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Risk of cardiovascular complications in patients with type 1 diabetes mellitus: focus on dyslipidemia and hyperglycemia

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Type 1 diabetes mellitus (type 1 DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic ß-cells leading to absolute insulin deficiency. In 2021, there were approximately 8.4 million people with type 1 DM worldwide. By 2040, the total number of cases is estimated to increase to 13.5-17.4 million. In Russia, according to the study in 2021, there are about 336 thousand patients with type 1 DM, by 2040 the number of patients is expected to increase 2.5-fold. People with type 1 DM have a 4-8 times higher risk of cardiovascular diseases (CVD) than the rest of the population. The underlying mechanisms of CVD development in type 1 DM are poorly understood. Optimal glycemic control without significant hypoglycemia is mandatory to reduce CVD in patients with type 1 DM. Although hyperglycemia plays an important role, CVD risk remains high even in well-compensated patients with type 1 DM, suggesting that other cardiovascular risk factors may be involved. Further studies are needed to research the factors involved in the premature development of CVD in patients with type 1 DM.

Keywords: type 1 diabetes mellitus, risk, cardiovascular diseases, atherosclerosis, complications.

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Type 1 diabetes mellitus: definition and epidemiology

Type 1 diabetes mellitus (type 1 DM) is a polygenic multifactorial disease based on immune-mediated or idiopathic destruction of pancreatic ß-cells leading to absolute insulin deficiency. Type 1 DM develops in the presence of genetic predisposition, which requires environmental factors that act as a trigger of autoimmune damage of pancreatic ß-cells. Both infectious and non-infectious factors can act as triggers [1].

In most individuals, changes in insulin secretion and glucose tolerance occur within 1 to 3 months after islet antibodies are detected. After a critical mass (it is not known exactly which one) of ß-cells is destroyed, disease manifestation occurs with the need for administration of exogenous insulin. Manifestation occurs after a "latent phase" that lasts from several months to many years, which in individuals with a genetic predisposition and several types of antibodies can be considered as asymptomatic type 1 DM.

The main mechanisms of trigger factors action are: activation of polyclonal lymphocytes (e.g., by infectious agents); molecular mimicry, i.e., the identity of protein sequence regions of an infectious or chemical agent and autoantigens; and increased immunogenicity, which induces an immune response. These mechanisms eventually trigger the development of autoimmune processes and lead to the production of various autoantibodies, the most significant of which are autoantibodies to insulin (IAA), glutamate decarboxylase (GADA), islet cells (ICA), tyrosine phosphatase-like protein (IA-2A), zinc transporter (Zn-T8A) [1].

In 2021, there were approximately 8.4 million people with type 1 DM worldwide: of these, 18% were younger than 20 years of age, 64% were aged 20–59 years, and 19% were aged 60 years or older. It is estimated that one in five deaths from type 1 DM occurred in people younger than 25 years of age due to hypodiagnosis. Traditionally, type 1 DM has been considered a disease that begins at an early age. However, the findings will demonstrate that numerically more adults than children are diagnosed each year (316,000 vs. 194,000 new cases worldwide in 2021), with a median age at diagnosis of 32 years. About 35,000 patients with undiagnosed type 1 DM died within 12 months of symptom onset. One fifth (1.8 million) of people with type 1 DM lived in low-income and lower-middle-income countries. In Russia, according to the study in 2021, there are about 336 thousand patients with type 1 DM. By 2040, the authors project an increase in the total number of cases to 13.5–17.4 million (60–107% more than in 2021), with the greatest relative increase in low- and lower-middle-income countries. It is expected that by 2040, the number of people with type 1 DM will increase 2.5-fold [2].

Type 1 diabetes mellitus and risk of cardiovascular diseases

Individuals with type 1 DM have a 4–8 times higher risk of cardiovascular diseases (CVD) than the general population [3,4]. The pathophysiology of type 1 DM is characterized by rapid and early autoimmune destruction of pancreatic β-cells, which leads to hyperglycemia and the need for lifelong insulin replacement therapy. Hyperglycemia is one of the most important cardiovascular factors; The highest all-cause mortality in people with diabetes was at HbA1c levels above 9.0% (HR=1.69; 95% CI 1.09 to 2.66) and in people without diabetes was at HbA1c levels above 6.0% (HR=1.74; 95% CI 1.38 to 2.20). However, both diabetic and non-diabetic populations with lower HbA1c levels (below 6.0% HR=1.57; 95% CI 1.14 to 2.17 and below 5.0% HR=1.19; 95% CI 1.04 to 1.36, respectively) had higher all-cause mortality [5]. Consequently, it can be argued that individuals with type 1 DM have a high risk of CVD, which remains the leading cause of death for this patient group. Despite improved control of some classic risk factors (RF), including effective glycemic control, cardiovascular morbidity and mortality are

still significantly higher than in the general population. In routine clinical practice, estimation of cardiovascular risk (CVR) in individuals with type 1 DM using scales or equations is often inaccurate because much of the evidence comes from pooled samples of people with type 2 and type 1 DM or from extrapolation of studies conducted on patients with type 2 DM. Given that type 1 DM occurs at a young age, long-term exposure to the disease and its consequences (e.g., hyperglycemia, changes in lipid metabolism, or inflammation) have a detrimental impact on cardiovascular health. It is therefore crucial to have tools that allow early identification of individuals at higher risk of CVD and thus be able to make the most appropriate management decisions on a case-by-case basis.

Atherosclerosis is known to be responsible for the majority of cardiovascular events (CVE). Individuals with diabetes have pathophysiologic changes that contribute to the development of atherosclerosis and may imply greater vulnerability to atheromatous plaques. Carotid atherosclerosis in type 1 DM is associated with many pathologies and changes associated with a higher risk of CVD. These include; high systolic blood pressure (SBP) [6], pre-eclampsia [7, 8], retinopathy [9, 10], insulin resistance [11, 12], excessive body weight [13], increased left ventricular mass [14], cerebral microhemorrhages [15], cognitive impairment [16], inflammation and endothelial dysfunction [17, 18].

Screening of subclinical atherosclerosis using various methods, mainly imaging, has proven valuable for predicting cardiovascular events. Its use allows the determination of CVD risk category and, therefore, the individualization of therapeutic treatment. However, the available data on individuals with type 1 DM are insufficient to reevaluate CVR. In a cross-sectional study involving 289 adults with type 1 DM without symptoms of peripheral arterial disease (PAD), an ankle-brachial index (ABI) level < 0.9 was determined in 6% and ABI > 1.2 in 26%. In 15% of patients with abnormal ABI, carotid atherosclerosis was detected by ultrasound, and 40% had asymptomatic PAD confirmed by ultrasound Doppler ultrasonography of lower limb arteries and/or ankle brachial index [19].

One meta-analysis showed that patients with type 1 DM had significantly greater carotid intima-media thickness (standardized mean difference (SMD): 0.89; 95% confidence interval (CI) 0.69 to 1.09; P < 0.001)), lower endothelium-dependent vasodilation (SMD: –1.45%; 95% CI -1.74 to -1.17; P < 0.001), increased carotid pulse wave velocity (SMD: 0.57; 95% CI 0.03-1.11; P < 0.001), and decreased glyceryl trinitrate-mediated carotid dilatation (SMD: -1.11; 95% CI -1.55 to –0.66; P < 0.001) compared with a control group of patients without DM [20].

International studies on cardiovascular diseases in type 1 diabetes mellitus

Analysis of data from clinical trials investigating the association of type 1 DM and CVD reveals some patterns. In a study using data from the Swedish and Scottish registers, 4070 and 3429 (men and women) with type 1 diabetes in Scotland and 4014 and 3956 (men and women) in Sweden aged 65 years and older had a 100% risk of developing CVD ≥10% in the next 10 years [21]. Also, when determining the 5-year model of CVR from data of the Swedish National Registry in patients with type 1 DM, the adjusted risk ratios for fatal/non-fatal CVD were 2.76 (2.21–3.44) for duration of diabetes; 1.47 (1.21–1.78) for patient age at onset of CVD; 1.26 (1.09–1.45) for the logarithm of the ratio of total cholesterol to high-density lipoprotein cholesterol; 1.19 (1.03–1.38) for the logarithm of HbA1c; 1.76 (1.27-2.46) for tobacco smoking; 1.52 (1.10–2.10) for macroalbuminuria (> 200 μg/min); 3.51 (2.54–4.84) for prior CVD, with a C-index of 0.83, with sensitivity and specificity of 72% and 77%, respectively, for the upper quartile of predicted risk [22].

27,195 people with type 1 diabetes and 135,178 controls without diabetes participated in another study based on the Swedish National Registry. During the follow-up period, 959 people with type 1 diabetes and 1501 controls died (median follow-up was 10 years). The corresponding risk ratios for individuals who developed type 1 DM at age 26-30 years were 2.83 — of which 3.64 were for all-cause mortality: 2.78 (2.29–3.38) — cardiovascular mortality; 3.85 (3.05–4.87) — for non-cardiovascular mortality. For CVD: 6.08 — for coronary heart disease, 5.77 — for acute myocardial infarction (MI), 3.22 — for stroke, 5.07 — for heart failure, and 1.18 (0.79–1.77) — for atrial fibrillation. And excess risk differed up to fivefold between age groups. The highest overall incidence rate observed for all-cause mortality was 1.9 (95% CI 1.71–2.11) per 100,000 person-years for people with type 1 DM [23].

Experts from the Steno Diabetes Center in Gentofte, Denmark, also proposed a CVR model based on data from 4996 adult patients with type 1 DM from 2001

to 2013. The final CVD prediction model was validated on another population of 2119 patients with type 1 DM. Over a median follow-up period of 6.8 years (interquartile range 2.9–10.9), 793 (18.4%) patients developed CVD. For the 5-year risk of developing CVD, the discriminatory C-index was 0.826 (95% CI 0.807-0.845) for the primary study and a C-index of 0.803 (95% CI 0.767–0.839) for the follow-up data. The Hosmer-Lemeshow test showed good calibration (P >0.05) in both cohorts [24]. The Epidemiology of Diabetic Complications (EDC) prospective cohort study conducted in Pittsburgh, USA included patients at age 27 years with type 1 DM which started in childhood (aged <17 years) and a mean duration of diabetes of 19 years/median of 18 years. Major atherosclerotic CVE (CVD death, MI or stroke) were associated with diabetes duration, albumin excretion rate, baseline SBP, smoking and mean HbA1c [25].

Glycemic control and cardiovascular outcomes in type 1 diabetes mellitus

Data from the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study provided evidence-based conclusions about the beneficial effects of better glycemic control on cardiovascular events in patients with type 1 DM. In the DCCT study, the incidence of cardiovascular events was very low in patients receiving intensive therapy and fewer cardiovascular events were observed than in the conventionally treated group, although without statistically significant differences. After completion of DCCT, 93% of patients agreed to participate in the EDIC follow-up study. Age-adjusted higher levels of mean HbA 1c levels estimated by the Cox proportional hazards model were associated with an increased risk of cardiovascular death (hazard ratio (HR)=5.19), acute MI (HR = 4.98), stroke (HR = 3.07), congestive heart failure (HR = 4.82), transcatheter coronary angioplasty/aortocoronary artery bypass grafting (HR = 5.40), and angina pectoris (HR = 4.75), but not with asymptomatic myocardial infarction (HR = 1.12) during 29 years of follow-up. Compared with conventional therapy, intensive treatment reduced the risk of any CVE by 51%; the risk of non-fatal MI, stroke, or death from CVD by 34%. [26]. In the DCCT/EDIC study, higher HbA1c levels were strongly associated with age and arterial hypertension in relation to CVD risk (HR = 3.94), [27]. According to the results of a meta-analysis, intensive glycemic control maintains the long-term incidence of serious CVD, especially in patients with diabetes duration <10 years at baseline, without increasing their prevalence of CVD during follow-up > 10 years [28].

Correction of lipid metabolism disorders in type 1 diabetes mellitus

Although lipid and lipoprotein levels are often within the normal range in patients with type 1 DM, low-density lipoprotein cholesterol (LDL-C) levels are a significant predictor of CVE and mortality in patients with type 1 DM, especially those with early onset type 1 DM (aged ⩽10 years) and a duration of DM >20 years [29–31]. It is known that even type 1 DM patients with good glycemic control have some changes in lipoprotein composition and functionality, which may be important for CVD risk in type 1 DM patients. In a Korean study, it was shown that statin therapy, during a mean follow-up period of 9.9 ± 3.7 years in 931 patients with type 1 DM (8.5%) was associated with a reduced risk of ischemic stroke and MI (adjusted HR 0.76; 95% CI 0.66–0.88; p < 0.001) [32], at the same time, ezetimibe was more effective in lowering LDL-C in patients with type 1 DM compared with patients with type 2 DM, and in the group with type 1 DM, ezetimibe lowered LDL-C more than statins [33]. PCSK9 concentration is known to be increased in young people with type 1 DM [34], and PCSK9 inhibitors reduce LDL-C levels by 47.8% compared to placebo in patients with type 1 DM [35].

Conclusion

Type 1 DM is associated with a higher mortality rate from CVD than the general population. CVD are a major cause of this mortality, but the underlying mechanisms are poorly understood. Lifestyle interventions and optimal glycemic control without significant hypoglycemia are mandatory to reduce CVD in patients with type 1 DM. Although hyperglycemia plays an important role, CVD risk remains high even in well-controlled patients with type 1 DM, suggesting that other factors of CVR may be involved. Further studies are needed to research the factors involved in the premature development of CVD in patients with type 1 DM to better predict and stratify CVD risk, and to clarify the age at which treatment with modern cardiovascular drugs should be initiated in young patients with type 1 DM. Potential targets for new therapeutic approaches to prevent the development and progression of sub-

clinical atherosclerosis in patients with type 1 DM should be identified.

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