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NEPHROLOGY – REVIEW

The role of obesity in kidney disease: recent findings and potential mechanisms

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Abstract Obesity epidemic is in rise in almost every industrialized country and continues to be a growing problem worldwide. In fact, obesity per se has been recognized as a chronic disease. Consequently, there has been a cascade of metabolic changes initiated by the markedly risen prevalence that contributes to the increased incidence of diabetes, hypertension, and cardiovascular disease. Moreover, obesity is also associated with an increased risk of chronic kidney disease (CKD). The majority of the studies indicate a direct relationship between body mass index (BMI) and CKD risk. Moreover, current evidence emphasized the fact that central obesity measurements, such as waist circumference, could be a better predictor of CKD progression and mortality than BMI. The detrimental effects of obesity on kidney outcome have been recognized in nondialysis-dependent (NDD)-CKD patients. However, survival in overweight or obese CKD patients undergoing maintenance hemodialysis is paradoxically opposed compared with the general population. This "reverse epidemiology," however, is valid mainly for the inflammated end-stage renal disease (ESRD) patients. In fact, renal transplant recipients with higher BMI have inferior patient and graft survival compared to patients with lower BMI. This review also provides perspectives concerning the mechanisms associated with obesity, such as the renin–angiotensin–aldosterone system (RAAS) activation, and the role of leptin, adiponectin, fetuin-A, and adipose tissue, as factors that contribute to the development of CKD. Prevention strategies for CKD patients are also discussed and should be considered by clinicians.

Keywords Obesity · Kidney · Chronic kidney disease

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Introduction

The markedly high prevalence of obesity contributes to the increased incidence of chronic diseases, such as diabetes, hypertension, sleep apnea, and heart disease [1–3]. Actually, obesity per se has been recognized as a chronic disease since 1985 [4], and the effects have also been recognized in patients with diagnosed kidney disease [5–10], as well as among the general population [11–19]. Moreover, obesity is a well-known risk factor for CKD [11, 14, 15, 20], independent of diabetes and hypertension [21, 22]. This review discusses the effects of obesity on kidney and mortality outcomes in the general population, in non-dialysis-dependent (NDD)-CKD patients, in CKD patients undergoing maintenance hemodialysis, and

in renal transplant recipients. Furthermore, it provides additional perspectives regarding the mechanisms of obesity as a factor that contributes to the occurrence of CKD. Finally, prevention strategies for kidney disease or obesity-related CKD patients, are also discussed and should be considered by clinicians.

Epidemiology of obesity and CKD

Over the past 20 years, the prevalence of obesity among adults aged 20–74 years has doubled, from 15 to 30% [23], and this increase occurred in both men and women, of all age-groups [23]. More recent data have shown that obesity afflicts 33% of the US population [24]. It is noteworthy that men were not more susceptible to these risk factors contrary to women [25].

Among adults, the body mass index (BMI) defines overweight and obesity as 25 kg/m^2 or greater and 30 kg/m^2 or greater, respectively. Among children and adolescents, overweight is defined as a BMI for age at or above the 95th percentile of a specified reference population. In 2003–2004, 32.9% of adults 20–74 years old were obese and more than 17% of teenagers (aged 12–19) were overweight [21]. Of note, children's obesity rate is lower; however, the increase in the prevalence of overweight is generally similar to the rise in obesity among adults [26].

Obesity initiates a cascade of metabolic and endocrine changes that contributes to an increased risk of diabetes, hypertension, and cardiovascular disease [1–3]. For example, it is suggested that 65–75% of the risk of hypertension is attributed to excess body weight [27, 28]. On the other hand, diabetes mellitus, which occurs with greater frequency in obese individuals [29], is the most common cause of CKD and end-stage renal disease (ESRD).

The specific risk level associated with a given obesity level may vary depending on gender, race, and socioeconomic condition [30]. Furthermore, race/ethnic differences in lifestyle and economic status may account for some of the race disparity in obesity-related diseases and outcomes [31]. On the other hand, socioeconomic status seems to play a strong role in the risk of obesity [32–34]. There is no evidence that obese or overweight patients receive inferior quality of care, compared with normal-weight patients [35]. Most of the excessive obesity trends have been noticed in communities with the highest rates of poverty and the lowest levels of education [36].

Obesity epidemic is in concert with the crescendo of adults with ESRD, a population that is expected to get doubled over the next decade [37]. CKD is a major worldwide public health problem [38], with an estimated prevalence of about 14.8% of the general population [39]. Both the incidence and prevalence of kidney failure treated by dialysis continue to increase [40] and during the past three decades they have been raising progressively [41].

Obesity and the risk for CKD

Obesity as a risk factor for CKD in epidemiological studies

Obesity epidemic has been paralleled by the increase in the incidence of CKD. In fact, there is a rapidly increasing prevalence of overweight and obese patients with CKD [23]. Obesity is not only a well-recognized risk factor for hypertension [42, 43] and diabetes [44], the most common etiologies of ESRD, [45] and indirectly linked to the development of CKD, but it predisposes directly to kidney disease, independently of diabetes and hypertension [17, 21, 22]. There is mounting evidence suggesting that increased BMI increases the risk of developing kidney impairment in the general population (Table 1). Noteworthily, long-term observational studies have shown a correlation between BMI and the incidence ESRD [11–19]. Hsu et al. assessed the impact of BMI on the risk of ESRD in a cohort of 330,252 persons from a large integrated health care delivery system in California, between 1964 and 1985. There was a strong dose–response relationship between the baseline BMI and the risk of ESRD. In particular, it has been demonstrated that the relative risk (RR) of ESRD was 3.57 [(95% coefficient interval (CI) 3.05,4.18)] compared to patients with an ideal BMI (18.5–24.9 kg/m), for those with stage 1 obesity (BMI 30–34.9 kg/m^2), 6.12 (95% CI 4.97,7.54) for those with stage 2 obesity (BMI 35–39.9 kg/m^2), and 7.07 (95% CI 5.37, 9.31) for those with morbid obesity (BMI $\geq$ 40 kg/m^2) [14]. In another study, Iseki et al., using data from a

Table 1 Obesity as risk factor for CKD in epidemiological studies

Studies	Follow-up-type of the study	Patients and ages	Primary endpoints	Results—conclusions
Iseki et al. [13]	Observational study 13-year follow-up	47,504 men 53,249 women, aged ≥20 years	Relationship between BMI and the development of ESRD	BMI for developing ESRD OR 1.273 (1.121–1.446) for men $P = 0.0002$) OR 0.950 (0.825–1.094) for women Higher BMI increased the risk of ESRD in men but not in women
Hsu et al. [14]	Observational study 8,347,955 person-years follow-up	320,252 adults	Association between BMI and risk for ESRD.	RR for ESRD 1.87 (1.64–2.14) for BMI, 25.0–29.9.9 3.57 (3.05–4.18) for BMI, 30.0–34.9 6.12 (4.97–7.54) for BMI, 35.0–39.9 7.07 (5.37–9.31) for BMI > 40 Higher BMI increased the risk of ESRD
HUNT-I study [17]	Retrospective cohort study, median 21-year follow-up	74,986 adults	Interaction between BP and body weight on the risk of ESRD on CKD-related death	In prehypertensive patients risk started to increase HR 1.21 (0.67–2.17) for BMI 18.5–24.9, HR 1.10 (0.59–2.00) for BMI 25.0–29.9, HR 2.66 (1.28–5.53) for BMI 30.0–34.9 HR 5.94 (1.94–18.20) for BMI 35.0 or >, Compared with BP less than 120/80 mmHg and BMI of 18.5–24.9 ($P = 0.02$ for trend). The risk of ESRD on CKD-related death associated with body weight started to increase from a BMI of 25
Framingham Heart Study [11]	Prospective cohort study, 18.5-year follow-up	2,676 adults 52% women; mean age 43 years	Association between BMI at baseline and incident stage 3 CKD(GFR < 59 ml/min/1.73 m^2 for women, GFR < 64 ml/min/1.73 m^2 for men)	There was no association between overweight individuals and stage 3 CKD incidence Obese individuals had a 68% increased odds of developing stage 3 CKD OR 1.68 (1.10–2.57) $P = 0.02$ which became nonsignificant in multivariable models OR 1.09 (0.69–1.73) $P = 0.7$
Ejerblad et al. [15]	Nationwide, population-based, case–control study	1,330 selected control subjects	The link between obesity and incident, moderately severe CKD	Relative to BMI < 25, BMI ≥ 25 at age 20 was associated with a significant 3-fold excess risk for CKD, BMI ≥ 30 among men and morbid obesity BMI ≥ 35 among women anytime during lifetime was linked to three- to fourfold increases in risk for CKD Two-to-threefold risk elevations were observed for all major subtypes of CKD
Ryu et al. [12]	Prospective cohort study 35,927 person-years follow-up	8,792 healthy men	Weight gain and the risk for incident CKD (GFR < 64 ml/min per 1.73 m^2)	U-shaped association between weight change categories and development of CKD Increases in body weight associated with an increased risk for CKD, even when the BMI remains within the normal range

Table 1 continued

Studies	Follow-up-type of the study	Patients and ages	Primary endpoints	Results—conclusions
Fox et al. [16]	Longitudinal cohort study 18.5-year follow-up	2,585 patients	Predictors of the development of new-onset kidney disease (GFR-MDRD $\leq$ 59.25 ml/min per 1.73 m^2 in women, $\leq$64.25 ml/min per 1.73 m^2 in men)	BMI increased the odds of developing kidney disease by 23% per SD unit OR 1.23 (1.08–1.43)
Elsayed et al. [18]	Prospective cohort study with a mean 9.3 years, follow-up	13,324 individuals	Association between anthropomorphic measures incident CKD and mortality	WHR, but not BMI, is associated with incident CKD and mortality
Gelber et al. [19]	Prospective cohort study with a mean 14 years, follow-up	11,104 healthy men	Association between BMI and risk for CKD (GFR $<$ 60 ml/min per 1.73 m^2)	Compared with participants in the lowest BMI quintile <22.7 those in the highest quintile >26.6 had OR 1.45 (1.19 1.76) *P* trend $<$ 0.001)

Abbreviations: *BMI* body mass index, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *OR* odds ratio, *RR* relative risk, *HR* hazard ratio, *BP* blood pressure, *WHR* waist-to-hip ratio, *HUNT-I* Health Study in Nord-Trondelag

community-based screening of 100,753 subjects, provided evidence that higher BMI at baseline increased the risk of ESRD after 17 years of follow-up only in men, but not in women [13]. Furthermore, a recent meta-analysis showed that overweight persons have a 40% higher risk of CKD and that obese persons have an 83% higher risk [46].

Obesity in individuals with normal renal function and in patients with mild and moderate CKD

The initial clinical evidence of kidney involvement in obesity is the presence of proteinuria, which usually precedes the glomerular filtration rate (GFR) decline by several years [20, 47]. In overweight and obese patients, the risk of incident dipstick proteinuria is 43–56% higher than in individuals with a BMI below 25 kg/m^2 [6, 48]. Proteinuria is less likely to be nephrotic [49] than in idiopathic focal and segmental glomerulosclerosis. In the Look AHEAD (Action for Health in Diabetes) Study, among 4,985 participants, the highest quartiles of BMI, [odds ratio (OR) 1.72 (95% CI 1.40–2.11)], and waist circumference (WC), [OR 1.75 (95% CI 1.42–2.15)], were significantly associated with albuminuria, compared to the lowest quartiles, after adjustment for covariates [50]. Results from the Framingham study cohort with more than 18.5 years of follow-up, 36% of whom were overweight and 12% obese, showed that 14.4% developed proteinuria and 7.9% stage 3 CKD. This increase in risk of stage 3 CKD was no longer significant after adjustment for cardiovascular risk factors. Thus, the relationship between obesity and stage 3 CKD may be mediated through cardiovascular disease risk factors [11].

Proteinuria is thought to be the result of glomerular hypertrophy and hyperfiltration due to hemodynamic changes. The question is whether interventions that reduce abdominal obesity could prevent the development of albuminuria. A recent meta-analysis showed that weight loss is associated with decreased proteinuria [51]; however there are no data to evaluate the effect of weight loss on CKD progression.

The effects of obesity on renal outcomes have been studied in patients with various kidney diseases, such as hypertensive kidney disease, specific glomerulopathies, or NDD-CKD [5–10] (Table 2).

In a cohort of 162 incident patients with biopsy-proven immunoglobulin A (IgA) nephropathy, the presence of elevated BMI at the time of the first biopsy was significantly associated with more severe pathological kidney lesions, increased proteinuria and subsequent development of CKD [6].

Table 2 Obesity-survival associations in mild and moderate CKD population

Studies	Follow-up-type of the study	Patients and ages	Primary endpoints	Results—conclusions
HDFP study, Kramer et al. [5]	Observational study 5-year follow-up	Incident patients with ESRD by year dialysis initiation	BMI in incident ESRD patients compared with the US population	BMI slope was approximately twofold higher in the incident ESRD population compared with the US population for all age-groups BMI is a risk factor for ESRD
Bonnet et al. [6]	Observational study	162 incident patients with biopsy-proven immunoglobulin A (IgA) nephropathy	Association between BMI and risk for CKD	Increased BMI is a predictive factor for the development of arterial hypertension and CKD
Obermayr et al. [8]	Longitudinal cohort study with follow-up period 5.5 ± 4.2 years	2,487 patients with mild CKD and 392 patients with moderate CKD	Relationship of BMI with earlier stages of CKD concerning cardiovascular mortality. Possible risk modification by proteinuria (mild CKD proteinuria and MDRD-GFR > 60 ml/min/1.73 m^2) (moderate CKD MDRD-GFR = 30–59 ml/min/1.73 m^2)	In moderate CKD for cardiovascular mortality HR 1.28 (0.33–5.82) at BMI 20 versus 25 HR 0.76 (0.38–1.50) at BMI 30 versus 25 HR 0.58 (0.13–2.64) at BMI 35 versus 25 In moderate CKD with proteinuria HR 9.43 (2.66–27.40) at BMI 25 HR 3.74 (0.93–15.70) at BMI 30 HR 1.95 (0.37–22.30) at BMI 35 In proteinuric CKD, BMI was associated with a reduced risk of death
Kovesdy et al. [9]	Prospective cohort with a follow-up for up to 5.5 years	521 male's age, 68.8 ± 10.4 years with CKD	Associations between BMI and all-cause mortality CKD(MDRD-GFR = 37.5 ± 16.8 ml/min/1.73 m^2)	HR for mortality versus <10th percentiles, HR 0.75 (0.46–1.22), BMI in 10th to 50th, HR 0.56 (0.33–0.94), BMI in 50th to 90th, HR 0.39 (0.17–0.87); BMI > 90th *P* (trend) = 0.005) Higher BMI was associated with lower mortality
Kwan et al. [10]	ARIC Study with a mean follow-up 10 years	15,355 participants 461 CKD patients	Associations between BMI and all-cause mortality CKD patients (stage 3 and 4)	U-shaped association of BMI with mortality In CKD patients, higher BMI associated with lower mortality
Evans et al. [7]	Population-based inception cohort with a median follow-up 5 years	920 patients aged 18–74 years with CKxD	Mortality rates in CKD patients Scr > 3.4 mg/dl, MDRD-GFR 17.5 ml/min/1.73 m^2 for men (Scr > 2.8 mg/dl, MDRD-GFR 15.9 ml/min/1.73 m^2 for women	Low BMI associated with higher mortality

Abbreviations: *BMI* body mass index, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate, *HR* hazard ratio, *HDFP* hypertension and follow-up program

However, in contrast with the above findings, other studies suggest beneficial effects of obesity in CKD patients. In a longitudinal cohort study with a more than 5-year follow-up period, the relationship of BMI with earlier stages of CKD concerning cardiovascular mortality as well as the possible risk modification of proteinuria was investigated. Impressively, it has been shown that in proteinuric CKD patients, BMI

was inversely correlated with the risk of death [8]. Prospective cohort studies with NDD-CKD participants investigated the association between BMI and mortality and showed that highly elevated BMI may reduce the risk of cardiovascular death [7, 9, 10] (Table 2).

Obesity in end-stage renal disease and dialysis patients

In a large cohort of 5,897 incident dialysis patients with hypertension from the Hypertension and Follow up Program (HDFP), significant associations of overweight and obesity with the development of ESRD were noted during a 5-year- follow-up, suggesting that obese adults with hypertension have an increased risk of ESRD [52].

In hemodialysis (HD) patients, already known key risk factors such as obesity, hypercholesterolemia, and hypertension are inversely related to mortality [53]. An increased number of epidemiological studies and analyses of large samples of dialysis patients (Table 3) indicated that high BMI is associated with improved survival [54–60]. Although studies in CKD patients undergoing peritoneal dialysis (PD) have yielded conflicting results, high BMI was shown to be an independent positive predictor of patient survival [61, 62]. In a recent large prospective study on a total of 5,592 patients, the association between BMI and mortality was examined. At the start of dialysis, patients were classified in four categories according to the BMI: underweight, normal range, overweight, and obese. Also, patient survival was analyzed according to five quintiles of body weight changes during the first year of HD treatment $<-5.8\%$, -5.8 to -1.1%, -1.1 to 1.7% (reference category), $+1.7$ to $+5.5\%$, and $>+5.5\%$. Survival was significantly lower in patients presenting the lower quintile of body weight change ($<-5.8\%$ in 1 year), whereas overweight and obese patients carried a significant lower mortality risk than patients in the normal and lower BMI ranges [55].

These findings are in contrast to the well-known association between over-nutrition and poor outcome among the general population. The association between under-nutrition and adverse cardiovascular outcome in dialysis patients, which stands in contrast to that seen in non-ESRD individuals, has been referred to as "*reverse epidemiology*". Even though the term is valid only for the inflammated patients, the etiology of this inverse association between conventional risk factors and clinical outcome in dialysis patients is not clear [63]. One possible explanation is that patients on HD with decreased nutritional reserve over time are not able to withstand inflammation, insufficient protein-calorie intakes, chronic acidosis, as well as vascular access failures, hospitalizations, and suboptimal small and middle solute clearance. Therefore, according to the aforementioned studies, HD patients with increased BMI may have a lower mortality risk [54, 55, 57, 60].

Obesity in kidney transplant patients

In the past years, a growing body of evidence has indicated that renal transplant recipients with elevated BMI have inferior patient and graft survival compared to patients with lower BMI [64–68] (Table 4). In a study including 292 renal transplant recipients, the impact of post-transplant weight gain on graft survival at the time of transplantation as well as 1 year post-transplant was explored. In multivariate analysis, patients with an increase in BMI of more than 5% at 1 year post-transplant had an increased risk of graft loss [64]. In a retrospective analysis of 51,927 primary, adult renal transplants registered in the United States Renal Data System (USRDS), BMI was significantly associated with outcomes after renal transplantation, independently of most of the known risk factors for patient and graft survival. Very high BMI was strongly associated with worse patient and graft survival [65]. In a retrospective study of 193 consecutive, adult renal transplant patients, with at least 6 months follow-up, those with a BMI ≥ 30 were less likely to experience graft loss. In this study, the rates of acute rejection were not increased in obese recipients, and the ratio of recipient-to-donor BMI did not influence graft survival. However, while mortality was not increased in the BMI > 30 group, morbidity, especially surgery-related, had an increased incidence [66]. On top of these, there is evidence that obesity in kidney transplant patients predicts increased cardiac risk, especially for chronic heart failure and atrial fibrillation [67].

It is now clear that the majority of the studies found a direct relationship between BMI and

Table 3 Obesity-survival data in dialysis patients (HD, PD)

Studies	Follow-up-type of the study	Patients and ages	Primary endpoints	Results—conclusions
Degoulet [56]	Prospective, observational study	1,453 HD patients	Association between BMI and risk of mortality	High BMI was found to be associated with significantly decreased cardiovascular mortality
Leavey et al. [54]	Prospective, observational study	9,714 HD patients	Association between BMI and risk of mortality	Relative mortality risk decreased with increasing BMI. ($P < 0.007$) Lower relative mortality risk (RR) as compared with BMI 23–24.9 was found for overweight (BMI 25–29.9; RR 0.84, $P = 0.008$), for mild obesity, BMI 30–34, 9; RR 0.73, $P = 0.0003$, for moderate obesity BMI 35–39.9; RR 0.76, $P = 0.02$
Joahansen [57]	Observational study with a 2-year average follow-up time	418,055 patients beginning dialysis	Relation between survival and BMI	High BMI was associated with increased survival even at extremely high BMI. This was not true for Asians
Chazot et al. [55]	Prospective study with mean follow-up 2.0 ± 1.6 years	5,592 incident in HD patients	Association between BMI and risk for mortality	HR 1.14 (0.96–1.35) for BMI < 24.9 1.074 (0, 67–0.9) for BMI 20–24.9 0.78 (0.56–0.87) for BMI ≥ 25 Overweight and obese significantly improved the survival
CANUSA study [61]	Prospective cohort study	680 PD patients	Relationship of adequacy of dialysis and nutritional status to mortality	1% difference in percent lean body mass was associated with a 3% change in the RR of death
Johnson, [62]	Prospective, observational study over a 3-year period	43 PD patients	Association between BMI cardiovascular outcomes and survival in PD patients Overweight BMI > 27.5 normal-weight BMI 20–27.5	BMI > 27.5 was shown to be an independent positive predictor of patient survival HR 0.09 (0.01–0.85) $P < 0.05$
Kaizu et al. [59]	Observational study with a median follow-up 13 months	45,967 HD patients	Relationship between survival and BMI	The lowest BMI group had a 42% higher mortality risk than the highest BMI tertile
Kopple et al. [60]	Retrospective study	Approximately 13,000 HD patients	Association between body composition and mortality	Patients who had greater weight for height percentiles had lower mortality rates
Kaizu et al. [58]	Observational study for up to 12 years	116 non-diabetic HD patients	Relation between survival and BMI	Patients with BMI < 16.9 and >23.0 showed lowered survival compared to patients with BMI of 17.0–18.9

Abbreviations: *BMI* body mass index, *RR* relative risk, *HR* hazard ratio, *HD* hemodialysis, *PD* peritoneal dialysis

cardiovascular risk. Furthermore, a continuous positive relationship between BMI and increased glomerular filtration fraction has been documented throughout the entire range from normal-to-abnormal BMI values [69], while other studies suggest a J-shaped association [14, 16]. There is growing evidence that overweight and increased BMI in adolescents is predictive of CKD in adult life [15]. Even in men as young as 18 years old, unadjusted estimated creatinine clearance is progressively higher in individuals with increasing BMI [70]. When BMI is in the normal range, the increase in body weight is independently associated with an increased risk of CKD [12]. On the other hand, as mentioned above in NDD-CKD population, higher BMI is associated with kidney function deterioration but with lower

Table 4 Obesity-survival associations in kidney transplant patients

Studies	Follow-up-type of the study	Patients	Primary endpoints	Results—conclusions
Duclux et al. [64]	Observational study 1-year follow-up	292 renal transplant recipients	Relationship between BMI and the development of ESRD	Increase BMI of more than 5% had an increased risk of graft loss HR: 2.82 [95% CI: 1.11–7.44], $P = 0.015$)
Meier-Kriesche et al. [65]	Retrospective study	51,927 primary, adult renal transplants	Association between BMI and risk for worse long-term graft survival	Very high and very low BMI were associated with significantly worse patient and graft survival
Massarweh et al. [66]	Retrospective study at least 6-month follow-up (mean 24 ± 14.1 months)	193 adult renal transplants	Association between BMI and risk for worse long-term graft survival.	Individuals with a BMI ≥ 30 were not more likely to experience graft loss (OR 0.93, 95% CI 0.50, 1.72).
Lentine et al. [67]	Retrospective study	1,102 renal allograft recipients at a single center in 1991–2004	Association between BMI at transplant patients and increased cardiac risk	Obesity at transplant kidney patients predicts increased cardiac risk, especially of CHF and AF
Kovesdy et. al. [68]	Prospective study	Cohort of 993 kidney transplant recipients	Association between BMI and waist circumference with all-cause mortality	Higher BMI was associated with lower mortality after adjustment for waist circumference (0.48 [0.34, 0.69], $P < 0.001$) Higher WC was more strongly associated with higher mortality after adjustment for BMI (2.18 [1.55–3.08], $P < 0.001$) WC appears to be a better prognostic marker for obesity than BMI

Abbreviations: *BMI* body mass index, *ESRD* end-stage renal disease, *OR* odds ratio, *RR* relative risk, *HR* hazard ratio, *WC* waist circumference, *CHF* chronic heart failure, *AF* atrial fibrillation

mortality rates [7, 9, 10]. Furthermore, all of the data in patients undergoing maintenance HD support the concept that mortality risk is decreased with increasing BMI. In contrast, in renal transplant recipients, higher BMI is associated with worse patient and graft survival.

Central body fat versus BMI

The next logical question is whether central obesity or BMI *per se* could be a stronger predictor of CKD. It has been suggested that central obesity with waist circumference measurement may be a better predictor than BMI [71, 72]. However, there is evidence that the central distribution of body fat is related to a variety of physiological abnormalities. Central body fat is associated with hypertension, hyperlipidemia, hyperinsulinemia, and atherosclerosis [72]. Furthermore, in a study of nondiabetic subjects, elevated waist-to-hip ratio (WHR) increased the risk of diminished GFR, whether they were lean, overweight, or obese [71]. In a recent study, patients with ESRD with large WC and low BMI were at the highest risk of overall and cardiovascular mortality [73]. On the other hand, BMI per se does not differentiate between fat and muscle mass. This is best exemplified by data from a recent study, in which the relationship between measures of fat, muscle mass, and mortality was examined in 1,709 patients during a median follow-up of 2.5 years. Triceps skin-fold thickness was used to assess body fat, and mid-arm muscle circumference was used to assess muscle mass. In multivariate analysis and adjusted models, lower quartiles of triceps skin-fold thickness, mid-arm muscle circumference, and BMI were all significantly associated with higher all-cause mortality [74]. In practical terms, body composition in ESRD patients bears a complex relationship to all-cause mortality. However, it is important to point out that in ESRD patients [73] and in kidney transplant patients [68], higher waist circumference was more strongly associated with higher mortality after

adjustment for BMI. Furthermore, higher BMI and waist circumference display opposite associations with mortality, and waist circumference appears to be a better marker of obesity than BMI [68, 73].

Kidney histopathology in obesity

It is clear from the foregoing discussion the adverse effect of obesity in patients with primary or with specific kidney disease [6, 52, 64–66]. In kidney biopsies of obese patients, the type of kidney disease that has become recognized is the so-called *obesity-related glomerulopathy* with or without focal segmental glomerulosclerosis [49]. The frequency has been increased from 0.62 to 1.0% during the last 5 years ($P = 0.02$) [75]. The biopsy specimens shows glomerulomegaly, increased mesangial matrix and proliferation, podocyte hypertrophy, lesions of segmental sclerosis and food process effacement, thickening of the glomerular basement membrane with interstitial fibrosis [49, 76, 77].

It should be acknowledged that the individual risk of developing glomerulopathy connected to obesity is very low. It is proposed that glomerular hyperfiltration/hypertrophy is *per se* not pathogenic in the absence of an enhanced glomerular blood pressure transmission, and the modest preglomerular vasodilatation that is likely present in the large majority of obese individuals is not sufficient to result in such increased blood pressure transmission [78]. In extremely obese people with normal kidney function prior to bariatric surgery, the majority had increased mesangial matrix mesangial cell proliferation, podocyte hypertrophy, and glomerulopathy. The risk factors of developing glomerular lesions were weight related [77]. These findings resembled those described at early stages of diabetic nephropathy and are observed even before the appearance of microalbuminuria [79].

Mechanism of kidney failure in obesity

Obesity, renin–angiotensin–aldosterone system activation and hypertension

The renin–angiotensin–aldosterone system (RAAS) is a well-coordinated hormonal mechanism that regulates adrenal, cardiovascular as well as kidney function by controlling fluid and electrolyte balance. A number of mechanisms have been proposed to be responsible for modifying blood pressure and renal function via homeostasis of renal salt and water, alteration in sympathetic nerve activity, and changes in vascular tone [80]. Furthermore, the RAAS regulates vasomotor tone, cellular proliferation, and structure in the kidney.

In obese individuals, commonly the RAAS is activated. It has been demonstrated that weight loss is accompanied by reductions in plasma renin activity (PRA) and aldosterone, and PRA reductions, irrespective of sodium intake [81]. For example, a 5% reduction in body weight can lead to a meaningfully reduced RAAS in plasma and adipose tissue, which may contribute to the reduced blood pressure [82].

The pathogenesis of obesity-related hypertension and kidney function impairment is highly complex. Vasoconstriction and sodium retention are promoted by several acting together factors [83]. Various factors need to be accounted for when you consider potential mechanism of kidney impairment related to obesity. Evidence is growing that local RAAS seems to be differently regulated in subcutaneous adipose tissue from obese patients with hypertension in comparison with normotensive obese patients and controls [84]. In particular, it has demonstrated the presence—and different levels of expression—of the various components of the RAAS system (angiotensinogen-AGT), angiotensin II type receptor (AT1), and angiotensin-converting enzyme (ACE) in human subcutaneous adipose tissue and in visceral adipose tissue. These observations highlight the different role and regulation of the system in the two tissues. Its high expression in visceral adipose tissue suggests that its regulation and function are involved in all conditions where visceral adiposity is present [85]. Angiotensin II (AgII), the final effector of the RAAS, is locally produced. The function of adipose RAAS is not well known; besides participating, together with other hormones and substances, in adipocyte differentiation and fat tissue growth, it could also be involved in the pathogenesis of the complications of obesity-related renal failure and obesity-related hypertension [86]. Positive and significant correlation was found between the expression of AGT in visceral adipose tissue and BMI. These data suggest that angiotensinogen may be determinant of fat

distribution and may be involved in the plurimetabolic syndrome of central obesity [87].

Adipose tissue, leptin, adiponectin, and fetuin-A

Adipose tissue is a prolific organ that secrets several immunomodulators and bioactive molecules [88, 89]. Leptin is a hormone with significant pleitropic actions on several systems [90, 91]. The role of leptin in the kidney is not completely defined. It seems to be a potential salt-regulating factor and may function pathophysiologically as a common link to obesity and hypertension [90]. It is also recognized that conditions of hyperleptinemia have been linked to renal structural changes that were particularly associated with obesity [92, 93]. Leptin is partly cleared by the kidney, and hyperleptinemia has been demonstrated in patients with kidney disease [94] and is elevated in HD patients [95]. Furthermore, in PD patients, the elevated body fat mass appears to contribute to more elevated leptin levels [96].

Insulin resistance, oxidative stress, and inflammation have all been implicated in albuminuria and renal dysfunction, although the picture is not entirely clear [97]. Elegant studies implicate low adiponectin in the pathogenesis of renal disease in obesity. Adiponectin is secreted by adipocytes [98] and circulates in plasma as various complexes, such as high molecular weight, low molecular weight, and trimeric forms. High molecular weight levels are in great quantity in women and fails gradually in obesity [98]. Low adiponectin levels are associated with higher prevalence of inflammation, type 2 diabetes, and atherosclerosis [98]. Furthermore, low plasma adiponectin was related to increased urinary albumin excretion in African-Americans, a group disposed to CKD and obesity [99]. Treatment with adiponectin reverses the fusion of podocyte foot processes in adiponectin-negative (-) mice and improved urinary albuminuria, glomerular hypertrophy, and tubulointerstitial fibrosis [99]. These changes were associated with the anti-inflammatory role of adiponectin in the kidney in accordance with its similar action in the vasculature and the other organs [100].

Another point of importance is the association of the glycoprotein fetuin-A with obesity in patients with CKD. Higher levels of fetuin-A are associated with obesity and insulin resistance both in the general population [101, 102] and in patients with CKD [103]. In particular, fetuin-A was recognized as a promoter of insulin resistance, because it inhibits the insulin receptor tyrosine kinase in the muscles and the hepatocytes. This action results in insulin resistance due to inhibition of the insulin signal transduction at the target tissue [104, 105]. It is also recognized that the high levels of fetuin-A have the same effects as the low levels of adiponectin because the two proteins have the same results but in the opposite direction [106]. There is a specific effect of fetuin-A on adiponectin. It is noteworthy that treatment with fetuin-A lowered adiponectin levels probably because fetuin-A inhibits the generation of adiponectin in the adipose tissue and furthermore fetuin-A suppresses mRNA encoding in cultured human adipocytes [107].

Potential interventions to prevent injury

In the aforementioned recent meta-analysis by Wang et al. was estimated that more than one-forth (24.2% in men vs. 33.9% in women) of CKD cases in the United States and one-fifth in industrialized countries (16.5% vs. 26.3%) could be prevented by eliminating overweight and obesity [46]. Undoubtedly, preventing obesity not only must be considered a public health priority, but it needs to be controlled as a chronic disease in an effort so that the ultimate goal is realized. It is reasonably the first attempt to be dietary. Curing obesity must be an ultimate goal as a modifiable risk factor in early nephropathy [108]. Weight loss improves the glomerular hemodynamic abnormalities associated with over obesity in subjects without overt kidney disease. Elevated GFR and renal blood flow (RBF) decreased after weight loss, and this reflect mainly decreased in a single-nephron plasma flow and a single-nephron GFR [109]. A lower pressure is transmitted to the glomerular capillaries due to decreased systemic arterial pressure and an increase in afferent arteriole resistance resulting in a diminished GFR [110]. Furthermore, the fractional excretion of albumin decreased following weight loss, possibly by altering glomerular permselectivity of affecting glomerular cell metabolism and the transforming growth factor (TGF-b) production [111–113]. Weight reduction results in a significant decrease in arterial pressure mediated in part through a reduction in peripheral resistance

[114], and this could be translated as prevention of renal and cardiovascular disease. Potential interventions with antihypertensive treatment that target RAAS may improve the kidney outcome in obese patients. In a recent study, the effects of treatment with Ag II type-1 receptor blocker (ARB) on the regulation of adipocytokines were determined. The ARB Olmesartan significantly blunted the age- and body weight-associated falls in plasma adiponectin both in genetically and in diet-induced obese mice, without affecting body weight, but had no effect on plasma adiponectin levels in lean mice. These results indicated that blockade of Ang II receptor ameliorates adipocytokine dysregulation and that such action is mediated, at least in part, by targeting oxidative stress in obese adipose tissue. Ang II signaling and subsequent oxidative stress in adipose tissue may be potential targets for the prevention of atherosclerotic cardiovascular disease in metabolic syndrome and also in metabolic syndrome-based CKD [115].

Conclusions

Obesity has reached epidemic proportions and continues to be a growing problem worldwide. What is more, it has increased the incidence of diabetes, hypertension, and heart disease and is associated with an increased risk for CKD worsening in this group of patients. Furthermore, it predisposes toward kidney disease independently of diabetes and hypertension. In fact, the presence of proteinuria is actually the initial clinical evidence of involving kidney and obesity. However, a significant percentage of CKD cases could be prevented by eliminating overweight and obesity. Hopefully, potential interventions that target RAAS may improve the kidney outcome in obese hypertensive patients.

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