Adipose tissue in renal disease: clinical significance and prognostic implications

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Abstract
Obesity is not only associated with the development of diabetes and hypertension, but is also a known risk factor for chronic kidney disease (CKD) and is a risk factor for progressive renal function loss. Abdominal obesity is especially related to incident CKD and mortality. The decline in fat mass over time has also been related to mortality in this population. In patients on peritoneal dialysis, intra-abdominal fat accumulation has been related to cardiovascular morbidity and mortality. The body mass index is a simple method to estimate fat mass in dialysis patients. Maximum abdominal circumference, triceps and subscapular skinfolds, and arm circumference have been proposed as alternative methods in assessing subcutaneous adipose tissue to overcome the altered hydration status associated with dialysis. Waist-to-hip ratio, waist-to-height ratio and the conicity index are used to estimate abdominal fat deposits. Dual-energy X-ray absorptiometry, bioelectrical impedance analysis, computed tomography and magnetic resonance imaging are more precise and reliable methods to estimate body composition in dialysis patients. Adipose tissue is the source of a novel group of hormonally active substances known as adipokines. Patients with CKD exhibit an increase in serum concentration of most of these substances. Besides, the kidney plays an important role in the regulation of adipokines, and altered renal handling of these substances might contribute to an increase in the uraemia-associated increased risk of cardiovascular disease and mortality. In particular, pro-inflammatory adipokines, such as leptin, tumour necrosis factor-alpha and interleukin-6, have been associated with an increased risk of mortality, whereas the link between adiponectin, an antiatherogenic adipokine, and survival is controversial in patients with CKD.

Keywords: adipokines; adipose; disease; kidney; obesity

Introduction
Adipose tissue consists of fat cells (adipocytes) and a component stromal/vascular in which the preadipocytes are found. Normally, the cellular content of adipose tissue is ~50% adipocytes, the remaining 50% being the vascular stroma, fibroblasts, endothelial cells, macrophages and preadipocytes. There are two types of adipose tissue and, therefore, two different types of fat cells: (i) white adipose tissue, which is the most abundant in adult human body and therefore the largest energy reservoir, and (ii) brown adipose tissue, which is responsible for thermogenesis. Adipose tissue is more than a passive store of triglycerides since numerous cytokines, commonly known as adipokines, are released by fat tissue. Normally, 80% of adipose tissue is located in the subcutaneous tissue, while visceral adipose tissue (VAT) is <20%. The VAT is composed of adipocytes of smaller size and less storage capacity, which are more vascular, with increased sympathetic innervation and a large number of β3-adrenergic receptors, which facilitates a higher metabolic activity [1].

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 subcutaneous peripheral adipose tissue (SAT). In fact, VAT is considered an important and independent predictor of risk for coronary heart disease as other known risk factors such as insulin, insulin resistance, hypertension, impaired glucose tolerance, diabetes and dyslipidaemia [2–5]. VAT correlates directly with intrahepatic triglyceride content, a better marker of the metabolic derangements associated with obesity [6]. Other fat depots such as abdominal subcutaneous, intra-organ and peri-organ fat may have metabolic activity between that of peripheral subcutaneous fat and VAT. Different factors such as capacity of preadipocyte differentiation, adipocyte apoptosis, lipolysis, lipogenesis, adipocyte receptors, and cytokines and adipokines secretion are also different among several types of fat depots [1].

When fat cells enlarge, for unknown reasons, they secrete factors that attract inflammatory cells or macrophages, which in turn release toxic factors, such as interleukins, responsible for causing damage to the liver and other organs, such as arteries, and promote insulin resistance leading to type 2 diabetes [7–9].
Recent studies have reported that abdominal fat plays an important role in metabolic syndrome, because it is predictive of sensitivity to insulin and is closely related to the development of type 2 diabetes, heart disease and cardiovascular mortality independent of total body fat [10,11]. Similarly, it has been reported that obesity adversely affects renal function and may be associated with morbidity and mortality in patients with chronic kidney disease (CKD). The objectives of this review are: (i) to analyse the relationship between the quantity and distribution of adipose tissue and different renal diseases, and (ii) to assess the role of adipokines in patients with kidney disease.

Adipose tissue and renal disease

Obesity-associated kidney injury. Obesity may be associated with different renal lesions such as micro- and macroalbuminuria, nephrotic-range proteinuria, and renal macroalbuminuria, diabetic nephropathy, urolithiasis, and renal sclerosis, diabetic nephropathy, urolithiasis, and renal sclerosis. Obesity and the progression of renal cell carcinoma [32,33]. Obesity may be associated with obesity-associated proteinuria, only weight loss in early stages of the disease remains the most effective measure to control definitively these renal changes [12,15].

The prevalence of diabetes and hypertension increases in parallel with obesity, and these are well-known risk factors for kidney disease. The kidney of an obese subject is more vulnerable to damage from hypertension and diabetes. Furthermore, the prognosis of the diseases that initially affect only the kidney is less favourable when they appear in obese people [14].

A high body mass index (BMI) is associated with increased risk of symptomatic urolithiasis and recurrent stone formation [18–23]. The main pathogenic mechanisms by which obesity increases the risk of urolithiasis are the increased urinary excretion of lithogenic substances such as calcium, oxalate and uric acid secondary to a high food intake and the lower urine pH caused by deficient ammonia production probably related to insulin resistance [21,24]. Although weight control may be considered one of the preventive modalities against recurrent stone formation, especially in first-time stone formers [22], some types of hypocaloric diets, especially low-carbohydrate diets, increase the risk of both calcium and uric acid stones. Moreover, bariatric surgery may cause hyperoxaluria with associated stone formation and even oxalate nephropathy [21,22].

Recent studies have established that obesity increases the likelihood of developing several cancers; among them is renal cell carcinoma [25–27]. Several pathogenic mechanisms such as lipid peroxidation [28,29], hormonal changes (high leptin, insulin, oestrogen and low adiponectin) [28,30,31] and immune malfunction [28] associated with high BMI have been implicated. Low serum total and high-molecular-weight adiponectin levels have also been reported in patients with metastatic renal cell carcinoma, suggesting that adiponectin might be a molecular link between obesity and the progression of renal cell carcinoma [32].

Obesity and chronic kidney disease. A positive association between high BMI and risk for CKD has been reported [33,34]. A high BMI is associated with many complications such as hypertension, dyslipidaemia, hyperglycaemia, insulin resistance, and glomerular hyperperfusion and hyperfiltration resulting in renal injury with proteinuria ‘obesity-related glomerulopathy’ [35–37]. As occurs in the general population, obesity, a traditional risk factor for atherosclerosis, is associated with inflammation also in CKD patients [38]. BMI has been considered as a common, strong and potentially modifiable independent risk factor for CKD [33]. In a large study performed in 320 252 adult volunteers, the adjusted relative risk for end-stage renal disease (ESRD) was 3.6 (95% CI, 3.05–4.18) for those with class I obesity (BMI, 30.0–34.9 kg/m²), 6.1 (95% CI, 5.0–7.5) for those with class II obesity (BMI, 35.0–39.9 kg/m²) and 7.1 (95% CI, 5.4–9.30) for those with morbid obesity (BMI ≥40 kg/m²) compared with persons who had normal weight (BMI, 18.5–24.9 kg/m²). This finding persisted even after additional adjustments for baseline blood pressure level and presence or absence of diabetes mellitus [33]. These results have been recently confirmed by the same group which evaluated risk factors for ESRD in 177 570 individuals in a 25-year follow-up study. In this study, excess weight and proteinuria were the two most potent risk factors for ESRD [33]. Hormonal changes, low-grade inflammation, oxidative stress and endothelial dysfunction are the main possible pathogenic mechanisms of renal damage in obesity [34,39–41]. Although the association between high BMI and risk for CKD has been reported by others [34], not all studies have been able to demonstrate a significant association after adjusting for known cardiovascular disease risk factors, considering that such association might be mediated by cardiovascular risk factors [34]. Lastly, other studies have shown that abdominal adiposity measured by waist-to-hip ratio (WHR) [42] or waist circumference (WC) [43] is associated with incident CKD [42,43] and mortality [42] irrespective of general adiposity estimated by BMI. Moreover, central fat distribution is a risk factor for diminished filtration not only in overweight and obese subjects, but also in lean subjects [44].

Obesity is also a risk factor for progressive renal function loss in patients with known renal disease [40,45,46]. Elevated BMI may promote CKD onset or progression by several mechanisms. On one hand, kidneys from obese...
people suffer from circulatory overload favouring protein loss in urine. On the other hand, excess weight is often accompanied by alterations in glucose and lipid metabolism, diabetes and hypertension which can induce renal disease. Lastly, a low-grade inflammatory response occurs in obesity and insulin resistance that causes an increase in macrophage infiltration into the adipose tissue and the kidney. The infiltration of macrophages gives rise to the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), nuclear factor kappa B (NF-κB) and cellular adhesion molecules. Hyperleptinaemia associated with obesity can cause vascular remodelling and disruption of renal function. Hyperinsulinaemia induces relaxation of theafferent arteriole, resulting in glomerular hyperfiltration and renal damage, and also stimulates angiogenesis and mesangial cell proliferation, associated with the development of diabetic nephropathy [39].

Obesity is the aetiology of CKD of 15% in men and 11% in women. This excess risk for CKD among obese people appears mainly to be driven by a high prevalence of hypertension and/or type 2 diabetes. Obesity (BMI ≥30) patients at any age is 3–4 times more likely to develop CKD. The link between obesity and CKD is strongest for diabetes-related kidney disease [46].

Elevated blood pressure has been reported to be related to an increased VAT [5]. In rodent models, metabolic syndrome is associated with perivascular adipose inflammation and oxidative stress, hypertensive resistance artery remodelling, and endothelial dysfunction secondary to decreased nitric oxide [47]. VAT produces adipokines that contribute to the pathophysiologic renal haemodynamic and structural changes leading to obesity-related nephropathy [48]. It has been suggested that VAT may represent an important clinical target in the management of elevated blood pressure [5].

Low serum high-density lipoprotein (HDL) cholesterol level is common in CKD patients. Although high BMI values have been associated with low HDL cholesterol levels across a spectrum of estimated glomerular filtration rate (eGFR), the magnitude of this association diminishes at lower eGFR, suggesting that other factors might contribute to low HDL levels in advanced CKD patients [49].

**Adipose tissue, and morbidity and mortality in dialysis patients**

Obesity is associated with several metabolic and cardiovascular complications in the general population, including hypertension, type 2 diabetes mellitus, dyslipidaemia, obstructive sleep apnoea and sleep-disordered breathing, certain cancers, and major cardiovascular (CV) diseases (heart failure, coronary heart disease, sudden cardiac death and atrial fibrillation) [50,51]. Also in CKD, there is a well-known relationship between body fat depots and cardiovascular morbidity and mortality [52,54].

**Adipose tissue and haemodialysis.** A low body fat mass estimated by BMI together with other markers of protein-energy wasting (PEW) such as hypoalbuminaemia, low serum cholesterol levels and reduced dietary protein intake are important predictors of mortality in CKD populations not only in pre-dialysis stages but also in haemodialysis (HD) patients [52–54]. This fact is important because, although body fat mass increases significantly in the first year of maintenance HD, especially in patients with poor nutritional status [55], more than one-half of the HD patients older than 65 years are usually malnourished [56].

On the contrary, whereas BMI predicts mortality in the general population, some studies have reported that high body fat mass estimated by BMI (>25 kg/m²) is associated with a reduced all-cause and cardiovascular (CV) mortality in HD patients (‘obesity paradox’), i.e. a high BMI is incrementally associated with better survival [53,57–62]. It would indicate that fat mass rather than lean mass plays a protective role against mortality in HD patients [61]. Several causes have been proposed for this ‘obesity paradox’ in these patients. Among them are genetic, biochemical (adipocytokines), haemodynamic and neurohormonal factors [59]. However, we should be cautious in interpreting the ‘obesity paradox’ as a true fact, due to the many confounders that are likely to affect the outcome in large epidemiological studies underpinning this hypothesis, and the conflicting data from Europe [63,64] and US HD patients [65]. Pros and cons on whether epidemiological data derived from the healthy general population may or may not be applicable to ESRD have been recently analysed [66,67]. Some authors consider, on one hand, that adequate energy stores are necessary to survive semi-starvation associated with dialysis and, on the other, that some established risk factors related to obesity might be less relevant in dialysis patients [66]. However, other authors think that observed discrepancies between the general population and dialysis patients might be related to several factors such as observation time and age between the general population and dialysis patients, as well as differences in ethnicity and nutritional intake [67].

Fat mass change over time has been considered as a risk factor for mortality in HD patients and has been proposed as a useful parameter for measurement of nutritional status in these patients [54,68]. In a study performed in 190 HD female patients with a similar initial body fat mass and followed up for 5 years, the decrease in annual fat mass estimated by dual-energy X-ray absorptiometry (DXA) was a significant predictor of all-cause mortality [68].

Although VAT has been related to lipid and carbohydrate metabolism and atherosclerosis in HD patients [69], a close relationship between subcutaneous fat accumulation (SFA) and insulin resistance or atherosclerosis in these patients has also been recently reported, suggesting that SFA plays important roles related to carbohydrate or lipid metabolism in HD patients [70]. Lastly, abdominal fat deposition in HD patients has been reported to be linked to both inflammation and PEW, resulting in an increased mortality risk [71].

**Adipose tissue and peritoneal dialysis.** Unlike HD, peritoneal dialysis (PD) patients tend to gain weight after starting renal replacement therapy, probably as a result of continuous glucose absorption [72,73]. Administration of glucose-containing peritoneal dialysis solution increases lipogenesis in the liver [74]. This weight gain is mainly due to the intra-abdominal fat accumulation [73]. This fact
has been proposed as one of the mechanisms by which the risk to develop cardiovascular morbidity and mortality in PD patients could be increased [73]. However, the relationship between overweight and/or obesity and mortality in PD patients has not been clearly established [75–77].

It has been recently reported that the level of VAT is related to parameters that measure arterial stiffness and endothelial dysfunction in PD patients. In fact, VAT estimated by multiple-frequency bioelectrical impedance analysis (BIA) was associated with an increase in pulse-wave velocity and a reduction in brachial artery flow-mediated dilation [78]. These findings have led some authors to consider the visceral fat as a risk factor for cardiovascular disease in these patients.

**Quantification of adipose tissue in renal disease**

In CKD patients, adipose tissue can be estimated by means of anthropometric and body composition assessment (Table 1). Dialysis per se can present special problems for anthropometry, including decreased functional status and increased co-morbidity that challenge nutrition assessment methodology [79]. Due to the altered hydration status associated with dialysis, it is recommended that both anthropometric and body composition analysis measurements be performed after dialysis. In comparison with healthy persons of the same ages, HD patients usually are, on average, lighter with less adipose and muscle tissue [79–82]. Diabetes is associated with increased body fat content in dialysis patients [83,84]. On the other hand, time on dialysis is also negatively related to body fat, showing greater loss of fat mass in patients with longer duration of dialysis [79,82]. HEMO Study data provide a clinical reference for the use of anthropometric parameters in assessing the nutritional status in HD patients [82]. Although BMI or Quetelet index, defined as the individual’s body weight divided by the square of his or her height, does not actually measure the percentage of body fat, it provides a

### Table 1. Pros and cons for the different methods for measuring fat mass in patients with chronic kidney disease

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td><strong>Anthropometric parameters</strong></td>
<td></td>
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<tr>
<td>BMI</td>
<td>Good correlation with total body fat</td>
<td>Does not actually measure abdominal fat</td>
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<td></td>
<td>Simple, reproducible and cheap</td>
<td>Unable to distinguish muscle and fat compartments</td>
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<tr>
<td>Waist circumference</td>
<td>Simple, cheap and reliable marker of abdominal fat</td>
<td>Influenced by fluid status and sex variable over time</td>
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<td></td>
<td>Strongly correlated with visceral fat</td>
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<td></td>
<td>Associated to cardiovascular disease risk factors</td>
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<td></td>
<td>Correlation with HDL cholesterol, and HOMA in men and with age, CRP and HOMA in women</td>
<td></td>
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<tr>
<td>Waist-to-hip ratio</td>
<td>Less influenced by muscle and bone mass than BMI</td>
<td>Limited in peritoneal dialysis</td>
</tr>
<tr>
<td></td>
<td>Associated with cardiac events and mortality</td>
<td></td>
</tr>
<tr>
<td>TSF and SSF</td>
<td>Best parameters for measuring subcutaneous fat on the limbs and trunk, respectively</td>
<td>Influenced by fluid status, sex and age</td>
</tr>
<tr>
<td>MAC</td>
<td>Useful in estimating subcutaneous fat in dialysis</td>
<td>Careful technique and some experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Influenced by fluid status, sex and age</td>
</tr>
<tr>
<td><strong>Body composition assessment</strong></td>
<td>Excellent precision in the evaluation of body fat content and nutritional assessment</td>
<td>Expensive</td>
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<tr>
<td>DXA</td>
<td></td>
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<tr>
<td>BIA</td>
<td>Can be applied for assessing body fat in non-obese clinically stable non-dialysed CKD patients</td>
<td>Little value in situations such as dehydration, oedema and ascites</td>
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<tr>
<td><strong>Morphological studies</strong></td>
<td>Proper assessment of the distribution of subcutaneous and visceral fat</td>
<td>Expensive</td>
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<tr>
<td>Abdominal CT</td>
<td></td>
<td>Requires long exploration time</td>
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<tr>
<td></td>
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<td>Ionizing radiation exposure</td>
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<td></td>
<td></td>
<td>Not feasible in clinical practice</td>
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<tr>
<td>Abdominal MRI</td>
<td>Discriminates adipose tissue with great precision</td>
<td>Lower reproducibility than CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not feasible in clinical practice</td>
</tr>
</tbody>
</table>

BMI, body mass index; TSF, triceps skinfold; SSF, subscapular skinfold; MAC, mid-arm circumference; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; HD, haemodialysis; HDL, high-density lipoprotein; CRP, C-reactive protein; HOMA, Homeostasis Model Assessment Index; CKD, chronic kidney disease.
Table 2. Clinical significance of adipokines in chronic kidney disease

<table>
<thead>
<tr>
<th>Adipokines</th>
<th>Biological significance</th>
<th>Clinical significance in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Reflects the content of body fat</td>
<td>Markedly elevated serum level</td>
</tr>
<tr>
<td></td>
<td>Control food intake</td>
<td>Clinical marker of body fat content in dialysis</td>
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<tr>
<td></td>
<td>Appetite</td>
<td>Absence of relationship between leptin and anorexia in dialysis</td>
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<td></td>
<td>Energy expenditure</td>
<td>Low bone turnover in dialysis</td>
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<tr>
<td></td>
<td>Bone turn-over regulation</td>
<td>Influence EPO sensitivity in ESRD</td>
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<tr>
<td></td>
<td>Pro-inflammatory adipokine</td>
<td>Associated to inflammation, atherogenic lipid profile and insulin resistance in CKD</td>
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<tr>
<td></td>
<td></td>
<td>Low leptin is an independent risk factor for mortality in HD</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Increases insulin sensitivity</td>
<td>Elevated serum level</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory and anti-atherogenic adipokine</td>
<td>Inversely associated with metabolic risk factors in uraemia</td>
</tr>
<tr>
<td></td>
<td>Bone turnover regulation</td>
<td>Inversely associated with CV events in HD</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Energetic metabolism</td>
<td>Improved survival and better outcome in dialysis patients</td>
</tr>
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<td></td>
<td>Immunity</td>
<td>Elevated serum level</td>
</tr>
<tr>
<td></td>
<td>Mimics insulin action</td>
<td>Anorexigenic</td>
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<tr>
<td></td>
<td>Pro-inflammatory adipokine</td>
<td>Decreased circulating levels of amino acids and triacylglycerols</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Pro-inflammatory adipokine</td>
<td>Mortality predictor in CKD?</td>
</tr>
<tr>
<td></td>
<td>Implicated in pathogenesis of obesity and insulin resistance</td>
<td>Elevated serum level</td>
</tr>
<tr>
<td></td>
<td>Correlates with BMI and body fat and hyperinsulinaemia</td>
<td>Enhanced gene expression of TNF-α in circulating blood cells in uraemia</td>
</tr>
<tr>
<td>IL-6</td>
<td>Pro-inflammatory adipokine</td>
<td>Elevated TNF-α associated to: Increased mortality in HD</td>
</tr>
<tr>
<td></td>
<td>Hyperglycaemia and hyperinsulinaemia</td>
<td>Anorexia and a poor nutritional status in PD</td>
</tr>
<tr>
<td></td>
<td>Insulin resistance</td>
<td>Elevated serum levels</td>
</tr>
<tr>
<td></td>
<td>Correlates positively with human obesity and insulin resistance</td>
<td>Reliable predictor of mortality</td>
</tr>
<tr>
<td></td>
<td>Predictive of type 2 diabetes</td>
<td>Better mortality predictor than TNF-α in CKD and HD</td>
</tr>
<tr>
<td></td>
<td>Associated with the appearance of coronary heart disease events, congestive heart failure events and stroke events</td>
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<tr>
<td>Resistin</td>
<td>Regulation of metabolism</td>
<td>Elevated serum levels</td>
</tr>
<tr>
<td></td>
<td>Inhibition of adipogenesis and inflammation</td>
<td>Similar levels in both HD and PD</td>
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<td></td>
<td></td>
<td>Associated to heart disease in dialysis?</td>
</tr>
</tbody>
</table>

EPO, epoetin; ESRD, end-stage renal disease; CKD, chronic kidney disease; CV, cardiovascular; IL-6, interleukin-6; BMI, body mass index; TNF-α, tumour necrosis factor-alpha; HD, haemodialysis; PD, peritoneal dialysis.

good correlation with total body fat. BMI is an appropriate, simple and cheap measurement, and low BMI value is closely associated with mortality in HD patients [85]. For that reason, it is generally used as a vague means of estimating adiposity and is being widely used for identifying individuals with underweight, overweight or obesity. However, due to the fact that BMI is unable to distinguish muscle and fat compartments, some authors have proposed that maximum abdominal circumference (MAC), in addition to height and weight, be included in studies relating body composition to outcomes in HD patients because this measure provides a better estimate of the metabolically active VAT pool in these patients [86,87]. In CKD patients, WC has shown a strong association with VAT and has been associated with cardiovascular disease risk factors similar to those observed for VAT, particularly in men, suggesting that this anthropometric parameter might be a simple, reliable and inexpensive tool to be used in epidemiological studies in CKD patients [87].

Triceps (TSF) and subscapular (SSF) skinfolds are the best anthropometric parameters for measuring subcutaneous fat thickness on the limbs and trunk, respectively. TSF has a moderate accuracy and utility and a very high reliability in assessing SAT, whereas the accuracy, utility and reliability of SSF are only moderate [79]. Arm circumference (AC) is other anthropometric parameter that can also be useful in estimating the SAT in patients on dialysis [79].

Several parameters are being used for estimating abdominal fat deposition such as WHR, waist/height ratio, conicity index and several predictive equations by means of variables such as age, sex, and waist and hip circumferences [71,88–91].

Among the methods most commonly used to analyse body fat in dialysis patients through body composition analysis are DXA and BIA. DXA has been used for body composition analysis in dialysis patients and has shown an excellent precision in the evaluation of body composition, fat content and nutritional evaluation [92]. BIA calculates an estimate of total body water (TBW) by means of the analysis of the opposition to the flow of an electric current through body tissues. TBW is then used to estimate fat-free body mass and, by difference with body weight, body fat. For non-obese clinically stable non-dialysed CKD patients, anthropometric and BIA can be applied equally well for assessing body fat; however, a weak correlation has been reported for overweight/obese patients [93]. BIA equations usually estimate decreased fat mass index in ESRD patients when comparing with healthy population [94].
VAT and SAT have been associated with CKD when defined using cystatin C-estimating equations but not when using a creatinine-based estimating equation [95]. At present, abdominal fat distribution (VAT and SAT) can also be quantified by computed tomography (CT) scan [70] and magnetic resonance imaging (MRI) [96] at the level of the umbilicus in HD patients for estimating cardiovascular risk. However, these techniques are expensive and not feasible in clinical practice.

**Adipokines in chronic renal disease**

Adipose tissue is considered currently as a hormonally active system in the control of metabolism and not only as a store of excess energy. It is the source of a number of pro-inflammatory adipokines, such as leptin, resistin, tumour necrosis factor-α (TNF-α) and IL-6, as well as one anti-inflammatory adipokine, adiponectin. Previous studies have found that ESRD patients have markedly increased circulating levels of pro-inflammatory and anti-inflammatory adipokines [97,98]. It might be due to an increase in their systemic production, a decreased renal degradation and an increased infiltration of adipose tissue by immunocompetent cells (CD68) with an increased expression of some, but not all, pro-inflammatory cytokines such as TNF-α [97–99]. In this setting, ESRD could lead to retention of pro-inflammatory adipokines, thus generating adipokine imbalance, and could lead to contribution to wasting, atherosclerosis and insulin resistance [57,100,101]. Adipokines influence systemic inflammation, endothelial health and appetite in CKD patients, and have been considered as morbi-mortality risk factors in both HD [102–104] and PD [72,105] patients (Table 2).

**Leptin.** The *ob* gene product leptin, a 16-kDa protein containing 167 amino acids, is secreted by adipocyte and reflects the content of body fat. This adipokine is related to the control of food intake, appetite and energy expenditure. Leptin has also been considered as a pro-inflammatory adipokine. It has been reported that an association between leptin and metabolic risk factors such as BMI, WC and high-sensitivity C-reactive protein (hsCRP) revealed a close link between metabolic syndrome, obesity and inflammation [106]. Some studies performed in type 2 diabetic patients have reported that leptin is regulated or affected by multiple factors including renal function [107].

Sera leptin concentrations are markedly elevated in CKD [108–113]. The kidney is not only a site of leptin metabolism but also a target organ for leptin action. In fact, leptin stimulates cellular proliferation, TGF-β1 synthesis and type IV collagen production in glomerular endothelial cells. Conversely, in mesangial cells, leptin upregulates synthesis of the TGF-β type II receptor, but not TGF-β1, and stimulates glucose transport and type I collagen production through signal transduction pathways involving phosphatidylinositol-3-kinase. These data suggest that leptin triggers a paracrine interaction in which glomerular endothelial cells secrete TGF-β1 to which sensitized mesangial cells may respond [114].

Recent studies have shown that adipokines may influence bone turnover [57]. Leptin is a major regulator of bone remodelling through a hypothalamic relay and by using two neural mediators: the sympathetic tone, and cocaine- and amphetamine-regulated transcript (CART), a brain-located peptide, both acting on the osteoblast [115,116]. This regulation of bone remodelling by leptin implies that bone may exert a feedback control of energy homeostasis [117]. On the other hand, leptin stimulates human erythroid development *in vitro* [118], and body fat mass and serum leptin levels influence epoetin sensitivity in patients with ESRD [119]. A reciprocal relationship between bone marrow adiposity and bone loss has been suggested [117,120].

Although leptin acts negatively on appetite, most studies have failed to demonstrate any relationship between leptin and anorexia in dialysis patients [121]. As occurs in healthy individuals, leptin correlates positively with body fat in CKD patients [110,112]. This hormone serves as a useful clinical marker of body fat content in both HD [109] and PD [108] patients. Moreover, leptin correlates strongly to changes in body fat during 12 months after starting PD [112]. On the other hand, leptin has also been associated with inflammation in CKD [122]. Uraemic patients with ongoing signs of inflammation (hsCRP levels) show higher serum leptin levels than patients with normal CRP [112].

An inverse association between leptin, bone mass and PTH in dialysis patients has been reported, suggesting that leptin may be implicated in low bone turnover in these patients [123]. Increases in serum leptin during PD are associated with inflammation and a decrease in lean body mass. Leptin has also been associated with atherogenic lipid profile and insulin resistance in CKD patients. In fact, leptin independently predicted total cholesterol and triglycerides [111], and correlated with plasma insulin concentrations independent of body fat content in CKD [124]. All these observations may contribute to the elevated cardiovascular risk that has been linked to hyperleptinaemia in CKD patients. On the other hand, a prospective long-term study in patients with CKD stage 5 on HD showed that reduced serum leptin concentration is also an independent risk factor for mortality in these patients [125], confirming that underweight is a mortality risk factor in this population.

**Adiponectin.** Adiponectin, a 26.4-kDa protein containing 244 amino acids specifically expressed in human adipose cells, is the most abundant adipokine in human plasma. This adipocyte-derived hormone increases insulin sensitivity and has anti-inflammatory and anti-atherogenic properties. Adiponectin has been shown to correlate negatively with glucose, insulin, triglyceride levels and BMI, and positively with high-density lipoprotein cholesterol levels and insulin-stimulated glucose disposal [126,127].

Serum adiponectin is invariably elevated in CKD [102–105,110,128–131]. In type 2 diabetic nephropathy, serum adiponectin levels are strongly and positively associated with fasting insulin levels and insulin resistance [132]. In uraemic patients, this adipokine is also inversely associated with metabolic risk factors, such as body mass index, blood glucose, insulin concentrations, and levels triglyceride and HDL cholesterol levels [128].

Adiponectin also plays a role in the regulation of bone turnover [133]. In a recent study, adiponectin was an independent predictor of bone mineral density in post-
Visfatin. Visfatin is an adipocytokine highly enriched in the visceral fat of both humans and mice, and whose expression and plasma levels increase during the development of obesity. It was isolated and identified recently by Fukuhara et al. [137]. Visfatin corresponds to a protein identified previously as pre-B-cell colony-enhancing factor (PBEF), a 52-kDa cytokine expressed in lymphocytes [138]. Apart from adipocytes, macrophages, dendritic cells and colonic epithelial cells might be additional sources of visfatin. In their initial study, Fukuhara et al. [137] found that visfatin exerted insulin-mimetic actions in cultured cells and lowered plasma glucose levels in mice. Mice heterozygous for a targeted mutation in the visfatin gene had modestly higher levels of plasma glucose relative to wild-type littermates. Surprisingly, these authors also found that visfatin was bound to an activated insulin receptor. Subsequent studies of visfatin in humans have generally not confirmed this initial study, which was, in part, retracted [139]. Visfatin is nowadays considered as a new pro-inflammatory cytokine with functions related to energetic metabolism, immunity and insulin action. Inside the cells, visfatin acts as a nicotinamide phosphoribosyltransferase involved in the biosynthesis of NAD⁺, thus exercising influence on cell energetic metabolism and the activity of NAD⁺/NADH-dependent enzymes [140]. Outside the cells, visfatin acts as an inducer of both pro- and anti-inflammatory cytokine expressions [141]. In CD14(+) monocytes, visfatin induces the production of IL-1β, TNF-α and especially IL-6. Moreover, it increases the surface expression of co-stimulatory molecules CD54, CD40 and CD80. Visfatin-induced effects involve p38 as well as MEK1 pathways as determined by inhibition with MAPK inhibitors, and an activation of NF-κB has also been observed [141]. Axelsson et al. [142] studied 189 patients with CKD and found that visfatin levels were greater in patients with CKD stage 5 than in those with CKD stages 3–4 or healthy controls. However, there were no significant differences between patients with and without diabetes. Visfatin level correlated with IL-6, hsCRP and soluble vascular cell adhesion molecule-1 (sVCAM-1), but not total or truncal fat mass, insulin resistance, or haemoglobin A1c level. Besides, high plasma visfatin level predicted mortality in patients with CKD after adjustment for age and sex, but not after additional correction for GFR, sVCAM-1, serum albumin and serum IL-6 levels. These authors suggest that circulating levels of visfatin are influenced by renal function but are not associated with fat mass or surrogate markers of insulin resistance in patients with CKD [142]. More recently, there have been reported novel links between visfatin and anorexia in CKD patients. Elevated circulating visfatin was associated with self-reported appetite loss and decreased circulating levels of amino acids and triglycerides in advanced CKD patients [143]. In summary, visfatin is able, on one hand, to bind to the insulin receptor and mimic insulin actions, and on the other hand, may induce the expression of IL-6 and other pro-inflammatory cytokines contributing to insulin resistance and vascular damage. Further studies are needed to understand the role of visfatin in the control of appetite in uraemia.

Interleukin-6. IL-6 is a pro-inflammatory cytokine similar to TNF-α that is not exclusively expressed in adipose tissue, although it is estimated that ~25% of systemic IL-6 is secreted by subcutaneous fat cells [152]. Visceral fat has a greater capacity to produce IL-6 in comparison with subcutaneous fat in vitro [153]. IL-6 circulates in multiple glycosylated forms ranging from 22 to 27 kDa and is a...
pleiotropic circulating cytokine with multiple effects ranging from inflammation to host defence and tissue injury.

Some epidemiological studies have suggested that plasma IL-6 concentrations correlate positively with human obesity and insulin resistance, and high IL-6 levels are predictive of type 2 diabetes [154]. IL-6 has been proposed to affect glucose homeostasis and metabolism directly and indirectly by action on skeletal muscle cells, adipocytes, hepatocytes, pancreatic beta-cells and neuroendocrine cells. IL-6 action contributes to, but is probably neither necessary nor sufficient for, the development of diabetes [155].

Several investigations have been reported showing that IL-6 serum concentrations are reliable predictors of mortality in patients with end-stage renal disease [156–160]. A recent survey, including a group of 120 HD patients, has shown that mortality was significantly higher in patients with IL-6 above the median value and also in subjects with TNF-α above the median values, with hazard ratio values of 6.38 and 4.56, respectively, thus suggesting that IL-6 is a better predictor of mortality than TNF-α in HD population [161]. A better predictor value for IL-6 in comparison with TNF-α has been confirmed in another survey of 125 patients with CKD at stages 2–5 [162].

Resistin. Resistin has been identified as a novel adipose-specific cysteine-rich protein. It is a 12.5-kDa polypeptide [163]. This adipokine has been involved in the regulation of metabolism, inhibition of adipogenesis and inflammation [164]. Resistin levels have been shown to be increased in patients with moderate renal failure, and this increase has been inversely related to glomerular filtration rate in patients with moderate renal failure, and this increase was associated with worse 1-year mortality in HD patients in the DOPPS database [165]. Dialysis (HD and PD) patients exhibit similar resistance to insulin compared with non-dialysis patients, and this resistance is associated with TNF-α and resistin, insulin resistance and vascular endothelial dysfunction in obese subjects. Arterioscler Thromb Vasc Biol 2008; 28: 1654–1659.


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ADQI 7: the clinical management of the Cardio-Renal syndromes: work group statements from the 7th ADQI consensus conference


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Introduction

Many patients with heart failure have underlying renal dysfunction, and similarly, patients with kidney failure are prone to cardiac failure. This has led to the concept of cardio-renal syndromes, which can be an acute or chronic cardio-renal syndrome, when cardiac failure causes deterioration in renal function, or acute and/or chronic Reno-Cardiac syndrome, when renal dysfunction leads to cardiac failure. Patients who develop these syndromes have increased risk of hospital admission and mortality. Although there are clinical guidelines for managing both heart failure and chronic kidney disease, there are no agreed guidelines for managing patients with cardio-renal and/or Reno-Cardiac syndromes, as these patients have typically been excluded from clinical trials. We have therefore reviewed the currently available published literature to outline a consensus of current best clinical practice for these patients.