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Obesity in CKD—What Should Nephrologists Know?

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ABSTRACT

Obesity, the epidemic of the 21st century, carries a markedly increased risk for comorbid complications, such as type 2 diabetes, cancer, hypertension, dyslipidemia, cardiovascular disease, and sleep apnea. In addition, obesity increases the risk for CKD and its progression to ESRD. Paradoxically, even morbid obesity associates with better outcomes in studies of ESRD patients on maintenance dialysis. Because the number of obese CKD and maintenance dialysis patients is projected to increase markedly in developed as well as low- and middle-income countries, obesity is a rapidly emerging problem for the international renal community. Targeting the obesity epidemic represents an unprecedented opportunity for health officials to ameliorate the current worldwide increase in CKD prevalence. Nephrologists need more information about assessing and managing obesity in the setting of CKD. Specifically, more precise estimation of regional fat distribution and the amount of muscle mass should be introduced into regular clinical practice to complement more commonly used practical markers, such as body mass index. Studies examining the effects of obesity on kidney disease progression and other clinical outcomes along with weight management strategies are much needed in this orphan area of research.

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Obesity has emerged as the largest pandemic in near history, with important implications of not only cardiovascular disease (CVD) but also CKD. Recent data from the United States indicate that the incidence and prevalence rates of obesity in maintenance dialysis patients largely exceed the corresponding figures in the general population.[1] A large European population survey documented that a high body mass index (BMI) ranks as one of the strongest risk factors for new-onset CKD.[2] The dimension of the obesity epidemic and the impact of the same epidemic on the kidney demand efforts for understanding the epidemiology and the mechanisms of CKD associated with excess adiposity. It also sets as an absolute public health priority for the development of treatment policies integrated across specialties and general practice to halt this much concerning problem. In this scenario, it is fundamental that nephrologists are updated on current knowledge about obesity in the setting of CKD. However, little attention is still paid to this issue in major nephrology journals. The suboptimal attention to the problem by major sources of dissemination of specialty information suggests that nephrologists may have scarce knowledge of how obesity should be assessed, its epidemiology, mechanisms whereby excess fat mass is conducive to CKD, and management of obesity in the catabolic uremic milieu.[3]

DEFINITION AND ASSESSMENT OF OBESITY

The most common method for defining obesity is based on BMI (*i.e.*, a person's weight [kilograms] divided by the square of his or her height [meters]). The World Health Organization (WHO) considers a BMI between 20 and 25 kg/m^2 as normal weight, a BMI between 25 and 30 kg/m^2 as overweight, and a BMI of $>$30 kg/m^2 as obese. It should be emphasized that population norms of BMI could be different based on ethnic and racial background (*i.e.*, the proportion of Asian people with a high risk of type 2 diabetes and CVD is substantial at a lower BMI).[4] Although BMI is easy to calculate and used in many nutritional guidelines, this metric is a poor estimate of fat mass distribution, especially in CKD.[5] Disease risk increases with a waist circumference (WC) and a waist hip ratio (WHR) of $>$102 cm and 0.9, respectively, for men and $>$88 cm and $>$0.8, respectively, for women. Although WHR and skin fold thickness are superior to BMI for the correct classification of obesity in CKD in cross-sectional studies,[6] WHR may not be a valid estimate

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of changes in visceral fat mass over time.[7] Fat measurement by single frequency bioimpedance is not superior to simple anthropometric measurements.[8] Because gold standard measurements of body fat content are problematic to perform in clinical practice, both WHR and skin fold thickness are recommended for routine use.[6] The conicity index is an easy anthropometric estimate using WC, height, and weight to model the relative accumulation of abdominal fat without requiring the hip circumference to assess fat distribution.[9] This method could be useful to identify CKD patients with abdominal obesity who are not necessarily overweight,[10] and it constitutes a risk estimate of the wasting component[11]:

$$C\ index = \frac{WC\ (m)}{0.109 \times \sqrt{\frac{Body\ Weight\ (kg)}{Height\ (m)}}}.$$

OBESITY—THE EPIDEMIC OF THE 21ST CENTURY

The increasing trend in obesity prevalence across regions, countries, and continents is a global concern, such that, in 2008, more than 1.4 billion adults were overweight.[12] During the next decade, this number is projected to grow by 40%.[13] Thus, obesity is a considerable public health problem that affects a sizeable part of the world population across all age and racial/ethnic groups. It should be emphasized that, when the society has become serious about addressing the obesity epidemic (through a combination of strategies involving public health, economics, behavioral change, and environmental change), it may take decades to turn back obesity rates to levels seen before the start of the epidemic 30–40 years ago. The obesity spreading patterns around the world are remarkably predictable, and low- and middle-income countries are presently going through the same rapid transition from normal weight to overweight and obesity as parts of Europe and the United States already have done. Recent studies show that the prevalence of obesity has also increased markedly in China,[14] India,[15] and Brazil.[16] Because the overweight prevalence growth rate is higher in individuals who are less educated and have low socioeconomic status, the social disparities represent important risk factors for obesity-related chronic diseases in developing countries.[17]

MECHANISMS OF OBESITY: WHY DO WE GET FAT?

As with any chronic disease that affects large populations, the pathophysiology of obesity is extremely complex, including but not limited to genetic predisposition, environmental changes, and individual preferences (Figure 1). To this date, more than 150 genetic loci have been associated with the development of obesity and type 2 diabetes.[18] A recent genome-wide association study showed that variants within the fat mass- and obesity-associated gene (*FTO*) located on chromosome 16 are associated with about 7% phenotypic variability of BMI.[19] Interestingly, a polymorphism within the FTO gene independently predicted all-cause mortality in CKD patients.[20] Although much progress in identifying epigenetic changes induced by (or inducing) obesity has been made, studies that have defined the responsible key loci in relevant tissues are lacking.[21] In the Framingham Cohort, there has been a remarkable growth of

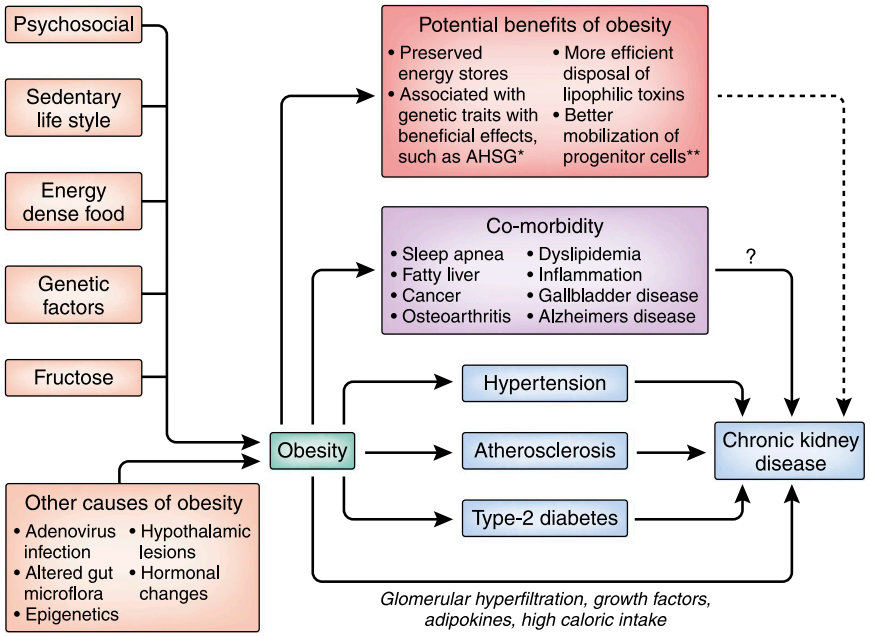

Figure 1. Relationships between obesity and chronic kidney disease. The pathophysiology of obesity is complex and includes both genetic (and epigenetic) and environmental factors associated with lifestyle. Many novel and/or hypothetical causes of the obesity epidemic are currently being investigated. Obesity is also associated with several comorbidities that, together with direct detrimental effects of obesity *per se*, significantly increase death risk. However, increased fat mass may be associated with some putative beneficial effects that could benefit uremic patients. By increasing the risk of hypertension, atherosclerosis, and type 2 diabetes, obesity may indirectly lead to CKD. Increased fat mass may also have direct pathophysiological effects on the kidney; through glomerular hyperfiltration, growth factors and adipokine alterations may lead to fibrosis, glomerulosclerosis, and kidney disease. *A study by Lavebratt *et al.*[113] shows that a common variant of α-Heremans–Schmid glycoprotein (AHSG) associated with lower fetuin levels is more common in lean than obese patients. Thus, it could be hypothesized that this genetic trait may protect obese dialysis patients from mineral stress and progressing vascular calcification by a genetic predisposition to higher systemic levels of fetuin-A.[114] **A study by Bellows *et al.*[115] shows that obesity promotes mobilization of progenitor cells.

the obesity prevalence at an almost fixed genetic background[22] linked to a substantial increase in sucrose (glucose and fructose) intake.[23] Increased fructose intake by stimulation of uric acid may not only promote metabolic syndrome and obesity[24] but also CKD.[25] There is also a strong link between decreased physical activity and obesity.[26] Because the WHO reported that physical inactivity is the fourth leading risk factor for worldwide mortality,[27] it has been suggested that a sedentary lifestyle should be regarded as a disease on its own.[28] Because increased adiposity results from the loss of the homeostatic control of caloric intake and energy expenditure, studies of obesity require a profound understanding of energy balance. Because the fixed idea of overeating as the single source of obesity has limitations,[29] the cause of the obesity epidemic may rather be because of researchers failure to understand the nature of this condition and the food industry's marketing-driven increased consumption of junk food. More energy-dense food with high glycemic index and the introduction of high-fructose corn syrup in soft drinks may have contributed to not only the obesity plague but also, the increased prevalence of type 2 diabetes, hypertension, gout, and CKD.[30] Other intriguing hypotheses of causes of the obesity epidemic include mutation of the uricase gene,[31] microRNAs,[32] adenovirus infection,[33] altered gut microbiota,[34] psychosocial stress,[35] and neurocognitive factors.[36]

OBESITY INCREASES THE RISK FOR DEATH AND COMORBIDITY

In the general population, being obese hastens death risk by more than 9 years.[37] A recent meta-analysis showed that, relative to normal weight, obesity was associated with higher all-cause mortality, although being overweight was not.[38] Obesity is associated with several comorbid conditions, including CVD, type 2 diabetes, metabolic syndrome, dyslipidemia, hypertension, gallbladder disease, fatty liver, osteoarthritis, and psychosocial problems (Figure 1). Moreover, a recent study showed a causal relationship between obesity and hypovitaminosis D.[39] Obesity is also linked to Alzheimer's disease,[40] and central leptin insufficiency (a feature of obesity) is recently associated with greater brain atrophy.[41] In the general population, obesity is also associated with worse outcome for many cancers, such as endometrial, breast, and colon cancer.[42] Obstructive sleep apnea is another increasingly recognized major health problem that is associated with both obesity and CKD.[43] Finally, obesity relates to persistent inflammation in both the general population[44] and CKD patients.[45] About 30% of obese patients seem to be protected against obesity-related metabolic complications.[46] This interesting subgroup of individuals with metabolically benign obesity is characterized by relatively low visceral fat mass, increased gluteofemoral fat mass, normal adipose tissue function, low macrophage infiltration, and normal insulin sensitivity,[46] and this seems to be protected against coronary heart disease and type 2 diabetes.[47]

OBESITY—A PREVENTABLE RISK FACTOR FOR CKD

Because the prevalence of obesity in North American ESRD patients increased by a rate far exceeding the general population,[1] the implication is that obesity is a risk factor for CKD.[48] However, few have studied whether obesity is a risk factor for progression in patients with early stages of CKD. Ejerblad *et al.*[49] showed that patients without diabetes or hypertension had a threefold increased risk for CKD if they were overweight at age 20 years. Hsu *et al.*[50] showed that higher baseline BMI remained an independent predictor for ESRD after adjustments for BP and diabetes mellitus. In a multivariable model based on data from 2585 individuals followed for 19 years, BMI predicted new-onset kidney disease.[51] A study based on the Prevention of Renal and Vascular Endstage Disease cohort[52] showed that, after adjustment for confounders, obesity was associated with a 70% increased risk of microalbuminuria compared to lean subjects. Components of the metabolic syndrome and CKD are strongly and consistently associated in many cross-sectional studies.[53] Moreover, European data based on 1271 incident dialysis patients showed that obesity is a strong risk factor for loss of residual renal function after initiation of dialysis therapy.[54] A meta-analysis of 25 cohorts, 3 cross-sectional and 19 case-control studies that met inclusion criteria confirmed that obesity increases the risk of CKD in the general population.[55]

Other than indirect effects on kidney disease incidence and progression (by type 2 diabetes, atherosclerosis, and hypertension), adiposity may also directly impact kidney function.[56] Indeed, Kwakernaak *et al.*[57] recently reported that a central body fat distribution was associated with an unfavorable renal hemodynamic pattern. As reviewed by Wickman and Kramer,[56] increased fat mass leads to mesangial expansion and increased renal metabolic demand that may promote glomerular hyperfiltration, glomerular hypertrophy, decreased podocyte density, increased foot processes, and increased filtration fraction (*i.e.*, alterations that promote proteinuria and glomerulosclerosis). These sequences of events stimulate a cascade of growth factors, such as the renin-angiotensin system and TGF-β, that further promote kidney damage. Obesity has been linked with FSGS since the mid-1970s.[58] Moreover, caloric restriction may prevent and retard kidney injury,[56] because the increased caloric intake that often accompanies obesity *per se* may promote kidney disease by downregulation of the enzyme Sirt1, which protects the mouse medulla from oxidative stress.[59] Obesity may also promote CKD through alterations in adipocyte-derived hormones, such as low adiponectin and high leptin levels. A study by Sharma *et al.*[60] shows that plasma adiponectin had a negative correlation to albuminuria in obese patients and that adiponectin administration reduced podocyte permeability to albumin and

podocyte dysfunction in cultured podocytes; their results imply that adiponectin is an important regulator of albuminuria.[60] Infusion of leptin causes proteinuria and glomerusclerosis, promotes renal fibrosis and oxidative stress, and increases the sympathetic nervous tonus.[61] Finally, obesity in CKD is independently associated with hyperparathyroidism,[62] and the intriguing relationships between parathyroid hormone, fat mass, adipokines, sympathetic activity, and osteoporosis deserve additional studies.[63]

OBESITY AND KIDNEY TRANSPLANTATION

Between 1987 and 2001, the prevalence of obesity among US patients awaiting a kidney transplant had increased from 11.6% to 25.1%.[64] In a retrospective study of 376 Italian kidney transplant recipients, obesity was an independent risk factor for graft loss and patient death.[65] In another retrospective single center study of 1132 deceased donor kidney grafts, multivariate analysis revealed recipient BMI and dialysis vintage as independent risk factors for delayed graft function.[66] Molnar *et al.*[67] reported that pretransplant overweight or obesity is associated with an incrementally higher risk of delayed graft function. Additionally, a recent study of 15,667 elderly kidney transplant recipients showed that obesity was associated with 19% higher risk of graft failure.[68] However, a study based on 10,090 hemodialysis patients showed that pretransplant obesity was not associated with poor 5-year post-transplant outcomes,[69] and the long-term effect of pretransplant obesity on outcome is currently not clear. Based on the higher risk for complications during and after surgery, there has been a debate regarding the eligibility for kidney transplantation of obese patients and which cutoff level of BMI should be used. Because BMI is a poor measure of body fat composition, additional research should define the optimal cutoff using more precise fat assessment methods and the relation between fat mass and clinical outcomes.

TREATMENT OF OBESITY IN CKD

Based on existing data, we have developed an approach for management of obese CKD patients (Figure 2). Many studies have shown that increased physical activity reduces the risk of developing many chronic diseases, such as hypertension, osteoporosis, metabolic syndrome, colon cancer, and type 2 diabetes,[70] and nephrologists should advice their patients to engage in higher levels of physical activity. Indeed, a sedentary lifestyle with more sitting time is associated with prevalent CKD.[71] Surprisingly, a recent randomized study of 5145 overweight or obese type 2 diabetic patients showed that, although many positive effects were observed, intensified lifestyle intervention focused on weight reduction failed to reduce the rate of cardiovascular events.[72] In contrast, a recent study showed that adherence to a healthy lifestyle (using a weighted healthy lifestyle score) was associated with a lower all-cause mortality in CKD.[73] However, only a few studies have studied the effects of a healthy lifestyle on kidney function.[74] Small studies suggested improvements in estimated GFR and/or albuminuria with low-calorie diets, especially when weight loss has been significant. Although even small amounts of regular physical activity (150 min/wk) reduce all-cause and particularly, cardiovascular mortality,[75] the effects of physical activity on kidney function have not been studied in obese CKD patients. Because Krikken *et al.*[76] showed that a high-sodium intake elicited hyperfiltration and a high filtration fraction only in subjects with a BMI$\geq$25 kg/m^2, a low-sodium intake should be advocated in obese CKD patients. Moreover, because angiotensin II suppresses 5′adenosine monophosphate-activated protein kinase activity in the kidney, which lead to enhanced salt sensitivity,[77] 5′adenosine monophosphate-activated protein kinase activation or angiotensin II inhibition represents a therapeutic target for obesity-related salt-sensitive hypertension. Indeed, in a *post hoc* analysis of the Ramipril Efficacy in Nephropathy trial, Mallamaci *et al.*[78] found that the angiotensin converting enzyme inhibitor ramipril reduced the rate of renal events better in obese compared with overweight and normal weight patients.

The effects of pharmacological treatment of obesity (such as sibutramine and orlistat) are not studied in depth in CKD patients. In a study of 33 obese type 2 diabetic patients and 27 obese nondiabetic patients, Tong *et al.*[79] reported that orlistat with a hypocaloric diet for 6 months reduced albuminuria and improved insulin sensitivity. In the general population, bariatric surgery has become the standard for effective intervention, with 50%–60% weight loss in morbidly obese patients.[80] Lower incidence of cardiovascular events after 15 years of follow-up has been reported in these patients as well.[81] A study including 1658 obese patients who underwent bariatric surgery and 1771 obese-matched controls showed that bariatric surgery was more efficacious in the prevention of type 2 diabetes than standard care. Another study reports a significant improvement in renal parameters after bariatric surgery.[74] Alexander *et al.*[82] reported that, in a series of 45 CKD patients who had undergone gastric bypass, nine patients had resolution, improvement, or stabilization of their kidney function. A study of 233 severely obese patients before and 12 months after bariatric surgery showed that mean estimated GFR increased in obese CKD patients.[83] Notably, there is a case report of recovery of kidney function in a dialysis-dependent patient after bariatric surgery.[84] In a study of 34 morbidly obese patients, surgically induced weight loss contributed to a decrease in markers of renal inflammation and BP.[85] Moreover, in a study of 255 morbidly obese type 2 diabetic patients, changes in BMI 12 months after bariatric surgery were the only independent predictors of albumin-to-creatinine ratio normalization.[86] In accordance, in a 5-year follow-up study in 52 obese type 2 diabetic

patients who underwent bariatric surgery, diabetic nephropathy resolved in 58%.[87] Turgeon *et al.*[88] reported that, although CKD patients had higher complication rates after bariatric surgery, the absolute incidence of complications remained less than 10%. In our opinion, although there is a somewhat higher risk for complications in CKD patients with morbid obesity and patients at risk for CKD progression, bariatric surgery is an underused treatment option in this population. Because bariatric surgery operations are likely to be more common in obese CKD patients, nephrologists should be aware of the risk of bariatric surgery-induced bone loss.[89]

SHOULD NEPHROLOGISTS PROMOTE WEIGHT GAIN IN DIALYSIS PATIENTS?

A controversial subject regarding obesity in CKD is the appropriate weight management of dialysis patients. The paradoxical finding that even morbid obesity predicts better outcome has befuddled the renal community since this phenomenon was first described 1999[90] and later confirmed in large US cohorts.[91,92] These observations have led some to argue that weight gain should be promoted in maintenance dialysis patients, regardless of body compartment (*i.e.*, fat or muscle mass). Indeed, obesity may be associated with better stem cell mobilization, more efficient disposal of lipophilic uremic toxins, better bone strength, and improved hemodynamic tolerance.[93] In addition, although obesity can be associated with muscle wasting and catabolism,[11] increased fat stores usually reflect well preserved energy stores and preserved appetite.[94] In this case, the overall protective nutritional effect presumably overrides the cumulative long-term metabolic adverse effects of obesity. Despite overwhelming epidemiologic data on this association, we believe that a generalization of this sort would actually be inappropriate, and additional consideration of certain phenotypic features is necessary for proper management of dialysis patients.[93] At

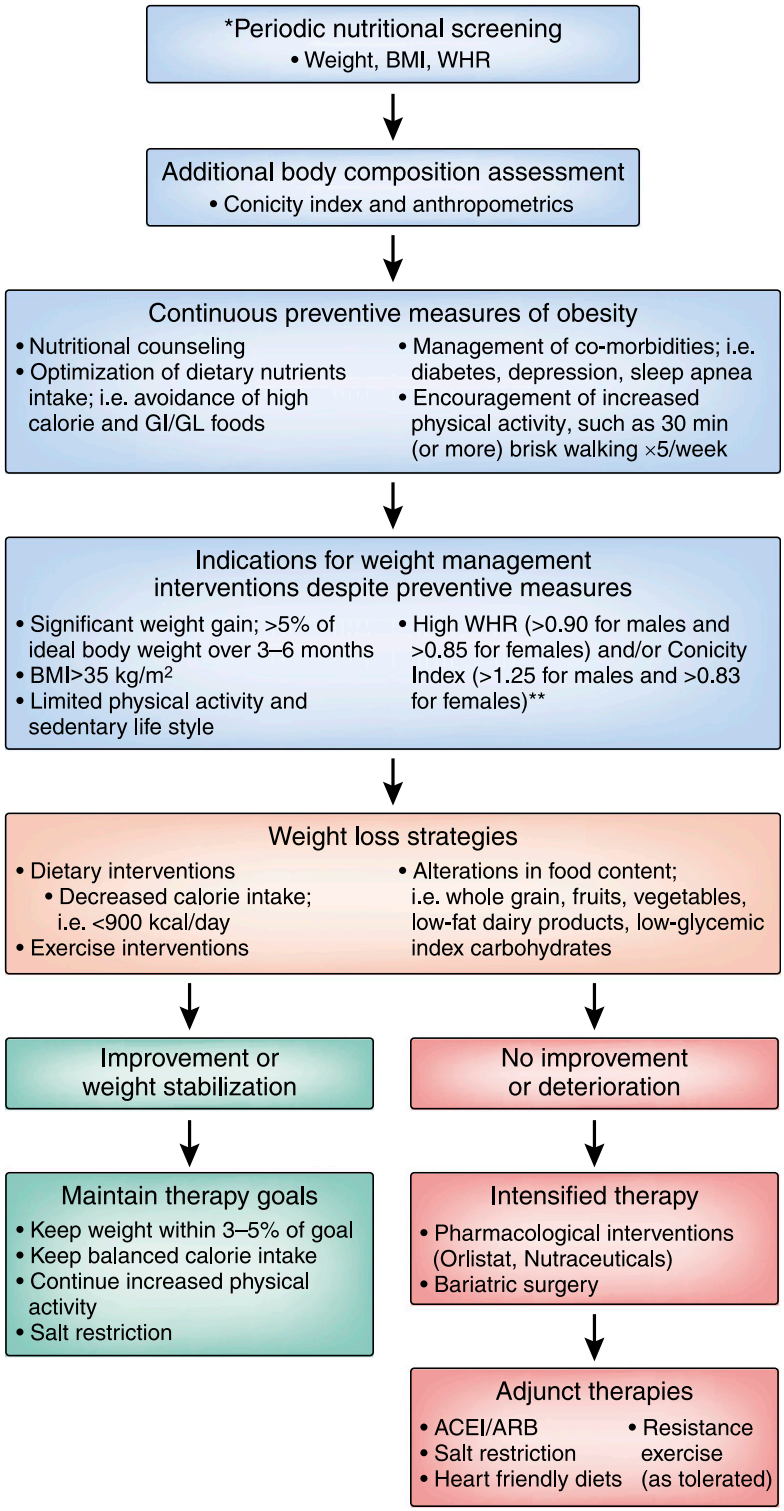

Figure 2. A proposed approach to management of obesity in CKD. *Screening every 3–6 months is recommended. Additional assessment is required for patients considered to be at risk. **A study by Pitanga and Lessa[116] showed that, in 968 adults, a conicity index of >1.25 predicted high coronary risk in men with a sensitivity and specificity of 73.9% and 74.9%, respectively. For women, a conicity index of >0.83 predicted high coronary risk with a sensitivity and specificity of 73.4% and 63.4%, respectively. ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; GI, glycemic index; GL, glycemic load.

first, in contrast to senior dialysis patients, younger patients with low or very high BMI had a substantially elevated risk for death.[95] Moreover, Deger *et al.*[96] reported that coexistence of overt diabetes and obesity exponentially increases mortality risk, a phenomena putatively mediated by adipocytokine imbalances. Because one study showed that African-American hemodialysis patients were reported to have a more consistent association between higher BMI and better outcome than other races,[97] race and ethnicity may also affect the association between high BMI and outcome.[98] However, in a recent study comparing 20,818 South Korean hemodialysis patients with 10,000 matched African-American and 10,000 matched white hemodialysis patients from the United States, race did not modify the association between higher body size and greater survival.[99] Assumptions of the existence of an effect modification by obesity may not be correct when the specific analysis is conditioned on a disease state that, in itself, is influenced by obesity.[98] Indeed, one study showed that ESRD does not modify the association between obesity and all-cause mortality in European hemodialysis patients when the general population was of comparable age and had equal duration of follow-up.[100] Also, the severity of kidney disease may affect the association between BMI and outcome. In accordance with the findings in the hemodialysis population, Evans *et al.*[101] and Kovesdy *et al.*[102] reported that a high BMI was protective in CKD stages 3–5 patients. However, Madero *et al.*[103] and Weiner *et al.*[104] reported that high BMI had no protective effect in CKD stages 3 and 4 patients. In a cohort also including patients with CKD stages 1 and 2, Hsu *et al.*[50] reported that high BMI, similar to the general population, predicts poor outcome. Taken together, most but not all studies indicate that, when renal function deteriorates, well preserved energy stores become more and more important for survival.

Additional data indicate that differences in body composition (*i.e.*, total fat mass versus muscle mass and visceral versus nonvisceral fat mass) could also lead to different morbidity and mortality risks in ESRD patients. Beddhu *et al.*[105] showed that the protective effect bestowed by high BMI is confined to those dialysis patients with normal or high muscle mass. A study by Noori *et al.*[106] using midarm muscle mass as a surrogate of lean body mass confirmed that high muscle mass constituted a survival advantage. Moreover, an observational cohort study in 808 Japanese hemodialysis patients showed that both increased fat mass and lean mass were associated with better outcome during 53 months of follow-up.[107] Because the metabolically more active visceral fat depots are the key factor in the development of insulin resistance, hypertension, fatty liver, type 2 diabetes, and atherosclerosis,[46] nephrologists should estimate fat distribution. Indeed, the gene expression differs markedly between visceral and subcutaneous fat depots,[108] and studies in the general population[109] and CKD[110] and dialysis patients[111] show that increased WC (or WHR) was related to a higher risk of death from major specific causes independent of BMI. In accordance, visceral obesity is linked to inflammation, protein energy wasting, and worse outcome in hemodialysis patients.[10] Signs of wasting and inflammation[45] are also commonly observed in CKD patients with abdominal obesity (obese sarcopenia) and herald poor prognosis.[11] Taken together, a disproportionally lower muscle mass in relation to increased metabolically active visceral fat mass is associated with poor outcome in ESRD. Introduction of more precise measures of body composition into clinical practice is necessary to individualize weight management. Moreover, because detectable levels of actin and low levels of gelsolin (an actin binder produced in muscle) predicted poor outcome in hemodialysis patients,[112] therapeutics that target muscle mass should be tested in this group of patients.

SUMMARY AND CONCLUSION

Increased fat mass not only promotes kidney disease indirectly through hypertension, atherosclerosis, and type 2 diabetes but also through direct renal effects. Indeed, a recent study by Friedman *et al.*[117] demonstrated that short-term weight reduction by 12% in patients with advanced diabetic nephropathy improved markers of glomerular filtration and risk factors for kidney disease progression. If conventional treatments do not result in sustained weight loss, bariatric surgery should be considered in obese CKD patients. It is crucial for nephrologists to learn how to assess fat mass distribution, identify metabolically benign obesity in the uremic milieu, and manage and treat obese CKD patients. Moreover, as a recent study demonstrates an important role for mitochondrial dynamics in the central regulation of energy metabolism,[118] further studies should address mitochondrial function in obesity and CKD. The treatment of obesity requires a multifaceted approach, including but not limited to weight reduction and physical exercise programs. Nephrologists should aim for interventions that increase muscle mass and decrease visceral fat mass. In this regard, a multidisciplinary approach with other health care providers (*i.e.*, dietitians and physiotherapists) is of paramount importance.

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DISCLOSURES

P.S. is a consultant for Abbott Renal Care, Bayer, Baxter Renal, Keryx, Amgen, and Takeda. C.Z. is a consultant for Abbott Renal Care, Shire, and Amgen. T.A.I. is a consultant for Abbott Renal Care, Abbott Nutrition, DSI, Inc., Baxter Renal, Amgen, Affymax, Inc., Fresenius Medical Care North America, Fresenius-Kabi, and Satellite Healthcare.

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