Type 1 Diabetes and Cardiovascular Diseases in Children (Literature Review)

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ტიპი 1 დიაბეტი და გულ-სისხლძარღვთა დაავადებები ბავშვებში (ლიტერატურის მიმოხილვა)

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აბსტრაქტი

შესავალი: ტიპი 1 დიაბეტი (T1D) ხასიათდება პანკრეასის ინსულინის სეკრეციის ბეტა უჯრედების შერჩევითი განადგურებით. 1 ტიპის დიაბეტის (T1D) განვითარების მექანიზმები ბოლომდე არ არის გარკვეული, თუმცა, საყოველთაოდ მიღებულია, რომ ტიპი 1 დიაბეტი გამოწვეულია გენეტიკური და გარემო ფაქტორების კომბინაციით.

ტიპი 1 დიაბეტით დაავადებულ პირებს აქვთ გულ-სისხლძარღვთა დაავადებების განვითარების ჭარბი რისკი და მცირე სიცოცხლის ხანგრძლივობა.

ჩვენი კვლევის მიზანია ტიპი 1 დიაბეტისა და გულ-სისხლძარღვთა დაავადებების ურთიერთკავშირის მიმოხილვა ბავშვთა ასაკში.

მეთოდები: ლიტერატურის ძიება ჩატარდა PubMed/MEDLINE, Web of Science, Google Scholar და Cochrane Library (The Cochrane Database of Systematic Reviews) მონაცემთა ბაზებში. გამოიყენებოდა შემდეგი საკვანძო სიტყვები "ტიპი 1 დიაბეტი", "გენეტიკური მიდრეკილება", "დისლიპიდემია ბავშვებში", „რისკის შეფასება“, „ანთებითი პასუხი“.

შედეგები: ლიტერატურის მიმოხილვამ აჩვენა, რომ T1D-ის მქონე ბავშვებში გულ-სისხლძარღვთა დაავადებების მოდიფიცირებადი რისკის ფაქტორებია: დისლიპიდემია, ჰიპერგლიკემია, სიმსუქნე, ინსულინრეზისტენტობა, ჰიპოდინამია, რაც გენეტიკურ წინასწარგანწყობასთან ერთად განსაზღვრავს გულ-სისხლძარღვთა დაავადებების განვითარებას.

დასკვნები: T1D-ის მქონე ბავშვებში საჭიროა გულ-სისხლძარღვთა დაავადებების რისკის ფაქტორების ადრეული გამოვლენა და პრევენცია;

აუცილებელია შესწავლილ იქნას გულ-სისხლძარღვთა დაავადებების რისკის ფაქტორები T1D-ის მქონე ბავშვებში პოპულაციური თავისებურებების გათვალისწინებით.

საკვანძო სიტყვები: ტიპი 1 დიაბეტი, კარდიო-ვასკულური რისკი, გენეტიკური ფაქტორები, რისკის მოდიფიცრებადი ფაქტორები.

Abstract

Background: Type 1 diabetes (T1D) is characterized by the selective destruction of insulin-secreting beta cells in the pancreas. The exact mechanisms underlying T1D are not fully clarified; however, it is widely accepted that type 1 diabetes is caused by the combination of

genetic and environmental factors. Individuals with T1D have an elevated risk of developing cardiovascular diseases (CVD) and a reduced life expectancy.

Our research aims to review the interrelationship between type 1 diabetes and cardiovascular diseases in children.

Methods: We performed a comprehensive literature search in the PubMed/MEDLINE, Web of Science, Google Scholar, and Cochrane Library (The Cochrane Database of Systematic Reviews) databases. Our search employed the following keywords and their combinations:

“type 1 diabetes”, “genetic predisposition”, “dyslipidemia in children”, “risk assessment”, “inflammatory response”

Results: A review of the literature showed that in children with T1D, modifiable cardiovascular risk factors include dyslipidemia, hyperglycemia, obesity, insulin resistance, and sedentary lifestyle. Along with genetic predisposition, these factors determine the development of cardiovascular diseases.

Conclusions: Early identification and prevention of cardiovascular disease risk factors are necessary in children with T1D.
In addition, cardiovascular disease risk factors in children with T1D should be studied considering population-specific characteristics.

Keywords: type 1 diabetes, cardiovascular risk, genetic factors, modifiable risk factors, pediatric population

Introduction

Type 1 diabetes (T1D) is caused by the autoimmune destruction of pancreatic β-cells. Genetic factors have a significant influence on this autoimmune process, while environmental factors serve as triggers. Genetic factors are primarily associated with HLA antigens. The process of atherosclerosis is accelerated in individuals with T1D and begins in early childhood at the endothelial level.

Studies have shown that 14–45% of children with T1DM have at least two CVD risk factors[1]. Moreover, children with T1DM already demonstrate evidence of subclinical CVD,

which can be manifested by reduced arterial elasticity, increased carotid intima-media thickness, and endothelial dysfunction. The risk of endothelial damage seems to be further heightened in patients with inflammatory activity, indicating a possible interaction between systemic inflammation and HLA in vascular injury. Consequently, patients with type 1 diabetes present with cardiovascular disease that mainly stems from endothelial damage[2].

The goal of our research is to review the interconnection between type 1 diabetes and cardiovascular diseases in pediatric populations.

Methods

A literature search was conducted using the PubMed/MEDLINE, Web of Science, Google Scholar, and Cochrane Library (The Cochrane Database of Systematic Reviews) databases. We used the following keywords: “type 1 diabetes,” “genetic predisposition,” “dyslipidemia in children,” “risk assessment,” and “inflammatory response.”

Inclusion criteria:

- Publications from January 2014 to December 2024, covering various research designs such as prospective and retrospective observational studies, case-control studies, cross-sectional studies, and randomized, placebo-controlled trials.

Exclusion criteria:

1. Studies performed on animals or cell cultures.
2. Publications whose full text or abstract is not freely available.

Results

Type 1 diabetes (T1D) is an autoimmune disease with a strong genetic component [3,4]. It may occur at any age but usually develops in childhood, hence referred to as “juvenile diabetes” [5]. T1D is characterized by the destruction of pancreatic β-cells, culminating in absolute insulin deficiency [6]. As of 2014 data, approximately 387 million people worldwide have diabetes, of which 5–10% have T1D [7].

A high prevalence of dyslipidemia among children and adolescents with T1D increases the risk of atherosclerosis [8]. Worsening of the lipid profile in T1D among children is mainly due to elevated serum triglycerides and VLDL concentrations. Even with relatively good glycemic

control, patients with T1D exhibit multiple qualitative and functional lipoprotein abnormalities that are potentially atherogenic[9].

Cardiovascular disease (CVD) is the leading cause of mortality in patients with type 1 diabetes (T1DM); the cardiovascular risk (CVR) remains high even in T1DM patients who achieve good metabolic control[10]. BMI, LDL, and HDL play a mediating role in the correlation between T1D and CVD. T1D has also been associated with small vessel stroke (SVS). Strategies focused on sustained reductions in HbA1c may potentially reduce the risk of CVD [11].

Adolescence is a period when the first signs of vascular complications appear and represents a critical window for interventions. Teenagers with T1D have early signs of cardiovascular complications due to multiple cardiometabolic risk factors. Poor glycemic control is one of the main risk factors and a primary target of therapy. However, only a small percentage of adolescents with T1D achieve the recommended glycemic targets. Hypertension, dyslipidemia, smoking, alcohol consumption, obesity, and insulin resistance are common cardiometabolic risk factors in this age group. Recent data confirm that screening for these risk factors is suboptimal, and the use of pharmacological interventions for hypertension and dyslipidemia remains low. Additionally, there is still insufficient data on non-insulin agents in this age group[12].

Risk factors are divided into modifiable and nonmodifiable (i.e., manageable and unchangeable) factors [13]:

Modifiable	**Nonmodifiable**
Obesity	Younger age of diabetes onset
Waist circumference	Family history
Insulin resistance	Longer diabetes duration
Hyperglycemia	
Hypoglycemia	
Glucose variability	
Hypertension	
Microalbuminuria	
Dyslipidemia	
Smoking	
Alcohol	

Avoiding these manageable factors reduces the risk of CVD. Worse glycemic control is observed in adolescent girls compared to boys, and they have a higher incidence of microvascular complications[16]. Girls also have higher mean BMI, fat mass adjusted for height, resting heart rate, insulin, triglycerides, and non-high-density lipoprotein cholesterol (HDL-c), along with lower muscle mass (adjusted for height) from birth or mid-childhood up to age 18. For instance, the average non-HDL-c in girls at birth is 0.07 mmol/L (95% CI: 0.04–0.10) higher than in boys, and by age 18, this difference increases to 0.19 mmol/L (95% CI: 0.16–0.23). Girls present lower glucose levels from mid-childhood onward, as well as lower systolic blood pressure and higher HDL-c from mid-adolescence[17].

The alarming global rise in obesity (with an estimated prevalence of 12.5–33%) also affects children with T1DM [18]; obesity itself is a risk factor for cardiovascular disease and can complicate optimal diabetes control. An important determinant of both diabetes and cardiovascular disease may be the early onset of a proinflammatory state[20]. Central obesity and physical inactivity correlate with a proinflammatory state, common even among overweight or obese young T1D patients. Compared to normal-weight children, overweight/obese youth with T1D have a significantly higher risk of CVD[20]. Nonetheless, low-grade inflammatory processes are also observed in normal-weight children with T1D[21]. Elevated levels of proinflammatory cytokines have been described in T1D[22,23]. Chronic, persistent systemic inflammation from childhood accelerates cholesterol plaque formation and fosters plaque growth[24].

Frequent infection recurrence appears to be an independent predictor of T1D risk[25]. About 45% of mothers report a gestational respiratory infection[25]. It is suggested that prenatal exposure may influence the immune system’s development after birth. Endothelial cell injury and inflammation occupy a central place in atherogenesis, participating not only in the onset and progression of atherosclerosis but also in complications such as myocardial infarction and stroke [26,27]. Both bacterial and viral infections are associated with pre-atherosclerotic changes in the arteries and coronary artery disease [28.29].

Vascular endothelial dysfunction, accelerated thickening of the arterial intima, and altered ventricular function enhance cardiovascular morbidity in T1DM. Studies have demonstrated left ventricular diastolic dysfunction. Children with diabetes show a significantly longer QTc interval compared to control subjects ($P < 0.001$). Diabetic children have higher hsCRP, increased circulating endothelial cells (CEC), thicker carotid intima-media thickness (IMT), and lower vitamin C levels than the control group ($P < 0.001$ for each). A positive correlation has been

detected between CEC and HbA1c (P = 0.004). Changes in myocardial function and endothelial dysfunction may begin early, associated with initial atherosclerotic changes, and are accelerated by poor glycemic control. The authors recommend early and careful monitoring of cardiac and endothelial function changes in diabetic children[30].

As noted, inflammation is an essential part of atherosclerosis, including in the early stages of type 1 diabetes. In one study, 314 diabetic patients aged 8–18 were compared with a healthy control group (n = 120) by measuring VCAM-1, ICAM-1, E-selectin, P-selectin, TNFα, IL-6, CRP, MCP-1, IL-18, MMP-9, and TIMP-1. Most markers were significantly higher in the diabetes group compared to controls. Except for MCP-1 and MMP-9, they showed a significant correlation with HbA1c; the correlation with VCAM-1 was negative. In the control group, significant correlations were not identified. These markers were only partially connected to traditional risk factors. The largest difference between diabetic patients and controls was for CRP, which also showed the strongest correlation with HbA1c[31].

The genetic contribution to T1D risk has been investigated through various study designs, mostly in European populations. Monozygotic twins show a concordance rate of 40–60%, while dizygotic twins have a concordance rate of ~8% (similar to sibling risk). The sibling risk is ~16 times higher than in the general population, indicating a significant Genetic contribution [32]. Unlike many other complex, multigenic diseases, T1D genetics is dominated by a single locus—the major histocompatibility complex (MHC) region on the short arm of chromosome 6 (6p21.3). The MHC region is ~4 Mb in size, contains >100 genes, and many of these genes function in adaptive and innate immune responses. The MHC region is associated with multiple autoimmune diseases. It has been shown that MHC genetic variability contributes ~40% of the genetic risk in T1D [33]. While there may be numerous potential candidate genes in the MHC, most studies have centered on the classical class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DPA1, HLA-DPB1) loci. Specific amino acid residues in HLA-DRB1 and HLA-DQB1 appear to influence the binding of foreign peptides (antigens), which underlies the autoimmune process [34]. Much of the genetic risk in the MHC appears to be associated with interactions among specific classical HLA alleles[35]. HLA genes, extensive linkage disequilibrium, and structural variations complicate the identification of causal variants, regulatory effects, and immunoregulatory mechanisms [36].

Genetic predisposition plays a major role in beta-cell autoimmunity and destruction. HLA regions are the most potent genetic determinants, contributing 40–50% of the risk for T1D

development. Other genes, such as INS, also increase disease risk. The mechanisms by which T1D-susceptible genes act may be related to their roles in antigen presentation, beta-cell autoimmunity, immune tolerance, and autoreactive T-cell responses. From an epigenetic perspective, pathogenic mechanisms leading to T1D can involve DNA methylation, histone modification, microRNAs, and molecular mimicry. These mechanisms can function through regulation of gene expression, prompting an immune response against beta cells [37].

Insulin resistance has been associated with the presence and progression of coronary artery calcification—a surrogate marker for coronary artery disease and a strong predictor of adverse outcomes. In patients with T1D, insulin-mediated suppression of free fatty acids is impaired[38].

A study conducted in Jordan showed that 36.7% of participants had dyslipidemia. There were no significant differences between dyslipidemic and normolipidemic individuals based on diet type, except for a significantly higher median vitamin B12 intake in the dyslipidemic group compared to the normolipidemic group (3.6 vs. 2.7 μg, P=0.046) [39].

Research has demonstrated that consuming fish, vegetables, fruits and berries, low-fat liquid dairy products, and vegetable oil-based fats, while limiting intake of sweet pastries, sweets, soft drinks, and salt, can be beneficial for reducing systemic inflammation in T1D[40]. Vitamin C supplementation may also reduce the risk of complications [41].

In individuals with T1D, the most significant risk factor for CVD is older age (HR 1.54 per 5 years; 95% CI 1.36, 1.73; Z=7.07, P<0.001). The next most significant factor is time-weighted average HbA1c (HR 1.31 per 1%; 95% CI 1.15, 1.50; Z=4.0, P<0.001). Other nominally significant variables included higher mean systolic blood pressure (Z=3.1, P=0.002), higher triglycerides (Z=3.0, P=0.003), higher mean pulse rate (Z=2.8, P=0.005), longer diabetes duration (Z=2.5, P=0.02), use of ACE inhibitors (Z=−2.3, P=0.03; protective), family history of myocardial infarction (Z=2.15, P=0.04), and higher mean LDL-c (Z=2.07, P=0.04) [42].

Three cornerstones of T1D management are glycemic control, nutritional therapy, and physical activity. The main objectives of therapy are to maintain blood glucose within a proper range (close to normoglycemia) with minimal episodes of hypo- and hyperglycemia, and to reduce macro- and microvascular complications.[43]

Even though clinical manifestations of cardiovascular diseases (CVD) usually appear in adulthood, vascular damage can start early in T1D, and evidence of subclinical CVD may already

be identified in adolescence. In T1D patients, the risk of death from cardiovascular events is 2–10 times higher than in the general population [44]. Therefore, the American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend periodic screening and, ultimately, appropriate treatment for hypertension, dyslipidemia, smoking, and nephropathy [45].

Conclusions

1. In children with T1D, early detection and prevention of cardiovascular risk factors are necessary.
2. Cardiovascular risk factors in children with T1D should be studied with attention to population-specific characteristics.

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