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The Role of Adipokines in Cardiovascular Pathology

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Abstract

The recent decades saw a steady growth of obesity incidence worldwide. Obesity is an independent risk factor for cardiovascular diseases (CVDs) and type 2 diabetes mellitus and is also associated with a shorter life expectancy. Not only hemodynamic but also hormone metabolic processes, arising from excessive accumulation of adipose tissue in human body, underlie the development of CVDs. Adipose tissue has now been proved to be a hormone-active substrate. Studies of the influence of adipokines will bring us closer to understanding cardiovascular pathogenesis and help personalize prophylactic strategies.

Introduction

The incidence of obesity has been steadily growing worldwide in the past decades and running into a pandemic. Modern medicine regard obesity not only as a chronic metabolic disease leading to excessive fat accumulation but also as an independent risk factor for the development of cardiovascular diseases (CVDs). Numerous studies have shown obesity to result in both structural and functional cardiac alterations that lead to the left ventricle (LV) hypertrophy, rhythmic and conduction disorders, and diastolic dysfunction; and marked morbid disorder, also to cause LV systolic dysfunction, which is certainly conducive to chronic heart failure (CHF) advancement [1], [2]. A determinant mechanism behinds the development of that the condition is cardiovascular system (CVS) remodeling that results from hemodynamic and hormonal metabolic alterations caused by excessive accumulation of adipose tissue in the human body [3]. Adipose tissue is known to secrete a lot of mediators (more than 250 described by now) called adipocytokines or adipokines. The “adipokine” term stands for any bioactive substance produced by adipose tissue.

Despite the indisputable finding that obesity is a CVD risk factor, epidemiological studies of CHF patients showed mortality to decrease as body mass index (BMI) rose. That is, obese and overweight CHF patients showed a better survival rate than patients with the lower BMI. That fact was termed “Obesity Paradox” [4], [5]. It prompted a tentative conclusion that some adipokines might have a beneficial effect, which led researchers to study adipose tissue physiology in more detail.

The era of adipokine studies began in 1994, with the discovery of leptin by Zhang. The new hormone name was named after its ability to suppress appetite and induce weight loss (λεπτός being the Greek for “slim” or “thin”). However, a decrease in its concentration, “leptin resistance” developing, or gene mutations promote obesity [6]. The discovery of the hormone marked the beginning of active studies of adipose tissue and the understanding that it is a hormone-active substrate.

Leptin is the best-studied adipokine, and its role in the development of CVS disorders is indisputable. Modern medicine is actively studying other obesity markers as well, some of which are described in this article.

Resistin

Resistin was discovered in 2001 by a group of researchers at the University of Pennsylvania. The name of this adipokine is derived from the phrase, "insulin resistance" [7]. It is produced by monocytes and macrophages as well as adipocytes, and its level rises with adipose tissue mass [8]. Modern literature contains a lot of data that relate resistin level to diseases of coronary and peripheral arteries, ischemic stroke, and congestive heart failure. Resistin does much to induce vascular and metabolic disorders in the human body, as it can provoke inflammation and insulin resistance and aggravate the advancement of atherosclerosis [4].

The adverse effect of resistin on the CVS is confirmed by the fact that patients who developed coronary artery disease (CAD) in young age had a higher level of resistin in their blood plasma compared to persons with intact coronary arteries [9]. Similar data were shown in another study that found considerably heightened resistin concentrations in the blood plasma of patients with unstable angina compared to stable angina patients' figures [10]. It was also proved that resistin is associated with recurrent cardiac events in patients' hospitalized for acute coronary syndrome (ACS) [11]. High resistin concentration in ACS was hypothesized to result from its release on atherosclerotic blood clot detachment [7], [12]. A heightened resistin level is predictive of not only coronary atherosclerosis but also recurrent stenosis after coronary stenting [13].

The negative effect of resistin on the development of coronary atherosclerosis primarily results from dyslipoproteinemia. A strong positive correlation between the concentrations of circulating resistin and triglycerides in fasting blood serum has been demonstrated. There is an opinion that resistin stimulates hepatic lipogenesis to increase the production of very low-density lipoproteins [13] and low-density lipoproteins [14]. Contemporary authors are discussing the possibility of targeting resistin to treat atherogenic dyslipidemia in obese and insulin-resistant persons.

An increasing number of publications are now dedicated to the discussion of arterial hypertension (AH) developed by hyper resistinemic persons [15]. The precise mechanisms of resistin's influence on arterial pressure (AP) remain unclear for now. Some researchers tend to believe heightened concentrations of resistin to activate the sympathetic nervous system. Smirnova and Shulkina show obese patients' AH to be associated with the high resistin, leptin, and insulin resistance index. The veritable correlations found between resistin concentrations in blood plasma and systolic and diastolic AP figures made it possible to regard this adipokine as an adverse marker of metabolic disorders in AH patients, whether obese or not [16].

Recent clinical studies have shown heightened serum resistin to be associated with development and severity of heart failure [17]. There is an opinion that hyper resistinemia is not only independently related to incident heart failure but is also predictive of adverse cardiac outcomes in patients with existing CHF [13], [18]. However, it remains unclear whether resistin is directly cardiotoxic or acts indirectly. It should be noted that resistin also promotes the development of myocardial hypertrophy [19].

Resistin is obviously related to type 2 diabetes mellitus (T2DM): The level of this adipokine is markedly heightened in obese T2DM patients. Experimental and clinical research done showed a resistin injection to be followed by reduced glucose absorption by tissues, which is conducive to the development of insulin resistance [12]. In the study by Kapłon-Cieślicka, observation of 284 T2DM patients proved resistin to be an independent predictor of such prognostically adverse events as: ACS, stroke, transitory ischemic attack, or early lethality. A resistin level above 11 ng/ml pointed to an increased risk of such events. Her findings suggest that in T2DM patients, resistin's relationship to unfavorable outcomes might be explained by its pro-inflammatory properties [20].

Apelin

Apelin was isolated in 1998. In addition to adipose tissue, it is produced in hypothalamic nuclei and is thus not only an adipokine but also a neurohormone. Synthesized together with vasopressin (anti-diuretic hormone) in supra-optic and paraventricular hypothalamic nuclei, apelin is the former's antagonist; consequently, this adipokine can inhibit water re-absorption in renal tubules and increase diuresis. The secretion of apelin is significantly reduced during fasting and increases with overeating, and is also influenced by water load, as heightened blood osmolarity suppresses its synthesis. The highest concentration of apelin is observed in obesity associated with hyperinsulinemia. In the recent years, attention is increasingly paid to its potential role in controlling the secretion of pituitary hormones and fluid and electrolyte homeostasis [4]. Most researchers are inclined to believe that apelin has complex vasomotor effects, as it can cause either vasodilation or vasoconstriction, depending on vasculature tone and associated conditions. Apelin can act through mechanisms of the central nervous system

to regulate the tone of peripheral blood vessels, and acts directly on endothelial cells to either stimulate nitrogen oxide (NO) and prostacyclin secretion, that causes vasodilation, or elicit endothelin production that causes vasoconstriction. However, it is a peripheral vasodilator to a greater extent and, besides, reduces systolic and diastolic AP considerably by increasing diuresis [4], [21]. The hypotensive effect of apelin was first described in 2000, when experiments on animals showed intra-peritoneal injection of apelin to reduce AP [22]. Its hypotensive effect was later confirmed on intravenous injection [21]. Research continued in that direction, and many publications on the topic appeared, particularly about experimental intravenous bolus injection of apelin that caused a considerable decrease of average pulmonary AP in acute pulmonary embolism [23]. The role of apelin in the development of pulmonary AH, pulmonary embolism, acute respiratory distress syndrome, obstructive sleep apnea syndrome, and chronic obstructive pulmonary disease is being actively studied now [24]. The concentration of apelin in circulation was established to increase as blood oxygen saturation decreased [25]. There are also publications that describe this adipokine's powerful positive inotropic effect on cardiac contractility, and its cardioprotective effect in severe myocardial ischemia [26]. Consequently, apelin's multi-factor positive effect on the CVS makes it a potential target for discovering new cardiovascular medications (e.g., apelin mimetics) intended to treat heart failure and arterial and pulmonary hypertension.

Adiponectin

Adiponectin is a hormone synthesized exclusively by adipocytes and more expressed in subcutaneous than in visceral fat. Adiponectin level is reduced in overweight and heightened in lean persons, and is thus negatively correlated with BMI and obesity. There is currently no exact answer about the causes and mechanism of this paradoxical phenomenon, for the mass of adipocytes (the main source of adiponectin secretion) increases in the case of obesity and naturally decreases on wasting. Since discovered a little more than 20 years ago, adiponectin has been closely studied by physiologists and clinical physicians, but its action in health and disease has not yet been completely established. The average concentration of this hormone in healthy people's blood is 10–16 μg/ml, or some 0.01% of all blood plasma protein [27]. The level of adiponectin is affected by many factors: Obesity and adipose tissue distribution in the human body; diet and exercise; smoking and lack of sleep; and genetic polymorphism and some medications [28].

Adiponectin possesses unique cardioprotective properties, and its reduced concentration is conducive to the advancement of atherosclerosis, development of lipotoxicity, and myocardial injury. The influence of adiponectin on the heart muscle results from its involvement in such metabolic processes in the myocardium as oxidation of glucose and free fatty acids, that is, from its direct effect on the production of energy substrates required for cardiac contractions. Hypoadiponectinemia has been proved to promote LV myocardial hypertrophy, for, with adiponectin level being normal, adenosine monophosphate is activated and, in turn, activates protein kinase and suppresses α-adrenoreceptor-stimulated cardiomyocyte hypertrophy. By hampering apoptosis, adiponectin has been shown to exhibit an anti-proliferative effect – incidentally, in all the tissues of the human body [1], [19].

Analysis of the data of patients with lipid disorders and such diseases as CAD, stroke, and atherosclerotic stenosis of carotid, renal, and peripheral arteries showed a low level of adiponectin to be closely related to atherogenesis. Adiponectin has been proved to be an anti-atherogenic and anti-inflammatory factor, and its deficiency has a pernicious effect on the vascular wall [28]. This mainly results from the fact that this hormone has an anti-apoptotic effect on endothelial cells, inhibits inflammation and, consequently, hinders the proliferation of vascular intima, and also hinders macrophage conversion into foam cells and suppresses adhesion of monocytes, reduces their phagocytic activity, and inhibits macrophage-induced cytokine production, which combines to reduce lipoprotein accumulation in the vascular wall [4]. In addition, adiponectin increases NO production. Notably, hypoadiponectinemy is a risk factor for disorders of vascular-thrombocytic and coagulatory hemostasis and, consequently, provokes blood clotting [19].

A study done in Japan showed people with adiponectin level below 4 μg/ml to be at a greater risk of vascular disorders and to have an unfavorable metabolic profile. On the contrary, the high serum adiponectin reduces the probability of acute myocardial infarction (AMI) considerably in men – irrespective of their family history, alcohol consumption, or T2DM or hypertension history [29], [30]. Observation of AMI patients, including some after a stroke, led to similar findings. The adiponectin levels were the lowest in the group of cerebral infarction patients, and the highest in the control group of healthy subjects [31]. The findings of the Framingham study also show a higher concentration of adiponectin to be veritably correlated with a lower risk of CAD development, which led researchers to suggest using this hormone as a valuable CAD prevalence marker [32].

Unique data were obtained by researchers who not just analyzed the overall level of adiponectin but studied five versions of its gene in persons who developed myocardial infarction in young age. To

this end, they examined AMI patients aged under 50, with healthy people of the same age and AMI patients aged over 50 included in control groups. Multivariate analysis veritably showed carriers of CC rs72563731:C>T and AA rs17300539:G>>A genes to have a higher incidence of AMI in young age. Furthermore, they were found statistically veritable differences between AMI patients younger than 50 and the healthy control group as regard the prevalence of those genes, with the CC genotype detected in 81.5% versus 15.9% and the AA genotype, in 19.3% versus 0.5%, respectively. Collation of AMI patients in different age groups also showed those genes' prevalence to veritably differ. The role of adiponectin and its genetic variants in AMI development in young age was thus proved [33].

Of interest is the findings of a study on mice with artificially induced hypoadiponectinemia that presented with rapidly advancing LV dilation, while adiponectin administered helped reduce their cardiac cavity sizes. On myocardial infarction, injections of this hormone given to mice reduced the zone of necrosis by slowing down cardiomyocyte apoptosis [2]. Analysis of the data of ACS patients with ST segment elevation who had undergone primary percutaneous coronary intervention (PCI) showed adiponectin to be an independent negative predictor of coronary blood flow disorders after PCI and is positively correlated with a better survival rate. It was finally concluded that adiponectin could reduce ischemic/re-perfusion myocardial injury and endothelial dysfunction in AMI patients [34].

According to the most studies, the level of adiponectin was inversely correlated with AP level and arterial stiffness figures [35]. As the adiponectin level decreases, AH develops as a result of activation of the renin-angiotensin and sympathetic nervous system and from the advancement of endothelial dysfunction and reduced urinary excretion of sodium ions [36].

Numerous studies done have proved the role of hypoadiponectinemia in the development and advancement of CHF in overweight patients. As a result of those works, it was proposed to determine adiponectin in obese patients and to regard it as a CHF development marker with a view to early prescription of preventive and therapeutic interventions [2], [37]. No less relevant is the issue of timely diagnosis of CHF. The use of adiponectin, as an early diagnosis and risk stratification biomarker, for this condition is also being discussed [38].

Hence, given its anti-inflammatory, anti-atherogenic, and cardioprotective effects, and anti-diabetic properties, adiponectin is currently regarded as a potential target in the development of medications for treating obesity and related diseases and as a marker of the development of some CVDs.

Visfatin

Visfatin was isolated in 2004. It is primarily produced by visceral adipose tissue and possesses insulin-mimetic properties. Its level grows in proportion to the degree of obesity, waist circumference, and insulin resistance index. Visfatin has been established to act biologically through insulin receptors as well as its specific ones [4], [37]. This adipokine is insufficiently studied by now, but modern findings make it possible to trace the relation between serum visfatin level and metabolic disorders in human body and vascular wall status, which led researchers to conclude that visfatin plays an important role in CVD pathogenesis. Thus, Vallejo established visfatin's adverse effect on vascular tone, realized through deterioration of endothelium-dependent relaxation, which, in turn, may provoke the development of persistent AH [39].

The involvement of visfatin in the development of atherosclerotic vascular lesions is being discussed. Its production was noted to rise in persons with unstable coronary and carotid atherosclerotic plaques [8]. A similar study of patients with coronary and aortal atherosclerosis detected increased visfatin production in perivascular adipose tissue [40], [41]. Dahl noted visfatin level to increase considerably in vascular wall lesions caused by atherogenic lipoproteins, which enabled researchers to conclude that the hormone is produced by macrophages as well as adipocytes [42]. Relation of visfatin to myocardial ischemia is actively being discussed in the modern literature. Meta-analysis of 15 studies with a total of 1053 CAD patients observed (and 714 in control groups) showed that an elevated visfatin concentration in peripheral blood might be a marker of CAD developing [43]. No less important conclusions were made in other studies that showed heightened blood plasma visfatin to be veritably associated with the risk of AMI. The data obtained enabled researchers to recommend visfatin as a marker for ACS diagnosis [44].

The findings of a major meta-analysis that included eight AH studies (1693 persons) and seven CHF studies (1696 persons) vividly showed blood plasma visfatin to be considerably higher in AH and CHF patients than in healthy subjects. The data suggested that AH and CHF might be associated with the higher visfatin levels in blood plasma. Elevated AP is associated with a higher risk of cerebrovascular disorders. A high visfatin level in blood plasma was established to promote vascular inflammation and de-stabilization of an atherosclerotic plaque, so some researches recommend using this adipokine as a marker to determine stages of essential hypertension. However, the role of visfatin in the pathogenesis of AH and cerebrovascular disorders remains unclear until now [45]. Of no lesser interest is the results of still another study that found an independent correlation between the higher visfatin and the presence of not only LV myocardial hypertrophy but also refractory AH [46].

Omentin

Omentin was initially termed intelectin or intestinal lactoferrin receptor, as it was first detected in the intestine, in Paneth cells. It was also found in endothelial cells and termed endothelial lactin. This adipokine was later presented as a new secretory protein typical of adipose tissue and involved in insulin regulation. Omentin is mainly synthesized by visceral fat adipocytes. Its concentration is directly proportionate to the levels of adiponectin and high-density lipoproteins and inversely proportionate to BMI and leptin content. Its synthesis is reduced in obesity. There are gender differences with the concentration of omentin in men is less than in women [47].

The findings of a study that determined omentin-1 level in the blood serum of early CAD patients, metabolic syndrome patients and healthy persons showed the CAD patients' omentin-1 level to be veritably the lowest. Yet, its concentrations in the groups of patients with acute phase myocardial infarction and post-infarction cardiosclerosis (several months or years after myocardial infarction) were not veritably different nor were any correlation with cardiac troponin T found. Those data enabled the researchers to recommend using omentin as a biomarker of precisely myocardial ischemia in all age groups [48]. The mechanisms of omentin's relation to CAD are not yet fully studied. Omentin is supposed to induce endothelium-dependent relaxation through NO and to increase sensitivity to insulin.

In the recent years, increasing attention has been given to the physiology of epicardial adipose tissue (EAT) and its role in CVS pathology. Ken Harada determined omentin level in the subcutaneous adipose tissue (SAT), EAT, and blood plasma of CAD patients and those without coronary pathology. The results obtained testify to increased EAT volume and higher omentin expression in it in CAD patients compared to the control group, while the adipokine's level in CAD patients' blood plasma was veritably lower than control. The influence of omentin expression on coronary atherogenesis is being discussed [49].

A number of studies established a correlation between omentin level and the risk of AH development. There is an opinion that decreased level of omentin in circulation in the presence of excessive fat mass is a risk factor for obesity-associated AH. According to the some data, serum omentin level is the most important marker of LV hypertrophy and LV diastolic dysfunction in T2DM patients [50].

There are now papers that prove a positive effect of omentin in the prevention of atrial fibrillation (AF). Tao *et al*. showed AF patients to have the lower serum omentin than patients with sinus rhythm, and permanent AF patients to have the lowest omentin figures [51], [52].

A reduced omentin level is associated with severe heart failure. Thus, the high NYHA class patients had lower serum omentin-1 concentrations than lower NYHA class patients. Patients with the low omentin-1 levels had more marked diastolic dysfunction than the group with the high omentin content. That may probably be explained by omentin potentiating an anti-inflammatory process that leads to deceleration of myocardial fibrosis [53]. The data currently available thus testify to omentin's cardioprotective, anti-inflammatory, and anti-arrhythmic effect.

Conclusion

The adipokines described in this article have a varying effect on the CVS. Some resistin and visfatin exert an adverse influence on the formation of metabolic and vascular disorders in the human body. The major population studies have vividly shown their ability to stimulate the proliferation of vascular smooth muscle cells, be involved in inflammation and promote the development and advancement of endothelial dysfunction and atherosclerosis. Their active negative metabolic effect made it possible to regard those adipokines as markers or even causative agents of CVD development.

Positive effects on the CVS are mainly attributed to adiponectin and omentin, though their concentrations decrease in obesity cases. Among the adipokines whose level is positively correlated with BMI, apelin has a beneficial effect. In aggregate, the above findings of various studies show those adipokines to have an anti-inflammatory and anti-atheromatic effects, potentiate regeneration processes in an injured myocardium, improves the metabolic process in cardiomyocytes and inhibits myocardial apoptosis and fibrosis, which ultimately has a beneficial effect on myocardial contractility function [54]. The medical community is actively discussing the potential use of adipokines in the treatment of AH, CAD, CHF, and pulmonary hypertension.

Further studies of adipokines will thus permit a more accurate understanding of CVD pathogenesis, as well as personalized prophylactic strategies.

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