Review Article

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The adipose tissue as a source of vasoactive hormones and cytokines with a potential role in the pathogenesis of cardiovascular and renal diseases

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SUMMARY

During the last decade white adipose tissue has been recognised as an active endocrine organ and a source of many hormones and proinflammatory cytokines in obesity. These adipokines may play an important role in the pathogenesis of cardio-vascular and kidney diseases.

The contribution to the vascular pathology of obesity of different cell types which compose the adipose tissue; adipocytes, preadipocytes, stromal/vascular cells and macrophages, is, however, different.

In this review we have summarized the present knowledge of some adipokines in patients with obesity, arterial hypertension and chronic kidney diseases.

Key words: leptin, adiponectin, resistin, interleukin-6, TNF-alpha, cardio-vascular.

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INTRODUCTION

The epidemic of visceral obesity, insulin resistance, noninsulin-dependent diabetes mellitus and obesity related arterial hypertension is a challenging health problem for modern societies. No solution to the increasing danger posed by these well known risk factors of cardiovascular morbidity and mortality has been yet pro-

posed. Propagation of an active life style and low caloric diet as well as anorexigenic medications are still insufficient to counterbalance an easy approach to high caloric products.

The last decade has seen adipose tissue rediscovered as an active endocrine organ and an important source of several proinflammatory cytokines[1,2]. Several of these may directly influence the function of the cardio-vascular system and the atherosclerosis process. An incomplete list of adipokines would run as follows: leptin, adiponectin and resistin, estrogens and glucocorticoids, renin, angiotensin II, PAI-1, tumour necrosis factor-α (TNF-α), interleukin-6, interleukin-8, interleukin-10, interleukin-1ß, acylation stimulating protein (ASP), prostaglandin E_2 (PGE_2), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin growth factor-1 (IGF-1), tissue factor (TF), complement factor D (adipsin), Agouti signaling protein (ASP), nitric oxide (NO)[3].

Adipose tissue is not a homogenous organ. It consists of a variety of different cell types such as adipocytes, preadipocytes, stromal/vascular cells and macrophages[3] (Table I). Each of these cells present their own secretion profile and specific regulation. It is already well known that mature adipocytes are the main source of leptin and adiponectin, that macrophages produce almost all TNF-α, while PGE_2, interleukins, VEGF, HGF are synthesized by stromal and vascular cells[3,4]. There are also some differences in the adipokines production between visceral and peripheral fat tissue (Table II). Adipokines released from the fat tissue may exert their action on the endocrine, paracrine or autocrine pattern. While this review mainly focuses on a discussion of the endocrine action of adipokines, the paracrine action can not be neglected in cardio-vascular diseases. An example of this is secretion of NO by the periadventitial fat tissue[5]. Its action on the neighbouring smooth muscle cells may actively influence the vascular tonus and arterial blood pressure[5].

The knowledge of adiposity related mechanisms devastating the cardio-vascular system and the kidneys may help in the design of new drugs for the prevention and treatment of the metabolic syndrome. The role of some adipokines in the pathogenesis of cardio-vascular and renal diseases is discussed in this review.

Leptin

Leptin is a protein predominantly produced by adipocytes[6]. It is encoded by the ob gene[6]. Initially, leptin was implicated in the regulation of appetite as a satiety hormone[6]. It was found that rats with homozygous nonsense mutation of the ob gene were suffering from marked obesity, while parenteral leptin substitution was decreasing their appetite and body mass[7]. A few years later leptin appeared mostly as a marker of nutrition unable to decrease food intake in obese humans, as opposed to what was initially expected. Obese individuals, especially females, are characterised by high plasma leptin concentrations[8]. Thus even highly elevated plasma leptin concentration does not suppress the appetite in these individuals[9].

According to Flier[10], leptin should not be regarded as an antiobesity hormone but as a sign of energy deficiency and integrator of neuroendocrine function. Low plasma leptin concentration – a 'starvation signal' – modulates the hypothalamic-pituitary-adrenal axis, suppresses thyroid and gonadal axes[10]. These endocrine changes resemble the clinical status of patients with *anorexia nervosa*[11].

Low plasma leptin concentration decreases energy expenditure and stimulates the search for food in deprived of food rodents[12,13]. Only in animals with low body fat stores it was demons-

TABLE I
The most important adipokines released by adipocytes and the matrix of adipose tissue

	Adipocytes	Tissue matrix
Prostaglandin E_2	+/-	+++
Prostacycline	+/-	+++
Adiponectin	+++	+
Leptin	+++	-
Resistin	+	+++
Interleukin 8	+	+++
Interleukin 6	+/-	+++
Interleukin 10	+/-	+++
Interleukin 1ß	+/-	+++
Tumor necrosis factor α (TNF-α)	+/-	+++
Platelet activator inhibitor 1 (PAI-1)	++	+++
Hepatocyte growth factor (HGF)	+/-	+++
Vascular epithelial growth factor (VEFG)	+/-	+++
Angiotensin II	+	+++

TABLE II
Comparison of gene expression of adipokines by adipocytes in human visceral or subcutaneous adipose tissue

	Visceral	Subcutaneous
Leptin	+	++
Adiponectin	+++	+
IL-6	+++	+
TNF-α	+	+
PAI-1	++	+
Angiotensinogen	++	+
Estrogens	+	+
IGF-1	+	+

trated that leptin is involved in the regulation of food intake and energy expenditure. Similarly, only in obese children with inactivating mutations of both leptin alleles, parenteral substitution of this peptide decreases appetite with a subsequent reduction of body mass[14].

It is well known that sexual maturation and fertility are linked to nutritional status and adiposity. Injection of leptin in the prepubertal female mouse causes earlier maturation of the reproductive tract[15], suggesting that leptin acts as a signal for puberty. Moreover leptin may promote angiogenesis and stimulate proliferation and differentiation of haemopoietic cells, including T cells[16,17]. In acute infections the shift of the immune system, stimulated by leptin, toward the predominance of the proinflammatory Th_1 T cells population seems to be beneficial[18]. Chronic stimulation of the immune system by leptin may lead to acceleration of atherosclerosis, as leptin-deficient mice are protected from atherosclerosis despite all the other metabolic factors that contribute to this vascular disease[19].

In obese humans leptin exerts a deteriorative impact on the cardiovascular system and kidneys by significant contribution to the pathogenesis of obesity related arterial hypertension. It was shown that high plasma leptin concentration stimulates the activity of the sympathetic nervous system via the receptors located in the brain trunk[20]. Moreover, leptin exaggerates insulin resistance in obese patients[21], stimulates activity of the renin-angiotensin system[22] and modulates the function of endothelial cell (vascular remodelling)[16]. Many of these above mentioned mechanisms interfere with the tubular sodium reabsorption. The contra-regulatory mechanisms responsible for the lack of arterial hypertension in 10-20 % of obese humans were not identified.

Leptin is also involved in the pathogenesis of obesity-related nephropathy and the progression

of chronic glomerulopaties[23]. Within the glomerulus, leptin directly stimulates endocapillary cell proliferation and mesangial collagen typ I and IV deposition[24,25]. In cultured rat endothelial cells, mouse recombinant leptin stimulates proliferation and increases TGF-ß mRNA and TGF-ß secretion[24]. It also stimulates the expression of TGF receptors[24]. Leptin infusion in rats enhances urinary protein excretion[24]. In addition, leptin induces overactivity of the sympathetic nervous, that may contribute to renal damage directly or indirectly via elevated blood pressure.

Patients with advanced chronic kidney disease (CKD) are characterized by markedly elevated plasma leptin concentration compared to body mass index and sex matched healthy individuals[26-28]. CAPD patient have even higher plasma leptin concentration than haemodialysis patients[26,27]. However, increased plasma leptin concentration in CKD is not accounted for by oversecretion of this hormone. Leptin gene expression is even lower in adipocytes of CKD patients than in healthy individuals[29]. In renal failure decreased renal clearance of leptin contributes to elevated plasma leptin concentrations[30]. Thus it is not surprising that plasma leptin concentration is normalized by successful kidney transplantation[31].

Elimination of leptin is partly independent from glomerular filtration rate[32,33]. Kinetic studies suggest that the active uptake of the peptide hormone by the renal tissue contributes to leptin catabolism[34]. Cumin *et al*.[32] studied plasma leptin in Zucker obese rats subjected to bilateral nephrectomy or bilateral ureteral ligation. Following the bilateral nephrectomy plasma leptin concentrations increased by 300%, more than the 50% increase observed after bilateral ligation of the ureters. Similarly in patients with noninflammatory, reversible acute renal failure requiring haemodialysis treatment, plasma leptin concentration although significantly higher than in healthy subjects was much lower than in CKD patients on haemodialysis[33].

In chronic uremia elevated plasma leptin concentration seems to participate in the pathogenesis of uremia-associated cachexia via signaling through the central melanocortin system[35]. On the other hand, it should be stressed that studies addressing the influence of plasma leptin concentration on future changes of the body mass in hemodialysis patients failed to find such a relationship[36,37].

Plasma leptin concentration may serve in these patients also as a marker of well being[36,38]. Elucidation of the mechanisms regulating appetite will be useful in our understanding of cachexia in uremic patients. From the other side it is well known that low body mass predominantly muscle mass is combined with the increased morbidity and mortality in these patients. Therefore there is no doubt that these new findings on the role of leptin in the pathogenesis of cachexia in uremia may have important clinical and therapeutic implications[35].

Adiponectin

Adiponectin is the cardio protective protein hormone secreted almost exclusively by adipocytes with antiatherogenic and insulin-sensitizing properties. It shows structural homology with collagen VIII, X and complement factor C1q[39]. Plasma concentration of adiponectin is relatively high (almost 0.01% of total plasma protein)[40]. In contrast to leptin its concentration is lower in obese than in non-obese subjects[40]. Lower adiponectinaemia was also found in males than in females, and in patients with coronary artery disease, diabetes mellitus type II and essential hypertension than in healthy subjects[41-43].

Adiponectin receptors are found in skeletal muscle, liver and endothelial cells[44]. It has been

suggested that adiponectin inhibits formation of initial atherosclerotic lesions by decreasing expression of adhesion molecules (VCAM-1; ICAM-1, E-selectin) in endothelial cells in response to inflammatory stimuli such as TNFα[45]. Adiponectin also suppresses production of cytokines, such as TNFα by macrophages[46]. Moreover, adiponectin suppresses accumulation of lipids in human monocyte-derived macrophages and inhibits transformation of macrophages into foam cells[47]. It also inhibits cell proliferation stimulated by oxydisized LDL and suppresses superoxide generation[48]. Finally, adiponectin interferes with atherogenesis in ApoE-deficient mice, a well known model of spontaneous atherosclerosis[49].

Adiponectin participates also in the stabilisation of atherosclerotic plaques by increasing expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) in infiltrating macrophages[50].

Adiponectin improves insulin sensitivity[41] by stimulating glucose utilization and fatty acid oxidation in skeletal muscles and the liver and by suppressing enhanced glucose production[51]. It has already been shown that low plasma adiponectin concentration is an independent predictor of the risk of developing insulin resistance and type 2 diabetes in the general population[52]. Adiponectin also modulates inflammatory processes by modifying expression of inflammatory cytokines, as shown in the model of anti-GBM glomerulonephritis[53]. Adiponectin deficient mice were more prone to renal injury after administration of anti-GBM serum[53].

Plasma adiponectin concentration is almost 3-times higher in haemodialysis patients with chronic kidney disease then in healthy subjects[54,55]. However increased plasma adiponectin concentration in these patients could not be explained by its oversecretion by adipose tissue, because the expression of the adiponectin gene (ApM1) is decreased in adipocytes of patients with advanced CKD[56]. The kidneys are the main organ participating in the biodegradation and elimination of adiponectin from the circulation. Thus as expected, successful kidney transplantation is accompanied by prompt reduction, but not normalization, of plasma adiponectin concentration[57]. In addition an inverse relationship between plasma adiponectin concentrations and GFR was found in patients with essential hypertension and apparently healthy individuals[43,58]. Measurements of plasma adiponectin concentrations in the renal veins and aorta of patients with haemodynamically important renal artery stenosis confirmed the role of the kidneys in the elimination of adiponectin[59].

Lower adiponectin gene expression in CKD patients may be partially caused by the microinflammation. Also in the general population, an inverse relationship was found between concentrations of adiponectin and CRP[60,61]. The same is true for haemodialysis patients[55,62,63]. Experimental studies indicating that TNFα and IL-6 inhibit adiponectin gene expression in cultured adipocytes[64,65] has already confirmed this clinical observation.

Low plasma adiponectin concentration is now recognised as a new potential risk factor in cardiovascular morbidity and mortality. In a large cohort of hemodialysis patients lower plasma adiponectin concentration was an independent predictor of fatal and non-fatal cardiovascular complications in these patients[54,55].

Resistin

Resistin is a large polypeptide which is produced exclusively by adipose tissue matrix[66]. Plasma resistin concentration is markedly elevated in obese overfed insulin-resistant mice and also in ob/ob and db/db mice with obesity and diabetes mellitus[67]. In mice, neutralization of resistin by anti-resistin antibodies lowers glu-

cose concentration and improves insulin sensitivity. Conversely, intraperitoneal administration of resistin causes glucose intolerance and insulin resistance in these animals[67]. Moreover, resistin impairs glucose uptake by adipocytes in vitro. It is important to stress that rosiglitazone, an agonist of peroxisome proliferator-activated receptor-γ (PPAR-γ), reduces gene expression and secretion of resistin[67]. In spite of this initial finding in mice, the true role of resistin in humans is unknown. In humans no association between plasma resistin concentration and adiposity or insulin resistance has been found[68].

Similarly to other adipokines, plasma resistin concentration is elevated with impairment of the kidney function[69]. However, no association between plasma resistin concentration and insulin sensitivity has been found in these patients[69].

Interleukin-6 (IL-6)

IL-6 is one of the main proinflammatory mediators primarily secreted by the immune system cells[4]. However 20-30% of these cytokines in the circulation is produced by the adipose tissue[70]. In obese subjects with high waist-hip ratio the participation is even greater[70]. In was also shown that omental adipose tissue releases 2-3 times more IL-6 than subcutaneous tissue[71].

The expression of IL-6 gene is related to the adipose cell size[72] and increases postprandially[73]. Moreover several studies have documented the positive relationship between BMI and plasma IL-6 concentrations[74,75].

In the liver, IL-6 stimulates synthesis of acute-phase response proteins including C-reactive protein (CRP), fibrinogen, serum amyloid-A and α-1 antichymotrypsine[76]. It is already well known that CRP is both a marker and important risk factor of cardiac events and atherosclerosis in the general population and CKD patients[77]. It is also worth stressing that IL-6 stimulates fibrinogen production and platelets activity, which increases the risk of clot formation[78].

In CKD patients plasma concentration of IL-6 is higher than in the general population, mainly as a consequence of prolonged plasma high-life of this cytokine and chronic infections such as Chlamydia pneumonia and others[79]. Elevated concentration of IL-6 and CRP are both strong predictors of mortality in haemodialysis patients[80,81].

Tumour necrosis factor alpha (TNF-α)

TNF-α is predominantly synthesized by macrophages infiltrating adipose tissue[82,83]. Subcutaneous adipose tissue is claimed to produce more TNF-α than visceral one[84]. This cytokine is involved in the genesis of inflammation and/or insulin resistance[85].

The excess of TNF-α production by adipose tissue is one of many factors influencing insulin resistance, but certainly not a fundamental one. Mice lacking TNF-α or TNF-α receptor function demonstrate only modest protection against hyperglycemia and insulin resistance when obese[86,87].

There are three mechanisms linking TNF-α with insulin resistance. The first is related to inactivation of the insulin receptor signaling pathway (involving NFkB and or INK) by phosphorylation[88,89]. The second mechanism engages adiponectin, the secretion of which from adipocytes is markedly reduced by TNF-α[46]. The third mechanism compromises induction of adipocytes lipolysis and stimulation of hepatic lipogenesis[90].

The consequence of elevated plasma TNF-α concentration in CKD patients[91] is until now only a matter of speculation.

Plasminogen activator inhibitor-1

Adipose tissue is a site of abundant PAI-1 synthesis[92]. PAI-1 is a pro-coagulative agent and inhibits fibrinolysis. Circulating plasma level of PAI-1 is an independent predictor of coronary artery disease[93]. These characteristics may explain coronary artery disease in obese patients. Increased PAI concentrations promote release of platelet-derived growth; factors which are known to play a role in vascular injury.

The renin-angiotensin system

All components of the renin-angiotensin system are found in adipose tissue[94,95]. It is still unclear whether angiotensin II secreted by adipose tissue has an important systemic haemodynamic and/or non-haemodynamic effects[96].

CONCLUSION

Visceral adiposity is the key feature of metabolic syndrome (Figure 1). Adipokines oversecreted by the excessive amount of visceral adipose tissue enables us to understand basic metabolic changes related to obesity, such as insulin resistance, dyslipidaemia and chronic microinflammation. Accelerated atherosclerosis, diabetes type 2 and obesity related hypertension are the most frequent causes of morbidity and mortality of the general population. Chronic kidney diseases are also common consequence of diabetic, hypertensive or ischemic nephropathies. Only in markedly (morbidly) obese humans obesity *per se* may directly impair the kidney function as an isolated entity – obesity related glomerulopathy.

However, even a moderate impairment of kidney function further increases the risk of cardiovascular morbidity and mortality[97].

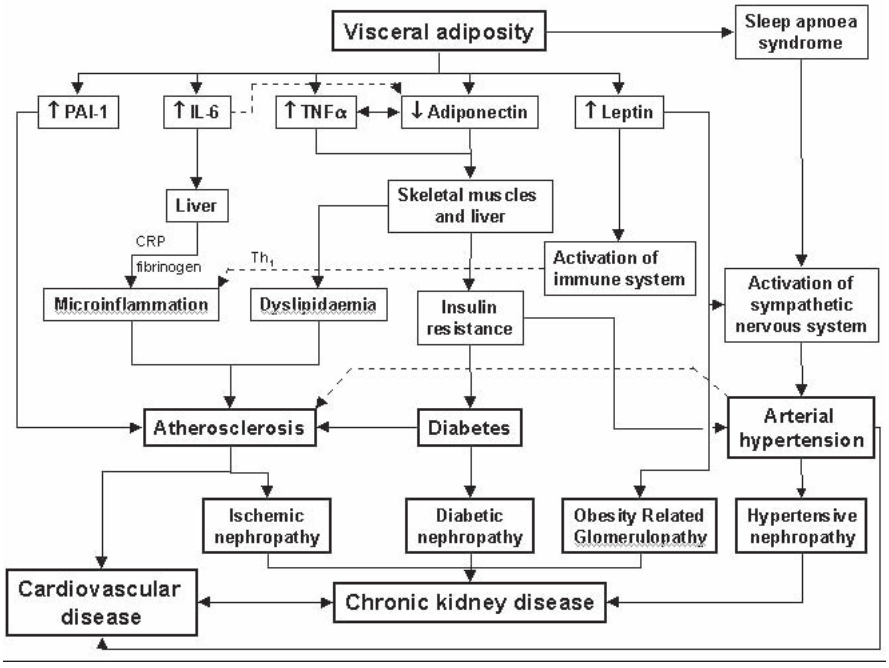

Figure 1 – Visceral adiposity and cardiovascular and kidney diseases.

Therefore it is expected that pharmacological intervention in paracrine/endocrine or immune activity of the adipose tissue may improve the outcome of metabolic syndrome and related, cardiovascular and renal complications in the near future, bringing new hope.

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