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SM Journal of Endocrinology and Metabolism

Mini Review

Adipokines at the Cardiovascular System: Role in Health and Disease

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Article Information

Received date: Aug 17 2015
Accepted date: Jan 15, 2016
Published date: Feb 01, 2016

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Keywords Obesity; Adipokines; Energy homeostasis; Cardiovascular diseases; Insulin resistance; Endothelial dysfunction

Abstract

Although a high body mass index is related to the development of cardiovascular risk factors, nowadays there are numerous evidences supporting the idea that the regional fat accumulation, its function and its endocrine products are more important than the excess of adiposity *per se* when considering the risk of cardiovascular disease development. In this review, we will focus on the function of the main adipokines and its role at cardiovascular level.

Introduction

The white adipose tissue (WAT) plays a crucial role in providing insulation, mechanical support, storage of energy and whole-body fatty acid homeostasis [1]. When there is an excess of nutrients, WATstores free fatty acids (FFAs) in the form of triglycerides through their esterification to glycerol, and releases them back into circulation in states of energy deficiency, representing the major source of FFAs in the postprandial fasting state for energy production through oxidative phosphorylation of adenosine triphosphate (ATP) high-energy bonds [1-3]. Although WAT function is essential for life in mammals, our new way of life (based on an increased intake of energy-dense foods and a decrease in physical activity due to the increasingly sedentary nature of many forms of work, changing modes of transportation, and increasing urbanization) is raising the prevalence of obesity and noncommunicable diseases associated to high body max index (BMI), such as diabetes, musculoskeletal disorders, some types of cancer and cardiovascular diseases (CVDs) [4].

In the last decades, a number of studies have shown an association between the adipose tissue pathological function and distribution and the higher risk to develop CVDs, mainly through the secretion of chemical mediators that act in an autocrine/paracrine/endocrine way to modulate not only cardiovascular function but also a wide range of biological processes. In this review we will summarize the implication of the adipose tissue in the cardiovascular risk and we will focus on the role of its main secretory products at cardiovascular level.

Adipose Tissue and Cardiovascular Risk

The association between the increase in BMI and cardiovascular risk has been widely described in the last decades and is nowadays thoroughly accepted [4]. Apart from the fact that chronic excessive body fat accumulation causes adaptations in the cardiovascular system to maintain whole body homeostasis (increased cardiac output, decreased peripheral resistance, increased stroke volume or ventricular remodeling), the contribution of the different fat depots to the development of CVDs vary according to their distribution and function [5].

White adipose tissue composition and function

The WAT is composed by several types of cells, including mature adipocytes, pre-adipocytes, fibroblasts, endothelial cells, T-lymphocytes and macrophages, as well as connective, vascular and neural tissues [6]. Adipocytes are the main component of the WAT, and in the postprandial period they accumulate FFAs from the circulation into triglycerides due to the anabolic and anti-lipolytic effect of insulin [7]. However, as adipocytes grow larger they become dysfunctional, insulin resistant and more sensible to the lipolytic effect of the adrenal medullary catecholamines epinephrine, and to a lesser degree norepinephrine, contributing to the release of FFAs into the circulation [8]. On the other hand, the cellular component of WAT (mainly adipocytes and macrophages) are able to release chemical mediators, termed adipocytokines or adipokines, which set a communication network between the WAT and other tissues, sympathetic nervous system and brain to modulate appetite, energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and homeostasis [6,8]. Thus, the WAT is nowadays considered as an endocrine organ with important functions not only regarding the management of energy homeostasis but also a wide

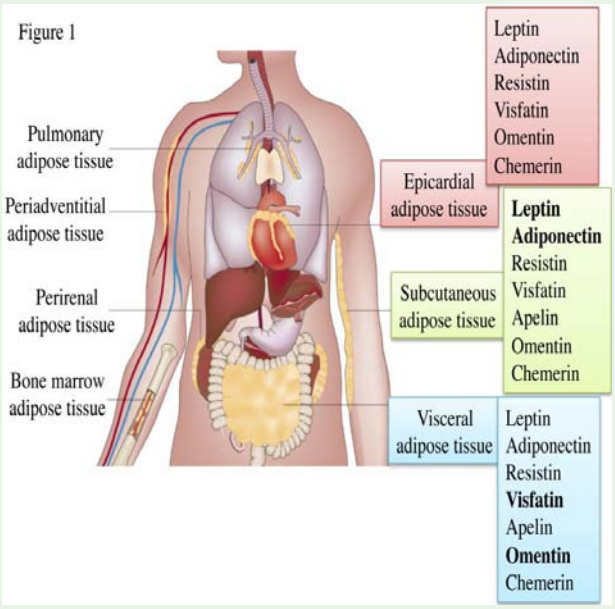

Figure 1: White adipose tissue distribution and comparative production of some adipokines in subcutaneous, visceral and epicardial adipose tissues. The White adipose tissue includes numerous discrete anatomical depots, being the subcutaneous and visceral fat its main locations. There are also numerous smaller adipose depots such as epicardial, pulmonary or bone marrow fat that may serve specialized functions related to their neighboring tissues. Differential adipokine secretion by each adipose tissue depot may selectively affect organ function and systemic metabolism. Adipokines in bold represent a higher production. Adapted from Ouchi et al. [12].

range of biological functions, and its physiological or pathological role depends on fat amount, distribution and the adipokine secretion pattern (Figure 1) [9].

White adipose tissue distribution and cardiovascular risk

The WAT is dispersed throughout the body in discreet depots, which are thought to constitute "separate mini-organs", being subcutaneous and visceral fat its major depots [8]. Subcutaneous adipose tissue (SAT) mainly accumulates below the skin in the abdominal, gluteus and femoral areas, and represents about 80% of body fat, while visceral adipose tissue (VAT) is distributed close to or even within the viscera of the abdominal cavity, and accounts for up to 10–20% of total fat in men and 5–8% in women, increasing with age in both genders [10–12]. Smaller fat depots have been described in other locations, including the heart, kidneys, bone marrow, joints, eyes, lungs and vasculature (Figure 1) [11,12].

SAT depots are the natural store for energy, but when its storage capacity is exceeded or its ability to generate new adipocytes is impaired, fat begins to accumulate in other areas [8]. In general terms, fat accumulation can be easily classified according to its distribution: "apple shaped" individuals have upper abdominal, central or android obesity (visceral fat) and are at a greater cardiovascular risk than those who are "pear shaped", with gluteofemoral, peripheral or gynoid obesity (subcutaneous fat) due to the fact that the type of adipocytes, their endocrine function, lipolytic activity, and response to insulin and other hormones are instead of is different between both fat depots (Figure 2) [8]. VAT contains a greater number of large adipocytes with a larger amount of β-adrenergic receptors on the cell surface compared to the SAT, which in turn leads to higher lipolytic activity due to catecholamine binding to β-adrenergic receptors and lower sensitivity to the anti-lipolytic effect of insulin (catecholamine-induced insulin resistance), with the concomitant FFAs delivery increase into the bloodstream and surrounded tissues [13,14]. VAT has a higher infiltration of macrophages, which contributes to the increase of pro-inflammatory adipokines release such as interleukin (IL)-6 or plasminogen activator inhibitor (PAI)-1, contributing to local and systemic inflammation and cardiovascular risk [9,11]. On the contrary to the SAT, in which venous drainage is through systemic veins, and because of its anatomical position, VAT venous blood is drained directly into the liver through the portal vein, releasing significant amounts of FFAs which stimulate hepatic glucose production and suppress hepatic insulin clearance, leading to dyslipidemia, hyperinsulinemia and insulin resistance at systemic level and contributing to the development of metabolic syndrome [11].

A wide number of epidemiological studies in the last two decades have contributed to demonstrate that the VAT accumulation is associated with the development of CVDs, while SAT is associated with a protective phenotype [11,15]. To this effect, the accumulation of visceral fat along with its key metabolic perturbations is now considered as a key modifiable CVD risk factor, which contributes to exacerbate CVD risk beyond classical risk factors such as insulin resistance, hyperinsulinemia, glucose intolerance, type 2 diabetes mellitus (T2DM), atherogenic dyslipidemia (high triglycerides, apolipoprotein B, small and dense LDL, low HDL), inflammation, altered adipokine profile, impaired fibrinolysis and increased risk of thrombosis, as well as endothelial dysfunction [5]. However, the

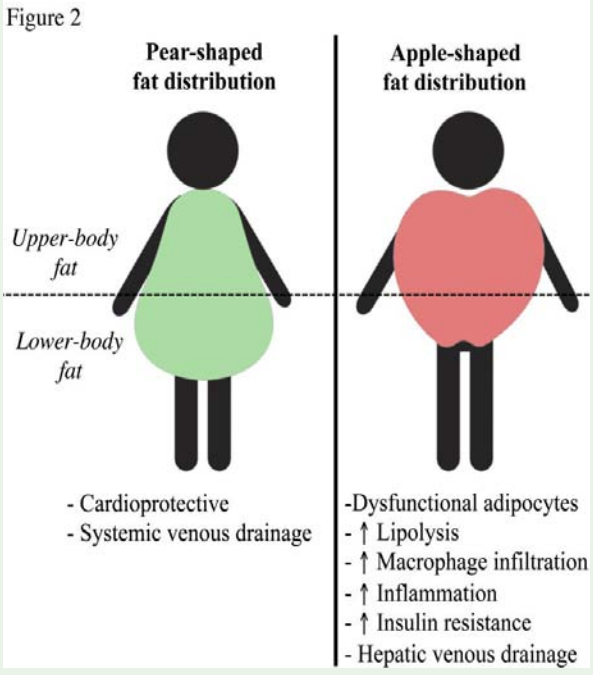

Figure 2: Fat distribution and cardiovascular risk.
Increased intra-abdominal/visceral fat (upper-body or apple-shaped obesity) promotes a high risk of cardio metabolic diseases, whereas increased subcutaneous fat in the thighs and hips (lower-body or pear-shaped obesity) exerts Little or no risk and may be protective.

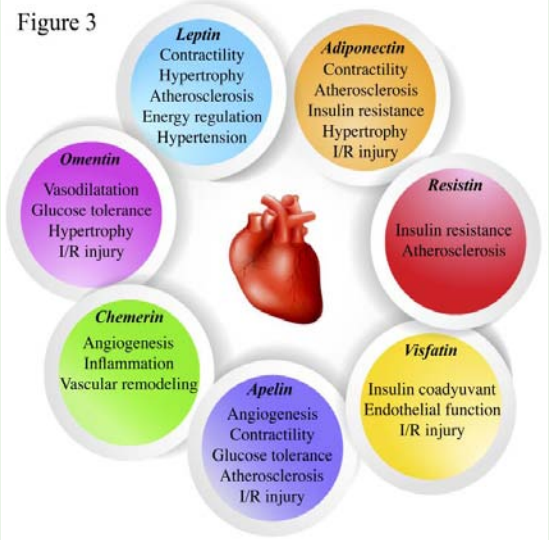

Figure 3: Adipokines and cardiovascular function.
Some adipokines exert important actions at the cardiovascular level by regulating a wide range of biological processes, including blood pressure, angiogenesis, insulin / glucose sensibility, inflammation or even heart contractility. Thus, their pathological production in obesity could contribute to the development of cardiovascular diseases.

underlying key molecular processes that link metabolic dysfunction with heart diseases need to be further studied and the secretion pattern of adipokines seems to be closely related to the pathophysiology of CVDs development.

Epicardial adipose tissue and cardiovascular risk

Epicardial adipose tissue (EAT) is a visceral thoracic fat depot distributed along the large coronary arteries and on the surface of the ventricles and the apex of the heart that constitutes about 20% of the total ventricular weight of the human heart while covering 80% of the heart's surface [16]. It has been defined as the intra-pericardial fat depot that is located between the myocardium and pericardium without a structure or fascia separating it from the myocardium and the epicardial vessels, sharing the coronary blood supply with the myocardium.Thus FFAs could diffuse across concentration gradients bidirectionally between the epicardial fat and the myocardium [16,17]. It has the potential to be a good storage depot for fatty acids, and potentially protects the heart against high fatty acid levels and acts as a local energy source of fatty acids during times of high energy demand by channeling fatty acids to the myocardium [16]. However, adipocyte/triglyceride infiltration into the myocardium wall/ cardiomyocytes may easily occur [16,17]. In obesity, EAT volume increases and it has been related to cardiac hypertrophy, impaired diastolic function and coronary artery occlusions [16].

As well as other WAT depots, EAT is considered an endocrine "mini-organ". It expresses and secretes a number of cytokines, pro- and anti-inflammatory adipokines, vasoactive factors, and growth factors that act at a paracrine / autocrine level to influence the myocardium and coronary arteries homeostasis [18]. The dysfunction of this local molecular cross-talk between EAT and the heart can trigger some of the mechanisms implicated in atherosclerosis and in the pathogenesis of cardiovascular disorders associated with obesity and diabetes.

Adipokines and Cardiovascular Function

The WAT releases a big number of different adipokines, working as an intricate network with effects at paracrine, autocrine and/ or endocrine level. This adipokine networking system is altered in obesity, contributing to an inflammation state and to the development of metabolic syndrome and CVDs (Figure 3) [6].

Leptin

Leptin was the first adipokine to be characterized, and its discovery in 1994 by Zhang et al. [19] implied a change in the point of view of the WAT from a mere storage organ to an important endocrine organ, and preceded the identification of a number of new adipokines. Leptin is a 16kDa polypeptide encoded by the obese (*ob*) gene, the murine homologue of the human gene LEP, which is mainly produced by SAT compared to VAT [20,21], but also produced by EAT [22]. Leptin acts centrally on the hypothalamus to reduce food intake and to increase energy utilization through the melanocortin system, and its circulating levels correlate directly with the WAT mass, so that obesity is associated with a state of leptin resistance [23]. Leptin receptors are expressed in both central and peripheral tissues, including the brain, WAT, liver, kidneys, skeletal muscle, pancreas, ovaries and heart [24–30], and in the same way, although the WAT is the main source of leptin, it is also produced by other peripheral tissues, such as the liver, the skeletal muscle, kidneys or heart [31–35]. Apart from its main function as an energy regulatory peptide, leptin can regulate inflammation through monocytes and macrophages activation to release the pro-inflammatory molecules IL-6, tumor necrosis factor (TNF) -α and IL-12 and, at the same time, pro-inflammatory signals such as TNF-α or the lipopolysaccharide (LPS) induce both leptin and leptin receptor expression [36]. Leptin has been involved in the development of different pathologies, including rheumatoid arthritis [37], insulin resistance [38], Alzheimer's disease [39] or some types of cancer [40], and acts as a key regulator of sexual maturation, ovarian and reproductive function [41-43].

Within the heart, leptin and its receptor are abundantly expressed in cardiomyocytes [34,35], where leptin signalling regulates the baseline physiology of the heart, including cardiomyocyte contractility, hypertrophy, fibrosis, apoptosis, and metabolism [44,45]. Leptin have been recently shown to enhance endothelial cell differentiation and angiogenesis in murine embryonic stem cells [46], however, it is also well documented that leptin plays an important role in the early stages of atherosclerosis development by initiating leukocyte and macrophage recruitment into the endothelial wall, by increasing platelet activity and the formation of atherosclerotic plaques, and by stimulating the production of vascular pro-inflammatory molecules, such as TNF-α, IL-2, IL-6 or Reactive Oxygen Species (ROS) that cause endothelial dysfunction through oxidative stress induction [47,48]. As well, *in vivo* studies have shown that mice lacking leptin (*ob/ob*) or its receptor (*db/db*) are resistant to atherosclerosis [48], and increased leptin serum concentrations in humans are associated with an increased risk of myocardial infarction and stroke independent of obesity status and cardiovascular risk factors [49,50], supporting the pathological role of leptin in the development of this disease. However, leptin has been suggested to protect against ischemia/reperfusion injury by reducing infarct size and protecting cardiomyocytes from hypoxia induced damage [48], and in rat cardiomyocytes it suppresses non-apoptotic cell death [51].

Some groups have shown that *ob/ob* and *db/db* mice have a cardiac metabolic profile in which carbohydrate uptake and utilization are reduced while FFAs uptake rates are increased, and the rescue of cardiac leptin receptors in *db/db* mice prevents myocardial triglyceride accumulation [44,52].These findings suggest a role for the disruption of leptin signaling in the development of the metabolic inflexibility observed in cardiac metabolism under pathological conditions, favouring fatty acid utilization and diminishing cardiac efficiency [44]. Leptin has also been described to induce autophagy in cardiac cells, but weather this effect is beneficial or harmful needs to be further investigated [53,54].

Different studies have shown a positive correlation between circulating leptin levels and blood pressure, suggesting that leptin could act as a hypertensive molecule [55], although studies in murine and humans have also reported a potent vasodilator function for leptin [48].

Adiponectin

Adiponectin is a 30 kDa adipokine discovered between 1995-1996 by various laboratories in an independent way, thus it has different nomenclatures: Acrp30, apM1, adipoQ and GBP28 [29,56,57]. It is mainly produced by SAT compared to VAT or EAT [58,59], and it circulates in monomers that bind to yield from trimers to do decamers, which are those with biological activity, at higher concentrations (μg/mL) than other adipokines such as leptin (ng/mL) [57,60]. In contrast to leptin, plasmatic adiponectin levels are decreased in obesity and correlate negatively with BMI, glycemia and circulating insulin levels, as well as with the risk to develop obesity, T2DM and CVDs [29,57,60]. Indeed, adiponectin gene knockdown in mice induces insulin resistance, glucose intolerance, dyslipidemia and an increase in vascular damage and atherosclerosis [57].

Adiponectin triggers the AMPK signalling cascade through the binding to its receptors (AdipoR1 and AdipoR2), being AdipoR1 plenty in skeletal muscle and AdipoR2 in liver [57]. In the brain, adiponectin receptors colocalize with leptin receptors and their activation induces energy expenditure through a mechanism independent of AMPK and food intake regulation [60]. At peripheral level, adiponectin signalling improves insulin sensibility and prevents atherosclerotic plaques formation by decreasing TNF-α production by macrophages, ROS production by endothelial cells and apoptosis, and by stimulating endothelial cell migration and vascularization [60,61]. AdipoR1 over expression has been shown to reduce lipid accumulation and hypertrophy in the heart of diet-induced obese mice [62], and the lack of AdipoR1 in T2DM mice has been shown to impair myocardial mitochondrial function and coupling [63], while myocardial mitochondrial and contractile function are preserved in normal mice lacking adiponectin [64], suggesting that adiponectin signalling may have different roles in the regulation of heart physiologyunder pathological and non-pathological conditions.Adiponectin has also been implicated in the protection against endoplasmic reticulum stress in the heart through different mechanisms, including the regulation of calcium mobilization and the inhibition of ROS production [65–68].

Low levels of circulating adiponectin are related to aortic vasodilatation dysfunction, endothelial dysfunction and hypertension [69–73] and in diabetic patients with coronary heart disease serum adiponectin concentrations are markedly decreased [74]. Adiponectin is implicated in the process of cardiac remodeling by limiting the extent of cardiac hypertrophy and it protects against ischemia/reperfusion injury [48,75–78]. TNF-α antagonism has been shown to ameliorate myocardial ischemia-reperfusion injury in mice by upregulating adiponectin expression [79], and a new orally active adiponectin receptor activator (AdipoRon) attenuates post-ischemic myocardial apoptosis through both AMPK-mediated and AMPK-independent signaling [80]. In murine, adiponectin protects against systolic dysfunction after a myocardial infarction and protects the myocardium against chronic intermittent hypoxia-induced injury via inhibition of endoplasmic reticulum stress, and in human circulating levels of adiponectin are negatively correlated with the severity of coronary artery disease and the risk of myocardial infarction [48,66].

However, despite of its well documented cardiometabolic benefits, high levels of circulating adiponectin have been shown to be associated with increased risk of atrial fibrillation in elderly (74±5years) [81].

Resistin

Resistin is a 12.5 kDa adipokine with a molecular structure similar to adiponectin [82,83]. In murine, resistin is mainly produced by SAT and VAT adipocytes, but in human it is produced by pre-adipocytes and macrophages, being its levels drastically decreased in mature adipocytes [60,82–84]. Although first studies showed that resistin gene expression was increased in obesity, its physiological role is not clearly understood [60]. Resistin expression was also found to be significantly lower in VAT of genetically obese rats in comparison with lean rats, while no differences were observed when SAT of the same animals were compared [84]. Mice lacking the resistin gene have lower fasting glucose levels and a better glucose tolerance and insulin sensibility, since resistin gene knock down allows AMPK activation and decreases the expression of gluconeogenesis related genes, while resistin over-expression is associated with insulin resistance and dyslipidemia [48,85].

At cardiovascular level, resistin exerts its actions mainly through the interaction with other adipokines, such as adiponectin or leptin. There seems to be a direct and reciprocal effect between resistin and adiponectin regarding endothelial cells inflammation: resistin induces the expression of adhesion molecules while adiponectin inhibits resistin action [48], and in *ob/ob* mice leptin administration suppress gene and protein expression of resistin in WAT along with reductions in glucose and insulin levels [86]. High plasma levels of resistin correlate with pro-atherogenic inflammatory markers, increased cardiovascular risk, unstable angina, poor prognosis in coronary artery disease, T2DM and metabolic syndrome [48,87]. Recently it has been reported an increased content of resistin in EAT of patients with advanced coronary atherosclerosis and history of myocardial infarction [88] and that circulating resistin levels correlate with oxidative stress and myocardial injury in patients undergoing cardiac surgery [89].

Visfatin

Visfatin was identified in 2005 by Fukuhara et al. as a new 52 kDa adipokine with high expression in VAT compared to SAT and EAT, with antidiabetic properties and with increased levels in obesity [90,91]. Visfatin acts similarly to insulin in mice; indeed, it can bind and activate insulin receptor (although in a different binding site)

and induce insulin receptor substrate (IRS)-1 phosphorylation and phosphoinositide 3-kinase (PI3K)/ protein kinase B (PKB/AKT) cascade signalling, inducing hypoglycemia by decreasing liver glucose release and stimulating glucose uptake in adipocytes and myocytes [85,92]. However, these observations are not corroborated in human, and some studies show a positive correlation between circulating visfatin levels with BMI, T2DM and obesity, while others do not find any correlation [83,85,93].

Visfatin has also been implicated in the regulation of endothelial function with contradictory effects. It has been described a pro-inflammatory role of visfatin by the stimulation of adhesion molecules production, oxidative stress and the release of pro-inflammatory cytokines at vascular level [48] and also an anti-inflammatory effect by increasing anti-inflammatory adipokines production, endothelial proliferation and angiogenesis [94,95]. There exists a positive correlation between circulating visfatin levels and HDL, being a positive effect regarding vascular cholesterol deposition, however, visfatin expression is increased in macrophages from atherosclerotic plaques in patients with unstable atherosclerosis [96,97]. On the other hand, visfatin induces endothelium vasorelaxation by increasing nitric oxide production, and it has a protective effect of ischemia/reperfusion injury by reducing the infarct area size [48,98]. However, plasma visfatin levels were recently found to be associated with major adverse cardiovascular events in patients with acute ST-elevation myocardial infarction [99].

Apelin

Apelin is an adipokine produced by SAT and VAT derived by the proteolytic processing of its 77 amino acids precursor, which can lead to 4 active isoforms: apelin-12, -13, -17 and -36, all with different binding affinity for the apelin receptor, and being apelin-13 the most active and abundant [93,100,101]. Apelin triggers the PI3K/AKT and extracellular signal-regulated kinases (ERK) 1/2 signalling cascades, and apart from the WAT it is produced by other tissues such as the brain, heart, lungs and kidneys [93]. It has been proposed to have beneficial effects on improving glucose tolerance through AKT and AMPK activation in both normal and insulin resistant murine models, and apelin injection in normal and obese mice decreases fat mass without modifying food intake, insulin or leptin levels, but increasing adiponectin circulating levels [93,102].

Circulating apelin levels are decreased in atrial fibrillation, paroxysmal supraventricular tachycardia, chronic heart failure and dyslipemic patients, and in those with high cholesterol, the therapeutic LDL reduction induces an increase in apelin plasmatic levels [48,103,104]. In dyslipemic animal models, apelin has been shown to exert an anti-atherogenic effect and to prevent the formation of aortic aneurysms by reducing macrophage-induced inflammation [105]. Plasma apelin levels are inversely correlated with the severity of coronary artery stenosis and positively related with the stability of atherosclerotic plaque in patients with acute coronary syndrome [106]. Apelin has also been demonstrated to induce angiogenesis and endothelium vasorelaxation by increasing nitric oxide production, as well as protection against ischemia/reperfusion injury [48,100]. Apelin gene therapy increases vascular density and alleviates diabetic cardiomyopathy by a mechanism involving activation of Sirt3 in diabetic mice [107]. Recently, it has been shown that post-infarct treatment with apelin improves myocardial function by increasing neovascularization and over expression of angiogenic growth factors in rats [108] and that it increases cardiac contractility through parallel and independent activation of PKC-ε and ERK1/2 signalling in the adult rat heart [109].

Chemerin

Chemerin is an 18 kDa adipokine secreted as an inactive form (prochemerin) that is subsequently transformed into an active protein by protease cleavage of the C-terminal domain [110]. It was described to act through the binding to its receptor (ChemR23), which is a G-protein coupled receptor, and more recently has also been found to bind to 2 other receptors, GPR1 (G-protein-coupled receptor 1) and CCRL2 (C-C chemokine receptor-like protein 2) [111–113].The binding of chemerin to ChemR23 has been shown to involve intracellular calcium release and the regulation of ERK1/2, nuclear factor (NF)-kB and PI3K/AKT signalling [114]. Initially, it was described as a chemotactic peptide which leads the macrophages and dendritic cells to inflammation sites, being related to adaptive and innate immune responses [111]. It is produced by endothelial cells, where chemerin production is increased by pro-inflammatory cytokines, resulting in angiogenesis induction and vascular remodeling [111]. Later on, it was shown that both chemerin and its receptor are expressed in WAT, and also produced by EAT, and its levels are increased by IL-1β and obesity, while after bariatric surgery its circulating levels decrease [111,115–117].

Chemerin has recently been proposed as a predictive marker of cardiovascular risk, since its circulating levels correlate with the severity of coronary artery disease, and patients with dilated cardiomyopathy and with acute myocardial infarction have higher concentrations of circulating chemerin [118–120]. Both chemerin and ChemR23 gene expression in human aortic, coronary artery and periadventitial adipose tissues are positively correlated with the severity of atherosclerosis [121].

Omentin

Omentin is highly secreted by VAT compared to SAT, and it is also produced in EAT, intestines and endothelial cells [111,122]. It is related to the increase of insulin signalling by PI3K/AKT activation and the glucose uptake in adipocytes [111]. Omentin circulating and expression levels in WAT are decreased in obesity, and correlate positively with plasmatic adiponectin and LDL levels, and negatively with abdominal perimeter, BMI, and insulin resistance [123]. It has also been proposed to act as a vasodilator by inhibiting catecholamine-induced vasoconstriction and increasing nitric oxide production in endothelial cells [48]. Omentin attenuates the pathological process of myocardial hypertrophy via the activation of AMPK in the heart [124], and ameliorates acute ischemic injury in the heart by suppressing myocyte apoptosis through both AMPK- and AKT-dependent mechanisms [125]. Decreased serum omentin-1 levels are associated with a poor cardiac outcome in patients with heart failure and are considered an independent risk factor for peripheral arterial disease and acute myocardial infarction [119,126,127].

Conclusion

The association between obesity and the cardiovascular risk has been described in multiple epidemiological studies and is at present clearly accepted. As a whole, overweight/obesity is associated with numerous cardiac complications not only due to the direct effect of fat

amount on the cardiovascular physiology, but also to fat distribution and function. In the last years, numerous studies have revealed the importance of the adipokine secretion pattern on the development of CVDs, and thus, a better understanding of the effects of adipokines on the cardiovascular system could help to treat/prevent CVDs.

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