

*Editorial Comment*

## The emerging biology of adipose tissue in chronic kidney disease: from fat to facts

Jonas Axelsson<sup>1</sup>

<sup>1</sup>Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska institutet, Stockholm, Sweden

**Keywords:** Metabolism; insulin resistance; renal disease; cytokine; adipokine

### Is uraemic fat different?

### Introduction

“No diet will remove all the fat from your body because the brain is entirely fat. Without a brain, you might look good, but all you could do is run for public office.”

George Bernard Shaw

Regardless of the implications, the incidence of obesity is increasing worldwide [1] and along with it the proportion of the population subject to hypertension [1] or type-2 diabetes mellitus [1]. Furthermore, the metabolic syndrome is an important risk factor for proteinuria and chronic kidney disease (CKD) independently of diabetes and hypertension [2]. For the nephrologist, this has resulted in both an increased influx of patients with CKD [2] and a larger and more obese end-stage renal disease (ESRD) population [3]. However, despite the generally reduced lifespan of obese patients not suffering from CKD [4], epidemiological studies of the impact of obesity on outcome in CKD remain conflicting, with several well-designed studies even suggesting a survival advantage for obese ESRD patients [5,6]. These studies were recently addressed in an excellent review in these pages by Mafra *et al.* [7] and will not be discussed in detail here. Instead, the present review aims to address the current lack of understanding of the biological basis for any effects attributed to obesity in the context of uraemia. Specifically, in order to better treat the obese CKD patient, we should ask ourselves what mechanisms may link fat to uraemic complications, and how the putative beneficial effects of obesity could be harnessed to benefit our patients.

It is now generally accepted that obesity produces insulin resistance [8], putatively through the induction of peripheral disruption of insulin signalling pathways by increased levels of circulating free fatty acids (FFA) [8] and an increase in inflammatory signalling [9]. In this context, it is noteworthy that a central function of adipose tissue may be to control whole-body lipid metabolism, thus effectively modulating both glucose and lipid homeostasis [8]. Indeed, adipose tissue is able to regulate metabolism through the dual pathways of adipokine excretion, exerting endocrinological control of insulin sensitivity and feeding behaviour [10] and the sequestration of FFA as triglycerides [8]. The advent of obesity is furthermore characterized by hypertrophy of individual adipocytes [11], which respond by recruiting tissue macrophages leading to a pro-inflammatory state of the fat [11], which stimulates adipocyte lipolysis, inhibits production of triglycerides and thus further exacerbates systemic insulin resistance [9].

In patients with CKD, obesity also predicts the classic metabolic syndrome, comprising dyslipidaemia, insulin resistance and hypertension [12]. The author is not aware of any studies investigating adipose tissue signalling pathways at the cellular level in uraemia. However, circulating FFA appear to be generally elevated in CKD [13], while multiple studies [14–22] have shown up to fivefold higher levels of the adipokines leptin and adiponectin in the circulation of CKD patients as compared to healthy controls. These adipokines also appear to increase concurrently with a decline in glomerular filtration rate (GFR), perhaps suggesting a compensatory mechanism or a reduced renal metabolism [16]. Thus, it would appear that uraemic fat tissue functions much as fat tissue in non-uraemic individuals, while the consequences of adipocyte signalling in uraemia remain to be elucidated.

### Insulin resistance and uraemic dysmetabolism

While insulin resistance in a large proportion of patients with CKD is mainly due to the presence of overt diabetes

*Correspondence and offprint requests to:* Jonas Axelsson, Department of Renal Medicine, K56, Karolinska University Hospital Huddinge, 141 86 Stockholm, Sweden. Tel: +46-8-5858-3981; Fax: +46-8-5858-3925; E-mail: jonas.axelsson@ki.se

mellitus, renal disease itself is also independently associated with an increase in glucose intolerance that is strongly and inversely correlated with GFR [23–25]. This uraemic glucose intolerance is characterized by low muscle glucose uptake [26], an elevated liver gluconeogenesis [27] and, in some cases, a blunted insulin response [27,28]. However, the extent to which general pathways, including elevated FFA, and pathways specific to uraemia, including accumulation of nitrogenous compounds [29,30], each contribute to produce insulin resistance in CKD patients remains unknown.

In non-diabetic CKD patients, insulin resistance correlates with body fat mass [31–33] and has been shown to contribute to muscle atrophy through defects in insulin receptor signalling [34,35]. The underlying mechanism demonstrated by Mitch *et al.* appears to be suppression of insulin receptor substrate-1-associated phosphatidylinositol 3-kinase activity resulting in stimulation of the ubiquitin-proteasome proteolytic system via caspase-3 [36]. Interestingly, muscle atrophy itself appears to be a more important predictor of outcome than fat mass, at least in ESRD patients [37]. Another factor that may contribute to uraemic insulin resistance is inflammation, which is present in a large proportion of CKD patients [38] and may act through specific pathways such as SOCS [39] and IKK- $\beta$  [40] to inhibit insulin signalling. Inflammation is in turn causally linked to oxidative stress, also elevated in most patients with CKD [41]. Oxidative stress is now recognized as a potent inducer of peripheral insulin resistance [9], as well as an important regulator of adipokine expression in CKD patients [42,43]. Of note, an experimental increase in FFA decreases the expression of myocyte mitochondrial antioxidant genes, thus linking FFA to oxidative stress and inflammation [44], while treatment of obese, diabetic mice with an inducer of antioxidant pathways reduced adiposity, increases adiponectin levels and improved insulin sensitivity [45].

Despite obvious applications, few studies have examined the links between inflammation, oxidative stress and insulin resistance in CKD. However, Ramos *et al.* [46] recently demonstrated that adiposity may amplify the oxidative stress and inflammation that accompany moderate to severe CKD, while we have shown that both inflammation and obesity in CKD are independently associated with insulin resistance assessed by the HOMA-IR index [31], as well as with pro-atherogenic dyslipidaemia [47]. Furthermore, Raj *et al.* recently published data linking an inflammatory response during HD to elevated SOCS-3 levels and insulin resistance [48].

### **Adipose tissue as the largest endocrine gland in the body**

The endocrinological role of adipose tissue was only recently realized with the discovery of leptin [49], but already a massive search for other novel proteins exclusively expressed in adipose tissue is ongoing. While many such adipokines have been proposed, few have been studied in detail and even fewer investigated in patients with

CKD. Perhaps most well studied in uraemia is adiponectin, an adipokine able to increase hepatic [50] and muscular [51] insulin sensitivity, improve endothelial function [52] and counteract pro-inflammatory signalling [52]. Hence, adiponectin has been proposed to be an autoregulatory mechanism whereby the detrimental effects of obesity would be ameliorated [20]. However, paradoxically and in contrast to many other adipokines, circulating levels of adiponectin drop as fat mass increases [53], and this drop parallels a risk of CVD [20,54,55].

In CKD patients, plasma adiponectin levels are elevated as compared to healthy controls [20,56], but it would appear that it is the patients with low adiponectin levels that have the greatest increase in mortality rate [20]. Further confusing the issue, adiponectin circulates in several distinct isoforms—which are simultaneously measured by most commercial ELISAs—characterized by multimerization of the original protein and the ability to activate different pathways dependent upon the number of molecules [57]. Furthermore, at least two specific adiponectin receptors have been cloned (AdipoR1 and R2), and simultaneous disruption of both these receptors is required to increase tissue triglyceride content, elevate oxidative stress and engender insulin resistance *in vivo* [58]. In CKD, Shen *et al.* [59] found both AdipoR1 and R2 upregulated on peripheral blood mononuclear cells (PBMCs) of HD patients in a manner unrelated to insulin resistance, suggesting that adiponectin signalling is an adaptive, protective mechanism in uraemia rather than a cause of dysmetabolism. As the expression of AdipoR1 and R2 is several-fold higher in muscle than in adipose tissue [60], a preserved muscle mass in CKD—recently shown to be associated with a better survival regardless of fat mass [37]—may also be associated with a better response to any compensatory increase in circulating adiponectin. However, this hypothesis remains to be tested.

Leptin was initially described as a modulator of feeding behaviour, and thus of fat mass, in rats [49]. While leptin signalling is more complex in humans, loss of renal function leads to inappropriately elevated serum concentrations of leptin [15]. In PD patients, we have shown [61] that serum leptin levels increase with initiation of PD, are inversely related to inflammation and predict longitudinal changes in lean body mass. In accordance, most [19,62], but not all [63], studies have demonstrated an association between inflammatory biomarkers and leptin in CKD suggesting that it may play a role in uraemic wasting. These data are corroborated by a study of non-renal patients, showing that leptin is able to initiate recruitment and activation of immunocompetent cells in adipose tissue [64], while leptin production can in turn be upregulated by local TNF- $\alpha$  levels [64]. Notably, serum leptin levels also appear to be an independent predictor of epoetin requirements in uraemia (even after adjustment for inflammation) [65,66] and the leptin receptor is expressed on haematopoietic stem cells [67].

### **Adipokines as uraemic toxins mediating anorexia**

Despite a large literature of epidemiological studies purporting a beneficial role of adipose tissue in uraemia [7],

so far relatively few studies have investigated the impact of fat and adipokines on common complications of CKD. An obvious target for such investigations is the highly prevalent dysmetabolism of CKD, which shares many similarities with the obesity-associated metabolic syndrome [68]. In uraemic rats, Mak *et al.* recently showed that leptin signalling in the central nervous system (CNS) is an important cause of anorexia [69]. In an elegant mechanistic experiment, they found that uraemic anorexia can be ameliorated by blockade of leptin signalling through the hypothalamic melanocortin-4 receptor [70]. In a follow-up study, the same group also found that injection of agouti-related peptide (a melanocortin-4 receptor antagonist) into the cerebral ventricles of uraemic mice resulted in a gain of body mass and an improved metabolic rate regulation [71]. These studies demonstrate the need for mechanistic investigations to support purported epidemiological facts, and while still needing confirmation in humans, may also be the first steps on a negotiable therapeutic strategy for uraemia-associated wasting.

Another proposed adipokine, nicotinamide phosphoribosyltransferase (Nampt), also known as visfatin and pre-B-cell colony-enhancing factor 1 (PBEF-1), is an ubiquitous intracellular enzyme involved in mitochondrial redox reactions [72]. It was proposed by Fukuhara *et al.* in 2005 to be a mediator of insulin resistance selectively upregulated in the adipose tissue of insulin-resistant rats, and having insulin-mimetic effects [73]. In humans, early data suggest that Nampt is present in increased concentrations in patients with type 2 diabetes [74,75], but that it is not in itself a mediator of insulin resistance [75–77]. Instead, it appears to regulate cell survival during periods of starvation [72] but also to mediate systemic NAD biosynthesis critical for pancreatic  $\beta$ -cell function [78]. In uraemia, Nampt appears not be associated with insulin resistance [79], but rather to correlate with endothelial dysfunction [80,81], perhaps due to its association with uraemic anorexia (Axelsson *et al.* Unpublished finding 2008).

### Fat as a source of inflammation in CKD patients

Inflammation is a ubiquitous feature of CKD associated with an adverse outcome [82]. As the biology and physiology of adipose tissue is re-examined in the light of recent findings, much attention is being drawn to the close and interdependent signalling pathways of inflammation and metabolic control expressed there [64,83]. Indeed, gene expression is highly similar between adipocytes and macrophages [64,83] and these two cell types also share functional capabilities, such that macrophages can take up and store lipids to become atherosclerotic foam cells, while preadipocytes under some conditions can exhibit phagocytic and antimicrobial properties and appear to even be able to differentiate into macrophages in the right environment [84]. Additionally, obesity is thought to be a state of aberrant immunological activation [11], and we [37,85,86] and others [12,46,68] have found that a large truncal (visceral) fat mass is associated with elevated circulating levels of pro-inflammatory cytokines such as IL-6 in patients with CKD. The current evidence suggests that this is because

adipose tissue growth in a state of overnutrition activates adipocytes to release chemokines that attract monocytes to infiltrate the fat as resident macrophages [11,87,88]. In uraemia, we recently found that circulating levels of sCD163, a marker of mature macrophages, correlates with fat mass, circulating levels of pro-inflammatory cytokines and increased circulating endothelial adhesion molecules [89]. Following adjustment for sCD163, the previously significant relationship between fat mass and inflammatory biomarkers (such as IL-6 or CRP) disappeared, while the relationships between fat and leptin remained significant, suggesting that pro-inflammatory signalling in uraemic fat is mainly derived from macrophages rather than adipocytes [89]. Furthermore, in the same study, we found that longitudinal changes in fat mass after the initiation of dialysis therapy were associated with changes in sCD163 and systemic inflammation, such that an increase in fat mass also engenders elevations in the levels of systemic sCD163 and inflammatory cytokines [89].

### Fat, bone and hypertension?

While the plethora of adipokines is just starting to be investigated, several novel findings from *in vitro* experiments and studies of non-uraemic individuals may have direct correlates in CKD. Perhaps most intriguing is the emerging connection between adipose tissue and bone [90]. Indeed, studies in elderly osteoporotics [91] as well as in young healthy individuals [92] have suggested a reciprocal relationship between bone marrow adiposity and bone loss, supporting basic research data indicating that osteoblasts and adipocytes share a common progenitor cell [90,93]. However, whether this relation represents a preferential differentiation of stromal cells from osteoblasts to adipocytes, or a passive accumulation of fat as bone is lost and marrow space increases with ageing, is unknown. More intriguing, recent data suggest that adipokines such as adiponectin [94] and leptin [95] may influence bone turn-over, while the bone-derived protein osteocalcin can stimulate expression of insulin in  $\beta$ -cells and adiponectin in adipocytes *ex vivo* and is able to endocrinologically improve glucose tolerance in a mouse model [90].

Another emerging pathway is the one between fat and the nervous system. While visceral obesity has long been known to increase the risk of hypertension [96], the mechanisms have been incompletely understood. Recently, it has become clear that adipose tissue expresses a full local renin-angiotensin (RAAS) system that is active at both the local and systemic levels [97]. However, the CNS also directly controls nutrient partitioning and adipose tissue accumulation through sympathetic nerve signalling [98,99], and in CKD the level of FFA in the circulation has been linked to  $\alpha$ 1-adrenoreceptor signalling and blood pressure control [100].

### Conclusion

While the controversies in nephrology regarding obesity and outcomes likely will continue for some time to come,

current research suggests that adipose tissue has both beneficial and detrimental ramifications in the unique milieu of uraemia. With the balance of physiological pathways studied so far, both similar to those active in the general population and harmful to the patient with CKD, it would appear that also for our patients too much of a good thing leads to unwanted results. However, until we fully understand the physiology of uraemic fat, and especially the causes of the accelerated mortality in CKD, it is hard to exclude that adipose tissue may indeed also exert beneficial effects in patients with CKD.

**Acknowledgements.** The author is supported by grants from the Swedish Heart and Lung Foundation's Renal Research Fund (grant 20070398), the Swedish Society of Medicine (grant 2007-20051), the Swedish Society for Medical Research and Karolinska institutet's Funds (grant 2007FoBi0121). Baxter Novum is the result of an unconditional grant from Baxter Healthcare Inc. to the Karolinska institutet. The author wishes to thank his patients for their continued support and interest, Prof. Peter Stenvinkel for his mentoring and most of all Prof. Bengt Lindholm for mentoring, teaching and unwavering support over the years.

**Conflict of interest statement.** The author does not declare a conflict of interest. The present article has not been published elsewhere wholly or in part.

## References

- Balkau B, Deanfield JE, Despres JP *et al.* International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* 2007; 116: 1942–1951
- Wahba IM, Mak RH. Obesity and obesity-initiated metabolic syndrome: mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 550–562
- Kramer HJ, Saranathan A, Luke A *et al.* Increasing body mass index and obesity in the incident ESRD population. *J Am Soc Nephrol* 2006; 17: 1453–1459
- Flegal KM, Graubard BI, Williamson DF *et al.* Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA* 2007; 298: 2028–2037
- Kalantar-Zadeh K, Abbott KC, Salahudeen AK *et al.* Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; 81: 543–554
- Beddhu S, Pappas LM, Ramkumar N *et al.* Effects of body size and body composition on survival in hemodialysis patients. *J Am Soc Nephrol* 2003; 14: 2366–2372
- Mafra D, Guebre-Egziabher F, Fouque D. Body mass index, muscle and fat in chronic kidney disease: questions about survival. *Nephrol Dial Transplant* 2008 Apr 3; E-pub ahead of print
- Guilherme A, Virbasius JV, Puri V *et al.* Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol* 2008; 9: 367–377
- Ozcan U, Cao Q, Yilmaz E *et al.* Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* 2004; 306: 457–461
- Ahima RS, Lazar MA. Adipokines and the peripheral and neural control of energy balance. *Mol Endocrinol* 2008; 22: 1023–1031
- Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. *J Clin Invest* 2003; 112: 1785–1788
- Kwan BC, Murtaugh MA, Beddhu S. Associations of body size with metabolic syndrome and mortality in moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2007; 2: 992–998
- Lee DM, Knight-Gibson C, Samuelsson O *et al.* Lipoprotein particle abnormalities and the impaired lipolysis in renal insufficiency. *Kidney Int* 2002; 61: 209–218
- Marchlewska A, Stenvinkel P, Lindholm B *et al.* Reduced gene expression of adiponectin in fat tissue from patients with end-stage renal disease. *Kidney Int* 2004; 66: 46–50
- Heimbürger O, Lonnqvist F, Danielsson A *et al.* Serum immunoreactive leptin concentration and its relation to the body fat content in chronic renal failure. *J Am Soc Nephrol* 1997; 8: 1423–1430
- Sharma K, Considine RV, Beckie M *et al.* Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. *Kidney Int* 1997; 51: 1980–1985
- Young GA, Woodrow G, Kendall S *et al.* Increased plasma leptin/fat ratio in patients with chronic renal failure: a cause of malnutrition. *Nephrol Dial Transplant* 1997; 12: 2318–2323
- Coyne DW, Dagogo-Jack S, Klein S *et al.* High-flux dialysis lowers plasma leptin concentrations in chronic dialysis patients. *Am J Kidney Dis* 1998; 32: 1031–1035
- Nordfors L, Lonnqvist F, Heimbürger O *et al.* Low leptin gene expression and hyperleptinemia in chronic renal failure. *Kidney Int* 1998; 54: 1267–1275
- Stenvinkel P, Marchlewska A, Pecoits-Filho R *et al.* Adiponectin in renal disease: relationship to phenotype and genetic variation in the gene encoding adiponectin. *Kidney Int* 2004; 65: 274–281
- Becker B, Kronenberg F, Kielstein JT *et al.* Renal insulin resistance syndrome, adiponectin and cardiovascular events in patients with kidney disease: the mild and moderate kidney disease study. *J Am Soc Nephrol* 2005; 16: 1091–1098
- Menon V, Li L, Wang X *et al.* Adiponectin and mortality in patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2599–2606
- Catena C, Soardo G, Melis A *et al.* Glucose metabolism in early renal failure. *Am J Kidney Dis* 2005; 46: 367; author reply -8.
- Eidemark I, Feldt-Rasmussen B, Kanstrup IL *et al.* Insulin resistance and hyperinsulinaemia in mild to moderate progressive chronic renal failure and its association with aerobic work capacity. *Diabetologia* 1995; 38: 565–572
- Crutchlow MF, Robinson B, Pappachen B *et al.* Validation of steady-state insulin sensitivity indices in chronic kidney disease. *Diabetes Care* 2007; 30: 1813–1818
- Foss MC, Gouveia LM, Moyses Neto M *et al.* Effect of hemodialysis on peripheral glucose metabolism of patients with chronic renal failure. *Nephron* 1996; 73: 48–53
- Di Mauro M, Papalia G, Le Moli R *et al.* Effect of octreotide on insulin requirement, hepatic glucose production, growth hormone, glucagon and c-peptide levels in type 2 diabetic patients with chronic renal failure or normal renal function. *Diabetes Res Clin Pract* 2001; 51: 45–50
- Kobayashi S, Maesato K, Moriya H *et al.* Insulin resistance in patients with chronic kidney disease. *Am J Kidney Dis* 2005; 45: 275–280
- Okada K, Takahashi Y, Okawa E *et al.* Relationship between insulin resistance and uremic toxins in the gastrointestinal tract. *Nephron* 2001; 88: 384–386
- Sautin YY, Nakagawa T, Zharikov S *et al.* Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 2007; 293: C584–C596
- Axelsson J, Bergsten A, Qureshi AR *et al.* Elevated resistin levels in chronic kidney disease are associated with decreased glomerular filtration rate and inflammation, but not with insulin resistance. *Kidney Int* 2006; 69: 596–604
- Tirirogoff ML, Shintani A, Himmelfarb J *et al.* Body mass index and fat mass are the primary correlates of insulin resistance in nondiabetic stage 3–4 chronic kidney disease patients. *Am J Clin Nutr* 2007; 86: 1642–1648
- Sanches FM, Avesani CM, Kamimura MA *et al.* Waist circumference and visceral fat in CKD: a cross-sectional study. *Am J Kidney Dis* 2008; 52: 66–73

34. Siew ED, Pupim LB, Majchrzak KM *et al.* Insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. *Kidney Int* 2007; 71: 146–152
35. Lee SW, Park GH, Lee SW *et al.* Insulin resistance and muscle wasting in non-diabetic end-stage renal disease patients. *Nephrol Dial Transplant* 2007; 22: 2554–2562
36. Bailey JL, Zheng B, Hu Z *et al.* Chronic kidney disease causes defects in signaling through the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. *J Am Soc Nephrol* 2006; 17: 1388–1394
37. Honda H, Qureshi AR, Axelsson J *et al.* Obese sarcopenia in patients with end-stage renal disease is associated with inflammation and increased mortality. *Am J Clin Nutr* 2007; 86: 633–638
38. Stenvinkel P, Ketteler M, Johnson RJ *et al.* IL-10, IL-6, and TNF- $\alpha$ : central factors in the altered cytokine network of uremia—the good, the bad, and the ugly. *Kidney Int* 2005; 67: 1216–1233
39. Ghanim H, Aljada A, Daoud N *et al.* Role of inflammatory mediators in the suppression of insulin receptor phosphorylation in circulating mononuclear cells of obese subjects. *Diabetologia* 2007; 50: 278–285
40. Arkan MC, Hevener AL, Greten FR *et al.* IKK- $\beta$  links inflammation to obesity-induced insulin resistance. *Nat Med* 2005; 11: 191–198
41. Dounousi E, Papavasiliou E, Makedou A *et al.* Oxidative stress is progressively enhanced with advancing stages of CKD. *Am J Kidney Dis* 2006; 48: 752–760
42. Kurata A, Nishizawa H, Kihara S *et al.* Blockade of angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation. *Kidney Int* 2006; 70: 1717–1724
43. Barazzoni R, Bernardi A, Biasia F *et al.* Low fat adiponectin expression is associated with oxidative stress in nondiabetic humans with chronic kidney disease—impact on plasma adiponectin concentration. *Am J Physiol Regul Integr Comp Physiol* 2007; 293: R47–R54
44. Richardson DK, Kashyap S, Bajaj M, *et al.* Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle. *J Biol Chem* 2005; 280: 10290–10297
45. Li M, Kim DH, Tsenovoy PL *et al.* Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. *Diabetes* 2008; 57: 1526–1535
46. Ramos LF, Shintani A, Ikizler TA *et al.* Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 2008; 19: 593–599
47. Axelsson J, Rashid Qureshi A, Suliman ME *et al.* Truncal fat mass as a contributor to inflammation in end-stage renal disease. *Am J Clin Nutr* 2004; 80: 1222–1229
48. Raj DS, Dominic EA, Pai A *et al.* Skeletal muscle, cytokines, and oxidative stress in end-stage renal disease. *Kidney Int* 2005; 68: 2338–2344
49. Zhang Y, Proenca R, Maffei M *et al.* Positional cloning of the mouse gene and its human homologue. *Nature* 1994; 372: 425–432
50. Berg AH, Combs TP, Du X *et al.* The adipocyte-secreted protein Acrp 30 enhances hepatic insulin action. *Nat Med* 2001; 7: 947–953
51. Yamauchi T, Kamon J, Waki H *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipohypertrophy and obesity. *Nat Med* 2001; 7: 887–888
52. Ouchi N, Kihara S, Arita Y *et al.* Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- $\kappa$ B signalling through a cAMP-dependent pathway. *Circulation* 2000; 102: 1296–1301
53. Arita Y, Kihara S, Ouchi N *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Comm* 1999; 257: 79–83
54. Iwashima Y, Horio T, Kumada M *et al.* Adiponectin and renal function, and implication as a risk of cardiovascular disease. *Am J Cardiol* 2006; 98: 1603–1608
55. Qi L, Doria A, Manson JE *et al.* Adiponectin genetic variability, plasma adiponectin, and cardiovascular risk in patients with type 2 diabetes. *Diabetes* 2006; 55: 1512–1516
56. Zoccali F, Mallamaci F, Tripepi G *et al.* Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002; 13: 134–141
57. Tsao TS, Tomas E, Murrey HE *et al.* Role of disulfide bonds in Acrp30/adiponectin structure and signaling specificity. Different oligomers activate different signal transduction pathways. *J Biol Chem* 2003; 278: 50810–50817
58. Yamauchi T, Nio Y, Maki T *et al.* Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med* 2007; 13: 332–339
59. Shen YY, Charlesworth JA, Kelly JJ *et al.* Up-regulation of adiponectin, its isoforms and receptors in end-stage kidney disease. *Nephrol Dial Transplant* 2007; 22: 171–178
60. Bluher M, Williams CJ, Klöting N *et al.* Gene expression of adiponectin receptors in human visceral and subcutaneous adipose tissue is related to insulin resistance and metabolic parameters and is altered in response to physical training. *Diabetes Care* 2007; 30: 3110–3115
61. Stenvinkel P, Lindholm B, Lönnqvist F *et al.* Increases in serum leptin during peritoneal dialysis are associated with inflammation and a decrease in lean body mass. *J Am Soc Nephrol* 2000; 11: 1303–1309
62. Pecoits-Filho R, Nordfors L, Heimbürger O *et al.* Soluble leptin receptors and serum leptin in end-stage renal disease: relationship with inflammation and body composition. *Eur J Clin Invest* 2002; 32: 811–817
63. Don BR, Rosales LM, Levine NW *et al.* Leptin is a negative acute phase protein in chronic hemodialysis patients. *Kidney Int* 2001; 59: 1114–1120
64. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005; 115: 1111–1119
65. Axelsson J, Qureshi AR, Heimbürger O *et al.* Body fat mass and serum leptin levels influence epoetin sensitivity in patients with ESRD. *Am J Kidney Dis* 2005; 46: 628–634
66. Hung SC, Tung TY, Yang CS *et al.* High-calorie supplementation increases serum leptin levels and improves response to rHuEPO in long-term hemodialysis patients. *Am J Kidney Dis* 2005; 45: 1073–1083
67. Cioffi JA, Shafer AW, Zupancic TJ *et al.* Novel B219/OB receptor isoforms: possible role of leptin in hematopoiesis and reproduction. *Nat Med* 1996; 2: 585–589
68. Beddhu S, Kimmel PL, Ramkumar N *et al.* Associations of metabolic syndrome with inflammation in CKD: results from the third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 2005; 46: 577–586
69. Cheung W, Yu PX, Little BM *et al.* Role of leptin and melanocortin signaling in uremia-associated cachexia. *J Clin Invest* 2005; 115: 1659–1665
70. Mak RH, Cheung W, Cone RD *et al.* Leptin and inflammation-associated cachexia in chronic kidney disease. *Kidney Int* 2006; 69: 794–797
71. Cheung WW, Rosengren S, Boyle DL *et al.* Modulation of melanocortin signaling ameliorates uremic cachexia. *Kidney Int* 2008; 74: 180–186
72. Yang H, Yang T, Baur JA *et al.* Nutrient-sensitive mitochondrial NAD<sup>+</sup> levels dictate cell survival. *Cell* 2007; 130: 1095–1107
73. Fukuhara A, Matsuda M, Nishizawa M *et al.* Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science* 2005; 307: 426–430
74. Chen MP, Chung FM, Chang DM *et al.* Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2006; 91: 295–299
75. Zhang YY, Gottardo L, Thompson R *et al.* A visfatin promoter polymorphism is associated with low-grade inflammation and type 2 diabetes. *Obesity (Silver Spring)* 2006; 14: 2119–2126
76. Berndt J, Klöting N, Kralisch S *et al.* Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes* 2005; 54: 2911–2916

77. Lopez-Bermejo A, Chico-Julia B, Fernandez-Balsells M *et al.* Serum visfatin increases with progressive beta-cell deterioration. *Diabetes* 2006; 55: 2871–2875
78. Revollo JR, Korner A, Mills KF *et al.* Nampt/PBEF/visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab* 2007; 6: 363–375
79. Yilmaz MI, Saglam M, Carrero JJ *et al.* Serum visfatin concentration and endothelial dysfunction in chronic kidney disease. *Nephrol Dial Transplant* 2008; 23: 959–965
80. Axelsson J, Witasp A, Carrero JJ *et al.* Circulating levels of visfatin/pre-B-cell colony-enhancing factor 1 in relation to genotype, GFR, body composition, and survival in patients with CKD. *Am J Kidney Dis* 2007; 49: 237–244
81. Yilmaz MI, Saglam M, Qureshi AR *et al.* Endothelial dysfunction in type-2 diabetics with early diabetic nephropathy is associated with low circulating adiponectin. *Nephrol Dial Transplant* 2008; 23: 1621–1627
82. Stenvinkel P. Inflammation in end-stage renal disease—a fire that burns within. *Contrib Nephrol* 2005; 149: 185–199
83. Wellen KE, Fucho R, Gregor MF *et al.* Coordinated regulation of nutrient and inflammatory responses by STAMP2 is essential for metabolic homeostasis. *Cell* 2007; 129: 537–548
84. Charriere G, Cousin B, Arnaud E *et al.* Preadipocyte conversion to macrophage. Evidence of plasticity. *J Biol Chem* 2003; 278: 9850–9855
85. Axelsson J, Qureshi AR, Suliman ME *et al.* Truncal fat mass as a contributor to inflammation in end-stage renal disease. *Am J Clin Nutr* 2004; 80: 1222–1229
86. Axelsson J, Wang X, Ketteler M *et al.* Is Fetuin-A/alpha2-Heremans-Schmid glycoprotein associated with the metabolic syndrome in patients with chronic kidney disease? *Am J Nephrol* 2008; 28: 669–676
87. Fain JN, Madan AK, Hiler ML *et al.* Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* 2004; 145: 2273–2282
88. Clement K, Viguerie N, Poitou C *et al.* Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *Faseb J* 2004; 18: 1657–1669
89. Axelsson J, Moller HJ, Witasp A *et al.* Changes in fat mass correlate with changes in soluble sCD163, a marker of mature macrophages, in patients with CKD. *Am J Kidney Dis* 2006; 48: 916–925
90. Lee NK, Sowa H, Hinoi E *et al.* Endocrine regulation of energy metabolism by the skeleton. *Cell* 2007; 130: 456–469
91. Griffith JF, Yeung DK, Antonio GE *et al.* Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy. *Radiology* 2005; 236: 945–951
92. Di Iorgi N, Rosol M, Mittelman SD *et al.* Reciprocal relation between marrow adiposity and the amount of bone in the axial and appendicular skeleton of young adults. *J Clin Endocrinol Metab* 2008; 93: 2281–2286
93. Schiller PC, D'Ippolito G, Brambilla R *et al.* Inhibition of gap-junctional communication induces the trans-differentiation of osteoblasts to an adipocytic phenotype *in vitro*. *J Biol Chem* 2001; 276: 14133–14138
94. Shinoda Y, Yamaguchi M, Ogata N *et al.* Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. *J Cell Biochem* 2006; 99: 196–208
95. Gordeladze JO, Drevon CA, Syversen U *et al.* Leptin stimulates human osteoblastic cell proliferation, *de novo* collagen synthesis, and mineralization: impact on differentiation markers, apoptosis, and osteoclastic signaling. *J Cell Biochem* 2002; 85: 825–836
96. Tobian L. Hypertension and obesity. *N Engl J Med* 1978; 298: 46–48
97. Sarzani R, Salvi F, Dessi-Fulgheri P *et al.* Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. *J Hypertens* 2008; 26: 831–843
98. Alvarez GE, Beske SD, Ballard TP *et al.* Sympathetic neural activation in visceral obesity. *Circulation* 2002; 106: 2533–2536
99. Nogueiras R, Wiedmer P, Perez-Tilve D *et al.* The central melanocortin system directly controls peripheral lipid metabolism. *J Clin Invest* 2007; 117: 3475–3488
100. Gadegbeku CA, Shrayyef MZ, LaPorte FB *et al.* Lipids enhance alpha1-adrenoceptor pressor sensitivity in patients with chronic kidney disease. *Am J Kidney Dis* 2004; 44: 446–454

Received for publication: 3.5.08

Accepted in revised form: 12.6.08