ENDOTHELIAL DYSFUNCTION SCORES IN CHILDREN WITH TYPE 1 DIABETES WHO HAVE SUFFERED COVID-19 INFECTION

[1]Sadirkhodjaeva Azizakhon Alavitdinovna, [2]Ashurova Dilfuza Tashpulatovna
[1,2]Tashkent Pediatric Medical Institute, Uzbekistan
https://doi.org/10.5281/zenodo.10884863

Abstract*. To analyze the relationship of endothelial dysfunction in children with type 1 diabetes mellitus who have suffered a COVID-19 infection. Research materials and methods. For our study, 140 children with type 1 diabetes who suffered from COVID-19 were treated in the children's department of the RSNPMC endocrinology aged 2 to 18 years. The comparison group was 65 children with type 1 diabetes, a group of 15 practical healthy children matched for age and sex without any signs or symptoms of cardiovascular disease was used as a control. The work uses biochemical, immunological research methods and statistical research methods. According to our studies, it was revealed that SD1 is an important risk factor affecting the clinical severity of COVID-19 disease. Immune and inflammatory response in children with 1 DM who have undergone COVID-19 infection leads to endothelial dysfunction with an increase in the concentration of HF CRP, and VEGF. A special response was also identified with an increase in AT to the myocardial antigen, which proved the role of myocardial damage.*
Keywords*: type 1 diabetes mellitus, children, endothelial dysfunction, COVID-19.*

Relevance. Currently, SARS-CoV-2 infection is also a potential trigger for the development of type 1 diabetes mellitus in children, which represents the most common chronic metabolic disorder in the pediatric population. There is growing evidence that many patients with COVID-19 may experience a wide range of post-acute consequences, including cardiovascular complications [3]. COVID-19 causes not only viral pneumonia, but also many extrapulmonary complications, such as cardiovascular or cerebrovascular diseases. COVID-19 can excessively stimulate the sympathetic system and cause an inflammatory cytokine storm and a state of hypercoagulopathy. These mechanisms can cause irreversible damage to the cardiovascular or respiratory system even after recovery from COVID-19. [8].

Type 1 diabetes mellitus (SD1) is one of the most common chronic diseases affecting children. In this disease, various micro- and macrovascular complications are often observed, which leads to at least a 10-fold increase in cardiovascular morbidity compared to healthy people of the same age [1,2]. Diabetes mellitus is characterized by a variety of cardiovascular complications. There is now strong evidence for a role in the formation of chronic endothelial dysfunction heart failure. The vascular endothelium has many functions. It is a key regulator of vascular homeostasis, maintains a balance between vasodilation and vasoconstriction, inhibition and stimulation of smooth muscle cell migration and proliferation, fibrinolysis and thrombosis, and is involved in the regulation of platelet adhesion and aggregation. Endothelial dysfunction underlies the pathogenesis of vascular complications of diabetes mellitus. It is now recognized that the vascular endothelium is a multifunctional organ. Endothelial cells are metabolically active and have the paracrine, endocrine and autocrine functions necessary to maintain vascular homeostasis under physiological conditions [4,5]. Endothelial functions include regulation of vascular integrity

and their permeability, angiogenesis, hemostasis. The endothelium is involved in immune responses. It plays a key role in the regulation of vascular tone, inflammatory reactions, control of tissue blood flow, maintenance of blood rheological properties [4,6]. As the main regulator of vascular homeostasis, the endothelium maintains a balance between vasodilation and vasoconstriction, inhibition and stimulation of smooth muscle cell migration and proliferation, fibrinolysis and thrombosis, and also participates in the regulation of platelet adhesion and aggregation [5]. Disruption of this regulated equilibrium leads to endothelial dysfunction [6]. Diabetes mellitus is a typical disease in which endothelial dysfunction is observed [7]. Therefore, understanding the mechanisms underlying the emergence and development of endothelial dysfunction in diabetes mellitus is an important focus in the prevention and treatment of vascular complications associated with all forms of diabetes mellitus [16,17].

Dysregulation of metabolism in SD1 goes far beyond hyperglycemia; In fact, SD1 is a combination of chronic inflammation and immune dysfunction that has harmful effects on the vascular system and blood clotting cascade, among others. On the other hand, COVID-19 is a hyperinflammatory disease that ultimately leads to multiple organ disease. Endothelial dysfunction and endothelial glycocalyx damage increase leukocyte and circulating inflammatory cell adhesion and promote vascular permeability and coagulation [10, 12, 13, 15]. The pathogenesis of endothelial microenvironment disorder in patients with 1 DM is closely related to hyperglycemia and subsequent oxidative stress [9]. Passive diffusion of glucose into endothelial cells and subsequent intracellular glucose accumulation during acute and prolonged hyperglycemia activate sorbitol, protein kinase C, and pentose phosphate pathways and increase NADPH/nicotinamide adenine dinucleotide (NAD) rates. These changes reduce the availability of nitric acid, increase vascular permeability, promote an inflammatory response by activating cytokines and adhesion molecules, and promote endothelial cell apoptosis and endothelial dysfunction [9,13].

SARS-CoV-2 directly affects the vascular system by targeting endothelial cells through ACE2 receptor binding, leading to severe endothelial disorders and inflammation. In addition, overproduction of pro-inflammatory cytokines during COVID-19 contributes to endothelial dysfunction. Patients with severe COVID-19 disease have elevated levels of proinflammatory cytokines, including the soluble interleukin 2 receptor (IL-2R), IL-6, and TNF-a. IL-6 promotes endothelial impairment and promotes procoagulation. Moreover, inflammation-mediated damage to the IL-6 or TNF- α glycocalyx increases vascular permeability, causing interstitial fluid shift and generalized edema. Histological studies have shown that endothelial cells damaged by SARS-CoV-2 lead to vasculitis and endothelitis in many organs [16,17].

Chronic endothelial dysfunction predisposes to severe COVID-19 infection, causing changes in glycocalyx and endothelial cells, which leads to increased leukocyte adhesion and contributes to a procoagulant and antifibrinolytic state. Chronic endothelial dysfunction in SD1 combined with direct damage to SARS-CoV-2 endothelial cells can lead to impaired endothelium and microcirculation, which contribute to the pathogenesis of acute respiratory syndrome and multiple organ failure [14,18].

The purpose of the study is to analyze the relationship of endothelial dysfunction in children with type 1 diabetes mellitus who have suffered a COVID-19 infection.

Research materials and methods. For our study, 140 children with type 1 diabetes who suffered from COVID-19 were treated in the children's department of the RSNPMC endocrinology aged 2 to 18 years. The comparison group was 65 children with type 1 diabetes, a group of 15 practical

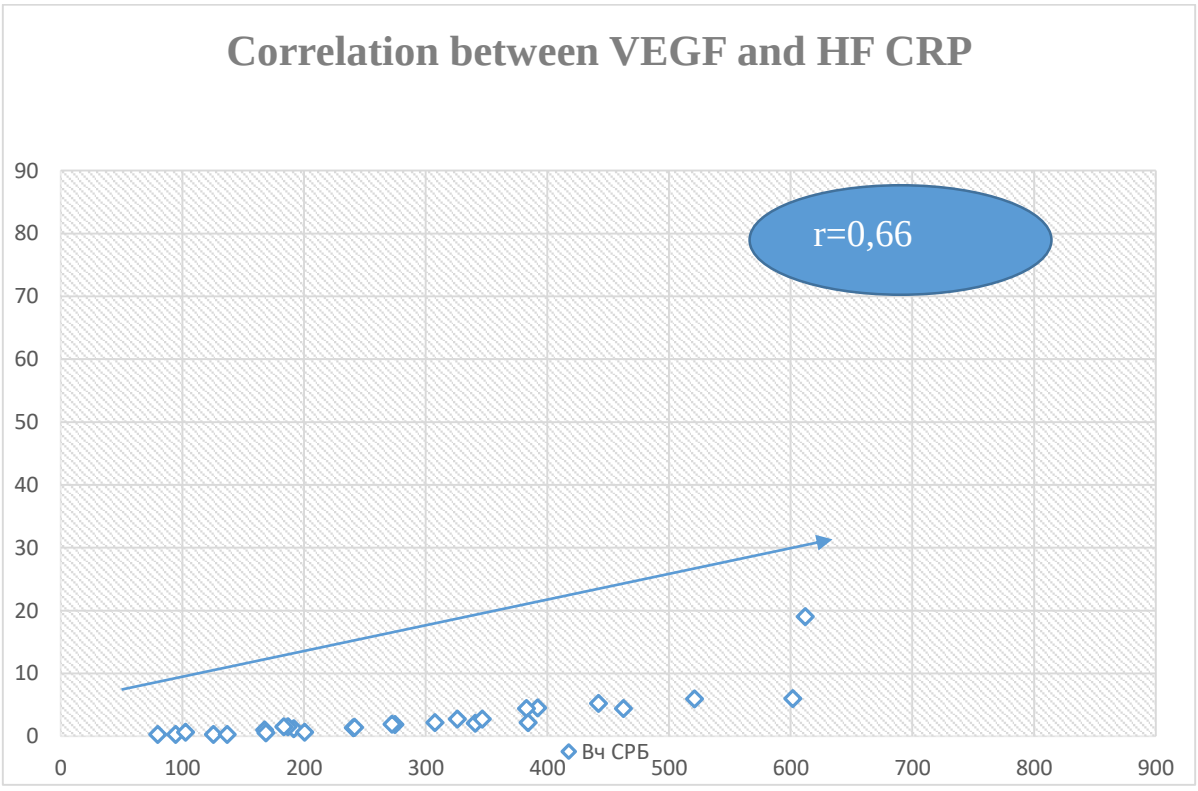
healthy children matched for age and sex without any signs or symptoms of cardiovascular disease was used as a control. The work uses biochemical, immunological research methods and statistical research methods. Statistical data processing was carried out in the Statistica 6.1 program.

Results and discussion. VEGF plays an important role in the development of complications associated with diabetes. In many tissues and cells, VEGF induces proliferation, migration, and vasoprotein of vascular endothelial cells. It has been identified as a major trigger for the development of both non-proliferative and proliferative diabetic retinopathy. It also plays an important role in the development of neuropathy and nephropathy in diabetic patients. Its activity is directly related to its expression. This means that small changes in its concentration affect physiological effects. Some studies have shown that serum concentration of VEGF corresponds to the clinical activity of various diseases, including tumor growth, coronary artery atherosclerosis, Kawasaki disease, synovial tissue neovascularization in rheumatoid arthritis, and diabetic microangiopathy. It also regulates inflammatory response and endothelial apoptosis. Despite a significant body of literature describing how VEGF contributes to diabetic complications, data analyzing the relationship between serum VEGF levels and aseptic vascular wall inflammation.

Table 1. VEGF and HF CRP

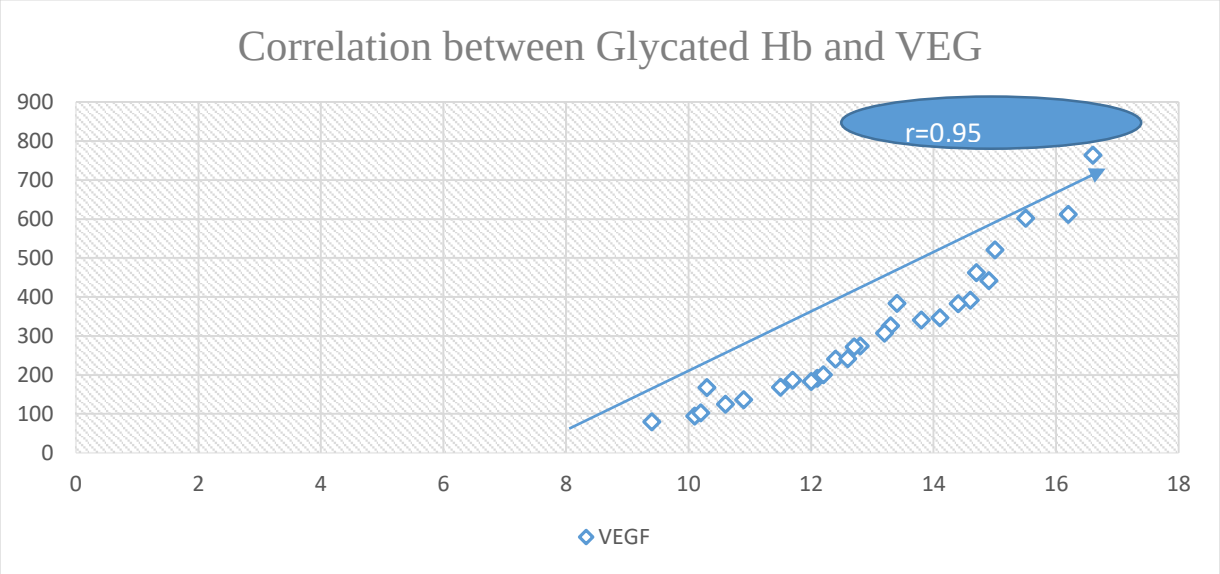
Indicator	Primary group	Comparative group	Check group
VEGF	305,3 ±132,59	2	2
HF CRP	4,62±1 0,1		
HbA1c (%)	10,9±1 0,35	±1,89	

According to our studies, there were increases in VEGF HV CRP in the main group of the comparison study with the comparison and control group, which proved the presence of endothelial dysfunction in children with type 1 diabetes who suffered a Covid-19 infection.



Correlation revealed a moderate positive relationship (r = 0.66) between VEGF HV CRP that proves vascular wall inflammation. VEGF is a predictor and risk factor for microalbuminuria and early diabetic nephropathy in children with diabetes.

Serum VEGF concentrations were increased in children with type 1 diabetes mellitus who had a Covid-19 infection. It has also been demonstrated that glycemic control affects serum VEGF levels and that the severity of microvascular complications is associated with a significant increase in serum VEGF levels in this group of patients.



Correlation revealed a strong positive relationship (r = 0.95) between VEGF and glycated Hb, which proves that a prolonged, uncontrolled level of glucose elevation

Antimyocardial antibodies are a collection of IgG class autoantibodies that are produced against most antigens in the heart muscle or in skeletal muscles.

An increase in the values of these antibodies indicates the development of myocarditis, DCMP, and also contributes to the accurate diagnosis and selection of rational treatment.

Antibodies to myocardial antigens are able not only to directly affect the heart tissue, but also to affect the metabolic cycle, provoking myocardial disorders, and, therefore, taking part in the deformation of the heart muscle.

The number of IgG class antibodies to cardiac muscle decreases sharply when the course of the disease worsens. This fact confirms that anti-myocardial antibodies may be harbingers of the disease leads to endothelial vascular wall dysfunction.

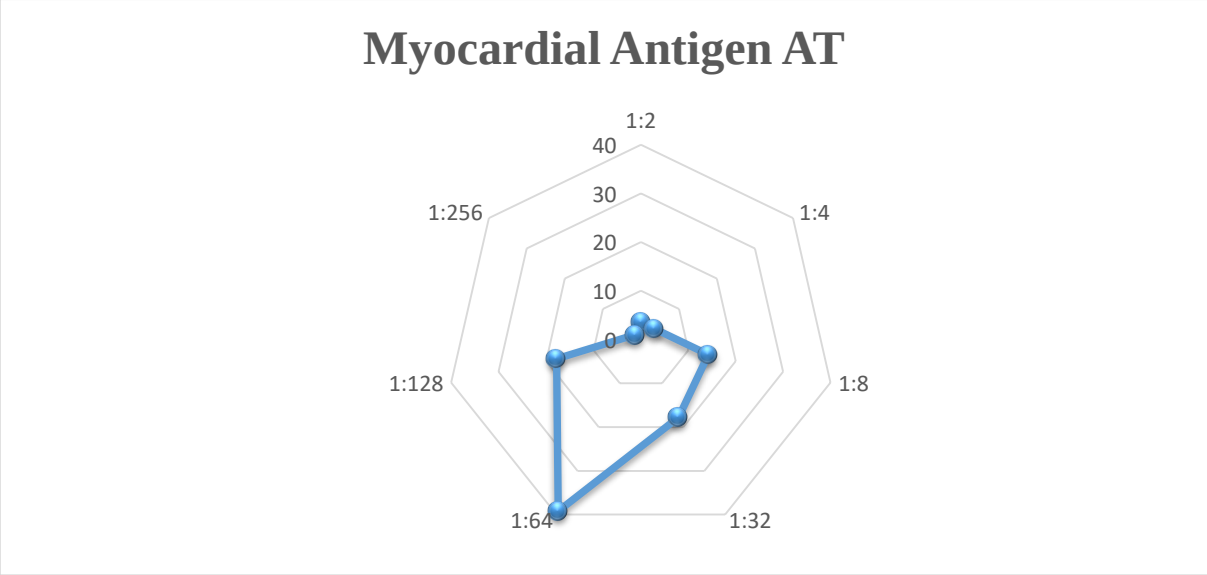
Autoimmune antibodies to the myocardium are protein structures that are produced in response to autoantigens produced by the heart muscle under the influence of certain factors.

Diseases such as cardiomyopathies, myocarditis, cardiac rheumatism, myocardial infarction lead to the production of myocardial autoantibodies.

Autoantibodies also appear after heart surgery and in rare cases in coronary disease.

Examination of patients with a defective cardiac muscle in diseases such as myocarditis, dilated cardiomyopathy (DCMP), together with the diagnosis of markers that determine the acute inflammatory process, also includes the determination of antibodies to heart tissue (myocardium).

During our studies, we found an increase in antibodies to myocardial antigen in children with type 1 diabetes mellitus who suffered a COVID-19 infection that proves the degree of myocardial damage after an infection.



Conclusions. According to our studies, it was revealed that SD1 is an important risk factor affecting the clinical severity of COVID-19 disease. Immune and inflammatory response in children with 1 DM who have undergone COVID-19 infection leads to endothelial dysfunction with an increase in the concentration of HF CRP, and VEGF. A special response was also identified with an increase in AT to the myocardial antigen, which proved the role of myocardial damage.

REFERENCES

1. Беленков Ю.Н., Агеев Ф.Т., Мареева В.Ю. Нейро-гормоны и цитокины при сердечной недостаточности: новая теория старого заболевания? // Сердечная недостаточность. 2000, №4 (1), С.135-138.
2. Берне С.А., Клименкова А.В., Шмидт Е.А., Авра-менко О.Е., Селезнева Е.С., Барбараш О.Л. Провоспали-тельные цитокины при остром коронарном синдроме в сочетании с сахарным диабетом 2 типа // Кардиоваскулярная терапия и профилактика. 2008, №7(6), Приложение 1, С.49.
3. Васина Л.В., Петрищев Н.Н., Власов Т.Д. Эндотелиальная дисфункция и ее основные маркеры // Регионарное кровообращение и микроциркуляция. - 2017. - Т.16. - №1. - С. 4-15.
4. Говорин А.В. Некоронарогенные поражения миокарда // Новосибирск: Наука, 2014. - 448 с.
5. Васина Л.В., Власов Т.Д., Петрищев Н.Н. Функциональная гетерогенность эндотелия (обзор) // Артериальная гипертензия. - 2017. - Т.23. - №2. - С. 88-102.
6. Мельникова Ю.С., Макарова Т.П. Эндотелиальная дисфункция как центральное звено патогенеза хронических болезней // Казанский медицинский журнал. - 2015. - Т.96. - №4. - С. 659-665.
7. Власов Т.Д., Нестерович И.И., Шиманьски Д.А. Эндотелиальная дисфункция: от частного к общему. Возврат к «старой парадигме»? // Регионарное кровообращение и микроциркуляция. - 2019. - Т.18. - №2. - С. 19-27.
8. Омельченко В.П., Затонский С.А., Демидова А.А., Демидов И.А. Прогнозирование прогрессирования хронической сердечной недостаточности ишемического генеза с

учетом иммунологических показателей // Фундаментальные исследования. 2014, №4, С. 325-329.

9. Chiarelli F., Spagnoli A., Basciani F., Tumini S., Mezzetti A., Cipollone F., Cuccurullo F., Morgese G., Verrotti A. Vascular endothelial growth factor (VEGF) in children, adolescents and young adults with Type 1 diabetes mellitus: Relation to glycaemic control and microvascular complications. *Diabet. Med.* 2000;17:650–656. doi: 10.1046/j.1464-5491.2000.00350.x.
10. Gregory J.M., Slaughter J.C., Duffus S.H., Smith T.J., Le Stourgeon L.M., Jaser S.S., Mc Coy A.B., Luther J.M., Giovannetti E.R., Boeder S., et al. COVID-19 Severity Is Tripled in the Diabetes Community: A Prospective Analysis of the Pandemic's Im-pact in Type 1 and Type 2 Diabetes. *Diabetes Care.* 2021;44:526–532. doi: 10.2337/dc20-2260.
11. Ilic I., Ilic M. Diabetes Mellitus after SARS-CoV-2 Infection: An Epidemiological Review. *Life.* 2023;13:1233. doi: 10.3390/life13061233
12. Mohseni Afshar Z., Babazadeh A., Janbakhsh A., Mansouri F., Sio T.T., Sullman M.J.M., Carson-Chahhoud K., Hosseinzadeh R., Barary M., Ebrahimpour S. Coronavirus disease 2019 (COVID-19) vaccination recommendations in special populations and pa-tients with existing comorbidities. *Rev. Med. Virol.* 2022;32:e2309.
13. Muñoz C.E., Chao L.C. Impact of COVID-19 on Youth with Type 2 Diabetes: Lessons Learned from a Pediatric Endocrinologist and a Psychologist. *Front. Endocrinol.* 2021;12:650492. doi: 10.3389/fendo.2021.650492.
14. Ng S.M. COVID-19 and children with diabetes: Emerging knowledge. *Pract. Diabetes.* 2020;37:147–148a. doi: 10.1002/pdi.2289.
15. Pal R., Bhadada S.K., Misra A. COVID-19 vaccination in patients with diabetes mellitus: Current concepts, uncertainties and challenges. *Diabetes Metab. Syndr.* 2021;15:505–508. doi: 10.1016/j.dsx.2021.02.026.
16. Sena CM, Pereira AM, Seiça R. Endothelial dysfunction - a major mediator of diabetic vascular disease. Biochimica Biophysica Acta. 2013;1832:2216-2231.
17. Torimoto K, Okada Y, Tanaka Y. Type 2 diabetes and vascular endothelial dysfunction. J Uoeh. 2018;40(1):65-75.
18. Wu Z., McGoogan J.M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA.* 2020;323:1239–1242. doi: 10.1001/jama.2020.2648.