Subclinical versus overt obesity in dialysis patients: more than meets the eye

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ABSTRACT

Background. Obesity is an important problem in the epidemic of chronic kidney disease (CKD). Obesity is usually diagnosed by body mass index (BMI), but this metric has limitations as a measure of adiposity in CKD patients. Simple anthropometric tools, like skinfold thickness measurements, have been shown to be a better test to classify obesity among those with CKD.

Methods. The prevalence of obesity was estimated by BMI (>30 kg/m²) and by skinfold thickness-estimated body fat (>25% in men and 35% in women) in two cohorts comprising 284 incident dialysis and 209 prevalent haemodialysis (HD) patients from Sweden. Patient characteristics were compared among individuals with differing diagnosis.

Results. BMI obesity cut-offs misdiagnosed many patients (>50%) with excess adiposity. Obesity, estimated by BMI, was present in 9% and 10% of incident and prevalent dialysis patients, respectively. When estimated by percentage of body fat, the prevalence of obesity rose to 64% and 65%. In both cohorts, a large proportion of patients (55%) were obese in the context of a normal BMI (termed as subclinical obesity).

Conclusion. A BMI of <30 kg/m² does not exclude the presence of excess adiposity. Subclinical obesity is a frequent condition in dialysis patients, and the clinical consequences of this finding deserve further consideration.

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health and/or reduce life expectancy. Currently, both overweight and obesity are the most common nutritional disorders in chronic kidney disease (CKD), and constitute an important risk factor in the CKD epidemic [1]. It has been proposed that the diagnosis of obesity can be inferred when the percentage of body fat exceeds 25% in men and 35% in women [2, 3]. An inherent problem with this definition is that gold standard measurements of body fat are problematic to perform in...
clinical practice. Because of the simplicity and ease of routine assessment, people are considered obese when their body mass index (BMI) exceeds 30 kg/m² [4]. This metric is recommended for nutritional assessment in guidelines on nutrition in CKD as well [5].

BMI, however, is an imperfect measure of excess fat. The main limitation of BMI is that it represents a composite measure of both lean and fat tissue, and therefore, the diagnosis of obesity by this technique is influenced by determinants of muscle mass, such as sex, ethnicity, age and health status. This is of relevance in the context of CKD, as most of these patients are elderly and frail with reduced muscle mass. In addition, the hydration status in CKD patients exerts an obvious influence [6]. The weaknesses of BMI as a metric of body fat in CKD patients were shown by Agarwal et al. [7] in US non-dialysed CKD patients, whereby a BMI of >30 kg/m² misclassified as many as 25% of the individuals when compared against the gold-standard technique of air-displacement plethysmography. This study was important because it showed that the vast majority of screened CKD patients were obese by means of excess body fat mass. In addition, this study also demonstrated that a simple anthropometric estimate of body fat using the skinfold thickness was an excellent discriminator of fat mass excess and could be used to better study obesity in CKD patients. The prevalence and clinical characteristics of obesity as estimated by fat mass excess are unknown in patients with end-stage renal disease (ESRD) undergoing dialysis. In this study, we assessed the diagnosis of obesity by both BMI and skinfold thickness in two independent cohorts of dialysis patients. Patient characteristics were compared among individuals with differing diagnosis.

**Materials and Methods**

**Patients**

This is a post-hoc, cross-sectional observational study performed in two different patient cohorts with CKD stage ≥5 [8, 9]. For the purposes of this analysis, patients were included if data on the primary variables of the study (BMI and skinfold thickness) were available. The first cohort is composed of CKD stage ≥5 patients referred to start dialysis therapy at the Department of Renal Medicine at Karolinska University Hospital Huddinge in Stockholm, Sweden [8]. Complete data of the primary variables were available for 284 individuals [128 men, median age 56 (10–90th percentile, 36–68) years old, glomerular filtration rate (GFR) 6.3 (3.7–9.0) mL/min]. The second cohort is composed of prevalent patients undergoing maintenance haemodialysis (HD) [10]. Complete data of the primary variables were available for 209 individuals [120 men, 67 (44–80) years old, dialysis vintage 28 (7–101) months]. Patient recruitment was performed at five dialysis units in Stockholm and one at the Uppsala Academic Hospital in Uppsala, Sweden. The protocol design of both patient materials has been described elsewhere in more detail [8–10]. The inclusion criteria in both cohorts were the absence of clinical signs of acute infection, active vasculitis, hepatitis or HIV at the time of evaluation and willingness to participate in the study. Additionally, only subjects aged ≤70 years were included in the incident cohort, whereas no age limit was considered in the prevalent cohort. Only patients on long-term HD (defined as >3 months on HD therapy) were included in the prevalent cohort. Most patients were on antihypertensive medications as well as phosphate and potassium binders, diuretics and vitamin supplementation in accordance with the clinical judgement of the treating physician. All subjects gave written informed consent, and the local ethical committees of the involved hospitals approved the protocols.

**Body composition and nutritional status**

Body weight, BMI (kg/m²) and anthropometric measurements were taken on a dialysis day immediately after the dialysis session for the prevalent HD patients, and for the incident dialysis patients, at the time of blood sample collection. Fat mass was assessed according to the formula of Durnin and Womersley [11], which is based on the four skinfold thicknesses (biceps, triceps, subscapular and suprailiac). The skinfold thickness was measured after the dialysis session when applicable in triplicates with a skinfold caliper (Cambridge Scientific Instruments, Cambridge, MD) by the same two well-trained and experienced nurses. The mid-arm circumference was measured with a plastic tape measure and normalized with measurements from healthy subjects [11]; the mid-arm circumference and triceps skinfold thickness were used to calculate the bone-free arm muscle area [11]. Handgrip strength was measured in triplicates using a Harpenden handgrip dynamometer (Yamar, Jackson, MI) in the dominant hand (in the incident dialysis cohort) or in the hand without a fistula (in the prevalent HD cohort). The average of the three measurements was computed and normalized with measurements from healthy subjects [11]. Subjective global assessment (SGA) [12] was performed on the same occasion as blood sampling and used as a surrogate of malnutrition (defined as an SGA >2). In addition, estimations of lean body mass and fat body mass by means of dual-energy X-ray absorptiometry (DEXA) using the DPX-L device (Lunar Corp, Madison, WI) were performed in the incident dialysis cohort.

**Blood sampling and biochemical measurements**

Blood samples were collected before the HD session after the longest interdialytic period for the prevalent HD patients or under fasting conditions for the incident dialysis patients and stored at −70°C if not analysed immediately. The GFR in incident dialysis patients was calculated from the mean of renal urea and creatinine clearances from a 24-h urine correction. In both cohorts, determinations of serum albumin (bromcresol purple) and cholesterol were performed by routine procedures in the Department of Clinical Chemistry at Karolinska University Hospital or Uppsala Academic Hospital. High sensitivity C-reactive protein (CRP) was measured by nephelometry. In prevalent HD patients only, insulin-growth factor (IGF)-1 was quantified in serum by commercial immunometric assays on an Immulite analyser (Siemens Medical Solutions Diagnostics, Los Angeles, CA).
Statistical analysis

Obesity was first defined with the established WHO cut-off of BMI ≥ 30 kg/m² [2]. In addition, the diagnosis of obesity, as assessed by skinfold thickness, was also considered when body fat exceeded 25% in men and 35% in women [2, 3]. We classified patients as ‘overt obese’ if they were considered so by both BMI and body fat composition. We classified patients as ‘subclinically obese’ if they were considered so only by skinfold thickness.

Normally distributed variables are expressed as mean ± SD and non-normally distributed variables are expressed as median and range (minimum and maximum) or interquartile range (25–75th percentile, IQR). Also, categorical values are expressed as number and percentage. Statistical significance was set at the level of P < 0.05. Bland and Altman plot analysis was applied to visually assess agreement between the DEXA-estimated and skinfold-estimated fat mass. The intra-class correlation coefficient (ICC) was used to test the reproducibility of the body measured by the DEXA and by skinfold. Coefficient values below 0.4 were considered indicative of poor reproducibility, values between 0.4 and 0.75, medium reproducibility and values above 0.75, good reproducibility. Comparison between the groups was done by the Kruskal–Wallis test or Chi-square analysis, as appropriate. Multivariable logistic regressions were fitted to study the association between the arm muscle area and obesity definitions. Statistical analyses were performed with statistical software using STATA Version 12.1 (Stata Corporation, College Station, TX).

RESULTS

Prevalence of overt and subclinical obesity in dialysis patients

In 284 incident dialysis patients, 25 (9%) were classified as obese based on BMI, while 164 (65%) were classified as obese based on their body fat composition. All individuals with a BMI of >30 kg/m² also had a body fat composition corresponding to obesity. Thus, 25 (9%) patients were considered overtly obese, while 159 (56%) were considered subclinically obese. The rest, i.e. 100 (35%) patients, were considered non-obese.

DEXA-estimated body fat was available in 234 of the incident dialysis patients. Body fat estimation by skinfold thickness was found to be in good agreement with DEXA measurements as shown by an ICC of 0.85 (95% CI 0.80–0.88). The Bland and Altman plot analysis showed that the mean difference between skinfold-derived and DEXA-derived fat body mass was −2 kg, while the 95% limits of agreements were 8.3 and −12 kg. No systematic error was observed between these methods (not shown). As a sensitivity analysis, when subclinical/overt obesity was defined according to DEXA-estimated percentage body fat, 20 (8%) patients were considered overt obese, while 103 (45%) were considered subclinically obese. The rest, i.e. 111 (47%) patients, were considered non-obese. As many as 28 patients classified as subclinically obese by skinfold thickness were considered non-obese by DEXA estimations.

In 209 prevalent HD patients, 23 (10%) were classified as obese according to the BMI, while 136 (65%) were classified as obese according to body fat composition. One patient with a BMI of >30 kg/m² had a body fat composition below the obesity cut-offs and was reclassified as non-obese. Thus, a total of 22 (10%) patients were considered overtly obese, while 114 (55%) were considered subclinically obese. The rest, i.e. 73 (35%) patients, were considered as non-obese.

Figure 1 shows the plot of BMI versus body fat for men and for women, combining both the cohorts. In men, the BMI misclassified 169 (59%) of obese individuals; in women, 104 (51%). There were no significant differences between sexes (chi square P = 0.08). We also studied the degree of misclassification among young and old (>60 years) patients. In young patients, the BMI misclassified 169 (59%) of obese individuals; in old patients, 84 (69%). The degree of misclassification by BMI was greater among the elderly (chi square P = 0.0005).

Clinical characteristics and body composition

To explore the determinants of subclinical obesity, Table 1 shows patient characteristics of incident dialysis patients
according to their obesity status. Body fat assessed by DEXA differed markedly among these three groups. When compared with non-obese patients, subclinically obese patients were older, more often diabetic and with history of cardiovascular disease (CVD). They also had higher cholesterol, triglycerides and CRP levels. They also presented with higher handgrip strength and arm muscle area values. When compared with overtly obese patients, subclinically obese individuals had lower muscle stores, depicted as reduced arm muscle area and a trend towards lower DEXA-estimated lean body mass.

Table 2 shows patient characteristics of prevalent dialysis patients according to their obesity status. When compared with non-obese patients, subclinically obese individuals were more often diabetic and presented with higher triglycerides and CRP levels. They also presented with higher handgrip strength and arm muscle area values. When compared with overtly obese patients, subclinically obese individuals had lower muscle stores, depicted as reduced arm muscle area and a trend towards lower DEXA-estimated lean body mass.

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We explored the strength of the association between the arm muscle area and the conditions of subclinical/overt obesity. For these analyses, non-obese patients were not included. Adjusted for age, sex, diabetes mellitus, CVD and GFR, a multivariable logistic regression model showed that, compared with overt obesity, the odds for subclinical obesity per 1 cm² reduced arm muscle area were 1.16 (95% CI 1.08–1.23, pseudo $r^2 0.30$) in the incident dialysis cohort and 1.08 (95% CI 1.05–1.11, pseudo $r^2 0.19$; instead of GFR, dialysis vintage was used as a covariate in the model) in the prevalent HD patients.

DISCUSSION

Because body fat is difficult to measure directly, the BMI is generally used in clinical practice to diagnose obesity. However, BMI does not only reflect fatness. At a community level, BMI correlates with percentage of body fat mass in a curvilinear fashion, being influenced by both sex and age; at an equivalent BMI, women and older persons have a higher percentage of body fat than men and younger persons. In addition, persons who have a large muscle mass can have an ‘obese’ BMI despite having a normal amount of body fat, while those with excess adiposity and reduced muscle mass can have a ‘normal’ BMI [10]. In CKD patients, additional issues such as volume overload and underlying protein-energy...
wasting may further limit the validity of BMI as a metric of adiposity [6, 7].

Our study shows that diagnosing obesity by BMI fails to detect a large number of people with excess body fat. The degree of misclassification of obesity by BMI was large and influenced, alike in the general population [2] by age and (to a lesser extent) by sex. Such observations expand the study of Agarwal et al. [7] in 77 non-dialysed CKD patients from the USA, where the prevalence of obesity as assessed by BMI was 65% but rose up to 90% when estimated by fat mass percentage. Altogether, our results in CKD patients are in line with observations at a general population level and summarized in the meta-analysis of Okorodudu et al. [3] who concluded that a BMI of >30 kg/m² has high specificity but low sensitivity to detect excess fatness.

Skinfold thickness is a non-invasive, inexpensive, and simple to implement technique that can be performed by an experienced operator in a few minutes. This method is not exempt, however, from limitations, and in particular skinfold thickness is subjected to technician’s error (intra and interobserver) and to the inherent difficulties of using the caliper in individuals with large amounts of adipose tissue or oedema. In our study, we tried to minimize these errors by performing the measurements in triplicate for each site, by the same two well-trained nurses and after the dialysis session when applicable. Accuracy limitations in obese individuals may have indeed occurred, but our study showed notwithstanding, that all BMI-obese individuals also had excess body fat. In our study, the agreement between skinfold-assessed body fat and DEXA estimations was relatively good but not precise, in accordance with preceding studies in pre-dialysis and dialysis patients [13–15]. In the study by Agarwal et al., skinfold thickness had a performance superior to that of BMI and of bioelectrical impedance measurements against air displacement plethysmography [8]. Although no assessment method is perfect, simplicity and availability is preferred in the clinical setting and skinfold thickness still gathers many advantages that justify its choice as a potential adjuvant in body composition assessment at the clinic [7,13,14,16].

Our study shows that a BMI of <30 kg/m² does not exclude the presence of excess fat in dialysis patients. Following a previously proposed nomenclature [7], we defined these two entities as ‘overt and subclinical obesity’. All BMI-obese individuals did have excess body fat, but a large proportion of patients presented excess fat in the context of a ‘normal’ BMI. The phenotype of these two entities was rather similar. Nevertheless, subclinically obese patients tended to be older, have more co-morbidity, as well as lower muscle mass stores and strength when compared with overtly obese patients. It is tempting to speculate that subclinically obese individuals fall into this category because of ageing and/or underlying muscle catabolism. Overtly obese individuals in our study did have

<table>
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<tr>
<th>Table 2: Clinical characteristics of 209 prevalent HD patients stratified according to the diagnosis of subclinical and overt obesity</th>
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<tr>
<td><strong>Number of patients, n (%)</strong></td>
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<td>---------------------------------------------------------------</td>
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<td>BMI, kg/m²</td>
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<td>Fat body mass, %</td>
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<td>Men, n (%)</td>
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<td>Diabetes Mellitus, n (%)</td>
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<td>Vintage, months</td>
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<td>Cholesterol, mmol/L</td>
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<td>Triglycerides, mmol/L</td>
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<td>CRP, mg/L</td>
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<td>Malnutrition (SGA), n (%)</td>
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<td>Albumin, g/L</td>
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<td>Handgrip strength, %</td>
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<td>Arm muscle area, cm²</td>
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<td>IGF-1, ng/mL</td>
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<td>*Different versus non-obese patients: *P &lt; 0.05, **P &lt; 0.01.</td>
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</table>
| †Different versus patients with subclinical obesity: †P < 0.05, ††P < 0.01; Categorical data are shown as a number of patients and percentage; continuous data as mean ± SD or median and interquartile range (25–75th percentiles), as appropriate.
larger stores of both muscle and fat, and tended to be better nourished according to SGA assessment, which could go in line with the protection conferred to these patients in the ‘survival obesity paradox’. Such thoughts would go in line with observational evidence showing that the survival advantage of high BMI in dialysis patients is not evident in older individuals [15], or that it is limited to those with normal or increased muscle mass [17, 18]. In non-CKD populations, subclinically obese patients were shown to present lower exercise capacity and increased CRP levels [19], higher prevalence of both metabolic syndrome and cardiovascular risk factors and, at least in women, higher risk of cardiovascular mortality [20].

Additional limitations of our study should be noted. First, the cross-sectional design provides associative, not causal, evidence. Second, there is no current consensus on the established healthy body fat ranges. The body fat categories used in our study were developed on the basis of age, sex and race and published healthy body fat ranges. The body fat categories used in the cross-sectional design provide associative, not causal, evidence showing that the waist circumference, a surrogate measure of abdominal body fat [22] or abdominal fat deposition by means of the conicity index [23], is associated with increased mortality irrespectively of BMI. The implications of subclinical obesity in CKD patients are unknown and warrant further investigation.

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CONFLICT OF INTEREST STATEMENT

B.L. is an employee of Baxter Healthcare Corporation BL.


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Resistin and all-cause and cardiovascular mortality: effect modification by adiponectin in end-stage kidney disease patients

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Keywords: adiponectin, end-stage kidney disease, interaction, mortality, resistin

ABSTRACT

Background. Resistin is a major adipose tissue cytokine implicated in insulin resistance, inflammation and vascular damage. This cytokine is raised in patients with end-stage kidney disease (ESKD) but the relationship between resistin and major clinical outcomes has not been investigated in this population.

Methods. We studied the mutual relationship between resistin and the two major adipokines (adiponectin and leptin) and the interaction between resistin and adiponectin (ADPN) and all-cause and cardiovascular (CV) mortality in a cohort of 231 haemodialysis patients followed up for 57 ± 44 months.