MARKERS OF ENDOTHELIAL DYSFUNCTION IN THE METABOLIC SYNDROME

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ABSTRACT

The metabolic syndrome (MS) has been represented as a “clustering” of strongly interrelated risk factors for cardiovascular disease (CVD). These include dyslipidemia, hypertension, obesity and insulin resistance. The components of metabolic dysfunction can act directly and indirectly on endothelial function. A common mechanism underlying endothelial dysfunction is related with increase of oxidative stress. Free radicals cause the initial disturbances of endothelial function, enhance the release of Endothelin-1 (ET-1), the main endothelial constrictor peptide, impair of NO metabolism and decrease of endothelium-dependent vasodilatation, stimulate release of proinflammatory mediators such as molecule 1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1), enhance the release of plasminogen activator inhibitor-1 (PAI-1) and von Willebrand factor (vWF), promote the PI3/Txα2, and to a prothrombogenic state, formatting represent a key early step in atherogenesis. Plasma ET-1, adhesion molecules VCAM-1 and ICAM-1, PAI-1 and vWF may serve as biomarkers pointing to endothelial dysfunction (ED) and increased cardiovascular risk. Significant increased plasma levels of these biomarkers along with other biochemical parameters can be seen in condition like obesity, diabetes of type 2 and others component of metabolic syndrome. Thus measurement of endothelial function might identify atherogenic risk individuals at the early stage long before clinical diagnosis of CVD. This may prove to be a useful means of assessing response to treatment aimed at reducing long-term morbidity and mortality from CVD.

Keywords: endothelial dysfunction, markers, oxidative stress, metabolic syndrome.

The metabolic syndrome (MS) has been described as a “clustering” of several risk factors for cardiovascular diseases (CVD), namely obesity (particularly abdominal obesity), dyslipidemia, insulin resistance and hypertension (1). CVD is a leading cause of death and disability in patients with diabetes or MS (2,3). In recent years, it has become clear that insulin resistance and endothelial dysfunction play a central role in the pathogenesis of atherosclerosis (4). Endothelial dysfunction (ED), which is one of the initial steps in the process of vascular disease, is often present in patients with diabetes or MS. It is important to elucidate the molecular mechanisms underlying ED and evaluate of prognostic biomarkers identifying this disease to isolate and evaluate potential therapeutic agents.

The vascular endothelium is dynamic tissue with a number of functions including regulation of vascular tone, platelet adhesion, coagulation and fibrinolysis. Dysregulation of one or more of these functions can occur in the metabolic syndrome. Although the precise mechanism(s) by which diabetes or MS causes ED remains to be elucidated, several possibilities exist. Hyperglycemia, hyperinsulinemia, increased oxidative stress and diabetic dyslipidemia can all contribute to ED individually or in concert with one another (5).

Endothelial dysfunction is an important component of insulin resistance syndrome and this is demonstrated by inadequate vasodilation and/or paradoxical vasoconstriction in coronary and peripheral arteries in insulin resistant states. Among important molecules synthesized by endothelial cells is nitric oxide (NO). In addition to being a potent vasodilator NO is a key vasoprotective agent influencing pathogenetic pathways including oxidative stress, smooth-muscle proliferation, chemotaxis and monocyte adhesion. Deficiency of endothelial-derived NO is believed to be the primary defect that links insulin resistance and endothelial dysfunction. NO deficiency results from decreased synthesis and/or release, in combination with exaggerated consumption in tissues by high levels of reactive oxygen (ROS) and nitorgen (RNS) species, which are produced by cellular disturbances in glucose and lipid metabolism (4,6).

Hyperglycemia and dyslipidemia increase DAG production and PCK activation leading to a decrease in bioactivity of eNOS and increases a production of endothelin -1 (ET-1). ET-1 is a strong vasoconstrictor and it stimulates

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also smooth-muscle proliferation and formation of extracellular matrix-collagen, lamin, growth factors. Significant and diverse changes in its concentration can be seen in conditions like diabetes and metabolic syndrome long before atherosclerotic changes appear in arteries. The imbalances between the release of NO and ET-1 may be involved in the pathophysiology of hypertension and also atherosclerosis in insulin-resistant states associated with endothelial dysfunction. ET-1, a product of endothelial cells, is one of the early circulating marker of ED in insulin resistant states (4,5).

Hyperglycemia and dyslipidemia via protein kinase C (PKC) pathway decreases endothelial-dependent vasodilatation and increases the production of growth factors by the endothelium, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and transforming growth factor (TGF-β). These reactions lead to the migration and proliferation of smooth muscle cells. In diabetic retinopathy, alteration of retinal microvasculature and increased vascopermeability are strongly stimulated by the interaction of VEGF with the endothelium (4). Activation of PKC by several factors such as triglyceride-rich lipoproteins, hyperglycemia, oxidized LDL and insulin itself increases secretion of plasminogen activator inhibitor-1 (PAI-1) by endothelial cells in tissue culture by (6,7). PAI-1 is a fast inhibitor of fibrinolysis that alters thrombotic-fibrinolytic equilibrium a favor of occlusion. Activity of PAI-1 is raised in young men surviving a myocardial infarction and predict recurrent events.

**OXIDATIVE STRESS - ENDOTHELIAL DYSFUNCTION**

![Fig 1. Markers of endothelial dysfunction and cardiovascular risk in the metabolic syndrome](image)

Von Willebrand factor (vWF) is synthesized and secreted by endothelial cells. vWF promotes thrombus formation by mediated of platelets to the injured vessel wall. Endothelial cells are the origin of all circulating vWF, and increased plasma levels may reflect the extent of vascular damage

Haidara Yudkin. Insulin resistance increases levels of PAI-1 and vWF, and C-reactive protein (CRP) appears to be the most determinant of this prothrombotic and proatherogenic state. They predispose patients with the metabolic syndrome to develop atherosclerotic events and atherosclerosis. (7,8,9)

In endothelial cells hyperglycaemia and dyslipidemia activates NF-κB and activator protein-1 (AP-1) which regulate expression of many proatherogenic mediators. NF-κB activates many proinflammatory chemokine receptors such as monocyte chemotactic protein-1 (MCP) and IL-1 and adhesion molecules vascular cell adhesion molecule-1 (VCAM-1), E selectin, which stimulate rolling adhesion, transmigration of mononuclear cells, and thus transformation of monocytes to macrophages and then to foam cells (3,4). Plasma soluble VCAM-1 levels are increased and related to hyperglycemia in type 2 diabetes.

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**ENDOTHELIAL DYSFUNCTION**

![Fig 2 Oxidative stress and endothelial dysfunction in the metabolic syndrome](image)

The oxidative stress that accompanies the metabolic syndrome is associated with both insulin resistance and endothelial dysfunction (2,6,10). Oxidative stress is defined as an increase in the steady state levels of reactive oxygen species (ROS) and may occur as a result of increased ROS generation and/or decreased antioxidant defense mechanism. The most important origin of ROS are mitochondrial respiratory process, NAD(P)H-oxidase system (3,11). Overloads of reactive oxygen species in insulin resistant states may be the initial event in endothelial cell dysfunction. ED occurs in association with increased ROS in insulin resistant states due to inactivation of NO by superoxide (O2-) (10). Antioxidant enzymes such as SOD revert this conditions.
Markers of endothelial dysfunction in the metabolic syndrome

ROS contribute to vascular dysfunction and remodeling through oxidative damage by reducing the bioavailability of NO and impairing endothelium-dependent vasodilatation and endothelial cell growth. ROS induce the expression of adhesion molecules (VCAM-1, ICAM-1) and proinflammatory mediators (IL-1,6, TNF) leading to endothelial dysfunction, an initial episode progressing toward hypertension and atherosclerosis (12). ROS can alter lipids and proteins and accelerate the formation of advanced glycation end products (AGE) which quench the NO and increased susceptibility to LDL oxidation (5,12). Administration of antioxidants (vitamin C and alpha-tocopherol) caused attenuation of the endothelial damage, as vitamin C administration caused a significant decrease in vWF, fibrinogen and increased HDL-cholesterol, while alpha-tocopherol caused a significant decrease in vWF (13). ED in the setting of diabetes or MS can subsequently result in the activation of a variety of pathways that alter vascular function and participate in the process of vascular remodeling and atherosclerosis. ED is early marker of CVD and can predict future coronary artery disease even before atherosclerotic changes appear in arteries. Damage to the vascular endothelium can be quantified by measuring plasma markers such as soluble (s) vWF, e-selectin, sICAM and plasma ET-1, PAI-1. High plasma levels of these markers may reflect of vascular damage. Thus measurement of endothelial function might indentify atherogenic risk individuals at the early stage long before clinical diagnosis of CVD. This may prove to be a useful means of assessing response to treatment aimed at reducing long-term morbidity and mortality from CVD.

REFERENCES