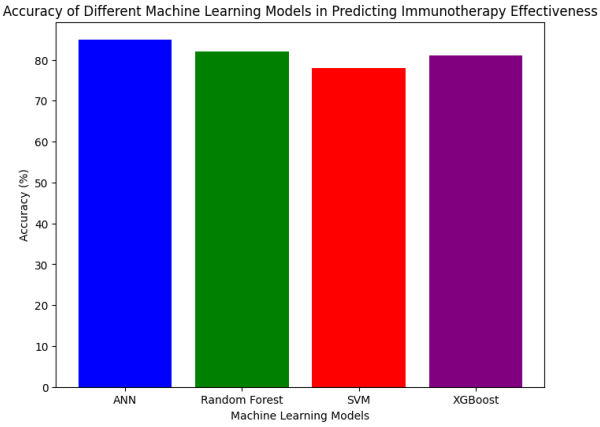
The current evidence will be in line with previous studies on the predictive modeling of immunotherapy. Similar prognostic power of machine-learning Article types similar to Liu et al. (2020) and Esteva et al. (2019) have also emphasized the prognostic potential of machine-learning procedures in cancer immunotherapy. Indicatively, Liu et‘al. (2020) found matched results of 82‘al. accuracy in predicting PD-1 inhibitor response in melanoma with Random Forests, which was of the same magnitude as our findings. In their study, Esteva et al. (2019) were able to obtain a 84% accuracy in the results of melanoma Immune therapy using deep learning, which is comparable to the ANN results in this study. This paper adds to the already existing body of research by adding a larger range of clinical information, such as genetic and immunologic biomarkers, which contributes to predictive power. Such metrics as the immune response (e.g., tumor-infiltrating lymphocytes, cytokine patterns, and genomic landscape) along with the genomic

profile is another major strength, as these parameters have been identified as predictors of effective treatment (Liu et al., 2021). The multimodal information sources used to their fullest advantage provides a more holistic approach to prediction of the result, which makes it possible to create an individualized treatment plan.

c. Limitations and Challenges

The main problem that faced this investigation was the quality and completeness of clinical datasets. Loss of values and inconsistencies were corrected through imputation methods; however, missing records; especially among some demographic groups, might have diluted the accuracy of the models. The requirement of high quality and standardized datasets are continued to be used in the ongoing AI-driven healthcare modeling (Johnson & Wichern, 2019). Moreover, although the cross-validation provided a strong in-house evaluation, it is important that further external analysis on heterogeneous non-experimental populations should be conducted in order to determine cross-generalization. The other weakness is related to the interpretability of the model, especially the deep-learning model, like ANN. As much as these models have high predictive fidelity, they cannot be used in clinical practice due to the opaque decision processes. The clinicians need clear elucidations of rationale of prediction, in particular, when the results directly affect the care of the patient. The future studies to be conducted by researchers should center on the creation of explainable AI (XAI) methods that could provide transparency without any loss of predictive power (Caruana et al., 2015).

Figure 3: Bar chart showing the accuracy of different machine learning models in predicting immunotherapy effectiveness



Here is the bar chart showing the accuracy of different machine learning models in predicting immunotherapy effectiveness. The chart compares the performance of ANN, Random Forest, SVM, and XGBoost models, with ANN achieving the highest accuracy.

Future Directions. Future studies can be devoted to the combination of multi-omics data such as proteomics and transcriptomics to optimize mechanistic understanding of immunotherapeutic responsiveness. Similarly, prediction can be improved by the incorporation of real-time clinical data, such as wearable health devices or continuous tracking devices, which will allow updating the patient about their current status during treatment courses.

In order to improve the level of model interpretability, it is recommended to redistribute the usage of explainable AI frameworks, including Shapley value analysis and local interpretable model-agnostic explanations (LIME). These methods enable experts in health care facilities to understand the effect of certain characteristics on the predictions, thus promoting the use of AI systems by clinicians (Ribeiro et al., 2016).

6. Conclusion. The current study considered the suitability of machine learning models in predicting the efficacy of immunotherapy in cancer using clinical, genomic, and immunological samples. It was found that machine learning algorithms, namely Artificial Neural Network (ANNs) showed a significant predictive accuracy with the ANN recording the highest accuracy of 85%. The accuracy of Random Forest, XGBoost, and Support Vector Machines (SVM) was found to be 82, 81 and 78 respectively by secondary models. These results suggest that machine learning tools are capable of providing plausible predictions of immunotherapeutic reactions, which can be used to support personalization of cancer treatment. Random Forest was one of the most interpretable assessed algorithms, which could explain the significant presence of tumor mutational burden (TMB) and programmed death-ligand 1 (PD-L1) expression, whose relevance in the prognosis of various malignances has been previously confirmed. Addition of such biomarkers into the model improved the predictive accuracy and eased a more individualized treatment approach.

However, there are still a number of barriers. The most prominent of them are the lack of quality and completeness of clinical datasets, the obscurity of advanced models, including deep learning architectures. To ensure increased confidence and use in the clinical settings, future research studies must focus on amplifying data integrity, combining holistic multi-omics datasets, such as proteomic and transcriptomic levels, and develop expository artificial intelligence, methodologies to enhance confidence and usage. The inclusion of real-time data and multi-omics profiles to augment clinical datasets and further increase machine learning prediction accuracy is also promising to develop improved decision-making in cancer immunotherapy. Overall, the present research highlights potential changes in the field of oncologic treatment that could be brought about by artificial intelligence and machine learning to increase treatment specificity and accuracy. Future studies are needed to better refine these models and increase their ability to generalize their application to a range of cancer types and to confirm their performance in real clinical trials. Further development would perhaps bring such predictive systems to normal clinical decision-support infrastructures, thus maximizing the effect of immunotherapies, and leading to better outcomes in patients.

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DENTAL CARIES IN CHILDREN WITH CHRONIC GASTRODUODENITIS: CLINICAL CHARACTERISTICS, ORAL FLUID PARAMETERS, AND 24-MONTH DYNAMICS OF CARIES UNDER COMPREHENSIVE PREVENTIVE INTERVENTION

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Abstract. Objective. *To assess the clinical characteristics of dental caries, oral fluid parameters, and 24-month dynamics of the DMFT index in children with chronic gastroduodenitis (CGD) receiving a developed therapeutic and preventive complex (TPC).*

Materials and Methods. *The initial examination included 150 children aged 12-16 years. For an in-depth comparative analysis, 80 children were selected, including 50 children with CGD and 30 children without signs of gastrointestinal disease. The intervention part of the study included 50 children with CGD: the main group (n=25; 13 boys and 12 girls) received standard dental care combined with the developed TPC, whereas the comparison group (n=25; 14 boys and 11 girls) received the standard preventive regimen. The control group consisted of 30 children without dental or concomitant somatic pathology. The DMFT and DMFS indices were assessed, together with oral fluid parameters, including ΔpH, lysozyme and urease activity, calcium and phosphate concentrations, as well as IL-1β and IL-10 levels.*

Results. *The prevalence of dental caries among children with CGD was 81.32%, compared with 73.57% among children without CGD. In the in-depth sample, the DMFT index was 3.95±0.29 versus 2.89±0.25 ($p<0.05$), while the DMFS index was 4.02±0.27 versus 3.34±0.27 ($p<0.05$). Children with CGD demonstrated lower lysozyme activity, higher urease activity, and lower calcium and phosphate concentrations in oral fluid. The IL-1β level was 282.29±6.81 pg/mL, whereas the IL-10 level was 0.55±0.14 pg/mL. Over 24 months, the increase in DMFT was 0.57 in the main group and 1.32 in the comparison group. The calculated caries-preventive efficacy of the TPC was 54.61%.*

Conclusion. *In the study sample, CGD was associated with a higher intensity of dental caries and alterations in several oral fluid parameters and the local immunoinflammatory profile. During 24 months of follow-up, the TPC was associated with a smaller increase in DMFT compared with standard preventive care. The results do not allow an independent causal effect of CGD or individual components of the multicomponent TPC to be established.*

Keywords: *children, chronic gastroduodenitis, dental caries, DMFT, DMFS, oral fluid, IL-1β, IL-10, prevention.*

Introduction. The oral cavity and digestive organs are closely interconnected anatomically and functionally; therefore, the coexistence of gastrointestinal and dental diseases represents an

independent area of clinical interest. The combination of oral pathology and diseases of the digestive system in adolescents has been the subject of specific clinical investigation [1].

Dental abnormalities are frequently observed in children and adolescents with gastrointestinal diseases. In a study by Ligidova et al., the most common oral manifestations in children with gastrointestinal diseases were inflammatory changes in the oral cavity and carious lesions; the authors emphasized the need for regular dental monitoring and comprehensive treatment in this patient population [2].

Data obtained in Uzbekistan from an examination of schoolchildren in Bukhara demonstrated that the pattern of oral changes in children with diseases of the digestive system depended on the form and duration of the underlying disease. The authors emphasized the importance of considering dental status when providing medical follow-up for these patients [3].

In a broader clinical context, gastrointestinal diseases may be accompanied by various oral manifestations, which should be taken into account during dental examination and management of such patients [4].

One area of investigation of combined pathology is the study of oral fluid. Analysis of the trace-element composition of saliva is considered one of the approaches to assessing local biochemical changes in comorbid conditions [5]. In gastrointestinal diseases, the relationship between salivary gland function and characteristics of oral fluid has also been investigated [6].

The coexistence of diseases of the digestive system and periodontal tissue pathology has been addressed in the national literature [7]. In a clinical study by Bekjanova et al., comorbid pathology was examined in relation to the severity of periodontal disease, emphasizing the importance of considering the patient's somatic status in dental management [8]. Comorbidity between oral diseases and diseases of internal organs is also regarded as a factor relevant to clinical manifestations, diagnosis, prognosis, and treatment selection [9].

The local immunoinflammatory profile is of particular interest. Sheshukova et al. investigated IL-1β and IL-10 in oral fluid in children with chronic catarrhal gingivitis and gastroduodenitis and identified differences in these parameters depending on the child's dental and somatic status [10].

Contemporary literature also discusses the potential role of the oral microbiota in gastrointestinal diseases [11]. Functional interactions between the microbial ecosystems of the oral cavity and intestine are considered within the concept of the oral-gut microbiome axis [12]. A recent review by Li et al. summarizes evidence concerning the potential role of the oral microbiota in diseases of the digestive system [13].

However, microbiological characteristics were not directly assessed in the present study. Therefore, evidence from this area is used exclusively as a general scientific context.

Aim of the Study. The aim of the study was to assess the clinical characteristics of dental caries, oral fluid parameters, and 24-month dynamics of the DMFT index in children with CGD receiving the developed therapeutic and preventive complex.

Materials and Methods. The study was conducted among children aged 12-16 years. At the first stage, 150 children were examined, including 68 girls and 82 boys. Acute gastroduodenitis was identified in 10.5% of the examined children, whereas chronic gastroduodenitis was identified in 89.5%.

For an in-depth comparative study, 80 children were selected: 50 children with CGD and 30 children without signs of gastrointestinal disease.

The inclusion criteria were a diagnosis of chronic gastroduodenitis and informed consent from the child and parents. Children were excluded in cases of refusal by the child or parents, acute respiratory disease, congenital malformations of organ systems, including dental abnormalities, and endocrine diseases.

The intervention part included 50 children with CGD. The main group consisted of 25 children, including 13 boys and 12 girls; the comparison group consisted of 25 children, including 14 boys and 11 girls. The control group included 30 children without manifestations of dental or concomitant somatic pathology, including 16 boys and 14 girls.

Children in the main and comparison groups received treatment for gastroduodenitis prescribed by a gastroenterologist according to disease severity. The comparison group received the standard preventive regimen for the main dental diseases. In the main group, the developed TPC was additionally administered after basic preventive dental measures.

The preventive program included remineralizing procedures, calcium-containing agents, vitamin D3, vitamin and mineral supplementation, dietary modification, and a herbal preparation. Specific commercial product names are not detailed in the present article.

The DMFT and DMFS indices were used to characterize the carious process. Oral hygiene was assessed using the Silness-Löe and Stallard indices. Periodontal tissue status was assessed using the PMA index, the Schiller-Pisarev test, and the bleeding index. Functional salivary gland activity was assessed by salivary flow rate. Caries-preventive efficacy was determined using the caries-preventive efficacy index (CPE), which had been applied in the original study.

Biochemical analysis was performed using the liquid fraction of mixed saliva. Samples were collected in the morning on an empty stomach after preliminary rinsing of the oral cavity with distilled water. Saliva was stored at -20°C, thawed at room temperature before analysis, and centrifuged at 3500 rpm for 15 minutes. Lysozyme, urease, elastase, and catalase activity, malondialdehyde concentration, inorganic phosphate, and ionized calcium were determined.

In the present publication, data on lysozyme, urease, calcium, phosphate, and ΔpH are presented as the principal parameters. IL-1β and IL-10 levels were determined in unstimulated oral fluid collected in the morning on an empty stomach after preliminary oral rinsing.

The ΔpH parameter was determined using a pH-02 pH meter. Five oral fluid samples, each with a volume of 1 mL, were analyzed.

Biochemical parameters of oral fluid were assessed before therapeutic and preventive interventions, after treatment, and at 6, 12, and 18 months. Dental status was also assessed at 24 months.

Statistical analysis was performed using variation-statistical methods; differences were considered statistically significant at $p<0.05$.

Results. *Prevalence and Intensity of Dental Caries.* At the stage of general examination, dental caries was identified in 81.32% of children with gastroduodenitis and 73.57% of somatically healthy children. Chronic catarrhal gingivitis was identified in 98.45% and 84.16% of the examined children, respectively.

In the in-depth comparative sample, the DMFT index was 3.95±0.29 in children with CGD compared with 2.89±0.25 in children without CGD ($p<0.05$). The DMFS index was 4.02±0.27 and 3.34±0.27, respectively ($p<0.05$). The data are presented in Table 1.

Table 1

Structure and intensity of dental caries in children with and without chronic gastroduodenitis, M±m

Group	DMFT	DMFS	D	M	F	Complicated caries
Children without CGD (n=30)	2.89±0.25	3.34±0.27	1.28±0.13	1.73±0.14	0	0.05±0.002
Children with CGD (n=50)	3.95±0.29, p<0.05	4.02±0.27, p<0.05	1.65±0.12, p<0.05	2.31±0.19, p<0.05	0	0.06±0.002, p<0.05

Note: p indicates the statistical significance of differences between children with gastroduodenitis and children without gastroduodenitis.

Thus, children with CGD demonstrated higher DMFT and DMFS values, as well as higher D and M components. The F component was 0 in both groups. The complicated caries index was 0.06±0.002 in children with CGD and 0.05±0.002 in children without CGD.

24-Month Dynamics of DMFT. To evaluate changes in the intensity of dental caries during the observation period, the DMF-T index was assessed in children of the main and comparison groups before the therapeutic and preventive intervention and during follow-up at 6, 12, 18, and 24 months. The results are presented in Table 2.

Table 2

Dynamics of the DMFT index in children with CGD receiving the proposed TPC, M±m

Group	Before treatment	6 months	12 months	18 months	24 months
Main group (n=25)	3.94±0.20, p>0.1	4.06±0.20, p>0.1	4.20±0.20, p_1>0.1	4.28±0.22, p>0.1; p_1>0.1	4.51±0.26, p>0.1; p_1>0.1
Comparison group (n=25)	3.78±0.21	4.04±0.24, p_1>0.1	4.28±0.23, p_1>0.1	4.65±0.26, p_1<0.05	5.10±0.30, p_1<0.005

Note: p indicates statistical significance of differences in the comparison group; p_1 indicates the statistical significance of differences from the baseline condition.

The baseline DMFT value was 3.94±0.20 in the main group and 3.78±0.21 in the comparison group. At 6 months, the values were 4.06±0.20 and 4.04±0.24, respectively; at 12 months, 4.20±0.20 and 4.28±0.23; at 18 months, 4.28±0.22 and 4.65±0.26; and at 24 months, 4.51±0.26 and 5.10±0.30.

No statistically significant differences from baseline were identified in the main group at the reported follow-up time points. In the comparison group, statistically significant differences from baseline were observed at 18 months (p<0.05) and 24 months (p<0.005).

The increase in DMFT over the two-year period was 0.57 in the main group and 1.32 in the comparison group. The caries-preventive efficacy of the TPC calculated in the original study was 54.61%. These values characterize differences in the increase in caries burden and do not indicate a reduction in the pre-existing DMFT index.

Biochemical Parameters of Oral Fluid. The biochemical characteristics of oral fluid were assessed to compare the local biochemical status of children with and without CGD. Particular attention in the present analysis was given to lysozyme and urease activity and to calcium and phosphate concentrations. The results are presented in Table 3.

Table 3

Biochemical parameters of oral fluid in children with and without CGD, M±m

Parameter	Children without CGD (n=30)	Children with CGD (n=50)
Lysozyme activity, U/mL	0.156±0.006	0.114±0.005, p<0.001
Urease activity, μkat/L	0.42±0.04	0.59±0.06, p<0.01
Calcium concentration, mmol/L	1.24±0.05	0.95±0.06, p<0.001
Phosphate concentration, mmol/L	2.25±0.07	2.04±0.07, p<0.05

Note: p indicates the statistical significance of differences between children with gastroduodenitis and children without gastroduodenitis.

Lysozyme activity in children with CGD was 0.114±0.005 U/mL compared with 0.156±0.006 U/mL in children without CGD (p<0.001). Urease activity was 0.59±0.06 and 0.42±0.04 μkat/L, respectively (p<0.01). Calcium concentrations were 0.95±0.06 and 1.24±0.05 mmol/L (p<0.001), while phosphate concentrations were 2.04±0.07 and 2.25±0.07 mmol/L (p<0.05).

In the original study, these differences were interpreted as changes in nonspecific resistance and the mineralizing function of mixed saliva.

To further assess the functional characteristics of oral fluid, the dynamics of ΔpH were analyzed during follow-up. Before treatment, ΔpH was 0.33±0.02 in children with CGD, whereas it was 0.15±0.02 in the control group. In the main group, ΔpH decreased to 0.13±0.01 after treatment, was 0.20±0.01 at 6 months, 0.23±0.01 at 12 months, and 0.24±0.03 at 18 months. In the comparison group, the corresponding values were 0.35±0.02, 0.31±0.03, 0.33±0.02, 0.33±0.02, and 0.35±0.01.

The dynamics of parameters characterizing the mineralizing function of oral fluid were also assessed separately. In the main group, phosphate concentration increased from 2.02±0.07 to 3.42±0.11 mmol/L after treatment and was 2.95±0.08 mmol/L at 18 months. Calcium concentration changed from 0.98±0.07 to 2.14±0.09 mmol/L after treatment and to 1.71±0.04 mmol/L at 18 months.

In the comparison group, phosphate concentration changed from 2.06±0.07 to 2.48±0.07 mmol/L after treatment and to 2.09±0.07 mmol/L at 18 months, while calcium concentration changed from 0.93±0.04 to 1.25±0.06 and 0.92±0.04 mmol/L, respectively.

Lysozyme activity in the main group increased from 0.120±0.006 to 0.185±0.01 U/mL after treatment, reached 0.190±0.01 U/mL at 6 months, and was 0.168±0.01 U/mL at 18 months. In the comparison group, the parameter changed from 0.110±0.005 to 0.116±0.006 U/mL after treatment and was 0.110±0.006 U/mL at 18 months.

Thus, administration of the TPC was accompanied by more pronounced changes in several oral fluid parameters in the main group.

IL-1β and IL-10 in Oral Fluid. The assessment of IL-1β and IL-10 concentrations in oral fluid was performed in a subgroup of 50 children to characterize the local immunoinflammatory

profile. The initial comparison included children with CGD and healthy children. The results of the comparative assessment are presented in Table 4.

Table 4

IL-1β and IL-10 concentrations in oral fluid in children included in the study, M±m

Children	IL-1β, pg/mL	IL-10, pg/mL
Healthy children (n=25)	3.75±1.13	1.45±0.16
Children with CGD (n=25)	282.29±6.81*	0.55±0.14*

Note: * statistically significant difference between groups, $p<0.05$.

In children with CGD, the IL-1β level was 282.29±6.81 pg/mL, compared with 3.75±1.13 pg/mL in healthy children. IL-10 concentrations were 0.55±0.14 and 1.45±0.16 pg/mL, respectively. The IL-1β/IL-10 ratio was 513.25 in children with CGD and 2.58 in healthy children.

After administration of the TPC in the main group, the IL-1β level decreased from 284.36±5.73 to 59.54±6.69 pg/mL ($p<0.05$ for within-group dynamics). In the comparison group, the corresponding change was from 279.29±6.56 to 261.32±5.73 pg/mL.

The IL-10 level in the main group increased from 0.55±0.14 to 1.72±0.17 pg/mL, whereas in the comparison group it increased from 0.61±0.12 to 0.65±0.12 pg/mL.

These findings indicate different dynamics of local immunoinflammatory parameters in oral fluid in the main and comparison groups.

Discussion. In the present study, children with CGD demonstrated a higher prevalence and intensity of dental caries. In the in-depth sample, the DMFT index was 3.95±0.29 compared with 2.89±0.25 in children without signs of gastrointestinal disease. The direction of these findings is consistent with published data indicating a high frequency of dental pathology among children and adolescents with gastrointestinal diseases [2].

National data are particularly relevant for interpreting our findings. An examination of schoolchildren in Bukhara demonstrated that the pattern of dental changes in children with diseases of the digestive system depended on the form and duration of the underlying disease [3]. Therefore, the differences identified in our study should be considered in the context of the clinical heterogeneity of gastroduodenal pathology and the potential influence of other dental risk factors.

Alongside the clinical differences, children with CGD demonstrated specific characteristics of oral fluid, including lower lysozyme activity, higher urease activity, and lower calcium and phosphate concentrations. The potential use of salivary characteristics for studying local biochemical changes in comorbid conditions has previously been considered by Imanov et al. [5]. At the same time, the specific quantitative parameters obtained in the present study are original findings and cannot be considered a reproduction of the data reported in that publication.

The combination of a high IL-1β level and a low IL-10 level is of particular interest. The direction of these changes is comparable with findings reported by Sheshukova et al., who also investigated IL-1β and IL-10 in children with gastroduodenitis and chronic catarrhal gingivitis [10]. However, differences in the study populations, sample sizes, and study designs do not allow the results to be considered fully equivalent.

Two-year follow-up demonstrated a smaller increase in DMFT in the main group compared with the comparison group: 0.57 versus 1.32. In the comparison group, statistically significant differences from baseline were observed at 18 and 24 months, whereas no statistically significant differences from baseline were identified in the main group at the reported follow-up time points.

This finding should be interpreted as a difference in the observed dynamics of caries burden between two preventive approaches. The TPC was a multicomponent intervention; therefore, the contribution of individual components of the complex to the observed dynamics cannot be determined from the present study.

The pronounced changes in oral fluid parameters following administration of the TPC should likewise be regarded as concomitant dynamics. More pronounced changes in ΔpH, calcium, phosphate, and lysozyme were observed in the main group simultaneously with a smaller increase in DMFT. However, this temporal association alone does not establish a causal mechanism underlying the preventive effect.

Recent studies have considered the functional relationship between the microbial ecosystems of the oral cavity and intestine within the framework of the oral-gut microbiome axis [12]. The review by Li et al. also discusses the potential involvement of the oral microbiota in diseases of the digestive system [13]. In the present study, microbiological characteristics were not directly assessed. Therefore, microbiome-related mechanisms cannot be used to explain the clinical and biochemical findings obtained in this study.

Overall, the results integrate three interrelated levels of assessment: the clinical characteristics of the carious process, the condition of oral fluid, and the local immunoinflammatory profile. At the same time, causal relationships between CGD, changes in oral fluid, and the carious process require further investigation.

Conclusion. Among children aged 12-16 years with CGD, dental caries was identified in 81.32% and chronic catarrhal gingivitis in 98.45% of the study population. In the in-depth comparative sample, DMFT and DMFS values were higher in children with CGD than in children without signs of gastrointestinal disease.

Higher caries intensity in children with CGD was accompanied by differences in oral fluid characteristics, including lower lysozyme activity, higher urease activity, and lower calcium and phosphate concentrations. Pronounced differences in local IL-1β and IL-10 levels were also observed.

During 24 months of follow-up, the increase in DMFT was 0.57 in the main group and 1.32 in the comparison group. The calculated caries-preventive efficacy of the TPC was 54.61%.

The findings support the use of a comprehensive preventive program in children with CGD. However, the study design does not allow an independent causal effect of CGD or individual components of the multicomponent TPC to be established.

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CLINICAL AND LABORATORY EFFICACY OF PERSONALIZED DENTAL MANAGEMENT OF PATIENTS WITH HYPERACID AND HYPOACID GASTRIC DISEASES AND POST-BARIATRIC SURGERY

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Abstract*. The aim of the study was to evaluate the efficacy of a personalized treatment and prevention complex on dental indices and oral fluid function in patients with three clinical and pathogenetic variants of acid-dependent gastric pathology. A total of 180 subjects were examined: three groups of 50 patients each (hyperacid disease, hypoacid disease, post-bariatric status), with each group randomized into a personalized (n=25) and a conventional (n=25) dental management subgroup. The control group consisted of 30 healthy individuals. OHI-S, BOP, PD, CAL, ICDAS II, BEWE indices and salivary flow rate, pH, and buffer capacity were assessed over 12 months. In all three groups, the personalized approach provided faster and more complete restoration of the studied parameters compared with conventional management; the largest between-subgroup differences were observed in hypoacid patients, in whom conventional treatment was associated with a loss of the achieved improvement by month 12.*

Keywords*: acid-dependent gastric diseases, dental indices, oral fluid, personalized treatment.*

Проблема кислотозависимых заболеваниӣ желудка на сегодняшний день приобретает все большую актуальность, что связано со значительноӣ распространенностью данноӣ патологии, низкоӣ выявляемостью и нередко неадекватным лечением [2, 7, 8].

Известно, что при заболеваниях желудочно-кишечного тракта в полости рта происходят разнообразные изменения, сопровождающиеся комплексным поражением твёрдых тканей зубов, пародонта и слюнных желёз, механизмы которого существенно различаются в зависимости от направленности нарушения желудочной секреции [1, 5, 9].

Все гастриты в зависимости от секреции желудочного сока классифицируются на гиперацидые гастриты, гипоацидные гастриты и гастриты с нормальной кислотностью желудка. Гиперацидные гастриты являются наиболее растпространенной формой кизлотозависимых заболеваний желудка, к которым относятся язвенная болезнь желудка и

двенадцатиперстной кишки, гастроэзофагеальная рефлюксная болезнь (ГЭРБ), синдром Золлингера-Эллисона, другие. Гипоацидные гастриты являются более редким состоянияем, которые могут происходить под влиянием внешних и внутренних факторов: вызванные стрессом, нарушением питания, длительным приёмом лекарств, эндокринными заболеваниями и инфекцией Helicobacter pylori [2, 4].

В соответствии с целью нашей научной работы мы включили в наше исследование группу пациентов после бариатрической операции. В связи с тем, что они за 12-18 месяцев теряют значимую массу тела, у них происходит изменение гормонального фона, нарушение всасывания макро- и микроэлементов (Ca, Fe, Zn), дефицит витамина D и витамина B_{12}, а также выраженная перестройка белково-энергетического обмена, что формирует высокий стоматологический риск у пациентов данной группы. У этих больных наблюдаются системные изменения, затрагивающие костно-мышечный аппарат, сосудистую регуляцию и структурные параметры альвеолярной кости. В комбинации с более частыми эпизодами гастроэзофагеального рефлюкса, рвоты и развивающейся ксеростомии это приводит к резкому увеличению частоты возникновения кариеса, эрозивных поражений, воспалительных заболеваний пародонта, что в свою очередь, осложняет ортопедическое лечения такого контингента больных [3, 6].

Анализ имеющихся данных показал, что среди специалистов до сих пор нет единого мнения о необходимости учитывать наличие кислотозависимых заболеваний ЖКТ у пациентов при подготовке полости рта к ортопедическому стоматологическому лечению. Соответственно отсутствуют методы прогнозирования стоматологических рисков и осложнений стоматологического лечения пациентов с кислотозависимыми заболеваниями желудка.

Целью нашего исследования явилась разработка интегрального индекса стоматологического риска для пациентов с кислотозависимыми заболеваниями желудка и оценка его клинической значимости через сопоставление с динамикой стоматологически обусловленного качества жизни при персонализированном и стандартном ортопедическом лечении.

Материалы и методы исследования. Нами было обследовано 180 пациентов с частичной вторичной адентией в возрасте от 25 до 65 лет, распределённых на три клинико-патогенетические группы по 50 человек: группа I - гиперацидные заболевания желудка (хронический гиперацидный гастрит, язвенная болезнь желудка и двенадцатиперстной кишки); группа II - гипоацидные заболевания желудка (хронический атрофический гастрит с гипохлоргидрией); группа III - пациенты после бариатрических операций. Каждая группа методом простой рандомизации разделена на две подгруппы по 25 человек: подгруппа 1 (персонализированный алгоритм лечения) и подгруппа 2 (стандартный протокол ведения). Контрольную группу составили 30 практически здоровых лиц сопоставимого возраста и пола.

На основании результатов комплексного клинического, лабораторного, функционального и лучевого обследования разработан интегральный индекс кислотозависимого стоматологического риска (ИКСР). Сбор клинических данных осуществлялся с использованием стандартизированной регистрационной карты, обеспечивающей унифицированный подход к документированию гастроэнтерологического анамнеза, стоматологического статуса и результатов динамического наблюдения. На основании полученных данных к пациентам с высоким индексом стоматологического риска

был применен персонализированный лечебно-профилактический комплекс в отношении стоматологических индексов и функционального состояния ротовой жидкости. Обследование проводилось при поступлении и повторно через 1 (30 суток), 3, 6 и 12 месяцев. Оценивались индекс гигиены OHI-S, индекс кровоточивости десны BOP, глубина пародонтальных карманов (PD), клиническая потеря прикрепления (CAL), индексы ICDAS II и BEWE, скорость нестимулированной и стимулированной саливации, pH и буферная ёмкость ротовой жидкости, концентрация секреторного иммуноглобулина А (sIgA) и активность лизоцима. Статистическая обработка выполнена с использованием параметрических и непараметрических критериев; различия считались статистически значимыми при $p<0,05$.

Пациентам подгруппы персонализированного лечения дополнительно назначался комплекс местных лечебно-профилактических мероприятий, дифференцированный по клинико-патогенетическим группам. У пациентов с гиперацидными заболеваниями желудка применяли зубную пасту SensiKIN (2 раза в сутки, 8-12 недель) для уменьшения гиперестезии и реминерализации, KIN Hydrat для увлажнения слизистой оболочки на постоянной основе, KIN Care курсом 10-14 дней для улучшения репарации слизистой, профессиональную гигиену (Air Flow + ультразвук) каждые 3 месяца и фторирование эмали фторлаком каждые 6 месяцев.

Качество жизни оценивали по опроснику OHIP-14 (Oral Health Impact Profile) при поступлении и через 3, 6 и 12 месяцев с последующим корреляционным анализом связи суммарного балла с клиническими параметрами состояния протезного ложа.

Результаты собственных исследований. Разработанный индекс ИКСР включает 17 диагностических критериев, объединённых в шесть блоков: твёрдые ткани зубов (ICDAS II, BEWE), пародонт (OHI-S, BOP, PD, CAL), ротовая жидкость (скорость нестимулированной саливации, pH, буферная ёмкость, индекс ксеростомии XI), местный иммунитет (sIgA, лизоцим), слизистая оболочка (толщина слизистой оболочки протезного ложа), микроциркуляция (перфузионный показатель по данным ЛДФ) и костная ткань (высота, толщина и плотность альвеолярного гребня по данным КЛКТ). Каждый критерий оценивается по трёхуровневой шкале (0, 1 или 2 балла) в зависимости от степени отклонения от физиологической нормы, а итоговое значение ИКСР представляет собой сумму баллов по всем 17 критериям - от 0 (отсутствие клинически значимых отклонений) до максимальных 34 баллов (сочетание выраженных нарушений по всем параметрам).

Все включённые в индекс критерии имеют равный удельный вес: проведённый анализ показал отсутствие единого универсального диагностического показателя, определяющего исход ортопедического лечения, - эффективность реабилитации зависит от совокупного влияния изменений твёрдых тканей зубов, пародонта, функционального состояния ротовой жидкости, местного иммунитета, слизистой оболочки, микроциркуляции и костной ткани. На основании суммарного балла пациенты стратифицируются на три категории риска, что позволяет определять объём необходимой предортопедической подготовки и обосновывать выбор конструкционного материала в сочетании с клинико-патогенетической моделью заболевания.

К пациентам с высоким индексом стоматологического риска был применен персонализированный лечебно-профилактический комплекс.

При первичном обследовании пациентов, страдающих заболеванием желудка с избыточной продукцией желудочного сока, средняя длительность гастроэнтерологического заболевания превышала 6 лет, а средний балл GERD-Q более чем в два раза превышал контрольные значения (10,3±2,2 и 10,5±2,3 против 5,2±1,5; p<0,001), что подтверждало хроническую кислотную экспозицию слизистой оболочки полости рта. Наиболее характерными находками являлись генерализованная гиперестезия, эрозивные изменения эмали на нёбных поверхностях верхних зубов и жевательных поверхностях моляров, а также снижение pH и буферной ёмкости ротовой жидкости.

Индекс OHI-S в подгруппе персонализированного лечения снизился с 2,01±0,43 при поступлении до 1,74±0,40 через 30 суток, 1,51±0,37 через 90 суток, 1,32±0,34 через 180 суток и 1,18±0,29 балла через 12 месяцев; в подгруппе стандартного лечения снижение было заметно более медленным - до 1,46±0,35 балла к 12 месяцам. Аналогичная закономерность отмечена по индексу BOP: снижение с 27,4±8,6% до 10,9±5,4% в подгруппе персонализированного лечения против снижения лишь до 17,4±6,1% в подгруппе стандартного лечения.

Через 12 месяцев в подгруппе 1 индекс PD снизился до 2,31±0,38 мм против 2,55±0,42 мм в подгруппе 2 (контроль - 1,50±0,04 мм; p<0,001 между подгруппами), CAL - до 2,63±0,49 мм против 2,87±0,58 мм. Индекс BEWE снизился с исходных 13,6±0,3 до 6,9±0,6 балла в подгруппе 1 против 8,5±0,3 балла в подгруппе 2, тогда как ICDAS II в подгруппе 1 стабилизировался на уровне 2,01-2,04 балла, а в подгруппе 2 продолжал нарастать до 2,82±0,5 балла к 12 месяцам.

Комплексная оценка функционального состояния ротовой жидкости в подгруппе персонализированного лечения показала последовательное восстановление всех изученных параметров (табл. 1). Наиболее выраженный прирост зафиксирован по нестимулированной саливации (+72,4%) и буферной ёмкости слюны (+65,3%), тогда как показатели местного иммунитета - sIgA и лизоцим - увеличились на 46,1% и 55,4% соответственно. Параллельно на фоне комплексного лечения суммарный балл GERD-Q снизился на 36,3%, а индекс ксеростомии - на 33,7%, что отражает сопряжённое улучшение гастроэнтерологического статуса и субъективного состояния полости рта.

Таблица 1. Динамика показателей ротовой жидкости и стандартизированного анкетирования у пациентов с гиперацидными заболеваниями желудка, подгруппа персонализированного лечения (M±SD)

Показатель ротовой жидкости (гиперацидная группа, подгруппа персонализированного лечения)	При поступлении	Через 12 месяцев	Прирост/ снижение
Нестимулированная саливация, мл/мин	0,29±0,08	0,50±0,07	+72,4%
Стимулированная саливация, мл/мин	1,23±0,17	1,46±0,15	+18,7%
pH ротовой жидкости	5,80±0,21	6,82±0,15	+17,6%

Буферная ёмкость, баллы	4,9±1,1	8,1±0,8	+65,3%
sIgA, мг/л	112,4±18,6	164,2±18,5	+46,1%
Лизоцим, мкг/мл	8,3±1,5	12,9±1,2	+55,4%
GERD-Q, баллы	9,1±2,6	5,8±2,0	−36,3%
Индекс ксеростомии (XI), баллы	24,6±7,3	16,3±5,7	−33,7%

Примечание: все изменения статистически значимы по сравнению с исходным уровнем (p<0,05-0,001).

У пациентов с гипоацидной патологией желудка динамика индексов носила принципиально иной характер: в подгруппе 2 (стандартное лечение) после кратковременного улучшения к 30-м суткам отмечался возврат показателей к исходному уровню - OHI-S снизился до 1,25 балла к 30 суткам, но к 360 суткам вырос до 2,38 балла (при исходном 2,60 балла), а BOP аналогично вернулся с 15,2% до 28,7% (при исходном 32,0%). В подгруппе 1 аналогичные показатели, однажды улучшившись, оставались стабильными весь период наблюдения. Скорость нестимулированной саливации, исходно наиболее сниженная среди трёх групп (0,15-0,16 мл/мин против 0,50 мл/мин в контроле), в подгруппе 1 восстановилась до 0,47 мл/мин против лишь 0,27 мл/мин в подгруппе 2.

У пациентов после бариатрических операций исходные значения индексов формировались на фоне сочетанного действия остаточного гастроэзофагеального рефлюкса и нутритивного дефицита. В подгруппе 1 к 12 месяцам достигнута стабилизация индексов ICDAS (сумма очагов) и BEWE, буферная ёмкость слюны выросла до 7,7 балла против 7,0 балла в подгруппе 2, а концентрация секреторного иммуноглобулина А - до 159,2 мг/л против 134,7 мг/л.

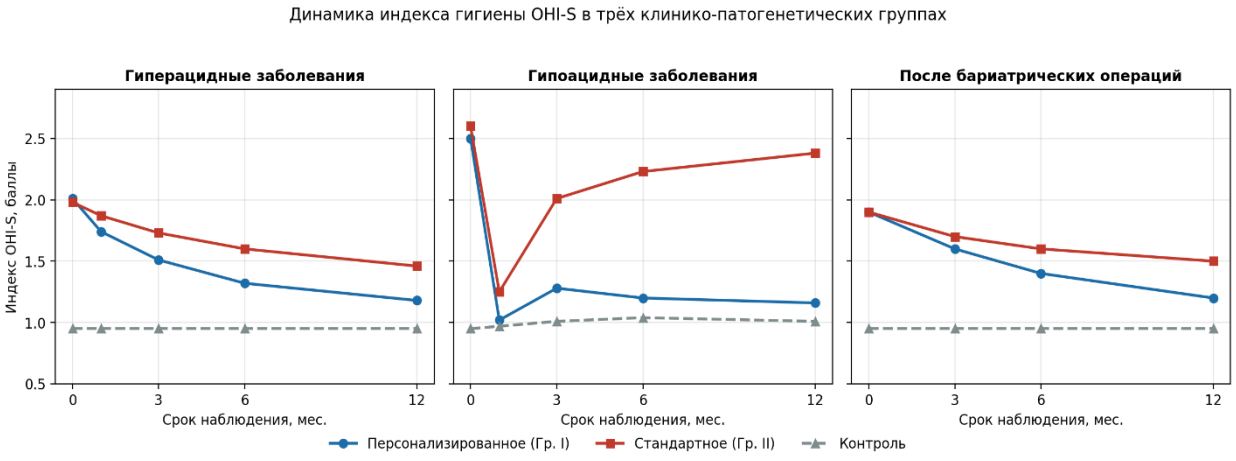


Рисунок 1. Динамика индекса гигиены OHI-S в трёх клинико-патогенетических группах

Примечание. Сплошные линии - динамика в подгруппах персонализированного и стандартного лечения; пунктир - контрольная группа. Обращает внимание

разнонаправленная динамика в подгруппе стандартного лечения гипоацидной группы: после улучшения к 30-м суткам показатель возвращается к исходному уровню.

Во всех трёх группах различия между подгруппами персонализированного и стандартного лечения достигали статистической значимости ($p<0,05$-$0,001$) по большинству изученных показателей уже к 6 месяцам наблюдения. Наиболее выраженный контраст между подгруппами зафиксирован в гипоацидной группе, где стандартная тактика сопровождалась не просто более медленным, а обратным развитием динамики - утратой достигнутого улучшения к концу периода наблюдения, что отражает нестойкость эффекта стандартного лечения при секреторной недостаточности, лежащей в основе данной клинико-патогенетической модели.

Анализ качества жизни пациентов показал, что у пациентов с гиперацидными заболеваниями желудка суммарный балл OHIP-14 снизился с 29,6-30,1 при поступлении до 13,5 балла через 12 месяцев в подгруппе персонализированного лечения (уровень, близкий к контрольному - 10,8 балла) против 19,8 балла в подгруппе стандартного лечения - снижение на 54% против 34%. У пациентов с гипоацидными заболеваниями - с 30,4-31,0 до 15,1 балла против 22,6 балла (снижение на 50% против 27%), что стало наименее полным восстановлением среди трёх групп и отражает более инертный характер компенсации секреторной недостаточности. У постбариатрических пациентов, у которых балл OHIP-14 возрастал почти в 1,7 раза непосредственно после операции (с исходных 18,4-18,8 до 31,8-32,4 балла), персонализированная тактика обеспечила снижение до 14,2 балла против 21,9 балла при стандартном ведении (снижение на 55% против 32%).

Таблица 1. Итоговое снижение балла OHIP-14 и ослабление корреляции с локальными симптомами через 12 месяцев.

Группа	**Снижение OHIP-14, персонал. (%)**	**Снижение OHIP-14, традиц. (%)**	**r с локальными симптомами, персонал.**	**r с локальными симптомами, традиц.**
Гиперацидные заболевания	54%	34%	0,25-0,34	0,55-0,62
Гипоацидные заболевания	50%	27%	0,28-0,36	0,57-0,65
После бариатрических операций	55%	32%	0,29-0,34	0,61-0,67

Примечание: r - коэффициент корреляции суммарного балла OHIP-14 с ведущими локальными симптомами группы (гиперестезия/BEWE - для гиперацидных; ксеростомия/воспаление слизистой - для гипоацидных; гиперемия/боль/зоны давления - для постбариатрических).

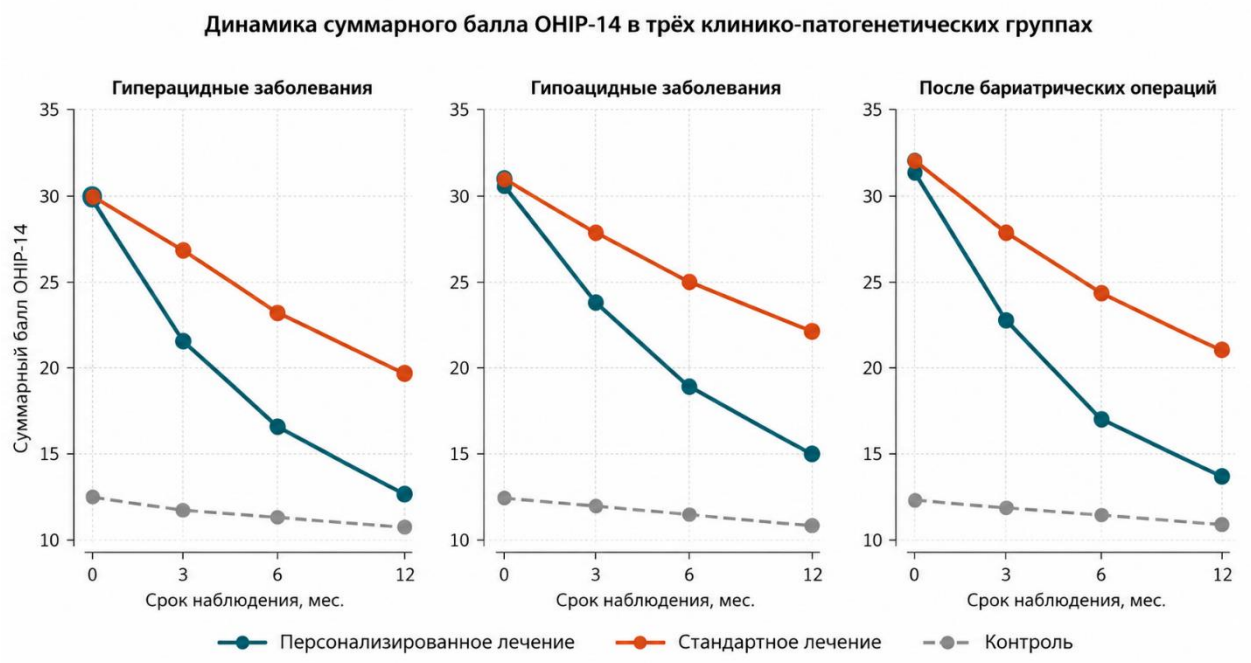


Рисунок 1. Динамика суммарного балла OHIP-14 в трёх клинико-патогенетических группах

Во всех трёх группах персонализированное лечение статистически значимо ослабляло корреляционную связь OHIP-14 с остаточными локальными проявлениями заболевания. У гиперацидных пациентов связь с гиперестезией и эрозивным индексом BEWE снижалась с r=0,55-0,62 (стандартное лечение) до r=0,25-0,34 (персонализированное лечение). У гипоацидных пациентов связь с ксеростомией и воспалением слизистой оболочки снижалась с r=0,57-0,65 до r=0,28-0,36. У постбариатрических пациентов связь с гиперемией слизистой оболочки, количеством зон повышенного давления и болевым синдромом по VAS снижалась с r=0,61-0,67 ($p<0,001$) до r=0,29-0,34 ($p>0,05$), тогда как отрицательная корреляция OHIP-14 со степенью функциональной адаптации к протезу, напротив, сохранялась и была статистически значимой в обеих подгруппах ($r=-0,52$ в подгруппе персонализированного лечения против $r=-0,69$ в подгруппе стандартного лечения).

Полученная закономерность - ослабление зависимости качества жизни от остаточной локальной патологии именно в подгруппах персонализированного лечения при сохранении и даже усилении этой зависимости в подгруппах стандартного лечения - свидетельствует о том, что персонализированный подход не просто ускоряет купирование отдельных симптомов, а изменяет сам патогенетический механизм формирования стоматологического дискомфорта, смещая его от зависимости к остаточной локальной патологии в сторону общей функциональной адаптации к ортопедической конструкции

ЗАКЛЮЧЕНИЕ

Разработанный интегральный индекс кислотозависимого стоматологического риска (ИКСР), объединяющий 17 клинических, лабораторных, функциональных и лучевых критериев в единую трёхуровневую систему оценки, обеспечивает объективную

стратификацию пациентов с кислотозависимыми заболеваниями желудка независимо от преобладающего патогенетического механизма.

Персонализированное стоматологическое сопровождение обеспечивает более выраженную и, что принципиально важно, более устойчивую нормализацию клинических индексов и функциональных показателей ротовой жидкости по сравнению с стандартной тактикой во всех трёх изученных клинико-патогенетических группах пациентов с кислотозависимыми заболеваниями желудка. Наиболее значимое клиническое преимущество персонализированного подхода - предотвращение рецидива патологических изменений, наблюдаемого при стандартном ведении гипоацидных пациентов, - подчёркивает необходимость учёта конкретного патогенетического варианта заболевания при планировании объёма и содержания стоматологического сопровождения.

Сопоставление динамики ИКСР и стоматологически обусловленного качества жизни подтверждает клиническую значимость разработанной системы: персонализированное лечение, ориентированное на снижение уровня стоматологического риска, во всех трёх изученных группах обеспечивает не только более полное восстановление качества жизни, но и качественное изменение механизма его формирования - переход от зависимости к остаточным локальным симптомам к определяющей роли функциональной адаптации к ортопедической конструкции.

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