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Risk Factors for Cardiovascular Disorders in Children with Diabetes Mellitus Following Covid-19 Infection

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Abstract: The aim of this study was to identify risk factors for the development of cardiovascular disorders and to improve the algorithm for their early diagnosis in children with type 1 diabetes mellitus following COVID-19 infection. This was based on a comprehensive assessment of metabolic, immuno-inflammatory, angiogenic, and functional indicators of the cardiovascular system. The study included 254 children aged 7 to 18 years with type 1 diabetes mellitus who received inpatient treatment at the pediatric department of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Yo.Kh. Turakulov from 2020 to 2023. The examination was conducted 6 months after COVID-19 infection. The main group consisted of 102 children, divided into 2 subgroups: the 1st subgroup - children with cardiovascular disorders and diabetic cardiovascular autonomic neuropathy (DCAN) (n=28), the 2nd subgroup - children with DCAN (n=74). The comparison group comprised 152 children without cardiovascular disorders and DCAN, while the control group included 30 generally healthy children who had COVID-19 infection without diabetes mellitus. The identified relationships confirm that metabolic decompensation and post-infectious inflammation play a key role in the development of early functional disorders of the myocardium and vascular regulation. This can be considered one of the leading mechanisms for the formation of cardiovascular neuropathy in children with type 1 diabetes mellitus in the post-COVID period.

Keywords: Type 1 diabetes mellitus; children; COVID-19; cardiovascular disorders; early diagnosis.

Introduction: In recent years, the issue of cardiovascular complications in children with type 1 diabetes mellitus (T1DM) has gained particular clinical significance in connection with coronavirus infection (COVID-19). It has been established that SARS-CoV-2 can cause cardiovascular system damage through direct impact on cardiomyocytes via angiotensin-converting enzyme-2 (ACE2) receptors, as well as through immunoinflammatory damage to the myocardium, endothelial dysfunction, and coagulopathy [1,2].

Recent studies show that even in previously somatically healthy children, functional changes in the myocardium can develop after COVID-19 infection, including decreased left ventricular contractility, heart rhythm disturbances, and signs of inflammatory damage to the heart muscle [3,4]. In the pediatric population, the frequency of cardiac disorders in COVID-19 reaches 30-35%, including the development of myocarditis, heart failure, and echocardiographic changes [5].

A special risk group consists of children with chronic metabolic diseases, particularly T1DM, in whom chronic hyperglycemia contributes to the development of systemic inflammation, endothelial dysfunction, and hypercoagulation syndrome [6]. In the context of COVID-19 infection, these disorders can be exacerbated due to the activation of pro-inflammatory cytokines, which contributes to the progression of vascular and myocardial changes [7].

It has been demonstrated that COVID-19 can affect glycemic control in children with T1DM, inducing metabolic decompensation and enhancing the

inflammatory response, which, in turn, increases the risk of cardiovascular complications developing in the post-infectious period [8]. In the long-term period after infection, children may also develop multisystem inflammatory syndrome in children (MIS-C), accompanied by pronounced myocardial dysfunction, decreased ejection fraction, and signs of heart failure [9].

Despite the existence of individual studies on cardiovascular system damage during COVID-19, the issues of early diagnosis of subclinical myocardial dysfunction and identification of risk factors for the development of cardiovascular neuropathy in children with T1DM remain insufficiently studied, especially in the post-COVID period [10]. Currently, there are no unified diagnostic algorithms based on a comprehensive assessment of metabolic, immunoinflammatory, angiogenic, and functional indicators of the cardiovascular system in this category of patients.

In this regard, identifying risk factors and developing an algorithm for early diagnosis of cardiovascular disorders in children with type 1 diabetes mellitus after COVID-19 infection represents an urgent scientific and clinical task in modern pediatrics and pediatric cardiology.

The aim of this study was to identify risk factors for the development of cardiovascular disorders and to improve the algorithm for their early diagnosis in children with type 1 diabetes mellitus after COVID-19 infection based on a comprehensive assessment of metabolic, immuno-inflammatory, angiogenic, and functional indicators of the cardiovascular system.

METHODS

The study included 254 children with type 1 diabetes mellitus aged 7 to 18 years who received inpatient treatment at the pediatric department of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after Academician Yo.Kh. Turakulov in 2020-2023. The examination was conducted 6 months after COVID-19 infection. The main group consisted of 102 children divided into 2 subgroups: 1st subgroup - children with CVD and DCAN (n=28), 2nd subgroup - children with DCAN (n=74). The comparison group comprised 152 children without CVD and DCAN, while the control group included 30 practically healthy children who had COVID-19 infection without diabetes mellitus. Immunoglobulins M and G (IgM and IgG) to the SARS-CoV-2 virus antigen and neutralizing antibodies to the SARS-CoV-2 virus antigen were determined using a semi-automatic immunofluorescence analyzer Finecare FIA Meter Plus (China).

RESULTS AND DISCUSSION

The established significant multidirectional correlations of varying strength between the diagnostic markers of children in the 1st group demonstrate causal relationships in the development of CVD.

A negative correlation between NT-proBNP and CK-MB (r=-0.78) indicates the opposite dynamics of markers for acute and chronic myocardial damage. A strong positive correlation between NT-proBNP and GLS (r=0.931) reflects a direct relationship between the level of natriuretic peptide and a decrease in myocardial contractile function. A highly significant positive correlation was established between the level of HbA1c and high-sensitivity C-reactive protein (r = 0.95), indicating a direct link between chronic hyperglycemia and the severity of the systemic inflammatory response. The relationship between HbA1c and VEGF (r = 0.93) indicates the influence of impaired glycemic control on the activation of the angiogenic cascade, which may be one of the factors contributing to the progression of vascular complications. The correlation between HbA1c and NT-proBNP levels (r = 0.756) reflects that increased glycemia is associated with increased myocardial overload, emphasizing hyperglycemia's contribution to the formation of heart muscle dysfunction in children with T1DM. A significant positive correlation between HbA1c and GLS (r=0.83) demonstrates the influence of metabolic decompensation on the reduction of global longitudinal myocardial strain. A direct correlation between EF and GLS (r =0.756) confirms the consistency between the global and longitudinal contractile function of the left ventricle. EF and NT-proBNP (r=0.23) weak positive correlation indicates initial signs of myocardial dysfunction with still compensated ejection fraction. hs-CRP and D-dimer (r=0.73) moderate positive correlation reflects the relationship between systemic inflammation and activation of fibrinolytic activity. Platelets and D-dimer (r=0.61) established an association between platelet

activation and increased thrombus formation processes. The relationship between TNF-α and HbA1c (r=0.69) confirms the involvement of chronic hyperglycemia in maintaining the inflammatory background. A high degree of correlation between VEGF and TNF-α (r=0.88) indicates cytokine-dependent regulation of angiogenesis in systemic inflammation. VEGF and hs-CRP (r=0.77) established a correlation between vascular activation and the acute phase inflammatory response. Fibrinogen and cholesterol (r=0.78) correlation reflects the participation of metabolic disorders in the formation of vascular inflammation (Table 1).

Table 1.

Correlation relationships of diagnostic markers of cardiovascular disorders

Correlation between indicators	Correlation coefficient (r)	Correlation between indicators	Correlation coefficient (r)	Correlation between indicators	Correlation coefficient (r)
NT-proBNP и CK-MB	0,51 (p<0,001)	HbA1c and GLS	-0,931 (p<0,01)	TNFα и HbA1c	0,756 (p<0,01)
NT-proBNP and GLS	-0,58 (p<0,001)	EF and GLS	0,23 (p<0,01)	VEGF и TNFα	0,78 (p<0,001)
HbA1c and hs-CRP	0,36 p<0,001)	hs-CRP и D-димер	0,66 (p<0,01)	VEGF hs-CRP	0,64 (p<0,01)
HbA1c and VEGF	0,95 (p<0,01)	Thrombocytes and D-dimer	0,83 (p<0,05)	Fibrinogen and cholesterol	0,8 (p<0,001)
EF and NT-proBNP	-0,78 (p<0,001)				

The correlation analysis conducted allowed for the systematization of diagnostic markers of cardiovascular disorders in children with type 1 diabetes mellitus following COVID-19 infection. These markers form interconnected pathophysiological circuits that reflect the key mechanisms of cardiovascular neuropathy development.

The identified statistically significant associations between metabolic indicators, markers of inflammation, angiogenic activity, coagulation potential, and parameters of myocardial contractile function indicate the multifactorial nature of cardiovascular system damage in the context of post-infectious metabolic dysregulation.

The set of established relationships demonstrates the interconnection of:

-glycemic control disorders with the activation of pro-inflammatory and pro-angiogenic mechanisms,

-systemic inflammatory response with changes in hemostatic potential,

-metabolic and immuno-inflammatory shifts with early signs of subclinical myocardial dysfunction.

The obtained data confirm the involvement of inflammatory-endothelial dysfunction and metabolically induced myocardial remodeling in the pathogenesis of cardiovascular complications in children with type 1 diabetes in the post-COVID period. This justifies the need for a comprehensive assessment of biochemical, immunological, and functional indicators in the early diagnosis of cardiovascular neuropathy.

CONCLUSION

Thus, in children with type 1 diabetes mellitus who have recovered from COVID-19 infection, the development of cardiovascular disorders is associated with the complex interaction of metabolic, inflammatory, endothelial, and hemostatic factors. The established significant correlations between indicators of glycemic control (HbA1c), markers of systemic inflammation (hs-CRP, TNF-α), angiogenic activity (VEGF), coagulation potential (D-dimer, fibrinogen), as well as parameters of the structural and functional state of the myocardium (NT-proBNP, GLS, EF) indicate a pathogenetic connection between chronic

hyperglycemia, immunoinflammatory activation, and subclinical myocardial dysfunction.

The identified relationships confirm that metabolic decompensation and post-infectious inflammation play a key role in the development of early functional disorders of the myocardium and vascular regulation. This can be considered one of the leading mechanisms for the formation of cardiovascular neuropathy in children with type 1 diabetes in the post-COVID period.

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