Adipokines and cardiovascular disease: A comprehensive review

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Adipokines are peptides that signal the functional status of adipose tissue to the brain and other target organs. In adipose tissue dysfunction, adipokine secretion is altered, and this can contribute to a spectrum of obesity-associated conditions including cardiovascular disease. Some adipokines have anti-inflammatory and cardioprotective effects (omentin, apelin, adiponectin). Others are pro-inflammatory with negative impact on cardiovascular function (leptin, visfatin, resistin, adipocyte fatty-acid-binding protein). In the first part, this article reviews the endocrine functions of adipose tissue in general, effects of the distribution and composition of fat tissue, and the roles of cortisol and the renin-angiotensin-aldosterone system in the development of the inflammatory state of addipose tissue. In the second part, the known cardiovascular effects of different adipokines and their clinical potential are discussed in detail.

Key words: adipokines, obesity, adipose tissue, cardiovascular effects, myocardial infarction, heart failure, omentin, apelin, adiponectin, leptin, visfatin, resistin, adipocyte fatty-acid-binding protein

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INTRODUCTION

Adipokines are hormones produced by fat tissue. They play a role in energy homeostasis, sugar and fat metabolism, thermogenesis control, reproduction and immunity. They also influence cardiovascular function, either by direct action on the vascular wall via paracrine effects or by affecting endothelial function through altered plasma and tissue levels of adipokines commensurate with the total mass of adipose tissue in the body[1]. The traditional view of adipose tissue functions as heat insulation, mechanical protection and as an energy reservoir, changed in the 1990s, with the first discovery of hormones produced by fat tissue. The understanding of adipose tissue as a mere passive reservoir of energy began to change and its endocrine functions in the human body came to the fore.

Apropos effects on the cardiovascular system, adipokines can be divided into cardioprotective adipokines (anti-inflammatory) and adipokines that adversely affect the cardiovascular system (pro-inflammatory). However, this division is not entirely accurate because, as described below, for a large proportion of adipokines, protective, as well as adverse effects are described and their global functions are not completely defined. The formerly used division of adipose tissue secretory products into cytokines produced by stromal vascular cell fractions and adipokines produced by adipocytes is not justified because some adipocytokines (resistin, apelin) are produced by two sources. Large amounts of adipokines are also abundantly produced outside adipose tissue which makes the classification of these substances even more complicated. Only a small portion of adipokines are produced exclusively by adipose tissue.

Fat depots: perivascular, epicardial, visceral and subcutaneous

Adipokines produced by perivascular adipose tissue (PVAT) have mostly paracrine effects. In a study on PVAT, perivascular fat tissue differs from subcutaneous and perirenal adipose tissue (SAT) in that there are large number of less differentiated adipocytes which produce increasingly pro-inflammatory cytokines, e.g. IL-6, IL-8 and MCP-1 (ref.[2]) and conversely, production of adiponectin in PVAT is reduced[2].

The secretory products of PVAT are also involved in proliferation and migration of smooth muscle cells of blood vessels. This process involves inter alia probable paracrine effects of some adipokines (e.g. visfatin and resistin) (ref.[3,4]). In response to vasoconstriction PVAT adipocytes react by the release of adipokines which induce anti-contractile effects on smooth muscle cells of adjacent blood vessels[5].

Epicardial fat is a type of perivascular adipose tissue that covers the surface of the heart and surrounding adventitia of coronary arteries. It is deposited more to the right heart sector than the left. Okura et al. assessed pericardial fat by CT and demonstrated that pericardial fat volume is directly proportional to the severity of coronary heart disease in patients with preserved ejection fraction[6]. The results of other large studies have revealed that the degree of coronary calcification correlates with the amount of pericardial fat, and that this correlation predicts progression of atherosclerosis in subjects with low calcification followed from the outset[7]. Increased number of macrophages, T-lymphocytes and mast cells in epicardial fat but not in SAT have been demonstrated in patients with coronary artery disease by several researchers

independently[8,9] and regression of epicardial fat has been observed in relation to weight reduction[10], exercise[11] or following administration of either atorvastatin[12] or ezetimibe[13]. Whether this reduction leads to a decreased cardiovascular risk remains unclear and needs to be further examined. The effect of epicardial fat on manifestation and progression of cardiovascular disease (CVD) is still insufficiently explored and warrants intensive research. Currently, epicardial fat is considered a marker of visceral fat (using echocardiographic evaluation) and cardiovascular risk[14,15].

Role of cortisol and the renin-angiotensin-aldosterone system in development of the inflammatory state of adipose tissue

In human adipose tissue, the hormone cortisol is produced from inactive cortisone precursor. Some studies suggest that the increased production of cortisol in visceral fat in obesity may be a key in the development of hepatic insulin resistance and type 2 diabetes mellitus. The cortisol formed in VAT has direct access via the portal circulation to the liver, where it can increase gluconeogenesis, synthesis of triglycerides etc.[16].

Up-regulation of the renin-angiotensin-aldosterone system (RAAS) characterized by high plasma renin activity and high levels of aldosterone was also reported in patients with visceral obesity[17]. Following weight loss, the levels of these hormones normalise[18]. Some components of the RAAS system are produced in adipose tissue, e.g. angiotensinogen[17]. Blockade of the renin-angiotensin-aldosterone system with ACE inhibitors, AT1-blockers or spironolactone is one of the basic approaches in the treatment of hypertension, congestive heart failure and coronary artery disease. Some studies suggest that mineralocorticoid receptors in adipocytes promote the expression of inflammatory adipokines and facilitate the effect of the pro-adipogenic effect of aldosterone and glucocorticoids[19]. Inhibition of these receptors in experimental studies decreases the expression of pro-inflammatory factors in adipose tissue and increases the expression of adiponectin in heart and adipose tissue[19].

Adipose tissue produces an as yet unidentified mineralocorticoid releasing factor which stimulates the production of aldosterone and glucocorticoids (please see Fig. 1). Both hormones by acting on mineralocorticoid receptors in adipocytes, potentiate macrophage infiltration and adipogenesis, which are important factors in the creation of pro-inflammatory acting adipokines (Fig. 1) (ref.[19]). In summary, increased amount of visceral adipose tissue induces production of aldosterone and glucocorticoids, and these hormones in turn facilitate the development of chronic inflammation in adipose tissue with subsequent overproduction of harmful adipokines (Fig. 1).

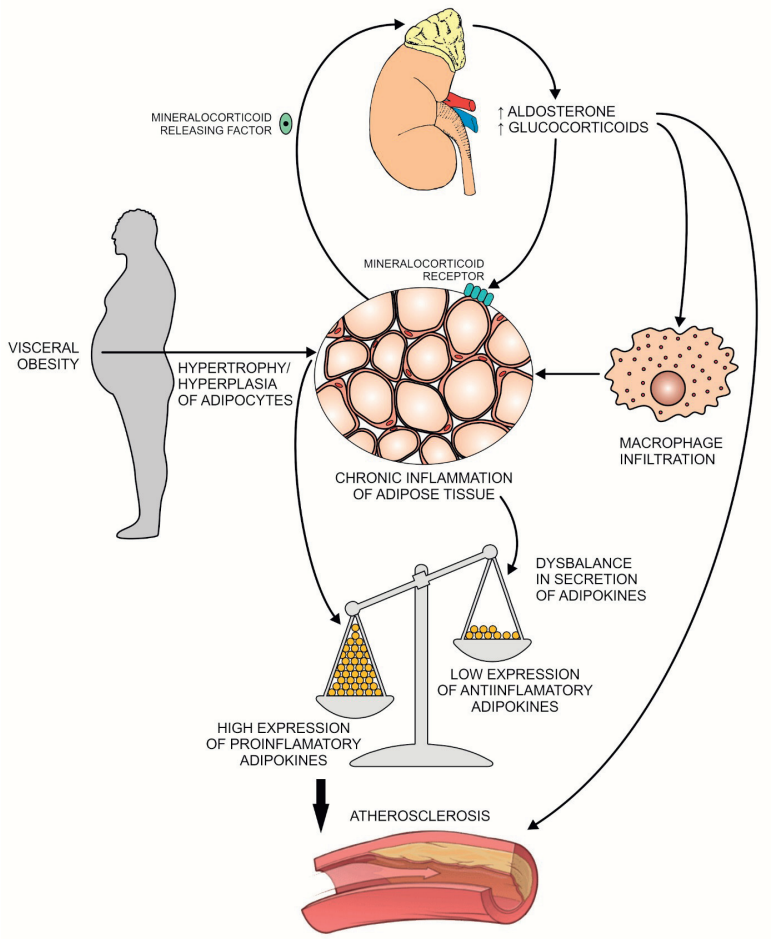

Fig. 1. Pathopysiological connections between adipose tissue, adipokines, renin-angiotensin system and atherosclerosis.

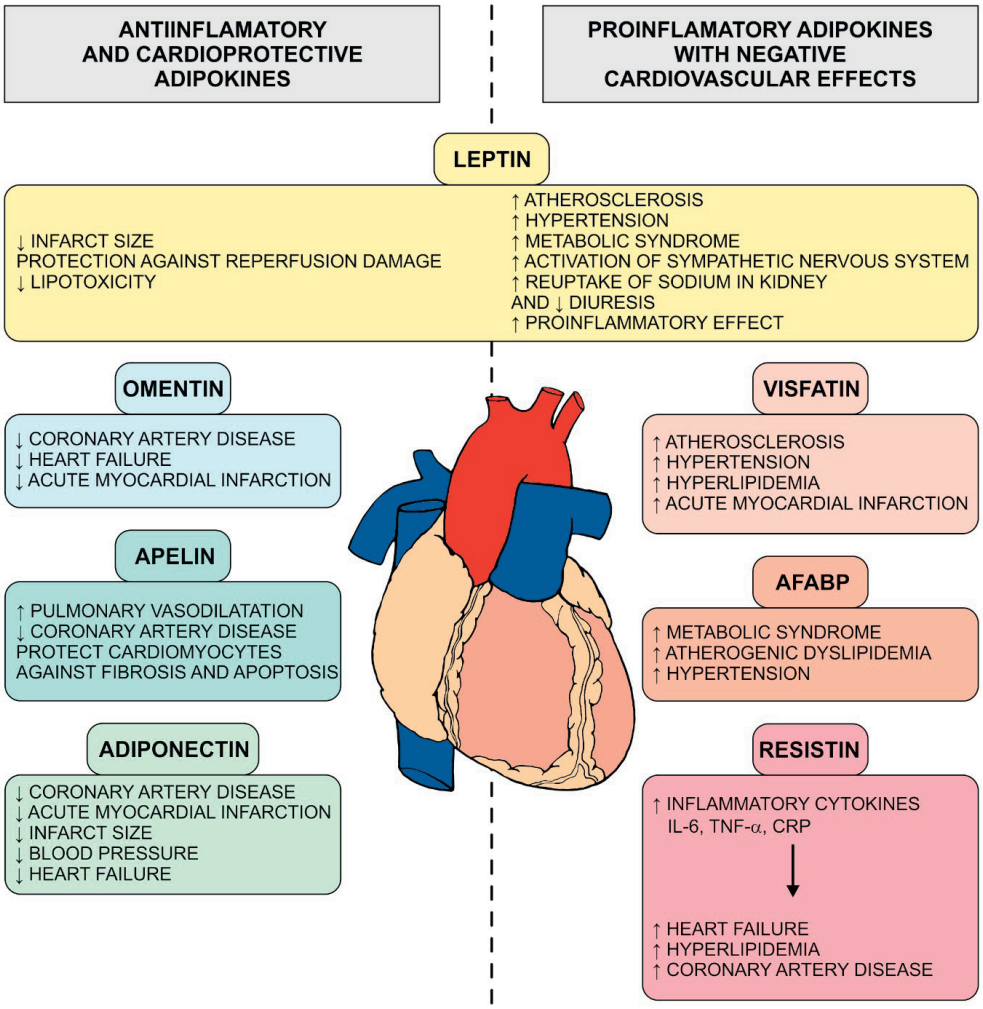

Fig. 2. Overview of positive and negative cardiovascular effects of major adipokines.

Fat distribution

Obesity with predominantly expanded SAT relative to VAT is a generally favorable cardiovascular risk profile. This is because obesity with predominantly subcutaneous fat is associated with improved insulin sensitivity, lipid parameters and cytokine profiles versus obesity with expanded VAT, which is more common in people with android obesity than in people with gynoid obesity. Extreme cases of impaired fat distribution are congenital and acquired forms of lipodystrophy, which lead to loss or lack of development of peripheral adipose tissue and its accumulation abdominally. Patients with this diagnosis are predisposed to developing atherosclerosis and CVD at a young age. In these patients, insulin resistance, diabetes, hyperlipidemia, fatty liver, hypertension, cardiac hypertrophy are relatively common at an early age, and levels of adiponectin and leptin are very low[20]. Administration of leptin in such individuals has led to improved metabolic control, reduction in food intake, decreased glucose and free fatty acid and triglyceride levels[21]. Liver steatosis virtually disappeared and there was significant improvement in insulin sensitivity in liver and muscle tissue[16].

Composition of fat tissue

Although adipose tissue consists predominantly of adipocytes (actually only about 50% of the cells) (ref.[20]), there are other cell types in fat tissue, including lymphocytes, macrophages, fibroblasts and vascular cells which have an important role in the control of the functional state of the tissue. Obese compared to lean people have more macrophages in adipose tissue, elevated levels of pro-inflammatory adipokines such as resistin,visfatin[22], IL-6, TNF-α, and, in turn reduced levels of adiponectin and apelin.

Lean people have small adipocytes. Obese individuals have large volume adipocytes due to accumulation of lipids. The size of adipocytes significantly affects their metabolism. Large adipocytes have reduced sensitivity to insulin and a higher proportion of macrophages to adipocytes is associated with insulin resistance. Most pro-inflammatory adipokines are closely related to the development of insulin resistence and this has broad implications for various organs, including heart muscle[23].

Obesity, insulin resistence and cardiac steatosis

Obesity and insulin resistence lead to increased lipidogenesis in the liver and increasing lipolysis in adipocytes,

which together result in increase in circulating triglycerides and free fatty acids. Hyperlipidemia and hyperinsulinemia in turn lead to the transport of free fatty acids into myocytes, where they exert lipotoxic effects[24]. Myocardial myocytes are subsequently damaged by the formation of reactive oxygen species, ceramide production, a drop in contractility due to Ca2+ depots in the sarcoplasmic reticulum, impaired insulin signaling and the development of mitochondrial dysfunction. Adiposity and insulin resistance may also lead to the accumulation of triglycerides in the myocardium and cardiac steatosis, which may contribute to the development of diastolic LV dysfunction[20]. Cardiac steatosis can be evaluated by magnetic resonance imaging.

Leptin

Leptin was the first discovered adipokine in 1994. It suppresses hunger, reduces food intake and increases metabolism. Currently it is shown that leptin levels positively correlate with body fat and its concentration is increased in obese people who are insulin resistent. Conversely they are reduced in lean individuals[25]. Elevated levels of leptin in obesity may be partially explained by leptin resistence, causing higher levels of SOCS3, an inhibitor of the signaling pathway of leptin[26]. Higher leptin levels and leptin resistence however are likely only an accompaniment of obesity with no causative role in its pathogenetics.

During fasting, leptin levels drop rapidly (up to 50% within one week). The formation of thyroid hormones will be reduced and there is increase in stress hormones. It is therefore possible that the main effect of leptin is adaptive response to starvation, and not the control of food intake[27]. In malnourished states, typically in patients with anorexia nervosa, this causes a reduction in metabolism and energy saving. One of the results of these processes is central amenorrhea. Administration of leptin in these patients results in recovery of menstruation[28]. Intravenous administration of leptin in human dietary intake (weight reduction programs) resulted in weight reduction compared to placebo[29]. Diet leads to inhibition of metabolism (lower levels of thyroid hormones, lower daily caloric expenditure). In another study, leptin administered at the end of a diet, led to expected faster normalization of metabolism[30].

Although exogenous administration of leptin, according to the studies mentioned above, had a positive effect on both the weight loss and the adaptive response of the organism to losing weight, its administration, according to current scientific knowledge, does not seem justified both owing to cost, and the need for subcutaneous (sc) or intravenous (iv) administration for which negative effects on the cardiovascular system have been described (eg. the development of hypertension after IV administration). Another major obstacle is the fact that the actual effect of administration of leptin in the general population is unproven . Interesting results could be achieved by administering leptin to certain categories of obese individuals, for example, obese people with low levels of leptin, who could be expected to significantly lose weight. This approach, however, requires further clinical research. For now, the only conditions where leptin administration has had notable success is in its use in obese patients with mutation of the leptin gene[31], which led to an almost normalization of weight and also in lipoatrophic diabetes[16].

The literature describes some of the cardioprotective effects of leptin which include reduced extent of myocardial infarction (MI) and protection against reperfusion damage by local autocrine effects (the heart itself also produces leptin) probably mediated through NO and also antilipotoxic effects[32].

Nevertheless, most authors consider leptin one of the 'bad' adipokines in its effect on the cardiovascular (CV) system. Hyperleptinemia in the general population is associated with atherosclerosis, hypertension and the metabolic syndrome[33]. The effects on the cardiovascular system are leptin mediated effects on blood pressure, sympathetic nervous system (SNS) activation, insulin resistance, platelet aggregation and pro-inflammatory effects.

Chronic intravenous administration of leptin increases heart rate and mean arterial blood pressure[34] by activation of the sympathetic nervous system and increased release of catecholamines[35]. Another mechanism described in the development of hypertension is indicated as leptin has been found to decrease diuresis and increased sodium reuptake in the kidneys[16]. Elevated leptin levels are associated with myocardial infarction and stroke, independently of traditional risk factors or obesity[35] and are associated with calcification of the coronary arteries irrespective of sex[36].

Visfatin

Visfatin is an adipokine discovered in 2005 by the team of Dr Fukuhara, who invented the name from the words visceral fat adipokine. Its levels are elevated in obesity, people with insulin resistance and Type 2 diabetes[37]. Via its insulin-mimetic effects, it reduces blood glucose[38], through as yet ill-understood mechanisms. Visfatin levels correlate with the amount of subcutaneous and visceral fat. Its production was confirmed in epicardial adipose tissue and of paraaortic fat in the same concentrations as in the abdominal fat and may thus act directly on the cardiovascular system via paracrine effects.

In a study comparing visfatin levels in 54 patients with acute myocardial infarction with ST segment elevation (STEMI), exertional angina and people without cardiovascular disease, visfatin levels were significantly elevated in patients with STEMI compared to the other groups[39]. Peak levels were reached 24 h after percutaneous coronary intervention (PCI) dropped to levels comparable to the control group after 1 week. The visfatin levels correlated with BNP, troponin I, CK-MB and the number of white blood cells. This temporary increase in the visfatin concentration in the first week after STEMI and its correlation with an increase in cardiac enzymes therefore indicate that the visfatin plasma level corresponds to the extent of myocardial disease.

In general, we can conclude that visfatin is probably involved not only in the pathogenesis of diabetes mellitus, obesity, dyslipidemia, hypertension, renal failure but also

in atherosclerosis[40], and growing clinical evidence supports the role of visfatin as a potential marker of inflammation and endothelial dysfunction in both metabolic disease[41] and in patients with acute coronary syndrome[39].

Resistin

In the past, the effects of resistin were examined particularly in connection with the development insulin resistence. These studies found a positive correlation between obesity and resistin[42]. Further research has shown, however, that these studies were inconsistent and often conflicting. Excessive production of resistin in acute and chronic inflamatory conditions[43] shows its closer relationship to the development of inflammatory conditions than to obesity and insulin resistance. This suggests that resistin is produced predominantly by macrophages outside adipose tissue than by adipocytes[44].

Several studies have described the effect of inflammatory cytokines on the expression and levels of resistin. The reverse is also possible, namely that resistin may act as a signaling molecule initiating the immune response and the production of pro-inflammatory cytokines (IL-6, TNF, CRP) and also PCSK9 and thus contribute to the progression of atherosclerosis. In non-obese patients with chronic coronary artery disease, elevated resistin levels are associated with higher levels of protease PCSK9 (ref.[45]), whose inhibition results in a significant decrease in LDL cholesterol. Serum resistin levels are elevated in people with heart failure and levels positively correlate with severity of heart failure according to the NYHA classification[46]. Interestingly, the opposite results were obtained in the case omentin (see below).

Adipocyte fatty-acid-binding protein (A-FABP)

One adipokine that adversely affect the cardiovascular system is the adipocyte fatty-acid-binding protein (A-FABP). The concentration of A-FABP in humans positively correlates with obesity and it has been confirmed that A-FABP is a marker of the metabolic syndrome[47]. AFABP levels positively correlate with metabolic and inflammatory cardiovascular risk factors, which include atherogenic dyslipidemia, hyperglycemia, hypertension and also some laboratory markers of inflammation (s-CRP and IL-6). For people with pre-existing coronary heart disease, a significantly higher concentration of AFABP4 predicted increased risk of cardiovascular death, nonfatal myocardial infarction or stroke[48].

Expression of the adipocyte fatty-acid-binding protein (FABP4) gene in macrophages can be induced by oxidized LDL cholesterol and decreased by administration of lipid-lowering drugs (statins), which inhibit cholesterol synthesis[49]. Treatment of patients with obstructive sleep apnea using CPAP favorably affects AFABP levels[50].

Omentin

Omentin is an adipokine discovered in 2004. It is produced by stromal vascular cells of visceral adipose tissue, while its expression in subcutaneous adipose tissue is negligible[51]. Its gene expression and serum levels are reduced in obese persons and negatively correlate with BMI, waist circumference, insulin resistance, and coronary artery disease. In contrast, there is a positive correlation with serum adiponectin and HDL (ref.[52]). Omentin also increases insulin-induced glucose reuptake and participates in the regulation of insulin sensitivity[51] and hence could have a protective role against deterioration in insulin resistance.

Regarding the influence omentin on the cardiovascular system, as mentioned above, lower levels of omentin have been described in people with coronary atherosclerosis[53]. In cases of heart failure, omentin levels were significantly lower in people who had, in a given period, more cardiac events (death, rehospitalization), and also in those with more severe symptoms (with NYHA classification IV compared to NYHA II and III) (ref.[54]).

Apelin

In 1992, the receptor for apelin, called APJ (also known as angiotensin-like receptor) was discovered. In structure it is strikingly similar to the receptor for angiotensin[55]. Angiotensin however, is unable to activate the receptor and so until 1998, when apelin was discovered[56], it was called an orphan receptor. Apelin is considered a cardioprotective factor because it has effects opposite those of the RAAS system. It is expressed in several organs, including the hypothalamus, vascular endothelium, heart, lungs and kidneys, fat tissue and gastrointestinal tract. The APJ receptor is expressed abundantly in the endothelium, smooth muscles and myocytes. In the systemic circulation, apelin induces NO-dependent vasodilation, prevents vasoconstriction caused by angiotensin II (ref.[57]), has positive inotropic and cardioprotective effects.

Plasma levels of apelin were significantly lower in patients with atrial fibrillation (AF) than healthy controls[58,59]. Recent studies suggest an increased risk of recurrence of AF in subjects with lower levels of apelin[60].

Apelin falls early after myocardial infarction (MI). After a few days, its levels start rising again, but remain reduced until 24 weeks post-MI. The decline is independent of degree of ventricular dysfunction and patient prognosis[61,62]. Generally, levels of apelin are lower in subjects with coronary heart disease (CHD). In patients with unstable angina and myocardial infarction, apelin levels are lower than in patients with stable forms of CHD. Levels are also negatively correlated with the severity of coronary stenoses[63]. Some studies have also demonstrated a positive effect in the reduction of reperfusion injury after myocardial infarction[64]. In the next phase of research, it will be necessary to prospectively monitor the levels of apelin as this could determine its use as a prognostic marker of cardiovascular disease. In the case of adiponectin, this potential has not been fulfilled up to now - see below.

In chronic heart failure patients, one study demonstrated increased expression and production of apelin in the left ventricle, whereas atrial apelin mRNA levels were unchanged while serum levels were reduced, as well as the expression of the receptor apelin AJP (ref.[65]). Other studies have confirmed reduced levels of apelin in heart failure[66]. Interestingly, the increased expression and tissue production was also demonstrated in subjects after implantation of mechanical left ventricular assist device[67].

According to some animal studies, the regulation of apelin is influenced by hypoxia. In the initial phase following hypoxia, there is increased production of apelin, followed by a normalization phase or a decline in production[68]. Chen et al. demonstrated higher levels of apelin in patients with heart failure and a lower NYHA class levels than healthy controls[67], but in patients with higher NYHA clasees apelin levels were low, commensurate with the biphasic response of apelin to hypoxia proposed by Andersen.

The positive inotropic effect of apelin has been demonstrated in isolated perfused rat hearts and was dependent on the apelin dose administered by infusion[69]. Acute administration of apelin in people with heart failure induced an increase of coronary blood flow, decrease in blood pressure and increase in cardiac output[70]. Further studies demonstrated an increase in cardiac index and ejection fraction that remained increased during a six-hour infusion, but heart rate increase occurred only during the first hour of the infusion[71]. However, until now, none of the positive inotropic substances has been demonstrated to improve survival in heart failure with left ventricular dysfunction.

Apelin appears to be a potentially attractive candidate for addition to the standard therapy of chronic heart failure without causing significant reflex tachycardia or severe hypotension. Its antagonistic effects on the RAAS system, an inherent therapeutic target of several currently used drugs in the treatment of heart failure, is promising. Another benefitial effect of apelin may be mitigation of angiotensin-2 induced cardiac fibrosis[72] and ischemia induced apoptosis of cardiomycytes[73].

Patients with pulmonary arterial hypertension (PAH) have lower plasma levels and reduced apelin expression in lung endothelial cells[74]. Chronic therapy with apelin alleviates the pulmonary hypertension and increases the contractility of failing right ventricle in mice with pulmonary hypertension induced by monocrotalin and hypoxia[68]. It is not clear, however, whether this effect is caused by the decrease in vascular resistance and right ventricular pressure or through direct effects on the myocardium of the right ventricle[68]. Acute vasodilatory effects of apelin on the pulmonary arteries are low (10-17%) and even lower in subjects with pulmonary hypertension, but this does not preclude good results of chronic apelin administration in the treatment of PAH, as shown in animal studies.

Patients with essential and masked hypertension have higher levels of apelin compared to normotensive subjects[75]. Apelin administration to rats with deoxycorticosterone induced hypertension led to a blood pressure decrease by inhibiting the RAAS system[76].

Despite a number of unanswered questions the therapeutic potential of apelin appears to be significant, particularly in the treatment of heart failure and pulmonary hypertension.

Adiponectin

Adiponectin is considered an anti-atherosclerotic factor that inhibits proliferation and migration of smooth muscle cells, inhibits the conversion of macrophages into foam cells, suppresses the production of reactive oxygen species (ROS) and increases the production of nitric oxide (NO). Adiponectin acts protectively against the development of diseases associated with obesity. Some studies have demonstrated an inverse relationship between adiponectin levels and inflammatory markers including CRP. Adiponectin levels are positively associated with HDL, negatively with TAG.

In most studies, the levels of adiponectin are decreased in individuals with obesity compared to lean persons. If obesity is combined with type 2 diabetes mellitus, optionally with documented coronary atherosclerosis, adiponectin levels are even lower[77,78]. In patients with angiographically confirmed coronary atherosclerosis and acute coronary syndrome, hypoadiponectinemia has been detected[79,80]. This association applies retrospectively in patients with proven coronary atherosclerosis, however, in prospective studies the results are very inconsistent.

According to some meta analyses there is no association between adiponectin levels and risk of cardiovascular disease[81-83], others indicate the opposite[84,85]. At the present time, adiponectin cannot be regarded as a predictor of cardiovascular diseases. The explanation for this phenomenon may lie in different effects of individual forms of adiponectin on the cardiovascular system. The structure of adiponectin is complex as it occurs in several isoforms – a low molecular hexamer (LMW, low molecular weight) and high molecular weight form (HMW, high molecular weight, mostly octodecamer). It is produced by adipocytes and serum levels are considerably higher than for other adipokines.

Adiponectin is bound by three receptors: AdipoR1, AdipoR2 and T-cadherin. AdipoR1 is mainly found in skeletal muscle, while AdipoR2 is expressed predominantly in the liver. AdipoR1 and AdipoR2 roles in heart muscle are not yet fully understood. T-cadherin is expressed ubiquitously. The highest expression is found in the aorta, carotid, iliac and renal arteries and also in the sarcolemma of cardiomycytes, where adiponectin binds as the high molecular weight form[86].

In T-cadherin deficient mice, no association of ANP with heart tissue can occur and its levels rise dramatically in the circulation. Pressure overload in T-cadherin deficient mice (induced by transaortic constriction) results in similar degree of LV hypertrophy increase as in adiponectin deficient mice. The degree of LV hypertrophy in these two groups is significantly higher than in healthy controls[86]. During ischemia-reperfusion injury, the absence of T-cadherin increases the extent of the infarction[86]. T-cadherin is more expressed in coronary arteries resistant, rather than susceptible to atherosclerosis[87].

Research suggests that the protective subtype is the HMW adiponectin, as indicated by the fact that T-cadherin binds only HMW adiponectin (see above). In contrast, LMW adiponectin has damaging and proinflammatory effects and possibly increases insulin resistance. It is therefore appropriate to measure the ratio of HMW adiponectin to total adiponectin[88]. Different functions and effects of ANP isomers could help explain the discrepancies in clinical trials.

Reduced adiponectin levels are associated with hyper-

tension through various mechanisms involving hyperactivity of the renin-angiotensin-aldosterone and sympathetic nervous systems, endothelial dysfunction and impaired renal pressure natriuresis. It is logical that hypoadiponectinemia should be associated with hypertension in obese individuals. One study has however shown that hypoadiponectinemia can lead to the development of hypertension in lean people as well[89]. Treatment with high doses of candesartan is associated with a significant decrease in the ratio of leptin / adiponectin levels (LA-ratio) and leads to an increase in circulating adiponectin levels[90]. Another study showed an increase in ANP with treatment by AT1 blockers and also ACEi (ref.[91]).

Despite the cardioprotective effects of adiponectin, there have also been described diseases and conditions which correlate positively with levels of adiponectin. Interesting is the demonstration of elevated levels of adiponectin in patients with chronic heart failure[92,80]. Several explanations for this have been offered and one of them could be resistance to adiponectin[92]. In patients with chronic heart failure ANP expression is increased in skeletal muscle and by deactivation of the PPAR/AMP signal the expression of AdipoR1 is lowered. High levels of ANP could thus be explained by resistance to ANP. A positive correlation between the level of ANP and natriuretic peptides was also demonstrated. In some studies, natriuretic peptides even enhanced secretion of ANP (ref.[93]).

Decreased biological response to ANP apparently may occur even in the initial period after MI, critical for the development of LV remodeling and heart failure. Wang and Gao demonstrated that after myocardial infarction, Adipo1R phosphorylated. This prevented the effect of adiponectin: it was not bound to myocardium and its metabolic, antiinflammatory and cardioprotective functions were prevented[94]. In patients with renal dysfunction, there is decreased clearance of adiponectin. Its levels are elevated and correlate with total cholesterol. The increased adiponectin levels could have a positive effect in reducing endothelial dysfunction triggered by dyslipidemia and other risk factors[95].

Other adipokines with potentially important cardiovascular effects

Fibroblast growth factor 21 (FGF21) is produced by adipose tissue, liver, and according to recent research also by cardiomyocytes. FGF21 improves insulin sensitivity, glucose reuptake, decreases lipogenesis and lipid oxidation[96]. High levels of FGF21 were associated with atherosclerosis, cardiac hypertrophy, coronary artery disease and diabetic cardiomyopathy[96]. Experimentally induced myocardial hypertrophy or infarction lead to increased expression of FGF21 (ref.[97]), which might prevent further progression of myocardial damage.

Chemerin regulates adipokine differentiation and has an important role in chemotaxis of dendritic cells and macrophages in inflammatiory tissues[98]. Levels of chemerin correlate positively with body mass index, blood pressure, serum LDL-cholesterol and triglycerides and negatively with serum HDL-cholesterol[99]. Because of its chemotactic effects, mediated decrease in NO production[100] and negative effects on plasma lipids, chemerin is linked to progression of atherosclerosis. Some studies showed positive association between chemerin levels and stable chronic coronary artery disease (CAD), but some found increased chemerin level only in patients with acute coronary syndrome and not in stable CAD (ref.[101]).

C-reactive protein (CRP) is an acute phase protein, produced in liver and adipose tissue. Small increases of CRP in high sensitivity analyses (hs-CRP) between 1-3 mg/L are, based on large epidemiology trials, traditionally linked with moderate risk of cardiovascular disease and levels >3 mg/L with high risk. Increase of hs-CRP accompany the increase of other cardiovascular risk factors – body weight, smoking or male sex. New data from genetic trials cast doubt on the causative role of CRP in the development of cardiovascular disease[102]. Decreasing CRP levels by CRP inhibitors in controlled clinical trials may help to confirm or rule out the causative role of CRP in cardiovascular disease[103].

Retinol binding protein 4 (RBP4) carries retinol in blood from liver to peripheral tissues. It plays an important role in the development of insulin resistence and type 2 diabetes mellitus, and its levels are increased in patients with CAD. One polymorphism in RBP4 was liked to CAD in a Chinese population but the presence of this polymorphism was not related to the severity of coronary atherosclerosis[104].

Vaspin is a serin protease, produced mainly by visceral adipose tissue. Levels of vaspin are increased in patients with diabetes mellitus and obesity[105]. Vaspin improves tissue sensitivity to insulin. Experimental administration of vaspin in obese mice decreased insulin resistence and food intake and normalized blood glucose[106]. Levels of vaspin were significantly increased in diabetics with CAD in comparison to diabetics without CAD (ref.[107]).

Conclusions and future prospects

In normal circumstances, the production of proinflammatory adipokines is in balance with antiinflammatory adipokines. With increasing obesity, especially perivascular and visceral, this equilibrium is disrupted and adipocytes overloaded by triacylglyceroles and energy produce increasing amounts of proinflammatory adipokines with several negative cardiovascular consequences.

In the near future, adipokines could find a clinical use in two areas. Firstly, they could be a marker of a number of pathological conditions and diseases, connected with obesity, metabolic syndrome and cardiovascular disease. Low serum levels of cardioprotective adipokines or increased levels of proinflamatory adipokines might be useful biomarkers of threatening or manifest cardiovascular disease. Currently, promising are low values of cardioprotective omentin, increased levels of visfatin as markers of acute coronary syndrome and AFABP as a marker of metabolic syndrome.

Second, at present an intensively investigated area, is the therapeutic use of adipokines. Currently, leptin is the only adipokine administered successfully in patients with leptin gene mutation and lipodystrophia. Sadly, this is much narrower spectrum for leptin use, than expected.

Apelin seems promising in patients with pulmonary hypertension and heart failure, due to its antagonist effect on the renin-angiotensin-aldosterone system. Another potential target is pharmacologic blockade of the production of cardiometabolically adverse adipokines or blockade of their receptors.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies on the role of the adipokines in the pathophysiology of cardiovascular disease. Data for this article were identified by searches of PubMed and Google Scholar databases and references from relevant articles using the terms "adipokine", "adipokines", "omentin, "apelin, "adiponectin", "leptin", "visfatin", "resistin", "adipocyte fatty-acid-binding protein", "adipose tissue", "cardiovascular disease", "myocardial infarction, "coronary artery disease" and "heart failure". All searches were up to date as of August 2016. Only articles published in English were included, abstracts and reports from meetings were not included. We gave preference to publications from the past 10 years.

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