Adipokines in obesity and metabolic diseases

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Abstract

Adipose tissue secretes many adipokines that regulate important physiological functions. Growing studies have highlighted that these bioactive molecules may contribute to the development of metabolic and cardiovascular diseases. Adipokines exert systemic metabolic effects and independent activity on numerous cells of the cardiovascular system, including cardiomyocytes and vascular cell walls. Adiponectin shows anti-inflammatory and anti-atherosclerotic activity on blood vessels. Conversely, resistin is endowed with pro-inflammatory effects and stimulates the proliferation of smooth muscle cells, thus promoting the development of atherosclerotic plaque. Leptin plays an important role in cardiac remodeling and blood pressure regulation through the activation of the sympathetic system. Obesity is a pathological condition associated with hypertrophy of white adipose tissue, which stimulates the production of pro-inflammatory adipokines while, it reduces the production of anti-inflammatory adipokines. The delicate balance among the production of pro-and anti-inflammatory molecules generated by adipose tissue affects, not only the development of metabolic complications associated with obesity, but also the onset and progression of atherosclerosis. Therefore, adipokines may be regarded as potential agents of clinical interest in the treatment of a wide range of metabolic disorders and as potential biomarkers useful for early detection of metabolic, cardiovascular and inflammatory diseases.

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Introduction

Adipose Tissue (AT) is a an organ whose cellular composition varies according to age, gender and tissue distribution.[1] For many decades it has been considered as a passive organ that functioned, under conditions of excess energy intake, only as lipid storage depot, to provide energy-rich substrates needed by other tissues.[2] Actually, AT it is recognized as a metabolically active organ, having endocrine and secretory functions, which synthesizes and secretes bioactive molecules such as adipocytokines.[3-5] These molecules contribute to regulate various physiological functions such as food intake, insulin sensitivity and inflammatory processes.[6] In mammals there are two different types of AT, *e.g.* white and brown tissue, which have different morphology and function. In humans, Brown Adipose Tissue (BAT) is present in infants and is less represented in adults. Brown adipocytes are smaller than white adipocytes. The main function of BAT consists in heat production (thermogenesis), through the oxidization of fatty acids present inside the adipocyte.[3,4,7] BAT takes the name by its colour, due to the presence of intense vascularization and the wide content of mitochondria.[8,9] On the other hand, White Adipose Tissue (WAT) is widely distributed throughout the body. It is mainly present in the dermis and in the subcutaneous region of the hollow organs and abdominal and mediastinal cavities. WAT has the function of mechanical cushion, reduction of trauma and allows the sliding of muscles filaments maintaining their integrity.[3,7] Furthermore, WAT acts as a thermal insulator.[4] It accumulates triglycerides, thus providing energy in the form of fatty acids.[9] WAT represents the largest endocrine organ in humans. It has been shown to secrete numerous hormones, growth factors, enzymes, cytokines, complement factors and matrix proteins involved in the regulation of different physiological processes, including food intake, energy consumption, metabolic homeostasis, immunity and blood pressure.[10,11] AT induce its effects through endocrine, paracrine and autocrine signals.[1,12] The endocrine functions of WAT were first hypothesized following the early observations showing that it influenced steroids conversion, and later in 1994 following the identification of leptin.[4,7]

Metabolic syndrome

The metabolic syndrome represents a clinical condition characterized by obesity, insulin resistance (decreased ability of the tissues to respond to the action of insulin) and hypertension. It is often associated with dyslipidaemias and Non-Alcoholic Fatty Liver Disease (NAFLD) and represents a risk factor for type 2 diabetes mellitus and cardiovascular disease.[13,14]

Obesity, especially abdominal obesity, which is considered a chronic inflammatory disease, has been shown to play a key role (Figure 1). The inflammatory condition associated with the metabolic syndrome is characterized by the presence high concentrations of pro-inflammatory molecules, such as C-reactive protein, TNF-α, Resistin, IL-6, IL-8, visfatin and adiponectin.[15] Low levels of adiponectins has been observed in both adults and children with metabolic syndrome. On the contrary, higher levels of adiponectins have been shown to exert a protective function against the onset of metabolic syndrome.[16]

Insulin resistance and adipokines

AT is a tissue that responds to the action of insulin which, in turn, stimulates the accumulation of triglycerides in the AT through various mechanisms.[17] Insulin resistance induced by obesity is related to an increased secretion of cytokines and bioactive substances by the AT, and to an increase in macrophages infiltrating the AT which account for a chronic inflammatory state.[13,18-20] These proteins are secreted by adipocytes and cells of the immune system, and in particular by macrophages. Many of these molecules such as Monocyte Chemoattractant Protein (MCP-1), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), IL-18, leptin, resistin, Plasminogen Activator Inhibitor (PAI-1), visfatin, Retinol-Binding Protein-4 (RBP-4) have pro-inflammatory activity, while others such as adiponectin, Secreted Frizzled-Related Protein-5 (SFRP-5) are anti-inflammatory adipokines.[21] TNF-α is a pro-inflammatory cytokine which can contribute to the pathogenesis of obesity and insulin resistance.[22] In humans, the expression of TNF-α is increased in obesity and in presence of insulin resistance. However, the correlation between TNF-α plasma levels and insulin resistance is relatively weak.[22,23] IL-6 is a cytokine associated with the development of insulin resistance in obesity.[24] In humans, 10-35% of the circulating levels of IL-6 are produced by adipose tissue, and its production increased following hypertrophic enlargement of adipocytes.[25] On the other hand, *in vitro* and *in vivo* studies have shown that IL-6 expression levels are positively associated with insulin.[26] However, the correlation between IL-6 and obesity or insulin resistance remains controversial. IL-18 is another pro-inflammatory cytokine produced by AT.[27] Circulating levels of IL-18 are increased in obese subjects and decrease following weight loss.[28] However, further studies are needed to confirm the role of IL-6 and IL-18.

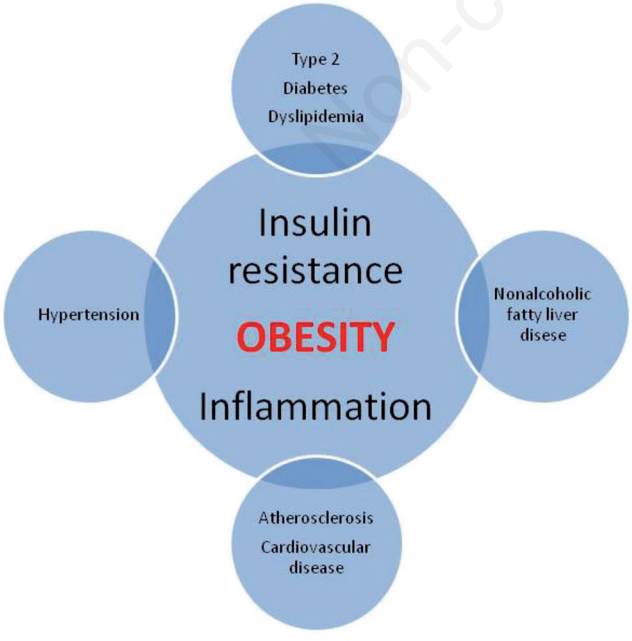

Figure 1. Obesity as a proinflammatory and pathogenic factor.

Leptin

The discovery of leptin as a product of the *ob* gene in obese mice dates to 1994.[29] Leptin is a protein secreted primarily from AT. Its plasma levels are increased in subjects with a higher fat mass. Leptin secretion increases after a meal, due to the increase in insulin secretion. Leptin is secreted, at lower concentrations, from placenta, gastric epithelium, bronchial mucosa and mammary gland. Glucocorticoids, acute infections and pro-inflammatory cytokines contribute to increasing leptin levels, while exposure to cold, adrenergic stimulation, Growth Hormone (GH), thyroid hormones, melatonin, cigarette smoking and thiazolidinediones reduce its circulating levels.[11,30-33] Circulating leptin is higher in women than in men, as a result of inhibition by androgens and stimulation by estrogens. This hormone plays an important role in regulating food intake, energy consumption and fertility. In the hypothalamus, leptin increases the synthesis of the anorexic peptides α-MSH and decreases the synthesis of orexic peptide (NPY), with a consequent reduction of the appetite.[34] In obese subjects, the circulating levels of the hormone are increased due to the onset of leptin resistance.[35] Furthermore, leptin receptors are expressed in the central reward processing pathway, These findings suggest that the reduction of food intake induced by leptin is not only related to its effect on hypothalamus.[36,37] Leptin reduces insulin secretion and its metabolic effects[38-41] while it increases fat oxidation.[42] Leptin promotes also apoptosis of adipocytes[43-46] and is endowed with pro-inflammatory effects. Consistent with these findings, leptin has been observed to promote the production of pro-inflammatory cytokines (IL-2 and IFN-γ)[47] and contributes to maintaining a chronic state of inflammation in obese patients.[48]

Resistin

Resistin is an adipokine secreted by adipocytes that promotes both inflammation and insulin resistance in mouse models.[49] Data on the correlation between resistin and metabolic disorders in humans are still controversial. In fact, although, some studies have reported a close relationship between resistin levels and obesity, insulin resistance or type 2 diabetes, other studies have highlighted no association between resistin and insulin resistance.[50,51] The circulating levels of resistin are increased in both experimental obese animals and humans, while they are reduced by rosiglitazone administration.[52,53]

Visfatin

Nicotinamide Phosphoribosyltransferase (NAMPT), also known as visfatin was initially described as an adipokine secreted mainly by visceral adipose tissue.[54] Subsequent studies in humans have shown that visfatin is also expressed in other tissues. However, its insulin-mimetic role appears controversial.[55,56]

Adiponectin

Adiponectin is an adipokine specifically secreted by adipose tissue.[57] There are three circulating isoforms of adiponectine, *e.g.* trimer, hexamer and multimeric complex.[58] Two adiponectin receptors have recently been identified. AdipoR1 is a receptor for globular adiponectin and is abundantly expressed in skeletal muscle, whereas AdipoR2, a receptor for full-length adiponectin, is mainly expressed in the liver. Two types of adiponectin receptors contain seven transmembrane domains have been identified, namely AdipoR1 which is expressed in skeletal muscle and AdipoR2 which is expressed in skeletal muscle and liver. The expression of these receptor results decreased in obesity-related insulin resistance.[59] A member of the cadherin super family, T-cadherin, has been identified as a potent receptor for the hexameric form and for an adiponectin oligomer.[60] Adiponectin induces an increase in insulin sensitivity. This molecule exerts anti-inflammatory and anti-apoptotic functions on various types of cells, and acts at hypothalamic level as regulator of energy homeostasis. In particular it increases energy consumption thus causing weight loss.[61] The circulating levels of adiponectin are decreased in presence of metabolic disorders.[61] On the other hand, adiponectin expression is reduced in adipose tissue, in obese subjects and in insulin resistant subjects compared to lean subjects. Furthermore, this phenomenon is associated with a reduced insulin sensitivity and a low expression of TNF-α in the adipose tissue.[62] The restoration of proper adiponectin levels could be of clinical relevance as a new therapeutic approach in the treatment of metabolic disorders associated with obesity.[63] In this context, synthetic orally active agonists of adiponectin receptors that bind and activate AdipoR1 and AdipoR2 receptors, *i.e.*, the so called AdipoRon, have been challenged on diabetics and obese mice. The results obtained were like those observed with adiponectin (*i.e.*, increase in sensitivity and tolerance to glucose, reduction of cardiovascular pathologies and cancer). In addition, these studies also showed an significant increase in the life span of mice. However, further studies are needed to better define the pharmacological and toxicological profile of these molecule and their long-term effects.[64]

Frizzled-related secreted protein- 5

Secreted Frizzled-Related Protein-5 (SFRP-5) is a protein endowed with insulin sensitizing and anti-inflammatory properties. It is highly expressed in the AT and exert beneficial effects on metabolic dysfunctions.[65] The results from emerging studies have highlighted a positive correlation between SFRP-5 levels and carbohydrate parameters in healthy and obese subjects. However, further investigation is needed to better assess this phenomenon.[66]

Apelin

Apelin is an adipokine involved in the regulation of glucose homeostasis.[67] The circulating levels of Apelin are increased in obese patients and in patients with insulin resistance and liver cirrhosis.[67,68] Conversely, decreased serum levels of Apelin hare associated with an improved insulin sensitivity, a phenomenon which does not appear to be associated with a significant weight loss.[68] Experimental *in vivo* studies in mice, indicate a possible correlation of Apelin with glucose homeostasis, obesity and related diseases. However further studies are needed in humans to better define these effects.

Vaspin

Vaspin is a novel serine protease inhibitor (serpin), with insulin-sensitizing effect, produced by visceral adipose tissue. It is also expressed in the hypothalamus, stomach, and pancreatic islets of rodents.[69] The underlying mechanisms which may account for the improving effect of Vaspin on glucose metabolism remain to be fully unravelled.[70]

Nesfatin-1

Nesfatin-1 is an adipokine expressed in central nervous system, pituitary gland, stomach, pancreas, testes, and in the adipose tissue. This new molecule appears to be involved in the regulation of food intake by acting through a leptin-independent mechanism.[71] Experimental observations in mice have shown that Nesphatin-1 is implicated in adaptive responses to stress conditions and has glucose-dependent insulinotropic effects.[72,73] However, studies on humans on the effective physiological role of this neuro-peptide are still lacking.

Dipeptidyl-dipeptidase-4

Dipeptidyl-Dipeptidase-4 (DPP-4) is an adipokine secreted by AT.[74] DPP-4 circulating levels correlate with the size of adipocytes and with the inflammatory conditions of the AT.[74,75] DPP-4 is present in the circulation in overweight and obese subjects[76] and may be responsible of the onset of insulin resistance in adipocytes and skeletal muscle. It is likely that the metabolic effects of DPP-4 could, at least in part, be related to its function. In fact, this adipokine is implicated in the degradation of GLP-1, an incretin that reduces peripheral resistance to insulin. This hypothesis is supported by the observations that the circulating levels of DPP-4 in insulin-sensitive obese patients are lower compared to those determined in insulin-resistant obese patients.[75] Therefore, the increased levels of DPP-4 may contribute to obesity and insulin resistance. The increased activity and concentration of DPP-4 in obese subjects may be useful as possible a therapeutic target in the treatment of obesity and related diseases.

Interleukin-1β

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine expressed and secreted by AT.[77] This cytokine is involved in inflammatory processes responsible of pancreatic beta cells destruction occurring in type diabetes 1.[78]

Adipokines and obesity and diabetes related diseases

Hypertension

Adiponectin levels are lower in patients with arterial hypertension than in normotensive patients. Therefore, the increased levels of this molecule appear to correlate with a reduced of the risk of hypertension. Adiponectin is an important biological modulator of vascular remodeling related to obesity and vascular disorders. This molecule regulates blood pressure through mechanisms mediated by the nervous system and endothelium.[79,80] *In vitro* studies have shown that it reduces the proliferation of smooth muscle cells and inhibits the expression and the biological effects of TNF-α in macrophages, thus reducing their molecular adhesion and transfor-

mation into foamy cells.[81] The anti-atherogenic properties of adiponectin are mainly due to the production of Nitric Oxide (NO) in endothelial cells[79,80] which induces relaxation of blood vessels relaxation and exerts anti- inflammatory and antithrombotic effects on the blood vessel walls.[82]

Chronic kidney disease

Chronic kidney pathologies and the related functional and structural changes of this organ caused by glomerulomegaly, glomerulosclerosis, diabetic nephropathy, renal carcinoma, nephrolithiasis, are related to obesity. Although endothelial dysfunctions are recognized as the pathogenetic mechanism of chronic kidney diseases, some adipokines such as leptin, proinflammatory cytokines and adiponectin can also contribute to kidney disfunctions. In addition, weight loss and decreased apodiponectin levels may hinder the progression of kidney damage.[83,84] However, the mechanisms responsible for the increased adiponectin levels observed in presence of kidney damage and the clinical significance of this phenomenon remain controversial. Further investigation are needed to better clarify these mechanisms.[85] Visfatin/nampt is also implicated in chronic renal pathologies. In particular, visfatin/nampt levels have been shown to be positively associated with some circulating markers of endothelial dysfunction including Vascular Cell Adhesion Protein-1 (VCAM-1), Intracellular Adhesion Protein -1 (ICAM- 1), Melanoma Cell Adhesion Molecule-1 (MCAM-1).[86,87] Conversely visfatin/nampt levels were inversely associated with the rate endothelial function expressed as brachial artery flow-mediated dilation or as rate of glomerular filtration rate.[88,89]

Diabetic retinopathy

Diabetic retinopathy is one of the most frequent microvascular complications, affecting 30-50% of diabetic patients.[90] Adiponectin levels were decreased in obese subjects and type 2 diabetes patients. In the latter case the levels of circulating adiponectin resulted lower in presence of diabetic retinopathy as compared to patients without retinopathy.[91] Furthermore, a positive correlation was observed between low plasma levels of adiponectin and severity of diabetic retinopathy.[92] In patients with proliferative diabetic retinopathy, Vascular Endothelial Growth Factor (VEGF) and adiponectin levels were significantly more elevated in the aqueous humor than in the control group.[93,94] This phenomenon could be due to either an increased permeability of the blood-retinal barrier or to the local reparative process of endothelial dysfunction. Adiponectin induces endothelial production of NO *in vitro*.[95] The administration of the angiogenesis inhibitor bevacizumab, may significantly reduce VEGF and adiponectin levels.

Dyslipidemia

The term dyslipidemia refers to an abnormal increase in lipids (cholesterol and triglycerides) in the blood. Dyslipidemia is often associated with obesity and is a well known risk factor for cardiovascular disease. Obesity related dyslipidemia is mainly characterized by increased plasma levels of Free Fatty Acids (FFA) and Triglycerides (TG), decreased levels of High Density Lipoproteins (HDL) and an abnormal Low Density Lipoproteins (LDL) composition.[21] An increased release of FFAs by adipose tissue can result a increased FFAs uptake from the liver. This effect, in turn, determines an enhanced release of TG from the liver associated with an increased production of Very-Low-Density Lipoproteins (VLDL), and inhibition of Lipoprotein-Lipase (LPL) in adipose tissue and skeletal muscle. These effects, in turn, give rise to hypertriglyceridemia. In addition, the increase of VLDL from liver can inhibit lipolysis of chylomicrons, thus contributing to the increase of plasma TGs. TGs of VLDL are exchanged with Cholesterol Esters (CE) from LDL and HDL from Cholesteryl Ester Transfer Protein (CETP), producing TG rich LDL and HDL. LDL and HDL of TGs are then hydrolyzed by the liver lipase, producing small and dense LDL and HDL. The decrease in HDL concentrations and the synthesis of small and dense LDL have been associated with an increase in cardiovascular risk.[21] On the other hand, a correlation between dyslipidemia and amount of visceral adipose tissue has been observed in patients with type 2 diabetes.[96] The onset of dyslipidemia is also influenced by inflammatory molecules released by adipose tissue, such as TNF-α, IL-6, IL-1, Amyloid Serum A (SAA) and adiponectins. In obese patients, the presence of infiltrating macrophages in adipose tissue is positively correlated with circulating TG levels, while it is inversely correlated with plasma HDL cholesterol levels.[97] Circulating TNF-α levels are increased in hyperlypidemic patients and correlate positively with VLDL concentrations.[98] TNF-α and IL-6 levels are increased in subjects with hypertriglyceridemia.[99,100] TG plasma levels remain elevated in the presence of increased levels of anti-inflammatory cytokines, such as IL-10.[101] In healthy subjects and in subjects with cardiovascular diseases, proinflammatory cytokines, such as TNF-α, IL-6 and IL-1, promote the increase in circulating levels of total cholesterol and LDL-cholesterol, by activating the cholesterol synthesis. These cytokines result also negatively associated with serum cholesterol-HDL levels.[102-104] However, a positive correlation was found between the concentrations of the anti-inflammatory cytokine IL-10 and HDL cholesterol plasma levels while, a negative correlation between IL-10 levels and high levels of total cholesterol and LDL cholesterol was noted.[101] Adiponectin has beneficial effects on lipid metabolism[105] and insulin sensitivity, as it stimulates fatty acids oxidation and the use of glucose through the activation of AMPK in the liver and muscle skeletal.[106] Furthermore, plasma adiponectin levels negatively correlated with TG levels while they positively correlated with HDL cholesterol levels.[107] On the other hand, decreased levels of adiponectin have been shown to be associated with dyslipidaemias and cardiovascular disease.[108,109] Recent studies have suggested the decrease of adiponectin levels in the blood as a useful marker for dyslipidaemias in subjects with polycystic ovary syndrome being at increased risk of dyslipidemia.[110]

Non alcoholic liver steatosis

Non-alcoholic liver steatosis (Non-Alcoholic Liver Disease, NAFLD) is the most common form of chronic liver inflammation and it is related to obesity.[111-113] The development of NAFLD is characterized by two phases: the first phase is characterized by hepatic steatosis (accumulation of TG in the liver), followed in the second phase, which is associated with inflammation and fibrosis (Non-Alcoholic Steatohepatitis, NASH).[113] The development of NAFLD and its progression to NASH are explained by the "two hits" hypothesis. According to this hypothesis, the "first hit" foster the accumulation of lipids in the liver, while the "second hit", causes hepatocytes damage, inflammation and fibrosis,[113] as a consequence of the release of proinflammatory cytokines, adipokines, mitochondrial dysfunctions, oxidative stress and lipid peroxidation. The "two hits" hypothesis has been renamed "multi-hits" hypothesis. This following the discovery of the contribute of various factors in the development of NAFLD, such as lipid dysfunction, imbalance of adipokines, inflammation in the AT, oxidative stress and insulin resistance.[114,115] In the "multi-hit" hypothesis, the imbalance between lipid metabolism and insulin resistance is considered as

"first-hit". Insulin resistance induced by hyperinsulinemia, causes liver steatosis by increasing *de novo* liver lipogenesis, FFA efflux from the AT due to increased lipolysis, by decreasing liver oxidation and reducing VLDL secretion. Following the onset of steatosis, the liver becomes more vulnerable to "multi-hit" factors, including bacterial toxins derived from the intestine, cytokine/adipokine imbalance, mitochondrial dysfunction, oxidative damage, unbalanced apoptosis in hepatocytes, release of pro-fibrogenic factors and inflammatory mediators from damaged organelles and activation of Kupffer cells. These factors contribute to stimulating inflammation, apoptosis, fibrosis, which lead to liver diseases progression.[116,117] In obese patients, the pro-inflammatory and anti-inflammatory factors secreted by the AT are associated with NAFLD.[118] In particular, it has been suggested that adiponectin possess anti-inflammatory activity, which may protect from hepatic steatosis and inflammation, and that, in the liver, it increases the suppressive activity of insulin on glucose production.[119] The circulating levels of adiponectin are lower in subjects with NAFLD than in healthy subjects[120] and are inversely correlated with biomarkers of normal liver function in healthy subjects.[121] On the other hand a low level of adiponectin is a marker of liver steatosis and increase the levels of enzymes characterizing liver damage in obese subjects.[122] Furthermore, in patients with NASH there is a reduction in the expression of adiponectin and its associated receptor AdipoR2 compared to patients with steatosis alone.[123]

Leptin is also involved in NAFLD, as it directly stimulates AMPK, which is involved in the activation of lipid oxidation (β-oxidation and glycolysis) and in the inhibition of lipogenesis.[124] There is a negative correlation between serum leptin levels and liver damage in humans[125] and a positive correlation between serum leptin levels and elevated serum ALT levels or hepatic steatosis. These effects has been shown to be independent from body mass index or body fat mass index.[126,127] Furthermore, in animal models while leptin increases in the presence of liver fibrosis, a decrease in its levels is correlated with a reduction in liver damage.[128] Moreover, leptin is a powerful mitogen and an inhibitor of apoptosis of Kupffer cells.[129]

Studies carried out in experimental animals have highlighted that resistin regulates glucose and lipid metabolism and that may act as a mediator insulin resistance in the liver. Increased resistin values are found in NAFLD patients[130,131] and in NASH patients compared to patients with pure steatosis. However, in humans, the role of resistin is still not well known. Therefore, further study are needed to unravel its functions TNF-α is involved in the early and late stages of NAFLD in both in animals and humans. In particular this cytokine appear to modulate the transition from NASH to NAFLD.[132-134]

Adipokines and cardiovascular diseases

Cardiovascular Diseases (CVDs) are the largest cause of death in the world. They are characterized by alteration of myocardial contractility, inflammation, and vascular damage. These pathological conditions include, hypertension, atherosclerosis, endothelial and myocardial cell dysfunctions. Risk factors for CVDs are hypertension, cigarette smoking, type 2 diabetes, overweight, hyperlipidemia, metabolic syndrome, and family history lifestyle (unhealthy diet and lack of exercise).[135] Adipokines also play an important role in the pathogenesis of CVDs.[136]

Adiponectin

In the heart, adiponectin mediates its action through the presence of three receptors *e.g.*, AdipoR1, AdipoR2 and T-cadherin.[60,137-139] Adiponectin receptors are also expressed in platelets, where they mediate the inhibiting effects of adiponectin on collagen-induced aggregation.[140] Adiponectin has anti-atherogenic properties, as it suppresses cell adhesion to the vascular endothelium and promotes angiogenesis.[105] This peptide is also endowed with anti-inflammatory properties, due to its ability in suppressing NF-kB factor, thus hindering the development of atherosclerosis. Adiponectin can also inhibit the conversion of macrophages into foamy cells and decreases LDL.[81] Adiponectin can also play a role in cardiac remodeling, which consists in thwarting i the extent of myocardial hypertrophy.[141] In humans, the plasma levels of adiponectin are inversely correlated with insulin resistance and the severity of coronary artery disease.[142] On the other hand, no correlations between serum adiponectin levels and risk of coronary heart disease have been reported. However, it has been suggested that the lack of correlation might be probably due to the different adiponectin oligomers tested.[143] However, increased adiponectin levels are correlated with a reduction in the risk of myocardial infarction in humans[144] and with a lower risk of coronary heart disease in diabetic patients.[145] However, unlike it may be expected, the circulating levels of this protein decreased after a myocardial infarction.[146] These findings indicate that adiponectin has a beneficial role in cardiovascular pathologies and atherosclerosis.

Leptin

Leptin is is not exclusively produced by adipocytes but also by cardiomyocytes and Smooth Muscle Vascular Cells (VSMC).[147,148] Leptin and its receptors have been detected in cardiomyocytes,[149] in VSMC,[150] in endothelial cells,[151] in the myometrium[152] and in cerebral and coronary vessels.[153,154] Humans hyperleptinemia is associated with atherosclerosis, hypertension and metabolic syndrome. In particular, this hormone has been shown to play an important role in the early stages of atherosclerosis development, and, in particular, during the recruitment of leukocytes and macrophages in the endothelial wall.[155] In humans, increased serum leptin levels are associated with an increased risk of myocardial infarction and stroke, which is independent from obesity and cardiovascular risk factors.[156] These effects have been, in part, explained with the ability of leptin to increase insulin resistance, to alter hemostasis balance and to induce vascular inflammation.[157] Besides its proinflammatory properties, leptin possesses pro-atherogenic properties. In fact this molecule has been reported to promote i) production of proliferative and profibrinotic cytokines, ii) to induces oxidative stress through Reactive Oxygen Species (ROS) generation,[158] iii) to stimulate cardiomyocyte hypertrophy[159] and VSMCs proliferation, iv) to stimulate platelet aggregation and v) to increase the expression of pro-atherogenic lipoprotein lipase.[160] On the other hand, there are conflicting results on the role of leptin in CVDs. While some of these studies find a positive association between leptin concentration and hypertension,[161] other studies have highlighted a significant vasodilator effect induced by leptin in coronary heart disease.[162] Leptin contributes to the development of obesity-related hypertension by increasing the secretion of pro-inflammatory cytokines such as TNF-α and IL-6, and by generating ROS in endothelial cells.[155,158] Increased leptin levels have been reported to be also associated with hypertension. Various mechanisms such as activation of the renin-angiotensin system, hyperactivity of the sympathetic nervous system, endothelial dysfunction and reduction of the effect of renal pressure on elimination may be involved in this phenomenon.[163] The heart itself produces leptin, which can act locally to induce its physiological effects.[164,165] Leptin has a nega-

tive inotropic effect mediated by NO[166] and regulates cardiac contractility,[167] size of cardiomyocytes and production extracellular matrix components.[168] Leptin has been also indicated to have beneficial effects, such as reduction of lipid toxicity on the heart,[169] protection of cardiomyocytes from the hypoxia-induced damages[170] and myocardial remodelling.[171] The protective effects of leptin from damages induced by ischemia is further supported by the "obesity paradox", *i.e.,* the unexpected reduction of co-morbidity and mortality associated with cardiovascular diseases in subjects with high body mass index.[165]

Resistin

Elevated plasma levels of resistin are correlated with pro-atherogenic inflammatory markers,[172] increased cardiovascular risk, unstable angina, adverse prognosis of coronary diseases and metabolic syndrome.[173,174] Resistin has a pro-inflammatory role in atherosclerosis, as it induces the expression of VCAM-1 and Intercellular Adhesion Molecule-1 (ICAM-1),[175] increases the expression of proinflammatory cytokines (IL-1, IL-6, IL-12, TNF-α);[176,177] and the release of endothelin-1. In line with these observations, studies on atherosclerosis carried out in experimental animal models, have shown that resistin levels correlated with the severity of the sclerotic lesion.[178] In addition, the action of resistin is inhibited by adiponectin.[175]

Visfatin

Visfatin is mainly produced and secreted in visceral fat. However, it is also present in perivascular and epicardial adipose tissue.[179,180] Visfatin expression is positively associated with lipid metabolism and atherosclerosis.[181] In particular, it has been shown that this molecule plays a role in the destabilization of atherosclerotic plaques[182] and inflammation. Consistent with these observations high levels of visfatin have been reported to induce the expression of VCAM-1 and ICAM-1, and to increase the expression of pro-inflammatory cytokines.[183] On the other hand, plasma visfatin levels result inversely correlated with vascular endothelial functions.[184] However, visfatin has been reported to exert beneficial effects. For instance, this hormone stimulates endothelial proliferation and capillary formation in human endothelial cells,[185] reduces apoptosis in human VSMCs.[186] Furthermore, experimental studies have shown that in rats, it reduces cardiac contractility and induces vasodilatation mediated by NO produced by the endothelium.[187] In an *in vivo* ischemia-reperfusion models, a single i.v. push of visfatin has been shown to reduce the size of the infarcted area by 50% and to protect from the damage due to reoxygenation of the cardiomyocytes.[188-190] In patients with coronary artery disease and acute myocardial infarction, visfatin levels are positively associated with unstable atherosclerotic lesions. Furthermore, visfatin promotes destabilization of plaques and their rupture in different types of acute coronary syndromes.[182] This molecule appears to play also a role in both atherosclerosis and endothelial dysfunctions.[191] *In vitro* studies and *in vivo* studies suggest that visfatin may have a neuroprotective role towards cerebral venous thrombosis ischemia.[192] Overall, visfatin can help to exacerbate angiogenesis caused by ischemic heart disease, diabetes or atherosclerosis, and could, therefore, be considered a new target for more effective treatments of these pathological conditions.[191]

Apelin

Apelin is a peptide produced and secreted by adipocytes, vascular stroma and cardiovascular tissues.[193] Apelin is expressed in endothelial cells of the endocardium while, its receptor APJ is expressed in cardiomyocytes. This suggest that the apelin system acts on the heart by increasing cardiac contractility and heart rate.[194-196] Plasma apelin levels are positively associated with body mass index and obesity, which is considered one of the major causes of CVDs.[197] On the other hand, decreased apelin levels are observed in patients with atrial fibrillation not associated with other CVDs[198] and chronic heart damage.[199] Overall, apelin is currently considered an adiponectin with a favorable effect for CVDs, as it reduces atherogenesis, macrophage activity, cardiomyocyte contractility, atrial fibrillation and heart damage. However, further studies are needed to clearly outline its role in different myocardial pathologies.[136]

Omentin

Omentin is an adipocytokine that is abundantly expressed in the adipocytes present in the vascular stroma. It has anti-inflammatory, anti-atherogenic and anti-diabetic properties.[200] Omentin plays an important role in the pathogenesis of vascular coronary diseases, mainly in coronary artery atherosclerosis.[201] Studies undertaken in mice have shown that omentin promotes cellular endothelial functions and revascularization in response to ischemia.[202] Serum omentin levels are lower in patients with acute coronary syndrome or with stable angina pectoris than in healthy subjects.[203] Omentine could be a potential biomarker to predict the development and progression of coronary heart disease in patients with metabolic syndrome.[204]

Chemerin

Chemerine is a relatively recent adipokine. Its cardiovascular properties have still not well established. Chemerin plasma levels are positively correlated with the metabolic syndrome and associated risk factors, such as body mass index, hypertension and hypertriglycaeridemia[205] Chemerin levels are increased in patients with severe obesity.[206] This adipokine appears to reduce inflammation in endothelial cells by inducing NO synthesis which, in turn, inhibits VCAM-1 mediated TNF-α induction and the consequent lymphocyte adhesion through the suppression of the activation of the NF-kB factor and that of the p38 signaling pathway.[207] It also promotes endothelial angiogenesis and the production and activity of matrix metalloproteinases[208] while reduces adhesion to endothelial walls[207] and enhances the contractile response to phenylepinephrine in VSCMs and in the endothelium.[209]

Adipokines and gestational diabetes mellitus

Gestational Diabetes Mellitus (GDM), is a frequent complication of pregnancy that can cause considerable risks to the mother and the fetus.[210] Untreated GDM, can progress to type 2 diabetes.[211] GDM occurs in 3-7% of pregnancies[212] and mostly in the second trimester of pregnancy, due to the increased insulin resistance and decreased function of pancreatic beta cells.[213] Normally, β-cells adapt to insulin demands for a given physiological context.[214] Following proliferative stimuli mediated by Placental Lactogen Hormone (HPL), prolactin and growth hormone, these cells increases up to 50% during pregnancy.[215] During pregnancy, selected insulin requirements in women are due to insulin resistance, which is related to HPL production, food intake, body weight intake, and to the fetal presence itself.[216,217] GDM increases the risk of developing type 2 diabetes and/or that of other complications in pregnancy, such as pre-eclampsia. These conditions may increase the possibility to resort to cesarean section and complications in problems, such as macrosomia. Children born from mothers with GDM have an increased risk to develop obesity and type

2 diabetes mellitus as adults, as well as hypoglycemia, hypocalcaemia, polycythemia, jaundice and respiratory distress syndromes.[213] Serum adiponectin levels progressively decrease during pregnancy.[218,219] In women with GDM, the increased secretion of inflammatory cytokine could reduce the secretion of adiponectin, whose excessive low levels contribute to insulin resistance. Adiponectin may be considered a factor related to insulin resistance and pancreatic beta cell dysfunction in the pathogenesis of type 2 diabetes.[214-216,220] Leptin is also secreted by the placenta. It regulates the secretion of Gonadotropin Releasing Hormone (GnRH) and activates the orthosympathetic nervous system. In normal pregnancy, leptin concentrations are 2-3 times higher than in non-pregnant subjects and peaks around the 28th week of gestation. Leptin has a potential role in embryo implantation, in the induction of the secretion of human chorionic gonadotropin, in the formation of trophoblastic cells and in the regulation of placenta growth. Furthermore, Leptin increases mitosis and promotes the absorption of amino acids.[220] The expression of leptin in the placenta is increased in pregnant women with GDM, compared to women with a normal pregnancy.[220] This could be explained with the presence of hyperinsulinemia in GDM.[220,221]

Discussion and conclusions

Adipokines are currently considered an exciting new link between obesity and insulin resistance, obesity and cardiovascular disease and hypertension and hyperlipidemia. Although the influence of adipokine on obesity in pathological conditions associated with obesity and metabolism has been well established, this phenomenon have been investigated more in detail. This review analyses and discuss the current findings of these studies. In general, adipokines can increase or decrease insulin sensitivity and can influence appetite and food intake.[6] The increased knowledge from studies on physiological and pathological functions of new adipokines suggests that adiponectin, visfatin, vaspin and omentin may also improve the effects of insulin.[55,56,200] Various studies have contributed to greatly increase our knowledge about the physiological functions of adiponectin. These studies have shown that elevated plasma levels of adiponectin are associated with a lower incidence of type 2 diabetes mellitus and that reduced expression levels of this this protein can be observed in insulin resistance.[16] Unfortunately, the clinical studies undertaken so far, has failed to highlight a direct sensitizing effect of adiponectin on endogenous insulin. However, preclinical *in vivo* studies have suggested that adiponectin, adiponectin receptor agonists and AMPK activators may be good candidates for developing new therapeutic options for the clinical management of type 2 diabetes and obese patients.[64] Furthermore, drugs that increase the expression of anti-inflammatory adiponectin in fats are also of potential interest. Other compounds including combined PPAR/PPAR-agonist could also mediate some of their effects on insulin sensitivity through similar mechanisms. On the other hand, the role of Visfatin, Vaspin and Omentin in human insulin resistance and obesity needs to be better clarified to define their therapeutic potential. Regarding the adipokine induce insulin resistance, the role of IL-6 in human insulin sensitivity and obesity is the best understood.[24,25] IL-6 increases glucose tolerance *in vivo*. Moreover, elevated baseline IL-6 levels are associated with an increased risk of developing a reduced glucose tolerance.[26] However, therapeutic approaches based on direct inhibition of IL-6 should not probably be feasible in the clinical practice, due to various expected side effects. TNFα and resistin appear as the main links between insulin resistance and obesity in rodents. However, their role in humans remain still uncertain.[15] In addition, clinical observations haves shown that the inhibition of TNFα has no effect on insulin sensitivity. Clinical studies on the physiological role PAI-1, SPARC/osteonectin, MCP-1 and RBP-4 are scanty so their role in insulin resistance and obesity, is still not well delineated. Leptin is the main appetite suppressant hormone. This adipokine is very effective in human leptin deficiency. However, the knowledge of mechanisms mediating leptin resistance in obesity it is of pivotal importance to find new therapeutic options to replenish central and peripheral leptin signaling. The results from numerous experimental and clinical studies reported in this review, highlight that various adipokines can be regarded as potential targets in the treatment of insulin resistance and obesity and related metabolic pathologies. It is now well established that the altered expression and secretion of adipokines, which occurs in obesity, especially in the visceral obesity, determines important circulatory and metabolic alterations. However, among the numerous signaling molecules and their associated effects identified by these investigations, those with potential clinical interest that might undergo to pharmacological modulation have to be still identified. Ultimately, advances in the knowledge of adipocyte biology may lead to a better understanding of the physiological functions attributed to the adipose tissue which, now is currently considered multi-functional organ rather than simply a passive storage site for excess energy.

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