

A review about biomarkers for the investigation of vascular function and impairment in diabetes mellitus

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Abstract: The aim of this review was to analyze the main biomarkers of vascular function and impairment in patients with type 2 diabetes. Medline, SCOPUS, Web of Science, and Google Scholar databases were searched. We concluded that proatherogenic adhesion molecules (soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and soluble E selectin) and inflammatory cytokines (high-sensitivity C-reactive protein, interleukin-6, and tumor necrosis factor- α) were elevated in type 2 diabetes mellitus. Their increased expression and release contribute to the accelerated atherogenesis typical of these patients. For these reasons, the early identification of high levels of these biomarkers will help to establish new strategies to reduce cardiovascular complications.

Keywords: biomarkers, vascular function, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus is responsible for high mortality rates, approximately twice that of the general population: micro- and macrovascular complications have been related to this disease.¹ Several epidemiological studies showed a strong relationship between type 2 diabetes and cardiovascular events:² diabetic patients have an incidence of triple vessel coronary artery disease or multivessel disease significantly higher compared to nondiabetics, and the severity of stenosis and total occlusion of vessels were more commonly seen in diabetic patients.³ This is because type 2 diabetes is involved and importantly implicated in the atherogenic process.⁴ Atherosclerosis is a well-known disease, where the progressive accumulation of cholesterol within the arterial wall plays the main role; this leads to the genesis of atheromatous plaques with consequent vascular narrowing. The rupture of these atheromatous plaques then leads to vascular occlusion, which may finally result in myocardial infarction, stroke, angina pectoris, or peripheral artery disease.^{5,6} Hyperglycemia, insulin resistance, hyperinsulinemia, hyperlipidemia (in particular elevated free fatty acids), and hyperhomocysteinemia are important pathophysiological components of type 2 diabetes mellitus that trigger systemic inflammation and impair nitric oxide (NO) bioavailability, with consequent impaired endothelial function.⁷

This review is aimed to analyze the biomarkers of vascular function and impairment in patients with type 2 diabetes; an early identification of these vascular abnormalities will allow study of new screening and therapeutic strategies in order to try to reduce the incidence of disease complications linked to atherosclerosis, especially in high-risk patients.

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Mechanism of endothelial damage in patients with type 2 diabetes

Hyperglycemia

Hyperglycemia, in particular postprandial fluctuations, has been linked to endothelial dysfunction, and, combined with absolute increases in glycemia, contributes to oxidative stress and endothelial impairment. Oral glucose tolerance test is the best experimental technique to estimate pancreatic response to a standardized glucose oral load. Previous published studies reported that Oral Glucose Tolerance Test increased some biomarkers involved in inflammatory response and endothelial impairment, such as high-sensitivity C-reactive protein (Hs-CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular adhesion molecule-1 (sVCAM-1), and soluble E selectin (sE-selectin).^{8,9} Hyperglycemia enhances the secretion of endothelin-1, a vasoconstrictor, in vitro and decreases NO production in the aorta of diabetic rats and coronary microvessels in humans. Moreover, postprandial glycemia induces glycation of protein, which forms cross-linked proteins termed advanced glycation end products, with consequent synthesis and release of cytokines, vasoadhesion molecules, endothelin-1, and tissue factor.

Insulin resistance and hyperinsulinemia

Under physiologic conditions, other than the hypoglycemic function, insulin has also a hemodynamic action at the endothelial level promoting the release of the precapillary sphincter, inducing vasodilatation.^{10,11} To do this, insulin directly regulates expression and activation of NO synthase, inducing NO production by endothelial cells. Actually, insulin regulates both vasoconstrictor (endothelin-1) and vasodilator (NO) mediators; in euglycemic patients, the vasodilator effect of insulin prevails, while in insulin-resistant patients, endothelin-1 production is preserved, but NO synthesis is altered.¹¹

Hypertriglyceridemia

Hypertriglyceridemia plays a role in the endothelial damage. We have already demonstrated in two previous studies we conducted that hypertriglyceridemia, in particular postprandial hypertriglyceridemia simulated by an oral fat load, is responsible for an elevated inflammatory state with an increase in metalloproteinase (MMP)-2 and MMP-9 and a decreased nitrites/nitrates ratio.^{12,13} The endothelial damage derived can cause an impaired release of smooth musculature endothelium-mediated, throughout an impaired release of NO.¹⁴

Hyperhomocysteinemia

Hyperhomocysteinemia is linked to cardiovascular diseases.¹⁵ Homocysteine is responsible for endothelial cell dysfunction and apoptosis of endothelial and smooth muscle cells involved in the atherothrombotic process.¹⁶ Homocysteine structure is characterized by a very reactive thiol group, easily oxidized to produce reactive oxygen species.¹⁷ On this basis, we can suppose that homocysteine induces cell dysfunction through autooxidation and oxidative damage. Moreover, homocysteine stimulates the production of several cytokines with proinflammatory action.¹⁸

Microalbuminuria

Microalbuminuria has been identified as a strong indicator of increased cardiovascular risk among patients with type 2 diabetes and also in patients without diabetes. Previous publications estimated that microalbuminuria causes a 2.4-fold increased risk for cardiovascular death compared to that in patients without microalbuminuria.^{19,20} If microalbuminuria is diagnosed, we must consider that cardiovascular risk is higher, and patient requires a more “aggressive” intervention for the prevention of cardiovascular events.²¹

Inflammatory markers

Inflammation plays a key role in the genesis and progression of atherosclerosis. In patients with type 2 diabetes, the inflammatory markers are higher than those in nondiabetic patients, as already shown in several studies.²²

In particular, TNF- α is one of the main characters in the acute phase reaction. It is produced mainly by activated macrophages and also by monocytes, T-cells, smooth muscle cells, adipocytes, and fibroblasts. TNF- α has important proinflammatory properties and regulates the innate and adaptive immunity, cell proliferation, and apoptosis.²³ TNF- α is also able to induce proatherogenic lipoprotein changes and to reduce insulin sensitivity.²³

Another important inflammatory marker is Hs-CRP, mainly synthesized by hepatocytes; high levels reflect active systemic inflammation. The Multiple Risk Factor Intervention Trial, for example, was the first trial to show a strong link between high Hs-CRP and high mortality from coronary heart disease.²⁴ These data were then confirmed by many other primary prevention, prospective epidemiological trials; in the area where ischemia and necrosis occurred, an increase in inflammatory cytokine has been reported.²⁵ The increase in Hs-CRP seems linked to the extension of infarct and with increased possibility of cardiac rupture.²⁶

On the other hand, myeloperoxidase (MPO) is a leukocyte-derived enzyme, it is the main protein in neutrophils, but it is also present in monocytes. MPO uses H_2O_2 to generate HOCl, producing reactive oxidant species.²⁷ Other than being a major character in the innate immune response, MPO-derived oxidants contribute to tissue damage during inflammation and atherosclerosis. MPO activates protease cascades, including both proapoptotic and prothrombotic pathways, involved in plaque rupture, and intracoronary thrombus generation during sudden cardiac death.^{28,29} However, MPO is also involved in several inflammatory-mediated diseases.³⁰

Increased levels of IL-6 have also been also linked to high risk of all-cause mortality. IL-6 is an important mediator in inflammation and has a central role for the acute-phase response.³¹ IL-6 is mostly produced by adipocytes, fibroblast, endothelial cells, and activated leukocytes and monocytes. IL-6 is a regulator of acute-phase inflammatory response; IL-6 stimulates the synthesis of C-reactive protein (CRP) by liver.³²

Serum paraoxonase-1 (PON-1) is associated with high-density lipoprotein and prevents lipoproteins from oxidation. It has a hepatic synthesis and production. PON-1 has a protective action against atherosclerosis. PON-1 has antiatherogenic properties, linked to the enzyme's ability to prevent low-density lipoprotein (LDL) and high-density lipoprotein oxidation, to reduce macrophage oxidation, to stimulate cholesterol efflux from macrophages, and to reduce oxidative status in atherosclerotic plaques. PON-1 also destroys active lipids in mildly oxidized LDL, with a consequent reduction in inflammatory responses in the artery wall cells. PON-1 also reduces monocyte chemotaxis and adhesion to endothelial cells and inhibits monocyte-to-macrophage differentiation. The absence of PON-1 was linked to an overexpression of adhesion molecules.³³ LDL oxidation is the first step in atherosclerosis genesis. The oxidized products are scavenged by macrophages that transform into foam cells, filled with cholesterol esters. They eventually become fatty streaks in the endothelium. Lower PON activity was found in patients with type 2 diabetes with neuropathy and retinopathy.^{34,35}

Endothelial damage markers

Endothelial dysfunction typical of diabetes plays a role in atherosclerotic lesions promoting the upregulation of adhesion molecules, the increase in chemokine secretion and leukocyte adherence, the increase in cell permeability, and an enhanced LDL oxidation, platelet activation, cytokine elaboration, and vascular smooth muscle cell proliferation and migration.³⁶

Nitrate and nitrite are an alternative source for NO. Vasodilation, inhibition of endothelial dysfunction, and inhibition of platelet aggregation are protective mechanisms against cardiovascular diseases.³⁷ NO mediates the regulation of vascular tone, with an increase in cyclic guanosine monophosphate and subsequent relaxation of vascular smooth muscle. NO suppresses systemic plasminogen activator inhibitor-1 (PAI-1) levels; elevated plasma PAI-1 levels are associated with endothelial dysfunction.³⁸ Circulating PAI-1 levels are high in diabetics, contributing to the prothrombotic and proatherosclerotic changes. In addition, plasma PAI-1 levels are elevated in insulin resistance.³⁹

On the other hand, cellular adhesion molecules play an important role in atherosclerosis, mediating margination, adhesion, and migration of circulating mononuclear cells from the blood stream to the extravascular compartment.⁴⁰ They also activate mononuclear cells to release matrix MMPs, promoting plaque rupture and the initiation of acute coronary syndromes.⁴⁰

In particular, sICAM-1 is linked to the subsequent incidence of coronary heart disease among healthy men and women.^{41,42} Two prospective cohort trials showed that levels of sICAM-1 are increased many years before a first myocardial infarction occurs;⁴¹ data on sVCAM-1 are not so clear.⁴³ Regarding sE-selectin, instead, it confirmed to be a reliable marker and to be strongly linked to traditional cardiovascular risk factors. E-selectin mediates leukocyte rolling on the endothelium and platelet-leukocyte interaction; it is expressed in activated endothelial cells and acts as an adhesive reactant. On activation, sE-selectin is released into the circulation. Patients with myocardial infarction had increased levels of sE-selectin; moreover, sE-selectin levels are related to blood pressure.⁴⁴

Matrix MMPs are proteolytic enzymes with the role of mediating changes in extracellular matrix. Humans have 24 matrix MMP genes. Matrix MMPs contribute to vascular remodeling and to the developing of atherosclerotic plaque. The activation of matrix MMPs modifies plaque architecture and may directly participate in the process of plaque rupture.⁴⁵ MMPs are extremely powerful proteolytic enzymes; thus, their biological actions are controlled by tissue inhibitor of MMPs. Among MMPs, MMP-2 and MMP-9 are the most important in vascular remodeling.⁴⁶ MMP-2 and MMP-9 are Zn^{2+} -dependent endopeptidases, synthesized and secreted in zymogen form. Increased MMP-2 and MMP-9 activities are associated with destruction of the elastic laminae of arteries and aneurysm formation in animals and humans.⁴⁷ MMP-2 and MMP-9 are elevated in patients with obesity,⁴⁸

hypertension,⁴⁹ type 2 diabetes,⁵⁰ and acute coronary syndrome.^{51–53} Moreover, plasma MMP-9 levels are a novel predictor of cardiovascular risk in patients with coronary artery disease and stroke.^{54,55}

Conclusion

Proatherogenic adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and inflammatory cytokines (high-sensitivity CRP, IL-6, and TNF- α) are elevated in type 2 diabetes mellitus. Their increased expression and release contribute to the accelerated atherogenesis typical of these patients. For these reasons, the early identification of high levels of these biomarkers will help to establish new strategies to reduce cardiovascular complications.

Disclosure

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