The obesity epidemics in ESRD: from wasting to waist?

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During the last six decades, from the World War II years on, the phenotype of human beings has changed profoundly. The dominant slim, pale and light phenotype of the 1920s has gradually been overthrown by the heavy, large and ponderous phenotype of obese people. Obesity is rampant in the USA (http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/, accessed on 20th July 2008) and, even though to a lesser degree, most European countries share the same epochal evolution [1]. Type 2 diabetes and cardiovascular diseases are the two most important non-communicable disease outcomes of obesity. Abdominal obesity is strongly associated, and at least in part in a causal manner, with hypertension, dyslipidaemia and impaired insulin resistance [2]. Well beyond these complications, neoplasia [3], greater exposure to drugs of various sort, sterility [4], asthma [5], non-alcoholic liver disease [6] and osteoarthritis [7] are all much concerning sequelae of this epidemics. The risk of disease and disability attributable to overweight and obesity starts early, just when the upper limit of the ideal body mass index (BMI) (21–23 kg/m²) is trespassed and rises linearly at progressively higher BMI levels [8,9]. The burden of disease attributable to excess BMI among adults in the USA is enormous. Obesity at age 40 years reduced life expectancy by ∼7 years in women and by ∼6 years in men in the Framingham cohort [10]. In Europe, more than 1 million deaths and ∼12 million life-years of ill health (disability adjusted life-years—DALYs) were counted in 2000 [9].

Obesity epidemics in the dialysis population

Until now the major focus of nutrition research in dialysis patients has been on low BMI and protein energy wasting [11]. The identification and elucidation of this pervasive condition in the dialysis population has certainly been a major achievement of modern nephrology. However, a thorough refoocusing of the problem is needed. In Western countries, overweight and obesity have now gained the ominous role of leading risk factors for chronic kidney disease (CKD) [12]. The pathophysiological underpinnings of obesity-related CKD are still unclear, but solid working hypothesis have been formulated and the issue is being intensively investigated in experimental models and in human studies [13]. From an epidemiologic point of view, the association between BMI and the incidence of ESRD has been convincingly established in population-based studies in Japanese men [14] and in American people [15]. Obesity is one of the most frequent risk factors for progressive CKD in the general population. For this reason, this condition has become highly prevalent in dialysis units (Figure 1). The problem was nicely described by Kramer et al., in synchronic analyses based on the USRDS and on the Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention [16]. During a relatively brief period (just 8 years, from 1994 to 2002), the mean BMI increased from 25.7 kg/m² among incident patients in 1995 to 27.5 kg/m² in 2002 and from 25.7 to 26.7 kg/m² in the total US population (Figure 2). Overall in 2002, almost one-third of incident dialysis patients were obese and, worryingly so, the prevalence of patients with stage 2 obesity (BMI > 35 kg/m²) increased by 63%. As expected, the prevalence of obesity was higher in diabetics than in non-diabetics with a forecasted 2007 prevalence of total obesity in these patients as high as 44.6%. The predicted population average of BMI for 2007 (∼28 kg/m²) clearly indicates that just a small fraction of dialysis patients in the USA have a normal or a low body weight. In a cohort of incident dialysis patients (1997–2004) in Europe (the Netherlands) [17], the average BMI was 25.3 kg/m² showing that in the other side of the Atlantic more than half of ESRD patients are overweight or obese. In brief, there is unmistakable evidence that the obese phenotype is at least as frequent in the dialysis population as it is in the general population. Thus, nutritional disorders in ESRD should be interpreted in a context that takes into appropriate account that fat excess rather than fat deficiency is the most common trait in dialysis patients.
The obesity epidemics in ESRD

Defining obesity and how to measure it is of fundamental importance if we are to develop disease-specific studies in ESRD. However, in broad terms, the very essence of obesity and how it should be measured in population studies is an unsettled problem. This is so in epidemiological research in general and in research specific to ESRD as well. Most of the progress on the understanding of the detrimental effect of fat excess on human health was made in studies based on the BMI. In recent years, this time-honoured metric has been under intense scrutiny and, on the basis of a thorough meta-analysis, eminent epidemiologists came to the conclusion that the BMI is an inadequate metric for the cardiovascular risk of obesity [28]. Authoritative claims have been made that BMI should be abandoned straightaway [29]. Which is the best metric of this condition remains highly controversial. Proper positioning of the indicators of obesity may be obtained by studying the inter-correlation between the various metrics, their relationship with clinical outcomes and by cogent biological knowledge. Detailed analyses of the relationship between BMI, overall fat mass, waist circumference and abdominal visceral fat (as measured by computed tomography) in Caucasian and African American population samples have been made [30]. Collectively, the mean correlation between BMI and fat mass in these populations was very high (r = 0.94). Of note, waist circumference correlated very well both with BMI (r = 0.93) and overall fat mass (r = 0.92). Finally, BMI (r = 0.72) as well as the other metrics (fat mass r = 0.73; waist circumference r = 0.77) correlated equally well with abdominal visceral adiposity by CT. Since the major factor implicated in the health risks of obesity seems to be the excess adipose tissue and/or some aspects of cell biology, the data on the relationship between BMI and overall fat mass may facilitate confusion between association and causation thus diverting clinical attention and scientific research from truly important issues related to risk factors modification in this population [23]. There is no question that obesity was a trait providing survival advantage to our ancestors at a time when famine and infectious diseases decimated the population and when the average duration of human life was 40 years or less [24]. The same survival advantage may apply to high-risk conditions such as cardiac disease, cancer and ESRD that are all characterized by a short life expectancy and by specific (non-Framingham) risk factors. Any case studying risk factors for survival in the dialysis population in no way imposes deviations from classic epidemiology principles. In this respect, there is absolutely no dissent on the fact that a high BMI per se should not be seen as a necessarily protective factor in ESRD. In fact, current guidelines in ESRD recommend a multidimensional assessment of nutritional status [25,26] both for prognosis and treatment while the very champions of the ‘reverse epidemiology’ concept accurately dissected the BMI–protein balance link when assessing the risk of malnutrition in this population [27].

How to measure the obesity burden in epidemiological studies

Obesity and the reverse epidemiology conundrum in ESRD

The term ‘reverse epidemiology’ has been widely adopted to describe the apparently paradoxical inverse association between mortality and BMI and other risk factors in ESRD. Studies in renal registries [18], in clinical databases [19] and in large, international studies [20] have coherently shown that BMI is indeed inversely associated with death risk. This phenomenon is not typical of ESRD being common also to other chronic conditions, including cardiovascular disease [21,22]. The term ‘reverse epidemiology’ has fierce opponents [23]. It was emphasized that rules of epidemiology have not been reversed in dialysis patients, and recent data in a European dialysis cohort documented that the relationship between the BMI and mortality does not deviate from that of the coeval background population [17]. In addition, most studies did not adequately control for potential confounders such as cancer and CHF, and smoking. The main reason of concern with the term ‘reverse’ is that such a definition may distract from the complexity of the ESRD population and...
would be against the contention that BMI is not a valid surrogate for fat mass, at least in apparently healthy adults in the community. The same reasoning applies to waist circumference. Since most of the variance in obesity-related anthropometrics is captured by BMI, some obesity experts see no reason to replace BMI by waist circumference or other metrics as a measure of obesity [30]. However, it has been argued that this position does not consider that analyses in apparently healthy subjects may not apply to patients with chronic conditions. Furthermore, simple analyses on inter-correlations between indicators of obesity in no way can surrogates the study of the relationship of these measurements with clinical outcomes, which is the ultimate, adjudicative criterion. In this respect, it is well demonstrated that waist circumference and the related metric waist hip ratio (WHR) add prognostic information at any level of BMI. In a large survey based on the III National Health and Examination survey within the three BMI categories of normal weight, overweight and class I obesity, a larger waist circumference coherently identified individuals at a higher health risk [31]. Likewise, the WHR was the strongest body size measure associated with myocardial infarction in the INTERHEART study, a world-wide extended case-control study [32]. Importantly, in this study, BMI lost substantial prognostic value in an analysis adjusting for WHR and other risk factors while the predictive power of WHR became stronger after these statistical adjustments, which is in line with biological evidence indicating that visceral fat is a relevant source of endogenous compounds impinging upon cardiovascular health. Whether metrics of waist circumference hold prognostic value for death and cardiovascular complications in patients with chronic diseases other than myocardial infarction is still unknown [33].

Obesity and protein energy wasting in ESRD: a two-dimensional problem

BMI is the most used anthropometric measure of overall body size in ESRD. The limitations of this metric are well known to nephrologists [11]. BMI does not distinguish between fat mass and lean mass. At similar BMI, percentage of body fat may differ considerably in people who exercise heavily and in sedentary people. Furthermore, in the elderly and non-Caucasian populations, the relationship between BMI and fat depots is different from that in the young and Caucasian populations [34]. Importantly, BMI does not give information on segmental fat distribution (abdominal versus peripheral fat), a phenomenon with metabolic and clinical bearings. Abdominal obesity is largely caused by the accumulation of visceral (or intra-abdominal) fat while peripheral obesity is mainly characterized by subcutaneous fat accumulation. Due to metabolic differences of the two fat depots, the two may differ in their role of predicting metabolic disturbances and clinical events. Although still not adequately emphasized, the notion that nutritional disorders in ESRD cannot be merely classified on the basis of BMI is well recognized. In 2003, Beddu et al. [35] looked at the problem of which body component (increased muscle mass or body fat) confers survival advantage in a large cohort of incident haemodialysis patients with high BMI. Twenty-four-hour urinary creatinine excretion prior entering regular dialysis treatment was used as a measure of muscle mass. Patients with high BMI had lower death risk than those with a normal or low BMI. However, high BMI patients with relatively low muscle mass (urinary creatinine ≤0.55 g/day) had higher risk of all-cause (HR, 1.14; P < 0.001) and cardiovascular (HR, 1.19; P < 0.001) deaths than patients with the same BMI but low muscle mass. Similarly, in a recent study by Honda in a relatively small cohort of ESRD patients in Sweden [36], protein-energy wasting (as measured by the subjective global assessment of nutrition) was equally prevalent in patients with low, normal and high BMI. In this cohort, BMI per se did not predict mortality. However, for each BMI group, protein-energy malnutrition was associated with increased death risk. Overall, these studies show that ‘obese sarcopenia’, i.e. a high body mass in the face of a low urinary creatinine or protein energy malnutrition, underlies a high death risk in ESRD patients thus indicating that the prognostic value of nutritional status in dialysis patients should be based on the BMI and on metrics of muscle mass and/or protein-energy balance.

Anthropometric measures of visceral fat accumulation such as waist circumference and the WHR are directly associated with all-cause and CV mortalities in the general population. Notwithstanding, ESRD is a chronic condition where nutrition disorders are exceedingly common, and no specific studies of these metrics are available in dialysis patients. Also in light of the rising tide of overweight and obesity in the ESRD population and of the adverse clinical outcomes observed in obese sarcopenia [35,36], the issue of simultaneously testing the prognostic value of metrics of overall body size (like the BMI) and segmental fat accumulation (waist circumference and WHR) in ESRD patients appears to be of major relevance. Very recently, relevant information on the validity of waist circumference as a measure of visceral fat accumulation has been gathered in patients with CKD [37]. In a series of 122 Brazilian patients with stage 3–5 CKD, this metric was strongly associated with visceral fat as measured by abdominal computed tomography and the association of this measurement with cardiovascular risk factors was of the same magnitude of that observed for visceral fat. These findings suggest that waist circumference is a simple and cheap instrument that may be applied for investigating the role of visceral fat on health outcomes in epidemiological studies in patients with renal diseases. In a combined cohort composed by patients enrolled in the Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Study (CHS), a larger waist hip ratio was associated with a 22% risk excess for incident CKD and a 12% risk excess for a combined outcome composed by incident CKD and death [38]. In the same study, BMI appeared protective for the composite outcome but did not predict the risk for CKD. Likewise, in another study in the same cohort [39], a large waist hip ratio was associated with an increased risk of cardiac events while obesity, defined on the basis of BMI >30 kg/m², did not predict these events. Overall these analyses indicate that, like in the general population, measures of abdominal fat accumulation maintain a direct association with the...
risk for CKD, cardiovascular events and death. Thus testing the value of these metrics in ESRD appears to be of foremost importance. This may be problematic in patients treated with peritoneal dialysis where other options for risk stratification can be envisaged [40]. Overall, combining estimates of overall body size such as the BMI and of abdominal fat accumulation such as waist circumference may indeed refine the prognostic power of these measurements and produce interesting hypotheses for future clinical trials in ESRD patients. For example, does weight loss confer a health benefit in patients with a high BMI and a high waist circumference? Conversely, does a relatively large waist circumference in the face of a normal or low BMI identify patients at the highest risk of adverse clinical outcomes? Does the relationship between waist circumference and the waist hip ratio with biomarkers of inflammation observed in the general population and in patients with cardiovascular diseases hold true in ESRD and is this relationship modified by the BMI in these patients? In light of the pervasiveness of the obesity epidemics (as defined on the basis of the BMI) in ESRD, studying anthropometric measurements of visceral obesity as related to health outcomes in this population appears to be an absolute research priority.

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References


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