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CARDIOVASCULAR RISK ASSESSMENT IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Abstract

Cardiovascular disease (CVD) is a major cause of death in type 1 diabetes mellitus (T1DM). Management of CVD risk factors in T1DM patients is based on evidence, mostly extrapolated from T2DM studies. Hyperglycemia, leading to the induction of oxidative stress, is considered a key pathophysiological mechanism for the development of micro- and macrovascular complications. Biochemical processes related to it directly damage monocyte function, and also indirectly affect the function of monocyte cells, through the synthesis of growth factors, cytokines and vasoactive mediators in other cells. However, the epidemiologic relationship between glycemia and CVD is not fully understood. The aim of the present review is a systematic analysis of potential laboratory biomarkers for the assessment of cardiovascular risk in T1DM patients, with particular attention paid to asymmetric dimethylarginine (ADMA), adiponectin (ADPN) and osteoporotegerin (OPG) as such. The available literature suggests a significant burden of CVD in patients with T1DM and poor management of risk factors. This is based on the poor evidence base for therapeutic management of CVD risk in T1DM patients. The clinical implications of the epidemiological and pathophysiological aspects of the relationship between T1DM and CVD are discussed. We have reviewed the available literature noting areas where sufficient clarity is lacking. More and more clinical studies are validating the capabilities of new classes of laboratory biomarkers that characterize cardiovascular changes in patients with T1DM.

Keywords: type 1 diabetes mellitus (T1DM), cardiovascular disease (CVD), hyperglycemia, oxidative stress, endothelial dysfunction, laboratory biomarkers.

Introduction

Cardiovascular disease (CVD) is a major cause of death in patients with type 1 diabetes mellitus (T1DM) 1. The evidence for this is mainly extrapolated from studies of patients with type 2 diabetes mellitus (T2DM). Based on a systematic analysis of literature data, it is established that a significant number of patients with T1DM are exposed to cardiovascular risk factors2. When following the progression of T1DM, it is reported that the first cases of clinically manifested

CVD appear at the end of the third and the beginning of the fourth decade of the patients' life, regardless of the duration of diabetes 1,2.

According to several epidemiological studies, there is no clearly established glycemic threshold for cardiovascular risk in patients with T1DM, which respectively necessitates the need for additional studies in this direction. Mechanisms that link hyperglycemia to CVD include formation of non-enzymatic glycation products, free radicals, etc. Besides having a direct damaging effect on endothelial cells, free radicals also oxidize non-enzymatic glycation products, thereby potentiating their atherogenicity. Accumulation of glycation end products in the extracellular matrix impairs gastrointestinal function through several pathways 3 .

Glycated collagen types I and IV inhibit the normal formation of intercellular substance and the cross-linking of molecules, in which the normal elasticity of arteries is reduced, the aglycated molecules of the matrix interact with mononuclear cells and with macromolecules such as LDL and act as oxidases. In addition, glycated plasma proteins can interact with corresponding receptors of different cell types - macrophages, monocytes, etc. 3,4 Validation of potential laboratory biomarkers is recommended for accurate prediction and diagnosis of cardiovascular disease (CVD) risk in T1DM.

Oxidative stress, single cell dysfunction and T1DM

Chronic hyperglycemia associated with oxidative stress is considered a key pathophysiological factor forming micro- and macrovascular complications in patients with diabetes 4. Hyperglycemia - induced overproduction of super oxides by the mitochondrial electron transport chain is assumed to be a key moment in the activation of all remaining pathways involved in the pathogenesis of diabetic complications4. Superoxide generation is accompanied by increased formation of nitric oxide (NO) by endothelial NO synthetase. Formed in large quantities, NO has a toxic effect. With an excess of superoxide radicals in the cell, they form with NO a permanent peroxynitrate anion that damages DNA and activates lipid peroxidation, potentiating the metabolism of arachidonic acid 3,5. The peroxynitrite anion stimulates the accumulation of Ca ions in the mitochondria, thereby disrupting the processes of tissue respiration and oxidative phosphorylation. As a result, acute endothelial dysfunction develops 5. The generation of NO from arginine under the action of nitric oxide synthetase (NOS) is subject to highly specific regulation. NO in physiological concentrations inhibits the adhesion of platelets and immune cells to the vascular wall and maintains the underlying vascular musculature at rest 6. There are three types of NOS: neuronal, immune, and endothelial. Neuronal type (nNOS) is expressed in the cytosol of nerve cells and is involved in the process of neurotransmission. The innate type (iNOS) is expressed in alveolar macrophages, other immune cells, and is involved in immune defense. Endothelial NOS (eNOS) is expressed in endothelial cells and is considered the largest determinant of vascular tone 6 . A cofactor of eNOS is tetrahydrobopterin (BH4). NAD(P)H-oxidase to produce superoxide, which in turn uncouples eNOS, causing even more superoxide to be produced. In the presence of prolonged hyperglycemia, tissue proteins such as collagen are non-enzymatically glycated, thus forming advanced glycation end products (AGES). AGES potentiate persistent chemical modification of proteins, stimulate cellular responses through specific antiproliferative receptors, and reduce the availability of endothelial NO5,6. Under normal conditions, the endothelium lowers vascular tone, limits leukocyte adhesion and inflammatory processes in the vascular wall. It maintains vascular permeability for nutrients, hormones, other macromolecules and leukocytes, inhibits platelet adhesion and aggregation through the production of prostacyclin and NO, limits the activation of the coagulation cascade through the interactions thrombomodulin/protein C, heparan sulfate/antithrombin and tissue factors/inhibitors of tissue factors. At the same time, it regulates fibrinolysis through t-PA and its inhibitor PAI-15,7,8. NO inhibits leukocyte adhesion and affects the cytokine-induced expression of VCAM-1 (vascular cell adhesion molecule 1) and MCP-1 (monocyte chemoattractant protein 1) – effects that are partly due to the inhibition of the transcription factor NF-kB (nuclear factor kB)3.

The duration of diabetes was a determinant of the presence of endothelial dysfunction, correlating negatively with endothelium-dependent dilatation. Endothelial dysfunction is usually observed already in the first decade of T1DM9,10. Children with T1DM have increased oxidative stress and reduced antioxidant protection compared to healthy children and their parents11. These results were similar among adolescents with T1DM12. Furthermore, endothelial progenitor cells are also reduced in children with T1DM, possibly associated with oxidative stress, compared to non-diabetic controls13. According to literature data, patients with T1DM and HbA1c above 6% show a significant impairment of endothelial function compared to patients whose HbA1c is below 6%, which respectively means that chronic hyperglycemia correlates positively with endothelial dysfunction in DM type 114. On the other hand, repeated episodes of hypoglycemia in patients with T1DM have also been found to induce endothelial dysfunction15. Acute hypoglycemia causes a rapid proinflammatory, platelet-aggregating, and antifibrinolytic response, as well as changes in hemostasis. The pathogenetic role of glucose variability is gaining increasing evidence and support, but its role is still not fully understood.

Microalbuminuria in patients with T1DM, in turn, is also positively correlated with endothelial dysfunction16. According to literature data, in patients with T1DM older than 5 years, poor glycemic control and microalbuminuria, flow-induced dilatation (FMD) is significantly impaired16 According to a study of 45 children with T1DM, a lower peak FMD response was reported and increased carotid artery intima thickness (IMT) compared to healthy children16 A directly proportional relationship between FMD and HbA1c was established in patients with T1DM and endothelial dysfunction16.

In contrast, according to some researchers, an inverse correlation was observed between FMD and mean HbA1c in the first 2 years after diagnosis of T1DM17. The most likely explanation for this is that endothelial function may be more affected by long-term versus short-term poor glycemic control, supporting the concept of metabolic memory. Therefore, the first years of T1DM are decisive for the development of potential endothelial dysfunction18. Whether endothelial dysfunction is an intrinsic feature of T1DM and whether moderate hyperglycemia is a sufficient cause of endothelial dysfunction is not fully understood in the available literature.

Inflammation and T1DM

Limited literature data suggest that inflammatory processes are more pronounced in primary T1DM patients compared to non-diabetic control patients4. Type 1 diabetes is an autoimmune disease characterized by immune-mediated destruction of pancreatic islet b-cells and subsequent insulin deficiency. This leads to metabolic disorders with chronic hyperglycemia as the main feature, which in turn determines the production of AGEs, activation of microphages, increased oxidative stress and production of inflammatory cytokines19.

Several recent studies have shown the relationship between acute hypoglycemia and indices of systemic inflammation, including increased CD40 expression and plasma CD40 ligand concentration, greater platelet aggregation, and increased circulating plasminogen activator inhibitor (PAI-1), interleukin-6 (IL-6) and platelet aggregation markers20. Soluble interleukin-2 (IL-2) receptor and CD40 ligand have been reported to have higher values in patients with type 1 DM than in non-diabetic patients. In addition, soluble IL-2 receptor levels correlate with CVD progression in T1CD4. These studies suggest that acute hypoglycemia in T1DM also leads to complex vascular effects associated with the activation of proinflammatory, prothrombotic, and proatherogenic mechanisms. The increased production of inflammatory cytokines in patients with T1DM suggests that they contribute to the instability of the atherosclerotic plaque. PAPP-A, placental growth factor PIGF, soluble intracellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule-(sVCAM-1) E-selectin are considered as potential biomarkers showing plaque instability5,6. There is increasing evidence that patients with T1DM and developed micro-macrovascular complications have high inflammatory activity expressed by the expression of cytokines, mainly C-reactive protein (CRP), IL-6 and tumor necrosis factor-alpha (TNF-a). 20. CRP is a positive acute phase protein synthesized in the liver. CRP production is induced by cytokines (interleukin-1 (IL-1), IL-6, TNF-a) and its level increases in infections, inflammatory and malignant diseases, tissue injuries and necrosis. According to literature studies, CRP is elevated in the first year of diagnosis of T1CD21 IL-6 is a cytokine produced mainly by T-cells and macrophages and involved in the immune response. Some other cells, such as adipocytes and osteoblasts, also secrete IL-6. TNF-α is mainly synthesized by activated microphages, but also by CD4+ lymphocytes, NK-cells and neurons. TNF-a participates in systemic inflammation and stimulates the acute phase response.

Inflammation and oxidative stress in patients with T1DM play a key role in the development of vascular damage and atherosclerosis, respectively, associated with a high risk of mortality. According to literature data, the degree of micro- and macrovascular complications in T1DM correlates positively with the serum concentrations of CRP and TNF-a compared to patients without vascular complications21. A worsened lipid status with increased total cholesterol, LDL-cholesterol and triglycerides has also been reported, which favors the accumulation of fat cells on the arterial walls and is therefore a prerequisite for increased inflammatory activity in T1DM22. Lipid levels of adult patients with well-controlled T1DM were found to be similar to those of healthy controls23. Poor glycemic control, high BMI and insulin resistance are associated with dyslipidemia, identified as a risk factor for the development of CVD both in the general population and in patients with T1DM24. Other relatively innovative markers of inflammatory processes associated with CVD in type 1 DM are lipoprotein-associated phospholipase A2, serum endogenous secretory RAGE - receptor for glycated end products (sRAGE), plasma fibrinogen, apolipoprotein B-rich modified immune complexes, adiponectin, asymmetric dimethylarginine (ADMA) and osteoprotegen (OPG)4,1.

Hypercoagulability and T1DM

In type 1 DM, pathological qualitative and quantitative changes occur in the coagulation system. Plasma levels of procoagulant factors are increased while fibrinolytic activity is decreased. Hyperinsulinemia results in increased hepatic synthesis of prothrombotic factors as a thrombogenic medium. In addition, due to glycation and oxidation of coagulation factors, functional changes occur in them, increasing the risk of thrombosis, respectively CVD4.

Laboratory biomarkers for CVD risk assessment in type 1 DM

In 2001 a working group of the American Institute of Health standardized the definition of a biomarker as a parameter that can be objectively measured and is an indicator of a normal biological process or response to a therapeutic intervention1,25. The biomarker can be measured in a biological sample, its value can be registered from an apparatus test (ECG, measured arterial pressure, etc.) or from an image test (echocardiogram, computer tomogram, etc.)25. Research interest in biomarkers has increased in recent years. According to data from MedLine in 1990 only 21 studies on cardiovascular biomarkers were registered, while by 2010 their number had increased to 2032, showing a significant increase in the penultimate decade26. In 2014, compared to 2013, 37% more laboratory biomarker studies were conducted. However, only a few of them are routinely used in clinical practice. For example, such are fasting blood glucose, glycated hemoglobin, cardiac troponin T (cTnT), cardiac troponin I (cTnI) and B-type natriuretic peptide (BNP). Biomarkers should have high analytical and diagnostic reliability. The laboratory method of detection should be fast and low-cost, and the biological samples should be easily

accessible through an invasive method (blood and/or urine). Bimarkers should be used for different purposes25,26 such as:

- Early detection of disease;
- Assessment of acute and chronic clinical conditions;
- Risk stratification;
- Differential diagnosis;
- Selection of appropriate therapeutic treatment;
- Monitoring the patient's response to treatment.

The identification of early laboratory biomarkers for non-infectious chronic diseases such as T1DM is of utmost importance for the subsequent therapeutic strategy. In order to maximally simplify the approach to the management of cardiovascular risk (CSR) in patients with type 1 DM and respectively applied in clinical practice, it is recommended to use relevant laboratory biomarkers or a combination of several markers to calculate the Z-score. The mean Z-score for the inflammatory markers (CRP, IL-6, S ICAM-1 and secretory phospholipase A2) correlates positively with cardiovascular mortality and morbidity in patients with type 1 DM4 (Table 1)

In the current selection of potential biomarkers for the evaluation of SSR in patients with T1DM, we consider in more detail the following parameters: asymmetric dimethylarginine (ADMA), adiponectin and osteoprotegerin (OPG).

Asymmetric dimethylarginine (ADMA)

ADMA is a single-gene inhibitor of nitric oxide synthetase (NOS). The primary cause of vascular complications in patients with T1DM, as we have indicated, is considered chronic hyperglycemia. The latter disrupts ADMA-regulated NO-biosynthesis27.

ADMA is formed as a result of post-translational modification of arginine residues of various specific proteins in the cell nucleus. Methylation is catalyzed by a group of enzymes called protein-arginine N-methyltransferases (PRMTs). The human body produces about 300 umol/d (60mg) of ADMA. Of this amount, about 50 umol/d (20%) is excreted in the urine. Therefore, the rules of interpretation of its values in patients with kidney damage require special attention27,28. The remaining 80% is broken down by a specific enzyme called dimethylarginine - dimethylaminohydrolase (DDAH) into dimethylarginine and citrulline. DDAH has two isoforms: DDAH I, expressing tissues containing Nnos , and DDAH II - expressing in tissues containing eNOS. The activity of DDAH depends on the cysteine residue in the active site of the enzyme: a region sensitive to oxidation and nitrosylation28.

Mechanisms for diabetes-induced endothelial dysfunction involve increased oxidative degradation of NO. NO deficiency increases vascular resistance and promotes atherogenesis. Chronic hyperglycemia impairs the function of DDAH, and this leads to accumulation of ADMA, respectively to impaired exchange of NO and glucose-mediated mitochondrial production of reactive oxygen species. ADMA, in turn, additionally "resides" eNOS, causing O 2 molecules to become a substrate for electron transfer, rather than a substrate for the L-arc - NO metabolic pathway28. Serum levels of ADMA were determined by enzyme-linked immunosorbent assay (ELISA), with cross-reactivity of ≤0.5% for symmetrical dimethylarginine and ≤0.02% for L-arginine27 reported in the literature.

According to the reviewed literature, circulating ADMA levels correlate with cardiovascular risk factors in individuals with diabetes, such as arterial hypertension, hypercholesterolemia, age and smoking28.

Increased plasma levels of ADMA are associated with subclinical atherosclerosis. A positive correlation was established with the thickness of the intima of the carotid artery - a hemodynamically unstable area, vulnerable to nitric oxide deficiency and the formation of atheromatous plaques29. Individuals with diagnosed coronary pathology and elevated ADMA concentrations have twice the risk of developing AMI and stroke compared to individuals whose ADMA values are within reference limits30. The correlation between glycemic control and measured serum ADMA levels is not fully understood. A variable effect was found in patients with T1DM and T2DM. On the one hand, elevated ADMA values are found, determining it respectively as an independent risk marker for previous CVD in diabetics27,31. In patients with T2DM, ADMA plasma concentrations are significantly higher in the presence of albuminuria and microangiopathy compared to diabetics without complications and good glycemic control32. Serum levels of ADMA have been reported to be higher in both patients with T1DM without vascular complications compared to healthy controls 32. On the other hand, according to a study of pediatric patients (T1DM), reported serum concentrations of ADMA were significantly decreased and inversely related to HbA1c and blood glucose27. This suggests that ADMA production is probably suppressed in infancy to compensate and protect against hyperglycemia-induced vasculopathy27. The mechanisms by which glycemia lowers ADMA are not fully understood. These may include reduced ADMA synthesis, impaired transport between tissues, or increased renal excretion. Further studies are needed in this direction.

ADMA is considered a promoter of atherogenesis, blocking the vasoprotective effects of NO. The increased concentration of ADMA potentiates the progression of atherosclerosis and increases the risk of cardiovascular events in T1DM. Adiponectin Adiponectin (ADPN) is a protein hormone secreted from adipose tissue inversely correlated with BMI. ADPN circulates in the circulation in the form of trimers, hexamers and wax molecular complexes (HMW), the latter of which are considered to fulfill its biological role33. ADPN exerts anti-inflammatory and anti-atherogenic effects, suppressing the adhesion of monocytes to vascular monolayers and exerting a retarding effect on growth factor-associated proliferation of smooth muscle cells in the vascular wall.

Adiponectin

Adiponectin suppresses the inflammatory processes associated with atherosclerosis by inhibiting the expression of cytokinin and adhesion molecules in vascular endothelial cells and macrophages. The higher the content of the hormone secreted by the meat cells, the lower the risk of CVD34. Adiponectin counteracts the

accumulation of fat in the walls of arteries and respectively reduces the risk of thrombogenesis. However, on the other hand, ADPN also exerts a pro-inflammatory effect33. HMW-ADN activates the NFkB transcriptional pathway and consequently induces the secretion of IL-6, monocyte-hematotactic protein I (MCP-I, CCL2) and interleukin 8 (IL-8, CXCL-8) from monocytes. The chemokines MCP-I and IL-8 direct the immune system to inflammatory processes and mediate the migration of monocytes to the subendothelium – an early stage in the atherogenesis process. Monocytes in turn participate in the innate immune response. Cytokines and chemokines released by them condition the development of premature atherosclerosis and suppress immune activity34. In our country, ADPN has been well studied as a risk marker in children with obesity in preschool35 and prepubescent age36,37. According to the reviewed literature, low serum ADPN concentrations are a In patients with type 1 DM, the correlation between ADPN and the presence of vascular complications is not fully understood. Patients with T1DM and microvascular complications had higher serum ADPN levels than patients without complications ($p<0.0001$)1. It is necessary to clarify whether the increased concentration of ADPN is pathologically associated with the development of microvascular complications in type 1 DM or is a marker of a compensatory immune response. Recent studies have reported that increased serum ADPN levels play a protective role on CVD risk in patients with type 1 DM35ssociated with an increased risk of CVD and retinopathy in patients with T2DM 33

OSTEOPROTEGERIN (OPG)

OPG is a glycoprotein involved in bone metabolism, with a regulatory role in the immune and vascular systems. It is a member of the TNF-alpha superfamily. OPG competes with the receptor activator of nuclear factor kappa B-RANK for binding to its ligand (RANKL), thereby preventing its action on cells, and inhibits osteoclast activation. Therefore, OPG suppresses osteoclastogenesis and increases bone mineral density due to binding and neutralization of RANKL. OPG also competes with TRAIL (TNF-related apoptosis-inducing ligand). Thus, acting as a competitive receptor for RANKL and TRAIL, OPG inhibits the regulatory effects of nuclear factor-Kb on inflammatory, skeletal and vascular systems and prevents TRAIL-induced apoptosis38. The OPG molecule has been described to contain a heparin-binding domain. In vitro studies have shown a rapid release effect of OPG from smooth muscle cells after heparin administration. In in vivo studies with intravenous infusions of heparin in healthy subjects, a 2.2-fold increase in circulating OPG levels was observed within 5 minutes compared to baseline OPG40 levels. In addition, OPG levels are age- and sex-dependent, which must also be considered before determining a threshold or risk stratification. In recent years, there have been a number of studies that indicate that a high serum concentration of OPG is positively correlated with the severity of the atherosclerotic lesion, the severity of heart failure, unstable angina and acute myocardial infarction40. The initial atherosclerotic lesion involves changes in the vascular endothelium, and patients with diabetes mellitus exhibit endothelial dysfunction as well as CVD-related risk factors such as hypertension, obesity, and dyslipidemia. Thus, diabetes plays a critical role in the development of CVD. Based on the reviewed literature, OPG is considered a reliable laboratory marker with predictive value for CVD in individuals with diabetes. In our country, OPG has been studied in detail in men with type 2 DM. In the early subclinical phase of diabetes evolution, in which there are no known cardiovascular diseases41. A significant positive correlation was reported between OPG and HbA values in patients with T1DM, respectively DM type 240. After a study was done for registered higher serum levels of OPG in children with T1DM compared to healthy controls ($p<0.0001$), and a directly proportional dependence with glucose concentrations ≥7 mml/L and albuminuria ≥30mg/24h39 was established.

On the other hand, as the duration of diabetes progresses in patients with type 1 DM, an inverse relationship of serum OPG with the progression of atherosclerosis is established. This suggests that the duration of diabetes has a greater predictive value for the development of atherosclerosis than the age of the patient38. We did not find studies on its role in type 1 DM in the Bulgarian literature.

Despite growing evidence, the exact mechanism by which OPG, DM, and CVD are linked is still not fully understood, and the actual role of OPG in atherosclerotic calcification remains speculative. The introduction of OPG as a potential laboratory biomarker could be useful for better CVD risk stratification in DM patients as well as for ensuring adequate treatment.

Conclusion

Despite the known higher risk of CVD in patients with type 1 diabetes mellitus, the pathophysiology underlying the relationship between CVD, CVD risk factors, and T1DM is not well understood. Proposed approaches to reduce SSR are largely extrapolated from experience with T2DM. The available literature suggests a significant burden of CVD in patients with T1DM and poor management of CVD risk factors.

The available literature suggests a significant burden of CVD in patients with T1DM and poor management of CVD risk factors. One of the reasons is a lack of sufficient evidence base for therapeutic CVD risk management. Non-invasive laboratory tests should be used more frequently to detect subclinical damage in patients with T1DM, to further investigate the risks and benefits of therapeutic approaches to their management.

Research interest in biomarkers has increased in recent years. A major challenge in the validation of laboratory biomarkers is the development of a personalized approach, as well as the active collaboration between laboratory and clinical specialists. Biomarkers may play a critical role in classifying T1DM patients into subpopulations. In the present review article, we performed a systematic analysis of potential laboratory markers associated with cardiovascular risk in patients with T1DM, with a recommendation for their diagnostic validation in clinical practice.

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