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Obesity and Chronic Kidney Disease

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Abstract

Background/Aims: The prevalence of obesity among U.S. adults has doubled within the past two decades, and if trends continue, over one-third of U.S. adults may be obese by the year 2008. Concurrent with the rising prevalence of obesity is an epidemic of chronic kidney disease (CKD) with an estimated 18 million U.S. adults currently affected. This review discusses the strong and consistent association between CKD risk and increasing body mass index noted in several observational studies. Potential mechanisms for obesity's role in the development and progression of CKD and secondary focal segmental glomerulosclerosis are also discussed. **Methods:** Literature review. **Results:** Although obesity is an important risk factor for diabetes and hypertension, the two most common etiologies of kidney failure, obesity itself may increase CKD risk by increasing the metabolic demands on the kidney, which leads to higher glomerular capillary pressures and glomerular hypertrophy. The hyperinsulinemia frequently linked with obesity may also accelerate structural damage by interacting with angiotensin II and increasing collagen production and deposition. The histologic changes in the kidney noted in some obese, especially morbidly obese, adults frequently mimic those changes associated with secondary focal segmental glomerulosclerosis, which may occur in disease states such as severely reduced nephron mass and hemodynamic stress. Given the presence of genetic susceptibility and/or reduced nephron mass, obesity may potentiate the development and progression of secondary focal segmental glomerulosclerosis. **Conclusions:** Obesity is an important risk factor for CKD. Treatment plans for obese adults with CKD should include weight loss and exercise because these interventions may simultaneously reduce the metabolic demands on the kidney, lower systemic and glomerular pressures, and improve insulin sensitivity. However, more studies are needed to further optimize the treatment and prevention of CKD associated with obesity.

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Epidemiology of Obesity

The U.S. and most other developed countries are facing a growing epidemic of obesity. Within the past 20 years, the prevalence of obesity among U.S. adults

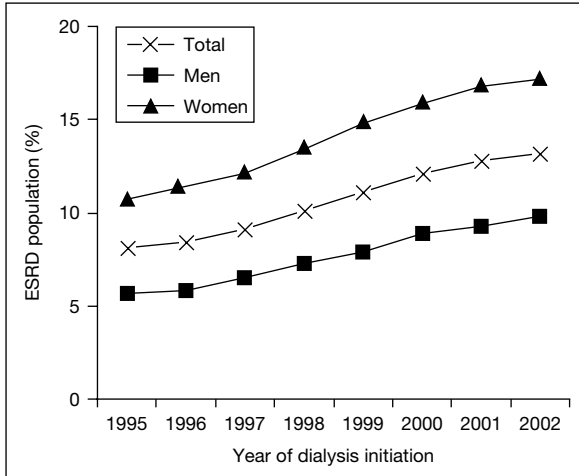


Fig. 1. Prevalence of obesity among incident dialysis patients by year of dialysis initiation. Adapted from reference [6].

has doubled from 15 to 30.5% [1]. If trends continue as projected, 39% of U.S. adults may be obese by the year 2008 [2]. Data from the 1999 to 2000 National Health and Nutrition Examination Survey show that approximately two-thirds of U.S. adults are now overweight or obese [1], a substantial increase from the 56% prevalence of overweight and obesity noted in the survey conducted during 1988–1994 period. The number of morbidly obese U.S. adults, defined as a body mass index (BMI) ≥ 40 kg/m² has quadrupled from 1 in 200 adults to 1 in 50 [3]. The prevalence of obesity worldwide has increased sharply from approximately 200 million adults in 1995 to over 300 million adults in 2000 [4]. Currently, the number of overweight or obese adults worldwide exceeds one billion [4]. Among developing nations, overnutrition now frequently coexists with undernutrition, especially in urban areas [5], and over 115 million people in developing countries now face obesity-related health problems [4].

Epidemiology of CKD in Overweight and Obese Adults

Evidence of the obesity epidemic may be witnessed in the changing demographics of the U.S. incident dialysis population. From 1995 to 2002, the rate of increase in mean BMI among the incident end-stage renal disease (ESRD) population was approximately 2-fold higher compared to the U.S. population and these findings were consistent across all age groups [6]. The increasing prevalence of obesity among incident U.S. dialysis patients is shown in figure 1.

In 2002, 13% of all patients initiating dialysis had a BMI ≥ 35 kg/m², an obesity level which may preclude transplantation. By 2007, this may increase to 18% [6]. Currently, 60% of all ESRD patients who receive a kidney transplant are either overweight or obese at the time of transplantation [7]. Not only is the average body habitus of the ESRD population expanding, but the total number of prevalent ESRD patients in the U.S. is expected to increase by 70% over the next decade exceeding 700,000 patients by the year 2015 [8].

In order to address the expanding number of patients with kidney disease, the National Kidney Foundation created guidelines for the detection and assessment of chronic kidney disease (CKD) [9]. These guidelines define CKD as the presence of kidney damage and/or a glomerular filtration rate (GFR) < 60 ml/min/1.73 m² body surface area for ≥ 3 months. Kidney damage may be indicated by increased urine albumin excretion, histological changes or abnormalities in the urine sediment and/or imaging tests. CKD has been divided into 5 stages depending on the estimated GFR. Stages 1 and 2 are defined as normal (≥ 90 ml/min/1.73 m²) or mildly decreased (60–89 ml/min/1.73 m²) GFR, respectively, given the presence of other markers of kidney damage such as increased urine albumin excretion. Stages 3–5 are classified as a GFR < 60 ml/min/1.73 m² regardless of other markers of kidney damage. Stage 5 includes patients with kidney failure or GFR < 15 [9].

The majority of information on CKD prevalence in the U.S. is based on data from national multistage complex probability health surveys called the National Health and Nutrition Examination Surveys (NHANES). These surveys provide estimates of health indicators and disease prevalence as if the entire non-institutionalized population had been surveyed. NHANES participants provide blood and spot urine samples which are analyzed for serum creatinine and albumin/creatinine ratios, respectively. GFR is then estimated using the modified Modification of Diet in Renal Disease (MDRD) GFR prediction formula [10] after calibrating serum creatinine values with the MDRD laboratory. Prevalence estimates of stages 1 and 2 CKD are based on persistent albuminuria (spot urine albumin/creatinine ratio ≥ 30 mg/g) in the setting of a GFR ≥ 60 ml/min/1.73 m². Due to sampling estimates, the number of adults with stage 5 CKD is extremely small and unreliable; thus, survey estimates focus on stages 1–4 CKD.

According to the NHANES completed during 1999–2000, stage 3–4 CKD (estimated GFR 15–59 ml/min/1.73 m²) is present among 3.8% of U.S. adults with a population estimate of seven million [11]. An additional 11 million U.S. adults have stages 1–2 CKD [11]. CKD prevalence is substantially higher among adults with hypertension or diabetes compared to healthy adults. In fact, only 1.4% of adults without hypertension or diabetes have stages 3–4 CKD. Prevalence of CKD also varies by BMI categories. For example, prevalence of GFR < 60 ml/min/1.73 m² increases from 2.9% among adults with an ideal BMI

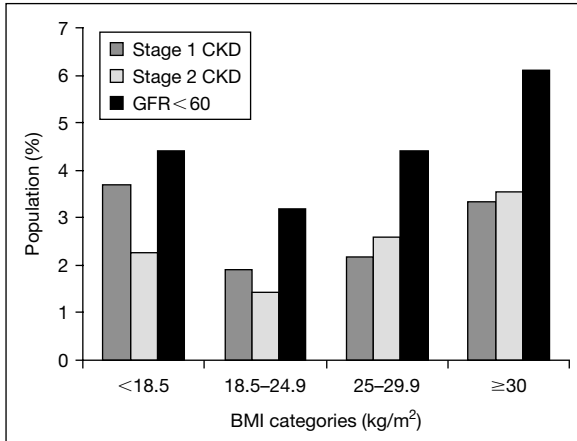


Fig. 2. Prevalence of CKD by BMI categories. National Health and Nutrition Examination Survey 1999–2000. Data are age adjusted for U.S. 2000 census. Unpublished data.

(18.5–24.9 kg/m²) to 4.5% among obese adults (BMI ≥ 30 kg/m²) [12]. Even after age adjustment, the prevalence of GFR < 60 ml/min/1.73 m² remains higher among obese adults compared to adults with an ideal BMI (fig. 2).

Using data from the Hypertension Detection and Follow-Up Program (HDFP), we tested the hypothesis that overweight and obesity are associated with incident CKD in hypertensive adults [13]. The HDFP is a multi-center, 5 year randomized trial comparing stepped care (SC) vs. referred care (RC) for the treatment of hypertension in approximately 10,000 White and African-American adults. Serum and spot urine samples were collected at baseline and at year five. CKD was defined as the presence of ≥1+ proteinuria on routine urinalysis and/or an estimated GFR < 60 ml/min/1.73 m² using the MDRD GFR prediction equation. After excluding participants with CKD at baseline, overweight (OR: 1.21; 95% CI: 1.05, 1.41) and obesity (OR: 1.40; 95% CI: 1.20, 1.63) were both associated with increased odds of incident CKD at year five after adjustment for covariates including diabetes mellitus (DM), blood pressure and hypertension treatment. Results did not change substantially after exclusion of participants with diabetes [13].

Similar results were noted in a cohort of approximately 11,000 healthy male physicians followed for 14 years in the Physicians Health Study, a randomized trial of aspirin and beta-carotene for primary prevention of cardiovascular disease and cancer completed in the 1980s [14]. CKD in this study was defined as an estimated GFR < 60 ml/min/1.73 m² using the MDRD GFR prediction equation. Participants in the highest BMI quintile (>26.6 kg/m²) at

baseline had a 45% increased odds (95% CI: 1.19, 1.76) of CKD at study end compared to participants in the lowest quintile (BMI < 22.7 kg/m²) after adjustment for age, smoking, exercise, alcohol consumption, and family history of premature cardiovascular disease [14]. The association between BMI and risk of CKD was not modified by physical activity, but further adjustment for baseline hypertension and diabetes decreased the odds of CKD to 1.26 (95% CI: 1.03, 1.54) [14]. A population based prospective study of Japanese adults without baseline proteinuria or renal insufficiency, defined as a serum creatinine >1.2 and >1.0 mg/dl in men and women, respectively, reported a 45% increased risk (95% CI: 1.13–1.86) of developing proteinuria over a 2-year period in obese adults compared to lean adults after adjustment for hypertension and DM [15].

Few studies have examined whether obesity increases risk of ESRD due to the large sample size needed to study this uncommon outcome. However, a study by Hsu et al. showed a very strong biologic gradient whereby increasing levels of BMI were associated with increasing risk of ESRD. The study cohort consisted of 320,252 adults who volunteered for a screening health checkup between 1964 and 1985 and were followed until death, ESRD or December 31, 2000. Cases of ESRD including transplantation, hemodialysis and peritoneal dialysis were ascertained by linking the Kaiser Permanente data with the U.S. Renal Data System registry. Compared to patients with an ideal BMI of (18.5–24.9 kg/m²), relative risk of ESRD was 3.57 (95% CI: 3.05, 4.18) for those with BMI of 30–34.9 kg/m², 6.12 (95% CI: 4.97, 7.54) for those with BMI 35–39.9 kg/m² and 7.07 (95% CI: 5.37, 9.31) for those with BMI ≥ 40 kg/m². Controlling for baseline blood pressure and presence of diabetes did attenuate the associations but the strong gradient between increasing body size and ESRD risk remained. Among 100,753 Japanese adults followed for 17 years, the cumulative incidence of ESRD was over 2-fold higher in adults with baseline BMI ≥ 25.5 kg/m² compared to adults with baseline BMI < 21.0 kg/m² [16]. However, after stratification by sex, the association between BMI and risk of ESRD was only noted in the men.

Obesity Is a Risk Factor for CKD Risk Factors

Obesity is a well-recognized risk factor for diabetes [17–19] and hypertension [20–22], thus, the global obesity epidemic translates into substantially heightened CKD risk factors worldwide. In fact, the number of adults with diabetes worldwide is expected to exceed 300 million by the year 2030 [4]. According to the World Health Organization, over half of the 177 million cases of DM worldwide in 2000 may be attributed to overweight and obesity [4].

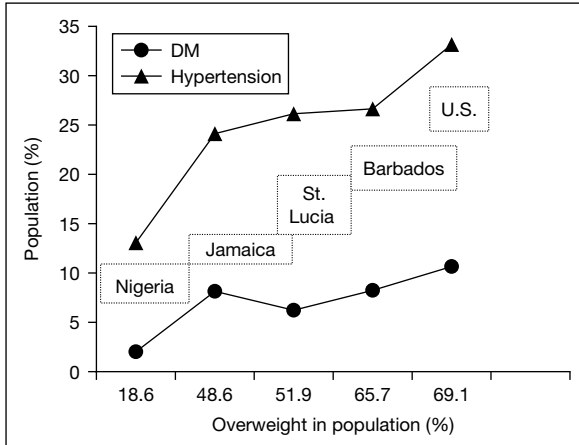


Fig. 3. Prevalence of diabetes and hypertension across the African diaspora by prevalence of overweight in the respective countries. Adapted from references [25, 26].

Among U.S. women, the prevalence of type 2 diabetes ranges from 2.4% with an ideal BMI to 7.1% in the overweight to almost 20% in the morbidly obese [23]. Prevalence rates of type 2 diabetes among men also increase steeply across BMI categories as well, but remain below levels noted among women [23]. Diabetes and hypertension remain the two most common etiologies of ESRD accounting for approximately 45 and 25% of all prevalent ESRD cases [24]. Incidence of ESRD secondary to diabetes has grown substantially over the past two decades with rates increasing from 12.5 per million population in 1980 to 146.8 per million population in 2000 [24]. Although incidence rates appear to have plateaued over the past several years [24], it is doubtful we will see rates of diabetic kidney failure decline substantially anytime within the next decade.

In the U.S., prevalence of hypertension, diabetes and kidney disease are substantially higher among African-Americans and Native Americans compared to whites, suggesting the role of genetic factors. However, international studies of populations of African origin have shown a strong gradient of hypertension and diabetes prevalence across the African Diaspora. This spectrum of risk is positively correlated with BMI and varies consistently with environmental factors, especially obesity and intake of sodium and potassium [25, 26] (fig. 3). Similar findings have been found among Pima Indians with diabetes prevalence 6-fold higher among those living in the U.S. compared to those living in Mexico [27]. Higher blood pressures are also noted among U.S. Pima Indians compared to Mexican Pima Indians [27]. Most of these differences can be explained by diet, physical activity and obesity, which is 4-fold more

prevalent among Pima Indians living in the U.S. compared to those living in Mexico [27]. These findings do not rule out genetic susceptibility among these populations, but they do demonstrate the importance of environmental factors, especially obesity, in the development of CKD risk.

Obesity, especially abdominal obesity, not only increases the risk of hypertension, but also makes hypertension more resistant to treatment [28]. The higher blood pressures associated with overweight and obesity are probably due to multiple factors and include activation of the sympathetic nervous and renin–angiotensin systems [19, 29], increased serum leptin levels [30–33], volume expansion [19, 29], and sleep apnea [34, 35]. Uncontrolled hypertension in obese adults may certainly accelerate loss of kidney function over time, especially when compounded by the additional CKD risks, which accompany obesity as detailed below.

Obesity as an Independent Risk Factor for CKD

Obesity may be the number one preventable risk factor for CKD due to its strong link with diabetes and hypertension, the two primary causes of CKD and kidney failure. Aside from its link with traditional CKD risk factors, obesity itself may increase susceptibility to CKD via several potential mechanisms. The fact that central adiposity modifies the association between overweight and obesity and measures of CKD point to the potential role of the metabolic syndrome [36–39]. The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study collected two 24-hour urine samples and one serum sample from 8,592 adults between the ages of 28 and 75 living in Groningen, The Netherlands who attended an outpatient screening program. The prevalence of microalbuminuria, defined as an average urine albumin excretion ≥ 30 mg/24 h, not only increased with increasing BMI, but was also higher in adults with central adiposity (waist to hip ratio ≥ 0.9 and ≥ 0.8 in men and women, respectively) in all BMI categories [40]. After adjusting for confounders such as age, sex, blood pressure and medication use, central adiposity among obese adults was associated with a 70% increased odds of microalbuminuria compared to lean participants. Odds of reduced creatinine clearance increased by 2.6-fold among obese adults with central adiposity compared to lean adults after adjustment for confounders [40].

Central adiposity is frequently accompanied not only by hypertension but also hypertriglyceridemia, low HDL cholesterol, inflammation, and a pro-thrombotic state. These metabolic changes reflect a state of insulin resistance and its interaction with obesity [41]. The clustering of these traits defines the metabolic syndrome which is delineated by the presence of three of the

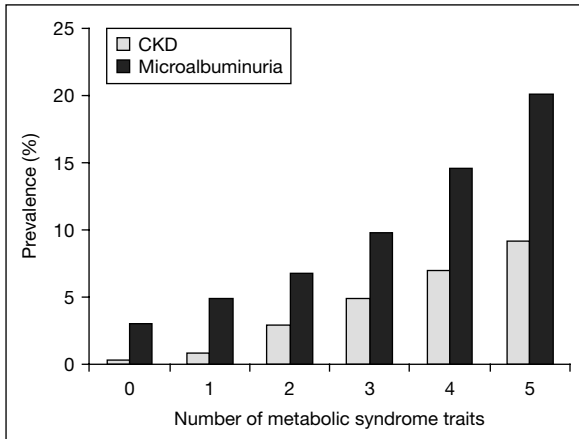


Fig. 4. Prevalence of CKD (estimated GFR < 60 ml/min/1.73) and microalbuminuria (spot urine albumin/creatinine ratio \geq 30 mg/g) by number of metabolic syndrome traits in the non-diabetic U.S. population. Adapted from reference [43].

following five traits: abdominal obesity, impaired fasting glucose, hypertension, hypertriglyceridemia, and low HDL cholesterol [42]. Cross-sectional studies have documented a strong and consistent association between the metabolic syndrome and measures of CKD [43–45]. For example, in a population survey of non-diabetic Native Americans participating in the Inter-Tribal Heart Project, the odds of microalbuminuria increased by 80% in the presence of one metabolic syndrome trait to 230% in the presence of 3 or more traits compared to no traits [44]. Similar results were reported in a study using data from a nationally representative sample of U.S. adults without DM [43]. Compared to presence of zero–one metabolic syndrome trait, presence of two metabolic syndrome traits was associated with a 2-fold increased odds of CKD, defined as an estimated GFR < 60 ml/min/1.73 m². Presence of five metabolic syndrome traits was associated with a 5-fold increased odds of CKD compared to presence of zero–one trait [43]. Prevalence of microalbuminuria was also positively correlated with number of metabolic syndrome traits (fig. 4) [43].

Metabolic syndrome represents hyperinsulinemia which may lead to structural changes via mechanisms not yet established but several theories have been postulated [46]. Renal mesangial cells cultured in the presence of insulin demonstrate increased synthesis of type I and III collagen [47, 48]. In dogs fed a high fat diet for 7 weeks with 64% increases in body weight, plasma renin activity and insulin concentrations increased by over 2-fold. Histologic kidney specimens showed mesangial expansion in obese but not lean dogs. No difference was noted in glomerulosclerosis score between obese and lean dogs, but

specimens from obese dogs exhibited 3-fold higher TGF- β 1 staining compared to lean dogs [49]. The heightened activity of TGF- β 1 may be due to the additive effects of insulin and angiotensin II [50], which could potentially promote production of extracellular matrix and accelerate glomerular damage [51–55]. Leptin levels, which are strongly and positively correlated with degree of adiposity, may also interact with TGF- β 1 and amplify its effects leading to increased collagen production [33].

Increased metabolic demands on the kidney may also mediate increased CKD risk in overweight and obesity. Given that nephron number is fixed at birth, weight gain increases the work of each individual nephron. Body size is positively correlated with glomerular size [56], and studies have demonstrated higher GFR and effective renal plasma flow (ERPF) in overweight and obese adults compared to lean adults [57–60]. These differences in GFR and ERPF are eliminated after correction for body size [57, 59, 61, 62]. Ribstein et al. [58] estimated GFR and ERPF by measuring clearances of technetium-labeled diethylene triaminopentaacetic acid and 131 iodine-orthoiodohippurate, respectively, in 40 normotensive adults and 80 never-treated hypertensives matched for age and sex. After stratifying normotensive and hypertensive study participants by presence of overweight, defined in this study as a BMI > 27 kg/m², GFR and ERPF were higher among overweight participants compared to lean participants but not after normalization for BSA. Higher filtration fraction (GFR/ERPF) was noted among hypertensive overweight participants compared to hypertensive lean participants, while no difference in filtration fraction was noted between overweight and lean participants who were normotensive [58].

Increased filtration fraction in overweight and obese individuals in the presence of increased blood flow suggests the potential existence of increased glomerular capillary pressure. As an individual gains weight, single nephron GFR must increase and this occurs at the expense of increased capillary pressures. Significant increases in GFR and renal plasma flow along with higher kidney weight and expansion of Bowman's capsule have been documented in dogs fed a high fat diet and gain weight compared to lean dogs [49]. Because increases in arterial blood pressure accompany the increases in renal plasma flow with weight gain, these hemodynamic changes result in increased glomerular capillary pressures. Experimental animal models have demonstrated that both glomerular hypertrophy and increased glomerular capillary pressures are risk factors for glomerulosclerosis [63–67]. In fact, acute increases in glomerular volume and capillary pressures are associated with increased TGF- β 1 expression [68, 69]. As discussed earlier, increased TGF- β 1 expression increases matrix production and deposition. The glomerular hypertrophy itself may also predispose the glomerular capillary wall to hemodynamic injury because capillary wall tension is a direct function of its diameter, which could potentially increase with glomerular

hypertrophy [70]. Because podocytes do not undergo adaptive replication in the setting of glomerular hypertrophy, the density of podocytes for a given glomerular surface area decreases. These podocytes then enlarge to compensate for the reduced density potentially leading to structural changes and detachment of the foot processes from the basement membrane [71]. Thus, in the setting of obesity, there are multiple stimulants of TGF- β 1, including increased insulin and angiotensin II levels and heightened glomerular volume and capillary pressures. These factors all interact and promote structural changes and glomerular damage.

Individuals with reduced nephron mass possess a high risk for CKD in the setting of overweight and obesity. The compensatory glomerular hypertrophy among individuals with reduced nephron mass is compounded by the increased metabolic load imposed on the kidney by overweight and obesity. These individuals are also at high risk for subsequent development of other CKD risk factors including hypertension [72, 73] and diabetes [74]. However, this cascade of CKD risk factors can be avoided if these individuals with reduced nephron mass maintain an ideal body weight.

Obesity and Focal Segmental Glomerulosclerosis

Obesity, especially morbid obesity, has been linked with focal segmental glomerulosclerosis (FSGS) since the 1970s when case reports of morbidly obese adults with proteinuria were first published [75, 76]. Several subsequent reports documented FSGS in patients with morbid obesity and sleep apnea [77, 78]. Investigators have also noted differences in the clinical and histologic features between patients with idiopathic FSGS and obese (particularly morbidly obese) patients with FSGS [70, 79]. Obese patients with FSGS frequently have higher serum albumin levels and less proteinuria and edema compared to non-obese patients with FSGS [78, 79]. Histologic differences most notably include larger glomerular size among the obese patients [79]. Heavy proteinuria has also been documented in morbidly obese adults in the absence of other glomerular abnormalities aside from glomerulomegaly [80, 81], although sampling error must be considered.

Obesity alone does not appear to be the sole mediator of the development of glomerulosclerosis as body size does not appear to predict percent sclerosed glomeruli [56]. However, body size is positively and directly correlated with glomerular size [56], and some investigators view glomerulomegaly accompanied by obesity and proteinuria as a specific disease entity termed obesity-related glomerulopathy [81]. In a single center study of 6,818 kidney biopsies collected over a 14 year period, obesity-related glomerulopathy was defined as presence of glomerulomegaly and/or FSGS in a patient with a BMI \geq 30 kg/m²

in the absence of other primary and secondary causes of FSGS such as HIV, heroin abuse, and reduced renal mass. All patients who fit these criteria were referred for kidney biopsy due to proteinuria [81]. Glomerulomegaly was noted in 10% of idiopathic FSGS cases vs. 100% of obesity associated FSGS cases. Foot process effacement was also significantly lower among patients with obesity associated FSGS vs. idiopathic FSGS [81]. The histologic differences may not necessarily indicate a new disease but rather evidence of secondary FSGS in these adults with glomerular hypertrophy, obesity and proteinuria.

Glomerular hypertrophy frequently antedates development of several experimental models of glomerular capillary hypertension such as the 5/6 nephrectomy animal model [65] and diabetic glomerulosclerosis [70, 71, 82]. In these models, structural alterations include increase in glomerular size, mesangial matrix expansion, and increased basement membrane thickness [71]. These same structural changes were noted in dogs fed a high fat diet for 7–9 weeks [49]. Histologic changes in some obese adults with FSGS may actually reflect structural damage due to increased glomerular capillary pressures and other factors which culminate in glomerulosclerosis and secondary FSGS. Secondary FSGS is the end result of adaptations to reduced functioning nephron population (e.g. primary kidney disease, reduced kidney mass from congenital or surgical means) [83–85] or hemodynamic stresses such as cyanotic congenital heart disease [86], pulmonary hypertension [87] or morbid obesity [56, 76, 78] accompanied by sleep apnea [77]. Clinically, secondary FSGS is frequently marked by absence of hypoalbuminemia, edema and high lipid levels and may be differentiated histologically from primary FSGS by increased diameter of non-sclerosed glomeruli, mild segmental foot process fusion over non-sclerosed segments and less visceral cell hypertrophy [70, 71].

Obesity itself is unlikely to be the sole mediator of secondary FSGS, given the rarity of this disease in the general population contrasted with the high prevalence of obesity. However, within a background of genetic susceptibility and perhaps other clinical risk factors including sleep apnea and reduced nephron number, obesity could potentiate development of secondary FSGS. These changes may begin with increased GFR and renal plasma flow in order to meet the increased metabolic demands associated with obesity. Glomerular capillary pressures and glomerular volume increase leading to a cascade of growth factors including TGF- β 1 and angiotensin II and subsequent increased matrix production and deposition. The hemodynamic changes associated with obesity damage visceral glomerular epithelial cells, which do not undergo cell division in this setting [71]. The same number of podocytes must now cover a larger surface area due to glomerular hypertrophy. Foot processes eventually become distorted and detached leading to increased hydraulic conductivity and proteinuria [71, 88]. These structural abnormalities may be compounded by

insulin resistance and hypertension [19]. Thus, obesity should be considered a 'high-risk state' for development of CKD and secondary FSGS as it represents the interaction of hemodynamic and metabolic abnormalities, which may lead to structural damage, matrix deposition and eventual glomerulosclerosis.

Interventions

Hypertension treatment with a blood pressure goal $<130/80$ mm Hg remains one of the most important interventions for any patient with CKD. Lifestyle modifications including maintaining a normal body weight, engaging in regular physical exercise and following a diet low in fat and sodium and high in potassium [89], should be included in all treatment plans. Among obese patients, weight loss should be viewed as an indispensable treatment for the prevention and treatment of CKD. Serial direct GFR measurements in normotensive morbidly obese adults who underwent gastric bypass surgery show that even moderate weight loss decreases GFR and renal plasma flow [61]. Among eight morbidly obese adults without hypertension (mean BMI 48 ± 2.4 kg/m²), directly measured GFR decreased from 145 ± 14 to 101 ± 4 ml/min ($p < 0.01$), while renal plasma flow decreased from 803 ± 39 to 698 ± 42 ml/min ($p < 0.02$). Urine albumin excretion decreased from 16 to 5 μ g/min [61]. These changes were noted despite the fact mean BMI remained at obesity levels (>30 kg/m²) after weight loss. Thus, an obese individual who loses even a moderate amount of weight will dramatically reduce the work of the kidney, and perhaps decrease his/her risk of CKD. Weight loss may also be beneficial in obese patients with established CKD. In a small study of 30 patients with a BMI > 27 kg/m² with established CKD and proteinuria due to either diabetic or non-diabetic causes, a 4.1% weight loss in the absence of oral protein restriction was associated with significant decreases in proteinuria from 2.8 to 1.9 g/24 h ($p < 0.005$) after 5 months. Patients assigned to the control group actually gained weight and showed increases in proteinuria during the 5-month period [90].

The renal benefits of weight loss in obese patients may be mediated not only by reduced systemic and glomerular [71] pressures but also by ameliorating insulin resistance. In the Diabetes Prevention Program Randomized Trial, lifestyle intervention, which aimed for a 7% weight loss and 150 min of exercise per week, decreased the 3-year cumulative incidence of metabolic syndrome by 25 and 40% compared to the metformin and placebo arms, respectively [91]. Compared to the baseline prevalence of metabolic syndrome, at study end the overall prevalence of metabolic syndrome actually decreased among participants in the lifestyle intervention group from 51 to 43% but increased in both the placebo and metformin arms [91]. This trial did not collect

information on kidney disease measures, but it seems intuitive that prevention and regression of metabolic syndrome with weight loss and exercise would decrease risk and progression of CKD.

Aside from weight loss, medications which block the renin–angiotensin system may provide additional benefits aside from lowering blood pressure. By binding to the angiotensin I receptor, angiotensin II inhibits the recruitment and differentiation of adipocytes [92]. Lack of adipocyte differentiation promotes storage of excess calories as fat in many tissues such as the liver, muscle and pancreas [93]. Drugs which inhibit the renin–angiotensin system will improve insulin resistance by promoting the recruitment and differentiation of adipocytes [93]. Several large randomized trials have shown significantly lower incidence rates of new-onset type 2 diabetes among participants assigned to medications which block the renin–angiotensin system compared to calcium channel blockers [94, 95], diuretics [94], β -blockers [96] or placebo [97]. Although angiotensin converting enzyme inhibitors and angiotensin II receptor blockers may provide protection from development of type 2 diabetes, the most common cause of ESRD, physicians should not overlook the benefits of weight loss and exercise, which may provide even greater payback than drugs and at lower cost.

Conclusions

Obesity is the number one risk factor for CKD risk factors, especially type 2 diabetes and hypertension, and may be the number one preventable risk factor for CKD. The development of CKD is rarely a ‘one-hit’ phenomena and is usually the culminating result of the interaction of multiple risk factors. Obesity represents one example of a ‘multi-hit’ state and given the background of genetic susceptibility and/or reduced nephron number, obesity may initiate and/or accelerate kidney damage. Because weight loss has been shown to improve glomerular hemodynamics and reduce urine albumin excretion [61], obese patients with CKD should be counseled on the benefits of weight loss. We are just now stepping on the iceberg of obesity and its link with CKD. Clearly, more studies are needed on the potential renal benefits of lifestyle interventions and medications for obese patients with all forms of kidney disease.

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