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Review paper

INSULIN RESISTANCE AND ATHEROSCLEROSIS

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Summary: Introduction of abdominal obesity as a crucial part of the metabolic syndrome pointed out that adipose tissue dysregulation might play a main role in the pathogenesis of insulin resistance and atherosclerosis. Excess of fatty acids in circulation creates resistance in periphery insulin by the added substrate availability and by modifying insulin downstream signalling. Patients with insulin have endothelial dysfunction with a partial or complete loss of balance between vasoconstrictors and vasodilatators, growth promoting and inhibiting factors, proatherogenic and antiatherogenic, and procoagulant and anticoagulant factors. Insulin resistant individuals may have a partial block to insulin action through PI(3)K pathway in skeletal muscle and endothelial cells with an intact MAPK pathway that may partially explain their increased cardiovascular risk.

Key words: atherosclerosis, insulin resistance, endothelial dysfunction

Introduction

Various hypotheses have been postulated in an attempt to explain the development of the process of atherosclerosis. There are three major hypotheses of atherogenesis and they include the »response to injury« hypothesis, »response to retention« hypothesis and the »oxidation hypothesis« (1).

According to the »response to injury« hypothesis, endothelial injury is a key event which initiates the inflammatory mechanisms associated with atherosclerosis (2), stating that the endothelial damage precedes smooth muscle cell migration and proliferation, deposition of the intracellular and extracellular lipid, and accumulation of extracellular matrix.

According to the »response to retention« hypothesis, the central atherogenic process is the sub-endothelial retention and accumulation of lipoproteins by extracellular matrix molecules, such as proteoglycans (3).

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According to the »oxidation hypothesis«, the central component of the atherogenic process is the oxidative modification of LDL, which acts as an immunogenic stimulus for monocyte recruitment to the vessel wall and phagocytic uptake of oxidized LDL by macrophages (4).

G. Reaven described in his historical paper the role of insulin resistance in human disease, postulating the existence of the so-called metabolic syndrome or Syndrome X (5). The term metabolic syndrome describes a cluster of cardiovasular risk factors, characterized by insulin resistance, dyslipidemia and hypertension, that is estimated to affect 15 to 25% of individuals in industrialized countries (6).

Recently, some controversy has emerged regarding how best to define the metabolic syndrome and whether the term should be used as a diagnostic label in clinical practice (7). The pathophysiology of the metabolic syndrome seems to be largely attributable to insulin resistance implicating an excessive flux of fatty acids. A proinflammatory state probably contributes to the syndrome.

The year 1761 was notable for the publication of *De Sedibus et causis Morborum per Anatomen Indagatis*, a landmark work establishing the anatomic basis of multiple diseases (8). Using a combination of clinical histories and autopsies, Morgagni identified

the association between intraabdominal obesity, hypertension, abnormal metabolism and extensive atherosclerosis (9). The concept of the metabolic syndrome has existed for at least 80 years. The constellation of metabolic disturbances which are all risk factors for cardiovascular disease was first described in the 1920s by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycaemia and gout (10). Later on, Himsworth (11) suggested the possibility that insulin insensitivity could have metabolic consequences. In the middle of the 20th century, attention was focussed on the upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with metabolic abnormalities related to type 2 diabetes and cardiovascular disease (12). The frequently simultaneous presence of obesity, high blood fat, diabetes and hypertension was first reported as the »plurimetabolic syndrome« in the 1960s, when the risk of coronary artery disease was described in people with this cluster of metabolic abnormalities (13). Since the first official definition of the metabolic syndrome by a WHO working group in 1998, a variety of alternative definitions have been proposed. The most widely accepted of these were produced by the European Group for the Study of Insulin Resistance (EGIR) and the US National Cholesterol Education Program (NCEP). The various definitions differed not only in the proposed components but also in the cut-off points used for each of these. Bearing in mind the urgent need for a single, universally accepted diagnostic tool that would be simple to use in clinical practice, IDF proposed a new definition of the metabolic syndrome that makes central obesity a necessary requirement (*Table I*).

Table I IDF definition of the metabolic syndrome

Central obesity
Waist circumference (ethnicity-specific; for the Europids: male ≥ 94 cm; female 80 cm)
Plus any two of the following
Raised triglycerides (1.7 mmol/L or specific treatment for this lipid abnormality)
Reduced HDL-cholesterol (< 1.03 mmol/L in male; < 1.29 mmol/L in females or specific treatment for this lipid abnormality)
Raised blood pressure (systolic ≥130 mmHg or diastolic 85 mmHg or treatment of previously diagnosed hypertension)
Raised plasma glucose (fasting plasma glucose ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes. If above 5.6 mmol/L an oral glucose tolerance test is strongly recommended, but is not necessary to define the presence of the syndrome)

The IDF definition takes into account the mounting evidence that central adiposity is common to each of the components of the metabolic syndrome. An increased waist circumference, an accepted proxy measurement for the abdominal adiposity, is now a necessary requirement for a diagnosis of the syndrome (14). However, a term »cardiometabolic syndrome« was recently proposed to describe the intricate connections among cardiovascular and metabolic abnormalities that predispose to cardiovascular disease – the leading cause of mortality in the Western world (15). The establishment of criteria or diagnosing what the ATP III report termed the metabolic syndrome represented an effort to acknowledge the importance of resistance to insulin action, and its consequences, as increasing the risk of cardiovascular disease (16). The individual criteria listed in *Table I* appear to have been selected because they tend to cluster together and to occur more commonly in insulin-resistant individuals (17), as well as because they have all been associated with increased cardiovascular risk. A variety of abnormalities and clinical syndromes may occur in insulin-resistant individuals (*Table II*).

Values for insulin-mediated glucose disposal vary continuously throughout a population of apparently healthy individuals, with at least a sixfold variation between the most insulin-sensitive and most insulin-resistant of these individuals (18). It was suggested that there is no objective way to classify an individual as being insulin-resistant, and that insulin resistance is not a disease but a description of a physiologic state that greatly increases the chances of an individual developing several closely related abnormalities and associated clinical syndromes (16). The primary value of the concept of insulin resistance is that it provides a conceptual framework for placing a substantial number of apparently unrelated biological events into a pathophysiologic construction. Insulin resistance has traditionally been defined with a glucocentric view – ie, when a defect in insulin action results in fasting hyperinsulinaemia to maintain euglycaemia. Yet, even before fasting hyperglycaemia develops, postprandial hyperinsulinaemia exists (19). Since abdominal obesity is a crucial part of the diagnostic criteria for the existence of the metabolic syndrome, an emerging paradigm supports the view

Table II Clinical syndromes associated with insulin resistance

Type 2 diabetes
Cardiovascular diseases
Essential hypertension
Polycystic ovary syndrome
Nonalcoholic fatty liver disease
Certain forms of cancer
Sleep apnea

that adipose tissue dysregulation might play a crucial role in the pathogenesis of insulin resistance and atherosclerosis. The net result of such a dysregulation is a state of low-grade, chronic, systemic inflammation that, in turn, links both the metabolic and the vascular pathologies (20). A major contributor to the development of insulin resistance is an overabundance of circulating fatty acids derived mainly from adipose tissue triglyceride stores through the action of the cyclic AMP-dependent enzyme hormone sensitive lipase. Fatty acids are also derived through the lipolysis of triglyceride-rich lipoproteins in tissues by the action of lipoprotein lipase. Insulin is important to both antilipolysis and the stimulation of lipoprotein lipase. Under the conditions of insulin resistance, increased amount of lipolysis in adipose tissue produces more fatty acids, which further inhibit the antilipolytic effect of insulin, creating additional lipolysis (19). Excess of fatty acids in circulation creates in peripheral insulin-sensitive tissues (especially in muscles) a state of insulin resistance by the added substrate availability and by modifying downstream insulin signalling. Earlier, it was proposed that such insulin resistance occurs as a result of fatty acid oxidation leading to inactivation of mitochondrial pyruvate dehydrogenase and ultimately decreased glucose uptake (21). Recently, accumulation of triglycerides and related lipid molecules in muscle (so-called intramyocellular lipids) have been explained by the defect in mitochondrial oxidative phosphorylation (22). Insulin resistance, inflammation and atherosclerosis appear to be linked via the metabolic syndrome and the question is the nature of the association being either a common molecular pathology related to insulin receptor signalling or vascular consequences of metabolic abnormalities of insulin resistance (1). It was demonstrated that, in humans and mice, increasing obesity is associated with increased oxidative stress in the fat compartment and in circulating markers of oxidative stress. As a consequence, the two potential mechanisms have been described: deregulation of the production of pro- and antiinflammatory cytokines, and the elevated levels of systemic oxidative stress mediated through increased oxidative enzymes (NADPH oxidase) and decreased antioxidative enzymes (Superoxide Dismutase). According to this hypothesis, obesity derived proinflammatory cytokines and reactive oxygen species may generate peripheral insulin resistance on one side, and on the other side may directly impact on the endothelium causing endothelial dysfunction and initiation of the atherosclerotic cascade (23). Insulin expresses its effect after binding for its own receptor at the cell surface. Binding of insulin for its own receptor results in rapid stimulation of glucose uptake (via the glucose transporter protein GLUT4) into insulin target peripheral tissues (muscle and fat). In metabolic tissues, phosphatidylinositol-3-kinase (PI(3)K) plays a central role in insulin-stimulated glucose uptake. In addition to the PI(3)K signaling pathway, insulin also activates the mitogen-activated protein (MAP) kinase cascade. The MAP kinase cascade is not involved in insulin--stimulated glucose transport or glycogen synthesis and may relate to cell survival and proliferation, that can be associated with the process of atherogenesis. The elements that control the balance between signaling through the PI(3)K and MAPK pathways may indicate trigger points in insulin resistance (1). Insulin is known to stimulate nitric oxide production in endothelial cells and glucose uptake in muscle and fat tissue through the PI(3)K and Akt pathways. In contrast, other effects of insulin action on the vasculature, including the stimulation of migration and growth of smooth muscle cells and the production of plasminogen activator inhibitor 1 (PAI-1), are mediated through the MAPK pathway (24). It was postulated that perhaps some individuals at risk for type 2 diabetes have some shared defects in the PI(3)K pathway in skeletal muscle, fat and endothelial cells, with an intact MAPK pathway, as it was previously described in an animal model of insulin resistance (Zucker rats). In theory, insulin resistant individuals could have a partial block to insulin action through PI(3)K pathway in skeletal muscle and endothelial cells with an intact MAPK pathway that could partially explain their increased cardiovascular risk (25). Plasma insulin concentrations associated with insulin resistance are in the concentration range that affects vascular cell and tissue responses *in vitro* and *ex vivo*. The mitogenic effect through the MAPK pathway in endothelial cells and VSMCs remains intact and responds normally to insulin, and its cell effects may even be enhanced instead of reduced. Predominance of insulin signaling effect mediated through the MAPK pathway may contribute to the progression of atherosclerosis with a concomitant increase in VSCM migration, expression of cell adhesion molecules (VCAM-1, E-selectin) and cell interaction between vascular cells and macrophage/monocytes (1). The major cells involved in atherosclerosis are endothelial cells (Ecs), vascular smooth muscle cells (VSMCs), monocytes/macrophages and T lymphocytes, and insulin has its own effect on each of them.

Stimulation of insulin receptors in endothelial cells activates the PI(3)K pathway which further on leads to an increase in the expression of the constitutively active endothelial nitric oxide synthase (eNOS) (26). Production of nitric oxide by the endothelial cells is viewed as a potentially vascular protective mechanism, since its increase leads to a lowering of intracellular free calcium, promotion of vasodilatation, inhibition of VSMC proliferation and regulation of angiogenesis. However, patients with insulin resistance demonstrate a phenomenon termed »endothelial dysfunction« which is at least partly a result of decreased production or increased clearance of nitric oxide and thus impaired blood flow. Endothelial dysfunction can be defined as the partial or complete loss of balance between vasoconstrictors and vasodi-

latators, growth promoting and inhibiting factors, proatherogenic and antiatherogenic, and procoagulant and anticoagulant factors (25). Endothelial dysfunction is an early pivotal event in atherogenesis that often precedes the development of clinically detectable atherosclerotic plaques in the coronary arteries. It is of interest that metformin improves endothelial vascular reactivity in first-degree relatives of type 2 diabetic patients with metabolic syndrome and normal glucose tolerance (27). Insulin vasodilatator action is regulated through PI(3)K dependent insulin receptor signaling, increasing the endothelial NO production. Under insulin resistance circumstances, endothelial NO production is impaired. Reduced NO production, beside its effects on endothelial cells, also has an impact on VSMCs. VSMCs in insulin resistance have an impaired responsiveness to NO. The ultimate effect is increased contraction that results in an imbalance of the vascular tone, leading to the impairment of glucose delivery to the muscles (1, 28). The insulin receptors on VSMCs are structurally and functionally similar to those in metabolic tissues and insulin signalling in VSCMs initiates proatherogenic cellular events such as proliferation and migration. Insulin-stimulated VSMC mitogenesis is mainly controlled through the MAPK pathway. Furthermore, stimulation of VSMCs through the MAPK pathway leads to an increase in the production of PAI-1. Increase in PAI-1 results in the reduction of fibrinolysis and increased vascular occlusion. Lipid retention in the vessel wall stimulates monocytes to differentiate into macrophages in an attempt of phagocytosis and remove retained lipid, transforming into »foam cells« which are deposited in the subendothelial space, and the atherosclerotic lesion develops around the lipid-laden macrophages (29). Insulin and IGF-1 receptors are present on circulating monocytes/macrophages while defective insulin signalling is implicated in macrophage foam cell formation. Macrophages from obese (ob/ob) mice are insulin-resistant and display a posttranscriptional increase in CD36, a key molecule in the recognition of modified LDL, as a direct result of decreased insulin signalling. The elevated level of CD36 is a result of decreased catabolism and results in increased binding, uptake and degradation of LDL that may contribute to the development of atherosclerosis in the insulin-resistant state (30). It was also suggested that, under insulin resistance conditions, the protective effect of insulin – to reduce macrophage apoptosis – may be lost because the PI(3)K pathway is blunted under these conditions (31). T lymphocytes do not have insulin receptors in the circulation, however, T lymphocytes have the unusual ability to express insulin receptors following the presentation of an antigen *in vivo* and an antigen or mitogen *in vitro* (32). Stimulation of the insulin receptor on T lymphocytes increases the cytotoxic effects, allows for differentiation of the cells and maintains the lymphocyte in an activated state after being presented with a mitogen or antigen. Plasma insulin levels *in vivo* have an inverse relationship with the number of insulin receptors on T cells *in vitro* following the presentation of an antigen (33).

Having in mind all the relevant data, it can be concluded that insulin resistance is associated with accelerated atherosclerosis and that the therapeutic options that can ameliorate insulin resistance may have a favourable effect on the course of the disease. This approach was supported by several studies showing the relationship between insulin levels and cardiovascular risk: the Paris Prospective Study; a study on over 1000 males in Finland; Multiple Risk Factor Intervention Trial (MRFIT) and the Insulin Resistance Atherosclerosis Study (IRAS) (8). However, treatment of insulin resistance with insulin sensitizers to decrease vascular disease has yielded mixed results, perhaps because insulin resistance in the vasculature may not promote atherosclerosis (8). At the present time, it appears that we still do not know all the answers to the questions about the complex interaction between insulin resistance and the process of atherosclerosis, and it seems that this fascinating area would be of interest for further scientific contributions in the future.

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INSULINSKA REZISTENCIJA I ATEROSKLEROZA

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Kratak sadržaj: Uvođenje abdominalne gojaznosti kao ključne komponente metaboličkog sindroma ukazalo je da disregulacija masnog tkiva može imati glavnu ulogu u patogenezi insulinske rezistencije i ateroskleroze. Suvišak masnih kiselina u cirkulaciji kreira na periferiji insulinsku rezistenciju kroz omogućavanje dodatnih supstrata i modifikovanjem nishodnog insulinskog signala. Bolesnici sa insulinskom rezistencijom imaju endotelijalnu disfunkciju sa parcijalnim ili kompletnim gubitkom balansa između vazokonstrikcije i vazodilatacije, faktora koji promovišu ili inhibiraju rast, proaterogenih i antiaterogenih i prokoagulantnih i antikoagulantnih faktora. Insulin-rezistentne osobe mogu imati parcijalni blok u delovanju insulina kroz PI(3)K putanju u skeletnim mišićima i endotelijalnim ćelijama sa očuvanom MAPK putanjom, što može delimično da objasni njihov povećani kardiovaskularni rizik.

Ključne reči: ateroskleroza, insulinska rezistencija, endotelijalna disfunkcija

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