

# Adipokines promote chronic kidney disease

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## ABSTRACT

The rapid growth in obesity worldwide contributes to an increase in metabolic syndrome and obesity-related kidney disease with an enhanced increased risk for chronic kidney disease, finally progressing to end-stage renal disease. Adipose tissue is a highly active endocrine organ secreting numerous factors that contribute to renal and cardiovascular complications. In renal damage, various adipokines are involved through mediating endothelial dysfunction, inducing oxidative stress and inflammation as well as stimulating renal sympathetic nervous activity, and it reduces cancellous bone but conversely increases cortical bone. Adipokines may also be involved in the development of renal anaemia. A balance exists between more protective adipokines (adiponectin) and factors mediating pathophysiological effects (angiotensin II, TNF $\alpha$ ). Obesity may cause a disruption of this delicate balance, thereby inducing renal disease. Consequently, weight reduction and lifestyle changes affecting all components of the metabolic syndrome are essential to disrupt this vicious cycle.

## INTRODUCTION

Beyond its effect on the development of cardiovascular disease and metabolic syndrome, the increasing prevalence of obesity worldwide is also linked to chronic kidney disease (CKD) and is a clear risk factor for progressive renal function loss. For example, data from northern California health care participants dramatically reveal the stepwise increase for risk of end-stage renal disease (ESRD) depending on body mass index (BMI). Compared with persons who had normal weight (BMI, 18.5–24.9 kg/m<sup>2</sup>), the adjusted relative risk for ESRD was 1.87 for those who were overweight (BMI, 25.0–29.9 kg/m<sup>2</sup>), 3.57 for those with class I obesity (BMI, 30.0 to 34.9 kg/m<sup>2</sup>), 6.12 for those with class II obesity (BMI, 35.0–39.9 kg/m<sup>2</sup>) and 7.07 for those with extreme obesity (BMI  $\geq$  40 kg/m<sup>2</sup>) [1]. Higher baseline BMI remained an independent predictor for ESRD after

additional adjustments for baseline blood pressure level and the presence or absence of diabetes mellitus [1].

Adipose tissue has more recently been recognized as a metabolically active organ system linking the endocrine and immune systems. It is the source of a variety of cytokines that are also called, due to their origin, adipokines or adipocytokines, such as adiponectin, leptin, tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), visfatin, interleukin-2 (IL-2), resistin or plasminogen-activator-inhibitor-1 (PAI-1). White adipose tissue is most abundant in the adult human body and is normally represented by a ratio of peripheral subcutaneous adipose tissue (SAT) of  $\sim$ 80% and visceral adipose tissue (VAT) that is normally  $<$ 20%. Fat tissue is composed of only up to 50% adipocytes; the other 50% comprise preadipocytes, fibroblasts, vascular structures, and endothelial cells. The secretory metabolic activity is highest in VAT and lowest in SAT. Different fat depots (abdominal visceral, abdominal subcutaneous, total subcutaneous and total body fat) are not equivalent from a functional point of view. VAT mass has a higher degree of metabolic activity compared with SAT. However, VAT as well as SAT secrete adipokines.

Obesity-related kidney disease is characterized by glomerulomegaly alone or in combination during different stages of secondary focal segmental glomerular sclerosis (FSGS). Early changes are associated with decreased podocyte density and number with mild foot process fusions, as usually also found in hypertensive or early diabetic renal injury [2].

The aim of this manuscript is to review recent data of the interactions/signalling from adipose tissue via characteristic adipokines to mechanisms involved in the progression of CKD (Table 1).

### Adiponectin

Adiponectin, the most abundant adipose tissue protein in human plasma has been suggested to be involved in anti-inflammatory, anti-atherosclerotic and insulin-sensitizing effects. Adiponectin has anti-inflammatory effects on the vascular wall by suppressing the expression of proinflammatory adhesion molecules and by interfering with endothelial

**Table 1. Characteristics of major adipokines and their impact in CKD**

Adipokine	Molecular weight	Major source	Change in CKD	Clinical impact in CKD
Leptin	16 kDa	White adipose tissue	↑	Atherogenic
				Inflammatory
				Oxidative stress ↑
				Modulation of immunity
				Bone turnover ↓
				Renal sympathetic activation ↑
				Erythropoietin sensitivity ↓
Adiponectin	26.4 kDa	White adipose tissue	↑	Anti-inflammatory
				Anti-atherogenic
				Oxidative stress ↓
				Proteinuria ↓
				Bone turnover regulation
TNF-α	26 kDa	Adipocytes, macrophages	↑	Inflammatory
				Macrophage infiltration ↑
				Profibrotic
				Epithelial to mesenchymal
				Transition
IL-6	21 kDa (soluble)	Visceral adipose tissue	↑	Atherogenic
	28 kDa (membranous)			Inflammatory
				Increased mortality
Resistin	12.5 kDa	Macrophages	↑	Inflammatory
		Visceral adipose tissue		Atherogenic
				Renal sympathetic activation ↑
Visfatin	52 kDa	Inflammatory cells (mainly macrophages)	↑	Inflammatory
		Visceral adipose tissue		Atherogenic
				Profibrotic
Angiotensinogen (effector: angiotensin II)	49.8 kDa (1.05 kDa)	Adipose tissue, mainly visceral adipose tissue	↑	Inflammatory
				Atherogenic
				Profibrotic

TNF, tumour necrosis factor; IL, interleukin; CKD, chronic kidney disease.

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nuclear factor kappa B (NF $\kappa$ B) signalling [3]. Adiponectin can reverse the endothelial effects of TNF- $\alpha$  as well as other cytokines that are involved in numerous proinflammatory effects.

Adiponectin also exerts anti-inflammatory properties both by suppression of the proinflammatory cytokines (for example TNF-alpha and IL-6) as well as by stimulating the expression

of the anti-inflammatory cytokine IL-10 in healthy persons and in patients with type 2 diabetes and cardiovascular disease [4]. Inoue *et al.* [5] could show *in vitro* and *in vivo* in glomerular mesangial cells that adiponectin is suppressed by aberrantly glycosylated immune globulin A-1 (IgA-1). In Italian patients with type 2 diabetes, plasma levels of intercellular leucocyte adhesion molecule-1 (ICAM-1) and adiponectin could predict albuminuria in multiple regression analysis, and plasma adiponectin positively correlated to adhesion molecule ICAM-1 [6]. Therefore, it was suggested that the anti-inflammatory and protective role of adiponectin in kidney injury might imply inhibition of ICAM-1. In contrast, others have shown that low adiponectin levels were predictive for albuminuria and diabetes [7]. Low levels of adiponectin are associated with higher levels of highly sensitive C-reactive protein (CRP) and IL-6, two well-known inflammatory mediators involved in the initiation and progression of atherosclerosis and renal disease [8]. For example, in diabetic Wistar rats overexpression of adiponectin significantly improved proteinuria in early stage diabetic nephropathy, an effect that was accompanied by an increase in nephrin expression, and an improvement of the endothelial dysfunction as shown by decreases in endothelin-1 (ET-1) and PAI-1, and an increase in endothelial nitric oxide synthase expression in the renal cortex [9]. In contrast, in adiponectin knockout mice, albuminuria and renal fibrosis are markedly increased in a subtotal renal ablation model compared with wild-type animals [10]. Therefore, adiponectin seems to play a protective role by reducing albuminuria through a direct or indirect 'stabilizing' effect on podocyte function as well as a reduction of inflammation and oxidative stress. In a study of patients with overt diabetic nephropathy, elevated adiponectin plasma levels could be measured despite increased urinary adiponectin excretion relatively compared with diabetic patients with normo- and microalbuminuria and normal renal function [11]. It was therefore suggested that adiponectin synthesis in adipose tissue and its secretion into the blood might be enhanced in overt diabetic nephropathy to mitigate microvascular damage [11]. Inversely, in patients with type 2 diabetes and overt diabetic nephropathy, low plasma adiponectin levels can predict progression of kidney disease [7].

### Leptin

The *ob* gene product leptin is secreted by adipocytes and, reflecting the content of body fat, is markedly increased in CKD. Obesity and hypertension are commonly found in combination which together can lead to renal injury and vascular dysfunction. In spontaneously hypertensive rats with a high-fat diet, plasma leptin and cholesterol levels are increased. This was associated with endothelial dysfunction as measured by the dilatatory response to acetylcholine [12]. A potential mechanism for leptin and cholesterol-induced vascular dysfunction is mediated by upregulation of reactive oxygen species (ROS) generation that can disturb the endogenous vasoactive response to acetylcholine and this may be attributed to the ability of leptin to increase oxidative stress and decrease nitric oxide (NO) bioavailability [13]. Endothelial dysfunction is linked with the development of renal injury, and the

presence of endothelial dysfunction is a predictor of cardiovascular risk and severity of renal disease. Serum leptin concentrations are elevated in patients with CKD and correlate with CRP levels, suggesting that inflammation and hyperleptinemia are associated with CKD [14]. Urinary concentrations of leptin are low in patients with CKD indicating that the increased serum levels of leptin in this situation are instead due to an attenuated degradation of the protein and not to a decrease in glomerular filtration rate [15]. Leptin production is associated with an increased size of adipocytes and is positively correlated with BMI [10]. The kidney expresses abundant concentrations of the truncated isoform of the leptin receptor *ob-Ra*, but only a small amount of the full-length receptor *ob-Rb* [16]. Leptin can bind to *ob-Ra* receptors expressed on glomerular endothelial and mesangial cells [16]. Leptin stimulates cellular proliferation via synthesis of transforming growth factor beta1 (TGF-beta1) and type IV collagen and also stimulates glucose transport and type I collagen production through signal transduction pathways involving phosphatidylinositol-3-kinase. This may also result in renal fibrosis and hypertrophy [16]. Leptin also mediates proinflammatory processes through its interaction with the innate and adaptive immune system. Studies of rodents with genetic abnormalities in leptin or leptin receptors revealed obesity-related deficits in macrophage phagocytosis and the expression of proinflammatory cytokines. Leptin deficiency enhances susceptibility to infectious and inflammatory stimuli and is associated with dysregulation of cytokine production [17]. Central leptin administration in *ob/ob* mice accelerates renal macrophage infiltration through the melanocortin system [18]. Leptin also stimulates central T-cell production and a peripheral shift in favour of T helper (Th) 1 adaptive proinflammatory immune responses. Leptin has been shown to modulate adaptive immunity by enhancing T-cell survival and stimulating production of proinflammatory cytokines such as interferon-gamma (IFN-gamma) and IL-2. The proinflammatory properties of leptin affecting the kidney seem to be partially explained by its effects on cellular proliferation and hypertrophy with an increase of extracellular matrix expression, and its effects on the innate and adaptive immune system.

### Visfatin

Visfatin is mainly, but not exclusively, secreted by adipocytes and is highly enriched in VAT, but is also produced by macrophages, dendritic cells and colonic epithelial cells. It is intracellularly involved in the biosynthesis of nicotinamide adenine dinucleotide (NAD<sup>+</sup>) and thereby influences cell energetic metabolism and NAD<sup>+</sup>-dependent enzymes; extracellularly it induces both proinflammatory and anti-inflammatory cytokines [19]. Circulating levels of visfatin are significantly increased in patients with CKD and correlate with renal function and are associated independently with the level of soluble vascular cell adhesion molecule-1 (sVCAM-1), a marker of endothelial damage.

Plasma visfatin levels are elevated in patients and animals with type 2 diabetic nephropathy. *In vitro*, visfatin is synthesized in renal glomerular mesangial cells and upregulated by high-glucose stimulation [20]. In addition, exogenous

visfatin stimulation in renal cells upregulated the synthesis of profibrotic molecules, including TGF- $\beta$ 1, PAI-1 and type I collagen. Thus, the pathophysiologic relevance of visfatin seems to be as a proinflammatory adipokine in type 2 diabetes and the metabolic syndrome.

### Resistin

Resistin is weakly expressed in human adipose tissue and is mainly produced in inflammatory cells, especially from macrophages residing in the VAT of obese patients. Its serum concentrations are increased in patients with type 2 diabetes mellitus and CKD. Resistin contributes to insulin resistance and to cardiovascular and atherosclerotic risk. In essential hypertensive subjects, higher resistin levels are associated with a decreased glomerular filtration rate. Moreover, the independent association of resistin glomerular filtration rate suggests involvement of resistin in the progression of kidney damage in the early stages of hypertension [21]. Plasma resistin also positively correlates with leucocyte counts, highly sensitive CRP and ET-1 [22]. Resistin is able to induce expression of adhesion molecules VCAM-1 and ICAM-1, an effect that is inhibited by adiponectin. In patients with CKD, resistin levels are markedly elevated and significantly correlated with inflammatory markers such as highly sensitive CRP, IL-6 VCAM-1 and ICAM-1 [23]. Elevated *resistin* levels in CKD are associated with a decreased glomerular filtration rate and inflammation. Plasma resistin levels are elevated in both genetic and diet-induced animal models of obesity. Both in CKD patients and in renal transplant patients, resistin is correlated to inflammation by the systemic increase of IL-6, TNF- $\alpha$ , highly sensitive CRP, VCAM-1 and ICAM [24]. Resistin strongly up-regulates IL-6 and TNF- $\alpha$  in human peripheral blood mononuclear cells via the NF $\kappa$ B pathway [25].

### TNF- $\alpha$

TNF- $\alpha$  is a potent proinflammatory cytokine and important mediator of inflammatory tissue damage. In addition, it has important immune-regulatory functions. Many experimental studies and clinical observations support a role for TNF- $\alpha$  in the pathogenesis of acute and chronic renal disease. TNF- $\alpha$  is mainly produced by macrophages infiltrating adipose tissue but can also be produced in the kidney and is markedly increased in obesity [2]. In the kidney, TNF- $\alpha$  synthesis in renal cells can be stimulated by several substances such as angiotensin II ANG II, advanced glycation end products (AGEs) or oxidized low-density lipoprotein (LDL) leading to local damage [2]. Neutralization of TNF- $\alpha$  in rats with renal failure decreases NF $\kappa$ B activity that is associated with a reduction in renal TGF- $\beta$ 1 and ET-1 production, and an improvement of NO release. These effects presumably reduce renal inflammation and fibrosis, as well as blood pressure, indicating a pivotal role for TNF- $\alpha$  in the progression of renal injury [26]. TNF- $\alpha$  has also been shown to induce the expression of monocyte chemoattractant protein-1 (MCP-1) via a p38 mitogen-activated protein kinase (MAPK) signalling pathway in renal mesangial cells [27]. Therefore, MCP-1, a key regulator in recruiting monocytes to the glomeruli, may also

contribute to renal damage at a later stage of kidney disease in obesity.

### Interleukin 6

Similar to TNF- $\alpha$ , IL-6 is a proinflammatory adipokine that correlates with body weight and insulin resistance. In a cross-sectional study on Caucasian subjects, higher systemic IL-6 levels and highly sensitive CRP correlated with microalbuminuria but not with renal function in linear regression analysis pointing to the link of inflammation and microalbuminuria [28]. In a large study of US patients with a 15-year follow-up, TNF- $\alpha$  receptor 2, white blood cell count, and IL-6 levels were positively associated with incident CKD [29]. Thus, elevations of most markers of inflammation predict the risk of developing CKD. Blocking the IL-6 receptor prevents progression of proteinuria and renal lipid deposit as well as mesangial cell proliferation associated with severe hyperlipoproteinemia [30].

### Progranulin

Progranulin is an adipokine induced by TNF- $\alpha$  in cellular models of insulin resistance. Progranulin knockout mice are resistant to high-fat diet-induced insulin resistance, adipocyte hypertrophy and obesity [31]. Progranulin-induced insulin resistance was suppressed by neutralizing IL-6 *in vivo* [31]. In patients with CKD stages 1–5, progranulin serum levels increased with deteriorating renal function and were independently correlated with IL-6 and adiponectin [32]. Thus, progranulin might directly contribute to the proinflammatory state frequently seen in renal dysfunction.

### Adipokines and renal sympathetic activation

The activation of the sympathetic nervous system through the central actions of leptin has been suggested as a major mechanism by which obesity contributes to the development of hypertension. In rabbits, exposure to a high-fat diet leading to visceral fat accumulation altered leptin sensitivity and elevated renal sympathetic nerve activity and arterial pressure [33]. Interestingly, resumption of a normal diet returned glucose, insulin, leptin and heart rate to control levels, but body weight, mean arterial pressure and renal sympathetic nerve activity remained elevated [34]. Hence, increased plasma leptin and insulin may contribute to the initiation of hypertension but are not required for maintenance of mean arterial pressure, which likely lies in alterations in the response of neurons in the hypothalamus. In contrast, adiponectin administration in rats was able to reduce renal sympathetic nerve activity blood pressure [35]. Resistin plasma levels are elevated in obesity and resistin can affect energy homeostasis through central mechanisms that include reduced food intake and reduced thermogenesis, and can also increase lumbar sympathetic nerve activity via a central action. Central resistin enhances renal sympathetic nerve activity via phosphatidylinositol 3-kinase but reduces the activity in brown adipose tissue via extracellular signal-regulated kinase 1/2 [36].



### Renin–angiotensin–aldosterone system

Elevated renin–angiotensin–aldosterone system (RAAS) activity, predominantly in the visceral adipose tissue, is characteristic of obesity. All components of the RAAS are expressed in, and independently regulated by, systemic RAAS. ANG II is mainly generated in the adipocytes and is delivered through circulation to the kidney. ANG II is the final effector of the RAAS and has emerged as a multifunctional ‘adipo’-cytokine, exhibiting many non-haemodynamic properties such as acting as a growth factor as well as a profibrogenic and proinflammatory cytokine, promoting ROS production and tissue fibrosis (for review see [37]).

### Adipokines and bone turnover in CKD

An inverse relationship between bone density and adiponectin, as well as a positive association between osteocalcin and adiponectin, could be shown in CKD stages 2–4 patients [38]. In male haemodialysis patients increased levels of serum adiponectin were associated with decreased bone mineral density [39] and similar data from both male and female haemodialysis patients regarding bone mineral density and high molecular weight adiponectin have been obtained [40].

In *ob/ob* mice, leptin attenuated renal 1- $\alpha$ -hydroxylase gene expression through the long form of the leptin receptor. Furthermore, leptin appeared to act indirectly on renal proximal tubules to regulate 1- $\alpha$ -hydroxylase gene expression [41]. Leptin directly stimulated bone-derived fibroblast growth factor-23 (FGF-23) synthesis by bone cells in *ob/ob* mice, suggesting that inhibition of renal synthesis of 1- $\alpha$ ,25-dihydroxyvitamin-D3 in these mice seems to be at least partly due to elevated bone production of FGF-23 [42]. Further observation to obtain more data regarding a possible bone/adipose pathway in CKD is required.

### Adipokines and renal anaemia

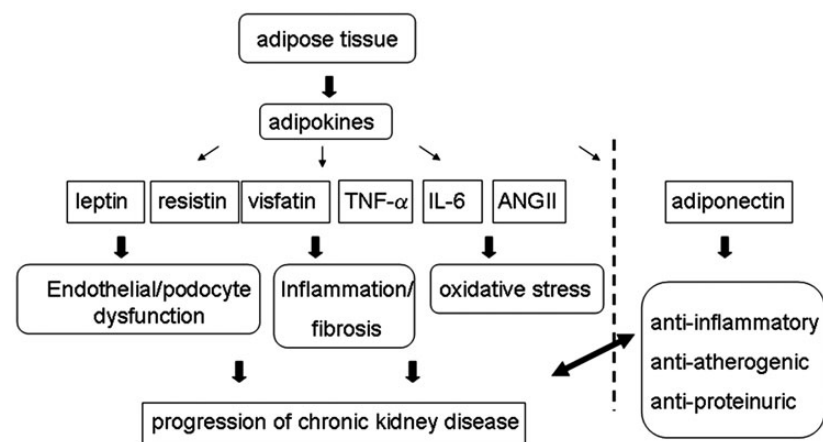
Body fat mass and serum leptin levels seem to influence epoetin sensitivity in patients with ESRD [43]. The authors consequently suggested that the leptin level may be a predictor of epoetin sensitivity, possibly through either direct stimulation of erythropoiesis or indirect stimulation by

associated adipokines. Although truncal fat is associated with secretion of proinflammatory cytokines, this secretion appeared not to have inhibitory effects on epoetin sensitivity in the presence of high leptin levels in this study [43]. Others have observed similar data but have interpreted this differently, suggesting that hyperleptinemia better indicates nutritional status and that the epoetin response in long-term haemodialysis patients reflects an increased energy intake by improved erythropoiesis (mediated in part by increased serum leptin levels) [44]. In a recent study of CKD patients, high-dose erythropoietin stimulating agents were associated with elevated inflammatory biomarkers and higher levels of the circulating soluble erythropoietin receptor but not with adipokines [45]. Nevertheless, the data are currently conflicting and further research is warranted.

### Newer adipokines and CKD

*Apelin*, derived from white adipose tissue, acts as a vaso-active peptide and has been identified as the endogenous ligand of an orphan G protein-coupled receptor called APJ. Apelin and its receptor have been found in the brain and the cardiovascular system; it has also been found to be highly expressed in rodent glomeruli while its level of expression is lower in all nephron segments including the collecting ducts that express vasopressin V2 receptors. Apelin has been correlated to endothelial dysfunction and inflammation in CKD patients and in kidney allograft recipients, and a correlation to adiponectin and adhesion molecules has been observed [46]. In experimental type 1 diabetes, apelin substitution was associated with inhibited whole kidney and glomerular hypertrophy, as well as renal inflammation, including MCP1 and VCAM1 expression, NF $\kappa$ B activation and monocyte infiltration [47]. Thus, apelin seems to exert a protective effect on the diabetic kidney.

*Chemerin* has been identified as a novel adipocyte-secreted factor playing a crucial role in adipocyte differentiation and insulin signalling. Chemerin is the recently identified natural ligand of ChemR23, a receptor highly expressed by plasmacytoid dendritic cells. Markers of renal function are independently related to circulating chemerin



**FIGURE 1:** Overview of major adipokines and their role in CKD (TNF, tumour necrosis factor; IL, interleukin; CKD, chronic kidney disease).

levels [48]. In dialysis patients, elevated chemerin was associated with a survival advantage despite its significant positive association with markers of inflammation and dyslipidaemia [49]. Serum chemerin was significantly elevated in type 2 diabetic patients with macroalbuminuria compared with control subjects and diabetic patients with normoalbuminuria and microalbuminuria. Whether chemerin is only a marker of kidney function or to what extent it is actually involved in the pathophysiological mechanisms of CKD needs further investigation.

## CONCLUSION

Adipose tissue is a highly active endocrine organ secreting numerous factors that contribute to renal complications. Adipokines are involved in kidney damage by mediating endothelial dysfunction, oxidative stress and changes in immune response and inflammation, and are associated with renal sympathetic nervous activity, bone turnover and perhaps even contribute to renal anaemia (Figure 1). The role and impact of each adipokine seems to induce a pathophysiological disbalance. Each adipokine has a role in the delicate balance between protective and pathophysiological impact. Although adiponectin has anti-inflammatory and anti-atherogenic properties, some studies have nevertheless shown that higher levels of adiponectin versus lower levels predict poor patient outcomes, indicating a complex relationship between various adipokines.

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## CONFLICT OF INTEREST STATEMENT

None declared.

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