

Editorial Comment

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

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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

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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- β [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- α 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 β -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 β -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 α 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.

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