THE DYSFUNCTION OF ADIPOSE TISSUE IN INFLAMMATION AND ATHEROSCLEROSIS

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Abstract

Adipose tissue, viewed as an active endocrine organ, secretes an increased number of mediators implicated in metabolic processes and is a key regulator of inflammation, coagulation, and fibrinolysis. Adipokines, biologically active peptides, secreted by adipocytes interfere with insulin actions and endothelial cell function and contribute to development of endothelial dysfunction, a preclinical stage of atherosclerosis. Obesity is associated with a chronic inflammatory state in white adipose tissue which releases proinflammatory cytokines that inhibit insulin action in liver, skeletal muscle and adipose cells and impaired glucose homeostasis.

Adipokines and low-grade inflammatory state may be the link between insulin resistance, obesity and cardiovascular disease.

***Keywords**: adipokines, atherosclerosis, inflammation, obesity*

Adipose tissue is no longer viewed a passive depot for triacylglycerol storage and a source of free fatty acids, but an active endocrine organ secreting an increased number of mediators that participate in diverse metabolic processes. Adipokines are biologically active substances found in the adipocytes of white adipose tissue, which act locally and distally through autocrine, paracrine and endocrine effects. In obesity, regarded now as a pro-inflammatory state, the increased production of most adipokines impacts on functions such as appetite and energy balance, insulin sensitivity, angiogenesis, haemostasis, lipid metabolism and blood pressure wich are linked to cardiovascular disease.

Adipose tissue is a rich source of proinflammatory mediators such as TNF-α, IL-6, leptin, plasminogen activator inhibitor (PAI)-1, angiotensinogen, resistin, C-reactive protein (CRP), which promote endothelial dysfunction, insulin resistance, and atherosclerosis. Other adipocyte products such as nitric oxide (NO) and adiponectin confer protection, but these appear to decrease in amount with increasing levels of obesity.

Leptin, a 16-kD cytokine, encoded by gene obese (ob) decreases food intake and increases energy consumption by inducing anorexigenic peptides such as CART (cocaine and amphetamine-regulated transcript), POMC (pro-opiomelanocortin) and suppressing orexigenic neuropeptides: NPY (neuropeptide Y), AgRP (agouti-related peptide) and orexin. [1] Leptin reduces intracellular lipid levels in liver, pancreatic beta cells, skeletal muscle, thereby improve insulin sensitivity.

In a group of patients with lipodystrophy and leptin deficiency, treatment with recombinant leptin result in metabolic benefits, reduce the glycosylated hemoglobin value and triglyceride levels. Have been

inrolled 9 female patients with lipodystrophy (five of the nine patients had congenital generalized lipodystrophy, or the Seip–Berardinelli syndrome, one patient had Dunnigan's familial partial lipodystrophy, the other three patients had acquired generalized lipodystrophy) and serum leptin levels under 4 ng/ml (age range 15-42 years, 8 with diabetes mellitus, all nine had hyperlipidemia). They received recombinant leptin therapy for 4 months, subcutaneously every 12 hours. During treatment, leptin level increase from 1.3±0.3 ng per milliliter at baseline to 11.1±2.5 ng per milliliter (0.9±0.2 nmol per milliliter) at the end of the fourth month. The eight patients with diabetes and poor metabolic control before treatment improve glycemic control (initially glycosylated hemoglobin value of 9.1±0.5 percent decreased by a mean of 1.9 percentage points). The fasting triglyceride levels had fallen by 60 percent, the liver volume by an average of 28 percent, the daily caloric intake decreased from a mean of 2680±250 kcal per day at base line to 1600±150 kcal per day after four months of leptin-replacement therapy.[2]

Adiponectin is almost exclusively expressed in white adipose tissue and circulates in the blood in different molecular forms and associated with insulin resistance, inflammation, risk for metabolic syndrome, type 2 diabetes. It has antiatherogenic properties and increases insulin sensitization, at least in part, by activation of AMPK in skeletal muscles and the liver, which increase fatty acid oxidation and reduces hepatic glucose production. Adiponectin serum concentrations are reduced in obese and insulin-resistant states.

Steven et all demonstrate low adiponectin levels corellates with atherogenic lipoproteins. 185 patients (66 diabetic, mean age 60 and 119 non-diabetic, mean age 64) undergoing coronary angiography and intravascular ultrasound (IVUS) have been enrolled. The median adiponectin level was 6.1 (2.5–9.3) µg/ml, lower in men than in women: 5.5 (3.4–8.4) vs. 8.7 (4.5–15.0) µg/ml and correlated with age, BMI, homeostasis model assessment, fasting insulin and with atherogenic lipoproteins (triglycerides, HDL cholesterol and small dense LDL cholesterol). Low adiponectin levels are associated with increased plaque volume, lipid-rich plaque, and IVUS-derived pathological intimal thickening in the total cohort, suggesting that low levels of adiponectin are associated with relatively early plaque development and risk of plaque maturation.[3]

Obesity is associated with a chronic inflammatory state in white adipose tissue that releases proinflammatory cytokines such as TNF-α and IL-6 into circulation. These cytokines inhibit insulin action in liver, skeletal muscle and adipose cells and impaired glucose homeostasis.

TNF-α, a multifunctional cytokine, synthesized and secreted by adipocytes and stromovascular cells, released in greater quantities by obese and patients with insulin resistance, also contribute to atherosclerotic lesion formation. TNF-α is involved in several cardiovascular processes. TNF-α levels are persistently elevated among post-myocrdial infarction patients at increased risk for recurrent coronary events and the excess risk of recurrent coronary events after myocardial infarction was seen for those with highest levels of TNF-α (a 3-fold increase)[4].

IL-6 , a pleiotropic cytokine secreted by lots of cells such as endothelial cells, skeletal muscle, adipose tissue immune cells has multiple effects and also correlate with human obesity and insulin resistance, IL-6 being often elevated in patients with metabolic disease. IL-6 increases basal and insulin-stimulated glucose uptake through an increased GLUT-4 translocation. Activation of AMPK by IL-6 seems to play an important role in modulating some of its metabolic effects. In humans, IL-6 stimulates the production of anti-inflammatory cytokines and suppresses TNF-α productions, offering protection against TNF-α induced insulin resistance. Insulin-stimulated glucose uptake in adipocytes is increased by IL-6 and decreased by TNF-α, and is totally abolished by the addition of TNF-α to IL-6.

Thereby high levels of TNF-α and low production of IL-6 are important factors in metabolic syndrome.

CRP is an inflammatory marker and participates in the process of atherogenesis by modulating endothelial function and this effect is potentiated by hyperglycemia. CRP induces the expression of VCAM-1, ICAM-1, selectins, and MCP-1 in cultured endothelial cells via increased secretion of ET-1, a potent endogenous vasoconstrictor, and IL-6. In the vascular smooth muscle cells, CRP upregulates angiotensin type 1 receptor (AT_1-R) mRNA and protein levels and increased AT_1-R expression on the cell surface and facilitates smooth muscle cell migration and proliferation, and vascular remodeling. CRP amplify the proinflammatory activity of other adipokines, like PAI-1, witch is a contributor to atherogenesis by promoting thrombus formation.

There is increasing evidence that the features of insulin resistance syndrome (abdominal obesity, hyperinsulinemia, high triglyceride, low HDL cholesterol, dyslipidemia and elevated plasminogen activator inhibitor-1 and fibrinogen concentrations) are all associated with increased CRP levels. Lemieux et all studied the relationship between abdominal subcutaneous and visceral adipose tissue accumulation and plasma CRP levels and examined their associations with glucose tolerance as well as with plasma insulin and lipoprotein concentrations in a sample of 159 men (BMI ranged from 21.0 to 41.0 kg/m^2, with no diabetes or cardiovascular heart disease, no medication known to affect insulin action or plasma lipoprotein-lipid levels, no anti-inflammatory treatment before or during the study). Total cholesterol was relatively normal (5.32±0.73 mmol/L), but with low HDL cholesterol (0.91±0.18 mmol/L) levels, leading to an elevated cholesterol/HDL cholesterol ratio (6.08±1.34). The average CRP level was 2.21±1.96 μg/mL and ranged from 0.17 to 9.67 μg/mL. All anthropometric variables were significantly correlated with plasma CRP levels. Among body fatness and adipose tissue distribution indices, total body fat mass was the variable that showed the highest correlation with CRP levels. It was also found a relationship between CRP concentrations and insulinemia. The insulin response to the 75-g glucose load was greater among men in the top CRP quintile compared with men in the first CRP quintile (P<0.05). This suggest that hyperinsulinemia resulting from insulin resistance is also associated with a state of low chronic inflammation. The highest plasma CRP concentrations were

observed among men who had simultaneous elevations in visceral adipose tissue accumulation and in total body fatness, whereas individuals with an elevated body fat mass alone had CRP levels that were not significantly different from men with elevated amounts of visceral adipose tissue alone. There was no relationship between lipoprotein-lipid variables and CRP concentrations.[5]

PAI-1, the main inhibitor of the fibrinolytic system is associated with atherothrombosis and increases the risk of developing cardiovascular disease. PAI-1 is also implicated in adipose tissue development, and in the control of insulin signaling in adipocytes, suggesting that PAI-1 inhibitors may control atherotrombosis and insulin resistance. PAI-1, a marker of ectopic fat depots is increased in obese subjects with metabolic syndrome, as well as in type 2 diabetes patients. Plasma PAI-1 decreases with the improvement of insulin resistance.

Resistin is a dimeric protein, containing 108 amino acids, founded in adipocytes, macrophages and other cells types, involved in insulin resistance. Neutralization of resistin by specific antibodies resulted in decreased blood glucose levels and improved insulin sensitivity thereby providing a more direct link between fat mass and insulin resistance. Resistin has also been demonstrated recently to have a proinflammatory effect on smooth muscle cells, induced human aortic smooth muscle cell proliferation and may play a role in the increased incidence of restenosis observed in diabetic patients [6]

Visfatin is an insulin-mimetic adipokine that was originally discovered in liver, skeletal muscle and bone marrow as a growth factor for B lymphocyte precursors. Visfatin levels correlate with white adipose tissue accumulation, visfatin mRNA levels increase in the course of adipocyte differentiation, and visfatin synthesis is regulated by several factors, including glucocorticoids, TNF-α, IL-6 and growth hormone.

Vaspin, another adipokine produced in visceral adipose tissue, was shown to decrease with worsening of diabetes and body weight loss. Administration of vaspin to obese mice improved glucose tolerance and insulin sensitivity, and reversed altered expression of genes that might promote insulin resistance.

Youn et al demonstrated that vaspin levels in normal glucose-tolerant female was 2,5 fold-higher than male subjects, differences that were not found in type 2 diabetic patients, suggesting that chronic hyperglycemia and decreased insulin-sensitivity modulated vaspin serum concentrations. The first week of physical training in untrained subjects increased vaspin levels improving insulin resistance, while high fitness level was correlated with low vaspin serum concentrations. [7]

Omentin-1, a novel adipokine of 40-kDa, preferentially produced by omental adipose tissue, decrease with obesity. Its local concentration in visceral fat may far exceed that in the circulation or in subcutaneous fat. Omentin may act as a paracrine factor to enhance insulin sensitivity and glucose metabolism and thereby modulate the distribution of body fat between visceral and subcutaneous fat depots. Omentin also play a role in nutrient storage, through its action at distant sites (muscle, liver). Treatment with recombinant omentin-1 enhanced insulin

stimulated glucose uptake in human subcutaneous and omental adipocytes.

Tan et all found a decreased omentin-1 mRNA expression and plasma omentin-1 levels in overweight women with PCOS (polycystic ovary syndrome), considerated an insulin resistance and prodiabetic state. They showed for the first time the down-regulation of omentin-1 by insuline and glucose, suggesting a mechanism for the development of insulin resistance in women with PCOS. [8]

Hepcidin, a liver produced peptide hormone, was later identified as an adipokine. It is a key regulator of body iron metabolism and it's production depends not only on iron homeostasis, but also on hypoxia, inflammatory stimuli and erythropoietic activity (17). Hepcidin level increase in disorders involving generalized inflammation, which results in hypoferremia due to a combination of decreased duodenal iron absorbtion and increased sequestration of iron by macrophages.

Apelin is a bioactive peptide known as endogenous ligand of the G protein-coupled APJ receptor. APJ receptor shares the closest identity to the angiotensin II type 1 (AT_1) receptor, but does not bind angiotensin II. Because APJ and AT_1 as well as apelin and angiotensinogen have significant similarity in tissue distribution, conclude that apelin and angiotensin II may affect the same biological processes. Boucher et all showed that apelin is expressed and secreted by both human and mouse adipocytes, with an increase in apelin expression during adipocyte differentiation stage. Apelin gene expression and secretion may be regulate by insulin, and this link is assert by a large decrease in apelin expression in streptozotocin-treated mice characterized by a dramatic fall in insulin production. Apelin is also significantly elevated but only in those states associated with hyperinsulinemia [9]

Although most of the physiological roles of apelin remain to be explored, it's demonstrated apelin's effects on cardiovascular system. Apelin is an arterial and venous dilator in vivo, decreasing blood pressure after iv administration of apelin in rats. The depressor effect of apelin is accompanied by tachycardia which is abolished by ganglion blockade (administration of mecamyilamine). [10]. Chen et all demonstrate that apelin is localized primarily in the endothelium of the coronary arteries and is found at a higher concentration in cardiac tissue after mechanical offloading. It seems that the apelin-APJ system is recruited to support the contractility of the failing heart in mild-to-moderate left ventricular dysfunction. Although plasma levels of apelin rise in early heart failure, they fall in late disease. [11]. Apelin is one of the most potent endogenous positive inotropic substances and that the inotropic response to apelin may involve activation of phospholipase C, protein kinase C, and sarcolemmal Na^+-H^+ exchanger and sarcolemmal Na^+-Ca^{2+} exchanger. [12]

Inflammation and atherosclerosis

Adipokines interfere with insulin actions and endothelial cell function. High concentration of proinflammatory adipokines contribute to development of endothelial dysfunction, through their proinflammatory properties, which is a preclinical stage of atherosclerosis.

Atherosclerosis involves an inflammatory process of arterial wall. The evolution of atherosclerotic plaque covers recruitment of mononuclear leucocytes to the intima with adhesion and migration into the subendothelial space by chemoattractant chemokines, where they become foam cells, the hallmark of the early atheromatous precursor, the fatty streak. Progression and complication of atheroma involves accumulation of smooth muscle cells which elaborate extracellular matrix macromolecules and thrombus formation with rupture of the plaque's protective fibrous cap.[13]

The variation in cytokine gene expression from adipose tissue such as increased levels of TNF-α, IL-6, resistin, PAI-1 and leptin, and reduced levels of adiponectin affect glycaemic homeostasis, coagulation system and the vascular endothelial function and accelerate the atherosclerosis process.. Adipokines and low-grade inflammatory state may be the link between insulin resistance, obesity and cardiovascular disease. Reduction of adipose tissue mass through weight reduction in association with exercise reduces TNF-α, IL-6 and PAI-1, increases adiponectin and is associated with improved insulin sensitivity and endothelial function and prevent the development of atherosclerosis.

Bahia et al investigated the relationship between adipokines, inflammation, insulin resistance, and endothelial function, in a cross-sectional study comparing obese subjects with metabolic syndrome to lean controls. 19 nonsmoking subjects with metabolic syndrome (7 males and 12 females, mean age 40.8 years, BMI=37.6 kg/m2, waist circumference 106.5 in women and 105.4 in men, waist-hip ratio 0.9 in women and 0.97 in men) and 8 healthy volunteers (4 males and 4 females, mean age 25.7 years, BMI=21.6 kg/m2, waist circumference 64.5 in women and 83.2 in men, waist-hip ratio 0.71 in women and 0.86 in men) were included in the study. Subjects with diabetes mellitus type 2, smoking habit, coronary heart disease or any major active medical issues were excluded.

Venous occlusion pletysmography measuring brachial forearm blood flow (FBF) and vascular resistance (VR) responses to intra-arterial infusions of endothelium-dependent (acetylcholine-Ach) and independent (sodium nitroprusside-SNP) vasodilators evaluate vascular reactivity, which indirectly assess endothelial function . Blood samples were obtained to evaluate C reactive protein (CRP), plasminogen activator inhibitor 1 (PAI-1), fibrinogen, adiponectin, resistin, and lipid profile (total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol). Patients were classified with regard to insulin resistance through the HOMA-IR index.

As expected, metabolic syndrome group had higher fasting plasma glucose, insulin and HOMA-IR. PAI-1, CRP and fibrinogen were higher, whereas adiponectin was lower in the metabolic syndrome group compared to the control group. Resistin values were not different between groups. Metabolic syndrome subjects had impaired endothelium-dependent and independent vasodilation. Adiponectin and PAI-1 were associated with insulin, HOMA-IR, triglycerides, and HDLc; and resistin with CRP. Adiponectin was associated with VR after Ach in the whole group and the relationship was not significant after adjustments to metabolic parameters and resistin was associated with FBF after Ach in

the metabolic syndrome group, but again, this relationship disappeared after adjustment for CRP levels.

In conclusion, an adipocyte-endothelium interaction might be an important mechanism of inflammation and vascular dysfunction leading to increased cardiovascular disease in obesity. Adiponectin and PAI-1 correlated with insulin-resistance markers, but resistin did not. The positive correlation between resistin and CRP found in this study suggests a direct proinflammatory role of resistin that might be involved in the inflammatory vascular process. [14]

Adipokines appear to play a central role and may serve as the cellular link mediating both the metabolic syndrome of insulin resistance and the endothelial dysfunction present in the obese state. Adipokine levels appear to correlate closely with adiposity, and with increasing BMI index values.

Weight loss after gastroplastic surgery in morbidly obese patients induces a significant decrease of CRP and IL-6 concentrations. The decrease in inflammatory markers improved insulin resistance, body-weight, and glycemia. Elevated levels of C-reactive protein (CRP) and interleukin-6 (IL-6), indicating chronic subclinical inflammation, have been associated with features of the insulin resistance syndrome and incident cardiovascular disease.[11].

Finally, it seems that the adipose tissue is a key regulator of inflammation, coagulation, and fibrinolysis.

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