Wasting, but not malnutrition, predicts cardiovascular mortality in end-stage renal disease

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Beddhu et al. [1] recently have reported that there were no positive associations of malnutrition with documented acute coronary syndromes requiring hospitalization in a large incident Medicare dialysis population. The authors state that their findings do not support our suggestion [2] of an association between malnutrition, inflammation and atherosclerosis (MIA hypothesis) in patients with end-stage renal disease (ESRD). No doubt the study by Beddhu et al. [1] is a well performed study conducted in a large group of dialysis patients. However, we feel that some fundamental issues regarding the nomenclature and definition of ‘malnutrition’ need to be discussed. First, as discussed by Mitch [3], the use of the word ‘malnutrition’ has often been used incorrectly in the renal literature, and, according to Mitch, ‘malnutrition’ should be used to describe a deficient nutritional status caused by insufficient nutrient intake. However, literally, the word ‘malnutrition’ (derived from the latin word ‘malus’) means, ‘not correctly nourished’. Thus, both under- and over-nourished (obese) patients could be considered to be ‘maldernourished’. Secondly, whereas malnutrition is usually defined as a consequence of insufficient food intake and low serum protein levels, the loss of muscle mass (i.e. cachexia or wasting) in the ESRD patients is usually the consequence of a number of catabolic mechanisms stimulated by renal insufficiency. Indeed, the aetiology of loss of lean body mass in ESRD is very complex and may include numerous factors apart from poor food intake (i.e. true malnutrition), such as delayed gastric emptying, hormonal derangements, inadequate control of acidosis, co-morbidity and inflammation [3].

Whereas Beddhu et al. [1] used a low body mass index (BMI) and low creatinine excretion in urine as a marker of malnutrition, we used subjective global assessment (SGA). It is obvious that SGA and BMI are crude surrogate markers of nutritional status that cannot be readily compared. In our opinion, BMI is not a very precise parameter of nutritional status, especially in patients in whom gross imbalances in fluid homeostasis are commonly observed, such as in patients with ESRD, congestive heart failure and liver disease. Also, protein malnutrition with loss of muscle mass (sarcopenia) is often associated with a relatively well-preserved fat mass in dialysis patients, resulting in small changes in BMI that may be obscured further by imbalances in fluid homeostasis. In fact, as BMI alone does not always capture adequately the joint relationship of body composition and body size to outcome [4], the waist circumference may have more potential in detecting overweight than BMI [5]. Indeed, although there may be a marked statistical difference in BMI levels comparing ESRD patients classified as well nourished (SGA = 1) or malnourished (SGA ≥ 2), there is a considerable overlap between the two groups (Figure 1). Thus, patients considered to be malnourished according to SGA may have a low as well as a high BMI (Table 1). Clearly, high-BMI patients could also have an ongoing catabolic wasting process, and low-BMI patients may show no signs of catabolism.

To be able to compare the results presented by Beddhu et al. [1], we have analysed the independent predictive power of both BMI and SGA in 271 incident ESRD patients classified as well nourished (SGA = 1) or malnourished (SGA ≥ 2), starting renal replacement therapy (Table 1). During the observation period (3.7 ± 0.2 years; range 0.1–9.2 years), 94 patients died (66 of cardiovascular disease; CVD). Like Beddhu et al. [1], we divided the patients into three groups according to their BMI. Whereas no differences in the prevalence of diabetes mellitus, clinical overt CVD or inflammation [C-reactive protein (CRP) ≥ 10 mg/l] were noted between the different BMI groups, the prevalence of malnutrition (according to SGA) differed significantly (Table 1). However, it should be noted that 38% of all patients in the low-BMI group were classified as having a normal nutritional status according to SGA, whereas 45% of the patients in the normal-BMI group and 17% in the high-BMI
group were considered to be malnourished according to SGA. Whereas a Kaplan–Meier survival analysis showed no impact of low BMI on cardiovascular death, a marked increase in the cardiovascular mortality rate was observed in ESRD patients classified as having SGA ≥2 (Figure 2). Moreover, analysis by the Cox proportional hazard model, adjusting for the impact of age, gender, diabetes mellitus, clinically overt CVD and inflammation (CRP ≥10 mg/l), showed that an increased SGA score [relative risk (RR) 1.34; 95% confidence interval (CI) 1.02–1.77; \( P < 0.05 \)] but not BMI (per kg/m²; RR 1.03; 95% CI 0.98–1.09), had an independent predictive impact on cardiovascular mortality.

Thus, our data not only confirm the results presented by Beddhu et al. [1] but also illustrate the fact that the classifications of ‘malnutrition’ based on BMI and SGA are not comparable. Indeed, as SGA is a combined subjective and objective test of the patient’s medical history and physical examination, including recent weight loss, dietary intake, gastrointestinal symptoms and visual assessment of subcutaneous fat as well as of muscle mass, it may be more of a marker of ‘cachexia’ or ‘wasting’ than reflecting only ‘pure malnutrition’ (although the latter component is included in the composite nutritional evaluation by SGA). Several large prospective studies have demonstrated that SGA is a reliable predictor of poor outcome in dialysis patients [6–8]. Although SGA has several advantages, such as its low cost, rapid performance and strong predictive value for mortality, it should be appreciated that visceral proteins are not assessed and that its sensitivity, precision and reproducibility over time have not been well studied. Although Cooper et al. [9] found that SGA performed poorly in detecting the degree of malnutrition, the same study demonstrated that SGA scoring can effectively discriminate malnourished patients from those with normal nutrition as assessed by total body nitrogen [9]. It should also be pointed out that although total body nitrogen may be the gold standard for evaluating protein malnutrition, it does not take energy malnutrition (an important component of a nutritional evaluation) into account.

A number of theoretical considerations support the concept that inflammation-associated wasting may contribute to an accelerated atherosclerotic process and poor clinical outcome. First, Kalanthar-Zadeh et al. [10] recently have shown a strong and consistent association between poor appetite and high levels of inflammatory biomarkers, linking inflammation and ‘pure malnutrition’, as well as a 4-fold increase in mortality in dialysis patients reporting poor appetite. Secondly, several inflammatory biomarkers associated with wasting, such as CRP, serum albumin, interleukin (IL)-6, tumour necrosis factor-\( \alpha \) (TNF-\( \alpha \)) and fetuin-A may have independent pro-atherogenic properties, such as promoting oxidative stress, vascular calcification and endothelial dysfunction [11]. Indeed, in other wasted and inflamed patient groups, such as in rheumatoid arthritis [12], systemic lupus erythematosus (SLE) [13] and human immunodeficiency virus (HIV) [14] patients, there is a documented increased risk of vascular disease. However, although it is possible that both inflammation and wasting may contribute to CVD, the effect of these two factors on the

Table 1. Baseline patient characteristics by BMI groups

<table>
<thead>
<tr>
<th></th>
<th>Low BMI (&lt;20 kg/m²)</th>
<th>Normal BMI (20–25 kg/m²)</th>
<th>High BMI (&gt;25 kg/m²)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>34</td>
<td>121</td>
<td>116</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49±2</td>
<td>52±1</td>
<td>54±1</td>
<td>By definition</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.4±0.2</td>
<td>22.5±0.1</td>
<td>28.6±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Males</td>
<td>47%</td>
<td>66%</td>
<td>66%</td>
<td>NS</td>
</tr>
<tr>
<td>Total fat mass (kg)a</td>
<td>9.9±0.8</td>
<td>17.3±0.5</td>
<td>28.9±0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lean body mass (kg)a</td>
<td>41.3±1.7</td>
<td>48.7±1.0</td>
<td>52.7±1.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wasting (SGA ≥2)a</td>
<td>62%</td>
<td>45%</td>
<td>17%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>33.3±1.1</td>
<td>32.7±0.6</td>
<td>33.1±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21%</td>
<td>29%</td>
<td>35%</td>
<td>NS</td>
</tr>
<tr>
<td>Clinical CVD</td>
<td>21%</td>
<td>36%</td>
<td>36%</td>
<td>NS</td>
</tr>
<tr>
<td>Inflammation (CRP ≥10 mg/l)</td>
<td>35%</td>
<td>34%</td>
<td>39%</td>
<td>NS</td>
</tr>
</tbody>
</table>

a\( n = 232 \); b\( n = 268 \). BMI = body mass index; CVD = cardiovascular disease; SGA = subjective global assessment; CRP = C-reactive protein; NS = not significant.
Wasting predicts cardiovascular mortality in ESRD

![Graph showing Kaplan–Meier curves for cardiovascular mortality](image)

Fig. 2. Kaplan–Meier curves showing the impact of body mass index (top) and subjective global assessment (bottom) on cardiovascular mortality in end-stage renal disease patients starting dialysis treatment.

development of CVD may be different and not easy to disentangle. Furthermore, the direct role of ‘pure malnutrition’ as such as a cause of poor clinical outcome may perhaps be even more difficult to delineate in clinical studies as ‘pure malnutrition’, wasting and inflammation often are present at the same time.

In conclusion, our results show that a low BMI at the start of dialysis treatment is not associated with subsequent cardiovascular mortality in ESRD patients, confirming the findings by Beddhu et al. [1]. On the other hand, an increased SGA score at the start of dialysis treatment, which probably is more a reflection of wasting than pure protein energy malnutrition [15], is an independent predictor of cardiovascular mortality. We agree that the MIA concept may partly be a misnomer (maybe WIA would be better?) because there is little support in the literature that pure energy protein malnutrition per se contributes to atherosclerotic CVD. However, as there is solid support in the literature that inflammation-associated wasting increases the risk of vascular disease, longitudinal studies, using adequate markers of nutritional status, are warranted to provide evidence of such a relationship also in ESRD patients. Finally, there is also a need to discuss further the appropriate terminology for the description of ‘malnutrition’, ‘pure malnutrition’ and wasting in ESRD patients, as pointed out by Mitch [3].

Conflict of interest statement. Bengt Lindholm is employed by Baxter Healthcare.

References


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