

Weight Loss Interventions in Chronic Kidney Disease: A Systematic Review and Meta-analysis

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Background and objectives: Obesity is an independent risk factor for development and progression of chronic kidney disease (CKD). We conducted a systematic review to assess the benefits of intentional weight loss in patients with non-dialysis-dependent CKD and glomerular hyperfiltration.

Design, setting, participants, & measurements: We searched MEDLINE, SCOPUS, and conference proceedings for randomized, controlled trials and observational studies that examined various surgical and nonsurgical interventions (diet, exercise, and/or antiobesity agents) in adult patients with CKD. Results were summarized using random-effects model.

Results: Thirteen studies were included. In patients with CKD, body mass index (BMI) decreased significantly (weighted mean difference [WMD] -3.67 kg/m²; 95% confidence interval [CI] -6.56 to -0.78) at the end of the study period with nonsurgical interventions. This was associated with a significant decrease in proteinuria (WMD -1.31 g/24 h; 95% CI -2.11 to -0.51) and systolic BP with no further decrease in GFR during a mean follow-up of 7.4 mo. In morbidly obese individuals (BMI >40 kg/m²) with glomerular hyperfiltration (GFR >125 ml/min), surgical interventions decreased BMI, which resulted in a decrease in GFR (WMD -25.56 ml/min; 95% CI -36.23 to -14.89), albuminuria, and systolic BP.

Conclusions: In smaller, short-duration studies in patients with CKD, nonsurgical weight loss interventions reduce proteinuria and BP and seem to prevent further decline in renal function. In morbidly obese individuals with glomerular hyperfiltration, surgical interventions normalize GFR and reduce BP and microalbuminuria. Larger, long-term studies to analyze renal outcomes such as development of ESRD are needed.

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Nearly two thirds of US adults are overweight (body mass index [BMI] ≥ 25 kg/m²), and of these, one half are obese (BMI ≥ 30 kg/m²) (1). Obesity not only is associated with an increase in morbidity, mortality, and reduction in life expectancy but also leads to an increase in the incidence of diabetes, hypertension, and dyslipidemia that are independent risk factors for chronic kidney disease (CKD) and coronary artery disease (2–5). Multiple mechanisms by which obesity may initiate and exacerbate CKD exist, and recent observational studies have established obesity as an independent risk factor for CKD and the development of ESRD (6–8).

Currently, >20 million Americans have CKD, and the projections for 2015 estimate that there will be $>700,000$ prevalent cases of ESRD in the United States (9). The health care costs that are associated with this increase are staggering. Diabetes and hypertension together account for $>70\%$ of the incident and

prevalent cases of ESRD. Given the epidemic of obesity in the United States and around the world, the numbers of obesity-related cases of diabetes, hypertension, and kidney disease are expected to increase. Several treatment options to prevent the progression of CKD have been tested. To date, the major impact on the progression of CKD and the incidence of ESRD has been through the treatment of proteinuria and hypertension (10,11). Although weight loss has been shown to reduce proteinuria in obese patients, the impact on progression of CKD and development of ESRD is less clear (12). Especially, with the increasing number of weight reduction surgeries being performed, intentional weight loss might be a therapeutic option for CKD if its benefits are proved (13,14). Hence, we conducted a systematic review to analyze the impact of weight loss interventions in patients with preexisting CKD and in patients with obesity-related glomerular hyperfiltration.

Materials and Methods

Data Sources and Search Strategy

MEDLINE (1966 through November 2008), SCOPUS (November 2008), and abstracts presented in the years 2004 through 2007 at the annual meetings of the American Society of Nephrology, National Kidney Foundation, and European Renal Association were searched using the following MESH terms: “kidney disease,” “weight loss,”

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“exercise,” “anti-obesity agents,” “resistance training,” and “bariatric surgery.” We used the bibliographies of relevant studies, the “Web of Knowledge Cited References” list, and the “Related Articles” link in PubMed to identify additional studies. Studies or review articles that discussed only the effects of obesity on renal function without a weight loss intervention were excluded, as were articles in languages other than English, studies that enrolled patients who were younger than 18 yr, and those that dealt with animals.

Study Selection

Two reviewers (S.D.N. and H.Y.) independently screened all abstracts and selected studies that met the inclusion criteria. Two major groups of studies were considered for inclusion: (1) An observational study or a randomized, controlled trial (RCT) aimed to analyze the impact of weight loss in patients with preexisting CKD and (2) studies that analyzed the impact of weight loss on renal parameters such as GFR in obese patients with glomerular hyperfiltration (GFR >125 ml/min) (15). We followed the National Kidney Foundation Kidney Disease Outcomes and Quality Initiative (KDOQI) definition for CKD (stage 1, GFR \geq 90 ml/min per 1.73 m² along with micro- or macroalbuminuria; stage 2, GFR 60 to 89 ml/min per 1.73 m² along with micro- or macroalbuminuria; stage 3, GFR 30 to 59 ml/min per 1.73 m², and stage 4, GFR 15 to 29 ml/min per 1.73 m²) (15). The intervention could be either nonsurgical (diet, exercise, and/or weight loss–inducing medications) or surgical for overweight patients and patients with any class of obesity (class I, II, or III or morbid obesity) with a follow-up of at least 4 wk duration. The following definitions for various classes of obesity were used: class I, BMI \geq 30 to 34.9; class II, BMI 35 to 39.9; and class III, BMI \geq 40 (16). Studies that analyzed multiple interventions were also considered for inclusion.

Exclusion criteria were (1) case reports and case series, (2) studies that used low-protein diets, (3) studies that analyzed the role of weight loss in dialysis patients, and (4) studies that assessed the impact of weight loss on albumin excretion in patients with normoalbuminuria. In studies that enrolled both non-dialysis-dependent patients with CKD and dialysis patients, only data relating to non-dialysis-dependent CKD were included in the analysis. Similarly, in studies that enrolled both patients with normoalbuminuria and microalbuminuria, only data pertaining to patients with microalbuminuria (when available) were extracted.

Study Outcome Measures

Pre- and postintervention data in the group that underwent nonsurgical or surgical interventions (in both observational and randomized studies) were extracted and included in the analysis. Even though we also intended to compare the outcome measures in treatment and control groups, this was not possible secondary to the lack of consistent reporting of these data in the included studies.

Primary outcome measures in the CKD population were postintervention changes in (1) GFR or creatinine clearance (ml/min) and (2) proteinuria (g/24 h). The secondary outcome measures in this population were postintervention changes in (1) BMI (kg/m²), (2) systolic BP (SBP) and diastolic BP (mmHg), (3) glycosylated hemoglobin (HbA_{1c}; %) and/or fasting blood glucose levels (mg/dl), and (4) lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in mg/dl).

Primary outcome measure in patients with glomerular hyperfiltration was the postintervention change in GFR or creatinine clearance (in ml/min) using measured values (inulin or iothalamate studies, 24-h urinary creatinine clearance). Data from studies that reported estimated

GFR were not included in this analysis. Other secondary outcome measures described already in the CKD population were also included.

Data Collection

Two reviewers (S.D.N. and H.Y.) extracted data after assessing and reaching consensus on eligible studies. Any discrepancies between the two reviewers were resolved by discussion. Authors were contacted when specific aspects of the data regarding primary outcome measures required clarification.

Study Quality

For observational studies, the Newcastle-Ottawa Scale was used to assess the study quality (17). A quality score was calculated on the basis of three major components: Selection of study participants (0 to 4 points), quality of the adjustment for confounding (0 to 2 points), and ascertainment of the exposure or outcome of interest in the case-control or cohorts, respectively (0 to 3 points). The maximum score was 9 points, representing the highest methodologic quality. The quality of RCTs was assessed without blinding to authorship or journal using the checklist developed by the Cochrane Renal Group. The quality items assessed were allocation concealment; intention-to-treat analysis; completeness to follow-up; and blinding of investigators, participants, and outcome assessors.

Data Analysis and Synthesis

Continuous variables (changes in creatinine clearance or GFR, proteinuria, BMI, BP, and lipid profile at the end of study period) were analyzed using the weighted mean difference (WMD) and its 95% confidence interval (CI). All *P* values are reported as two-sided. Results from individual studies were pooled using the DerSimonian-Laird random effects model when appropriate (18). Few studies did not report SD values for pre- and postintervention GFR and proteinuria; therefore, not all studies could be included in these analyses. Heterogeneity across the included studies was analyzed using heterogeneity χ^2 (Cochrane Q) statistic and *I*² test. *I*² values of >25, 50, and 75% were considered evidence of mild, moderate, and severe statistical heterogeneity, respectively (19). If substantial statistical heterogeneity was noted, then we planned to explore individual study characteristics and those of subgroups of the main body of evidence if an adequate number of studies was available.

Separate analyses were performed for (1) nonsurgical interventions (dietary interventions, exercise, and/or antiobesity agents) and (2) surgical interventions because the effect size would differ for these interventions and pooling them together would introduce substantial heterogeneity. Sensitivity analyses to explore the influence of statistical models (fixed and random-effects model) on effect size and the influence of each study by excluding one study at a time to assess the robustness of the results for primary outcome measures was conducted. Prespecified sensitivity (subgroup) analyses that were based on the type of study (observational study *versus* RCT) were also carried out. Because some studies reported renal function after adjusting for body surface area and some did not adjust for body surface area, a separate *post hoc* analysis was conducted to assess whether any difference existed among these studies (in patients with CKD). All analyses were undertaken in RevMan 5 (Nordic Cochrane Centre, Copenhagen, Denmark).

Results

Search Results

We identified 762 potentially relevant studies in MEDLINE, SCOPUS, and conference proceedings. A total of 733 studies

were rejected because they were review articles or studies that did not specifically address the impact of weight loss in patients with kidney disease and because of search overlap. Twenty-nine full-text studies were further reviewed in detail, and 13 studies (11 observational and two RCTs) in 14 publications were included in the final review (Figure 1) (20–33).

Study Characteristics

Nonsurgical Interventions. Six studies assessed the impact of weight loss attained through nonsurgical interventions (diet, exercise, and/or antiobesity agents) in patients with pre-existing CKD (20–25). In these studies, the baseline kidney disease was due to diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, obesity-related glomerulopathy, or undefined proteinuria. In most studies, the cause of CKD was based on clinical diagnosis rather than biopsy-proven. Among the studies that analyzed the effects of diet and/or exercise, four were observational studies (21,22,24,25) and two were randomized studies (20,23). Dietary intervention included hypocaloric diets with no protein restriction in most studies. Only one study included a co-intervention with Orlistat (24). Length of follow-up ranged from 4 wk to 1 yr among the included studies with a mean follow-up of 7.4 mo. Most studies reported 24-h protein or albumin excretion. Renal function was reported using 24-h urinary studies (21–23) and Cockcroft-Gault formula (20). A few studies reported renal function after adjusting for body surface area, whereas some did not. Other outcomes analyzed in the included studies were the effects on diabetes, such as fasting blood glucose, oral glucose tolerance test, HbA_{1c}, and insulin secretion, as well as BP, lipids, and liver function tests. All other study characteristics are outlined in Table 1.

Surgical Interventions. Seven studies (eight publications) analyzed the effects of surgical interventions on GFR in patients with glomerular hyperfiltration (26–33). Except for the study by Alexander *et al.* (23), most studies assessed the impact of

weight loss on renal parameters in patients with normo- and microalbuminuria. Surgical interventions included gastric bypass, gastroplasty, and biliopancreatic diversion. All surgical intervention studies were observational in nature (26–33), and few studies used healthy control subjects as comparators. Length of follow-up ranged from 1 to 2 yr among the included studies. Most studies reported 24-h protein or albumin excretion. Renal function was reported using 24-h urinary studies (26–28) and inulin clearance (29). All other study characteristics are outlined in Table 2.

Study Quality

The quality of the observational studies varied from 3 to 8 points, with a mean of 5 (suggesting that these are low- to moderate-quality studies). Allocation concealment was unclear in both of the included RCTs, and participants, investigators, and outcome assessors were not blinded in either of these trials. None of these trials was analyzed on an intention-to-treat basis. There were no dropouts in either treatment or control group of these RCTs.

Study Outcomes

Effects of Nonsurgical Interventions

GFR or Creatinine Clearance. For patients who received the nonsurgical interventions, weight loss did not result in a change in GFR or creatinine clearance at the end of study period (five studies, 87 patients, WMD 4.25 ml/min; 95% CI –3.30 to 11.81; $P = 0.27$) (20,21,23,24). A mild statistical heterogeneity was noted among the included studies (heterogeneity $\chi^2 = 6.29$, $I^2 = 36%$, $P = 0.18$; Figure 2). There was no significant difference in the GFR or creatinine clearance among studies that adjusted for body surface area (WMD 4.35 ml/min per 1.73 m²; 95% CI –4.42 to 13.12) and that did not adjust for body surface area (WMD 1.78 ml/min; 95% CI –13.15 to 16.71) with no significant differences noted between the groups ($P = 0.56$).

Morales *et al.* (20) reported that the creatinine clearance did not differ in the treatment group (between baseline and 5-mo of follow-up), whereas it declined from 61.8 ± 22.1 ml/min to 56 ± 19.9 ml/min during a 5-mo period in the control group. Praga *et al.* (23) demonstrated no difference in creatinine clearance between the group that received captopril and the group that underwent hypocaloric therapy.

Proteinuria. Weight loss that was attained through nonsurgical interventions reduced the proteinuria at the end of study period (four studies, 75 patients, WMD –1.31 g/24 h; 95% CI –2.11 to –0.51; $P = 0.001$) (20–23) with significant heterogeneity noted among the included studies (heterogeneity $\chi^2 = 4.12$, $I^2 = 75%$; $P = 0.04$, Figure 3). Vasquez *et al.* (25) reported that eight of 24 patients regressed from microalbuminuria to normoalbuminuria at the end of the study period.

BMI. Weight loss attained through nonsurgical interventions resulted in a significant decrease in BMI at the end of study period (five studies, 107 patients, WMD –3.67 kg/m²; 95% CI –6.56 to –0.78; $P < 0.001$; 20–24) with significant statistical heterogeneity noted among the included studies (heterogeneity $\chi^2 = 40.33$, $I^2 = 90%$, $P < 0.001$). Vasquez *et al.* (25) reported BMI values at baseline but not in the follow-up; how-

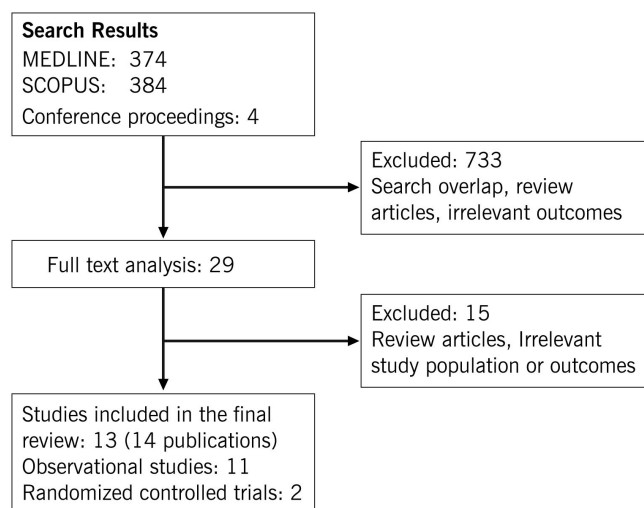


Figure 1. Flow chart showing number of citations retrieved by individual searches and number of trials included in the review.

Table 1. Characteristics of studies that analyzed the effects of dietary and pharmacologic interventions to reduce weight on renal parameters

Reference	Type of Study	Baseline Kidney Disease	Preintervention BMI (kg/m ²)	Comorbidities	No. of Patients	Intervention	Follow-up	Renal Outcomes	Nonrenal Outcomes ^a
Observational Cook <i>et al.</i> (24), 2008	Prospective cohort	Stage 2 through 4 CKD and ESKD	35.7 ± 4.5	NA	44 (total) 19 (predialysis) 22 (dialysis) 3 (transplant)	Hypocaloric (500 kcal less than usual), low-fat, renal diet plus exercise 3×/wk plus orlistat 120 mg thrice daily	12 mo	eGFR	Exercise capacity, functional ability
Saiki <i>et al.</i> (21), 2005	Prospective cohort	Creatinine <265 mmol/L and proteinuria >300 mg/d	30.4 ± 5.3	Diabetes	22	Hypocaloric diet (11 to 19 kcal/kg per d) using formula diet	4 wk	24-h creatinine clearance, 24-h proteinuria	Lipid profile, HbA _{1c} , visceral fat analysis using CT scan
Solerte <i>et al.</i> (22), 1989	Prospective cohort	Proteinuria >500 mg/d	33.5 ± 1.6	Diabetes, retinopathy	24	Hypocaloric diet (1410 kcal/d)	12 mo	GFR (Tc injection), 24-h creatinine clearance, 24-h proteinuria	Lipid profile, BP, HbA _{1c}
Vasquez <i>et al.</i> (25), 1984 ^b	Prospective cohort	Proteinuria	36.1; 47.6; 39.1	Normal, borderline diabetes	37	Hypocaloric diet (500 kcal/d less than usual)	82 to 110 d	Serum creatinine, 24-h proteinuria	BP, albumin, liver function tests
Randomized Morales <i>et al.</i> (20), 2003	Randomized study	Proteinuric nephropathies with Cr <2.0 mg/dl	33 ± 3.5	Diabetes, hypertension	30	Hypocaloric diet (500 kcal less than usual); protein intake 1.0 to 1.2 g/kg per d <i>versus</i> usual dietary intake	5 mo	CG creatinine clearance, 24-h proteinuria	Lipid profile
Praga <i>et al.</i> (23), 1995 ^c	Randomized study	Proteinuria (>1 g/d) with Cr 0.8 to 2.3 mg/dl	37.1 ± 3.1	Hypertension	17	Hypocaloric diet (1000 to 1400 kcal/d) <i>versus</i> captopril 50 to 150 mg/d	12 mo	24-h creatinine clearance, 24-h proteinuria	Lipid profile

CG, Cockcroft-Gault; Cr, creatinine; CT, computed tomography; eGFR, estimated GFR.

^a All studies measured BMI and change in weight over time.

^b Proteinuria data from these studies were not included in the analysis because of the lack of adequate information. This study had three arms: Normal control subjects, patients with borderline diabetes, and patients with type 2 diabetes.

^c We used the pre- and postintervention data from the hypocaloric arm only for the analysis.

Table 2. Characteristics of studies that analyzed the effects of surgical interventions to reduce weight on renal parameters

Reference	Type of Study	Baseline Kidney Disease	Preintervention BMI (kg/m ²) or Body Weight (kg)	Comorbidities	No. of Patients	Intervention	Follow-up	Renal Outcomes	Nonrenal Outcomes ^a
Agrawal <i>et al.</i> (30), 2008	Retrospective	Microalbuminuria	49.1 ± 7.4	Diabetes, metabolic syndrome	94	Roux-en-Y gastric bypass	12 mo	Urine albumin-creatinine ratio	Hs-CRP, BP, diabetes
Alexander and Goodman <i>et al.</i> (31), 2007	Prospective cohort	ESRD, CKD	NA	NA	45 (total) 23 (CKD) 22 (dialysis)	Roux-en-Y gastric bypass	Up to 13 yr	Serum creatinine	NA
Brochner-Mortensen <i>et al.</i> (32), 1980	Prospective cohort	Glomerular hyperfiltration	136.4 kg	None	8	End-to-side jejunioileostomy	1 yr	Serum creatinine, GFR (using EDTA)	Extracellular volume
Chagnac <i>et al.</i> (29), 2003	Prospective cohort	Glomerular hyperfiltration	48 ± 2.4	Hypertension	17	Gastroplasty	12 to 17 mo	GFR (using inulin clearance), renal plasma flow, filtration fraction, albuminuria	Oral glucose tolerance test, BP
Navarro-Diaz <i>et al.</i> (27), 2006 ^b	Prospective cohort	Glomerular hyperfiltration	53.6 ± 9.6	CAD, hypertension	85	Gastroplasty	24 mo	24-h urinary creatinine clearance, proteinuria	BP
Palomar <i>et al.</i> (26), 2005	Prospective cohort	Microalbuminuria and overt proteinuria	46.9 ± 6.3	Hypertension, diabetes, obstructive sleep apnea	35	Biliopancreatic diversion	12 mo	Proteinuria, nephrolithiasis	Lipid profile, BP, hematologic parameters
Serra <i>et al.</i> (28), 2006 ^b	Prospective cohort	Microalbuminuria	53.3 ± 9.6	Hypertension	70	Roux-en-Y gastric bypass	12 mo	24-h urinary creatinine clearance, proteinuria	Lepin, adiponectin, lipid profile, insulin level, BP

CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein.

^a All studies measured BMI and change in weight over time.

^b Same set of patients were included and different outcome measures were reported, and only study with longer duration of follow-up was used for analysis.

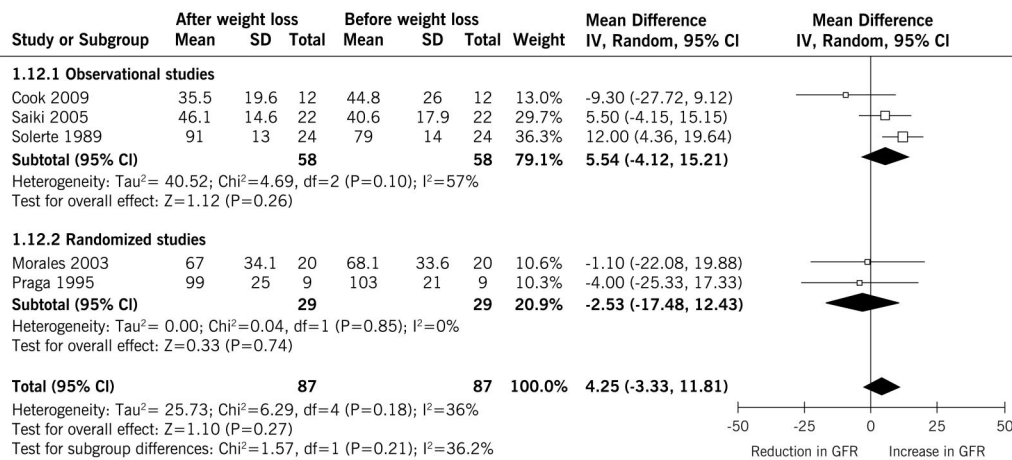


Figure 2. Effect of nonsurgical interventions on GFR in CKD.

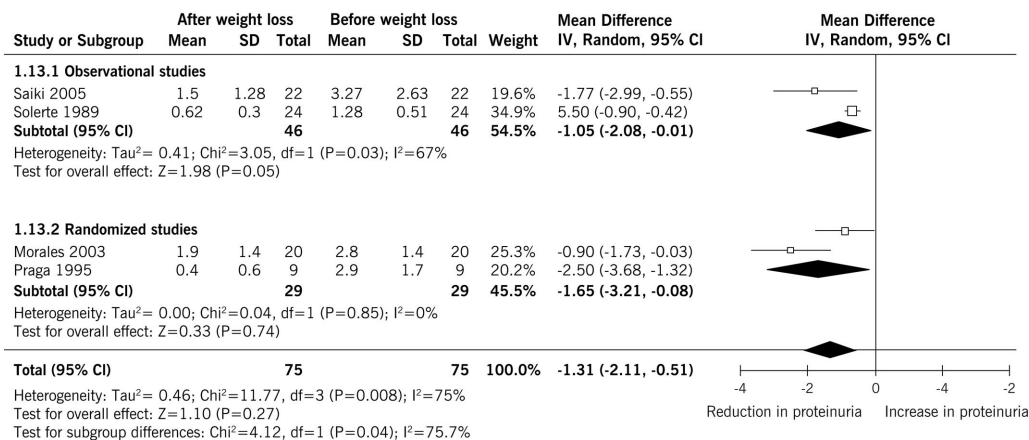


Figure 3. Effect of nonsurgical interventions on urinary protein excretion in CKD.

ever, they reported a significant decrease in body weight with hypocaloric diet ($P < 0.05$).

Systolic BP. Nonsurgical interventions resulted in a significant decrease in SBP at the end of the study period (three studies, 66 patients, WMD -8.98 mmHg; 95% CI -14.23 to -3.74 ; $P < 0.001$) (20–22) with low statistical heterogeneity noted among the included trials (heterogeneity $\chi^2 = 2.81$, $I^2 = 29%$, $P = 0.24$).

Lipids. Nonsurgical interventions resulted in a significant decrease in total cholesterol (four studies, 75 patients, WMD -16.61 mg/dl; 95% CI -31.83 to -1.38) (20–22) at the end of study period; however, there was no significant change in triglycerides (four studies, 75 patients, WMD -47.99 mg/dl; 95% CI -102.80 to 6.82) (20–23) or HDL cholesterol levels (three studies, 66 patients, WMD 4.79 mg/dl; 95% CI -1.61 , 11.20) at the end of study period.

Glycemic Control. Pre- and postintervention HbA_{1c} and fasting blood glucose levels were not reported consistently in the included studies to conduct a meta-analysis. Solerte *et al.* (22) reported a decrement in fasting blood glucose along with a reduction in insulin dosage after diet therapy. Saiki *et al.* (21) reported that the HbA_{1c} decreased from 7.11 ± 1.42 to $6.68 \pm$

$1.21%$ ($P < 0.05$) in 22 obese patients who received a low-calorie, normal-protein diet.

Effects of Surgical Interventions

GFR. Weight loss that was attained through surgical intervention resulted in normalization of GFR (three studies, 77 patients, WMD -25.56 ml/min; 95% CI -36.23 to -14.89 ; $P < 0.0001$) in patients with glomerular hyperfiltration (26,27,29) with no heterogeneity noted among the included studies (heterogeneity $\chi^2 = 0.78$, $I^2 = 0%$, $P = 0.68$; Figure 4). Alexander *et al.* (31) reported nine of 45 patients for whom the renal function remained stable after gastric bypass surgery.

Proteinuria. Agrawal *et al.* (30) reported that there was a significant decrease in urinary albumin-creatinine ratio in patients who had microalbuminuria and underwent Roux-en-Y gastric bypass surgery (median urinary albumin-creatinine ratio 66 mg/g [39 to 106 mg/g] to 13 mg/g [8 to 21 mg/g]). Data related to patients with microalbuminuria alone were not reported in studies that had both patients with normoalbuminuria and microalbuminuria (26–29).

BMI. Weight loss that was attained through surgical intervention resulted in a significant decrease in BMI at the end of study period (three studies, 104 patients, WMD -16.53 kg/m²;

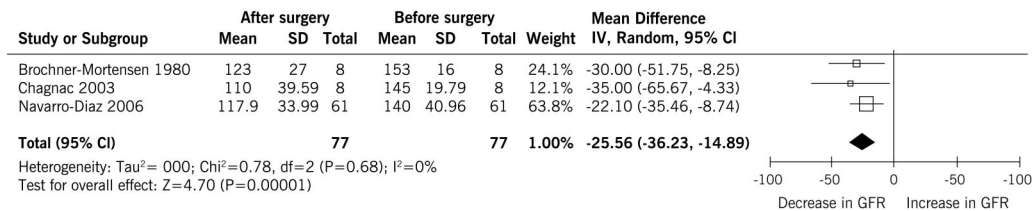


Figure 4. Effect of surgical interventions on glomerular hyperfiltration.

95% CI -19.59 to -13.48; $P < 0.001$) (26,27,29) with significant heterogeneity noted among the included studies (heterogeneity $\chi^2 = 9.04$, $I^2 = 78\%$; $P = 0.01$).

Systolic BP. Surgical interventions resulted in a significant decrease in SBP at the end of study period (three studies, 104 patients, WMD -22.63 mmHg; 95% CI -26.19 to -19.07; $P < 0.001$) (26,27,29) with significant heterogeneity noted among the included trials (heterogeneity $\chi^2 = 14.70$, $I^2 = 86\%$; $P = 0.006$).

Exploration of Heterogeneity

There was a mild to moderate significant heterogeneity in the analysis of primary outcome measures that could be attributed to the differences in the interventions used in each group, study type, study duration, patient population, and formulas used to calculate GFR. This heterogeneity was further explored in the sensitivity analysis.

Random-Effects versus Fixed-Effects Model. The fixed-effects analysis of GFR yielded effect sizes that were similar in direction and significance to those obtained from random-effects analysis.

Study Exclusion. The sensitivity analysis of proteinuria with weight loss after the exclusion of one study at a time yielded effect sizes similar in magnitude and direction to the overall estimates in the analysis of nonsurgical interventions. Exclusion of the study by Solerte *et al.* (22) resulted in an elimination of heterogeneity in the GFR analysis because that study reported an increase in GFR after weight loss in contrast to other studies, which showed no changes in GFR.

Type of Study. In the GFR analysis (impact of exercise and/or medications), subgroup analysis including RCTs alone yielded similar results (WMD -2.53 ml/min; 95% CI -17.48 to 12.43) to that of subgroup analysis that included observational studies (WMD 3.54 ml/min; 95% CI -7.38 to 14.45; Figure 2). In the proteinuria analysis, subgroup analysis including RCTs alone showed greater reduction in proteinuria (WMD -1.65 g/24 h; 95% CI -2.62 to -0.69) than observational studies (WMD -1.05 g/24 h; 95% CI -2.08 to -0.01; Figure 3).

Discussion

The results of our systematic review show that in patients with CKD, weight loss that was attained through nonsurgical interventions was not associated with a change in GFR, but statistically significant improvement in proteinuria was observed during a short period of follow-up. Conversely, weight loss that was attained through bariatric surgery was associated with a normalization of glomerular hyperfiltration (*i.e.*, decre-

ment in GFR to normal range). After weight reduction that was achieved through either intervention, SBP and total cholesterol levels were reduced. There is a lack of long-term studies that analyzed the impact of these various weight loss interventions on patient-centered data such as development of ESRD.

Obesity contributes independently both to the development of CKD (*i.e.*, development of obesity-related glomerulopathy) and to decline in renal function in patients with preexisting CKD. Adipose tissue releases several biologically active compounds that regulate energy balance, insulin sensitivity, angiogenesis, BP, and lipid metabolism (34,35). In obesity, these adipokine and cytokine profiles are such that there are increased levels of TNF- α , IL-6, resistin, and leptin and reduced levels of adiponectin with resultant increase in the insulin resistance, blood lipids, endothelial function, fibrinolysis, and inflammation (36,37). Ramos *et al.* (38) reported that the detrimental effects of oxidative stress and inflammation noted with obesity are augmented in patients with CKD. These negative effects subsequently contribute to the decline in renal function and increased cardiovascular disease, as evident from the available observational study results (6–9).

In this analysis, we compared the pre- and postintervention data in patients who had CKD and underwent weight reduction. There was no significant change in the GFR that could be interpreted as “no treatment benefit”; however, this could be viewed as “treatment benefit” for following reasons: (1) A decline in GFR occurred in the control groups of the included studies and (2) the GFR stabilized in a mean follow-up of 7.4 mo. Unfortunately, GFR data of both treatment and control groups were not reported consistently in these studies to be pooled together.

We considered the impact of weight loss on glomerular hyperfiltration as a separate outcome because of the documented detrimental renal effects of obesity, which include elevated GFR, elevated renal blood flow, and renal hypertrophy, that subsequently lead to the development of obesity-related glomerulopathy. Given the lack of universal definition for glomerular hyperfiltration, we chose the cutoff of 125 ml/min on the basis of the normal range of GFR (15) and previous studies in the literature. Bariatric surgery currently offers the most effective durable weight loss treatment in morbid obesity while at the same time ameliorating obesity-related comorbidities (39,40). In the morbidly obese population, weight loss that is attained through bariatric surgery results in an improvement in insulin resistance, oxidative stress, and vascular endothelial function (41,42). These improvements may contribute to the

observed better long-term outcomes after bariatric surgery in the general population (43,44). Our review shows that bariatric surgery is associated with a decrease in BMI with resultant normalization in glomerular hyperfiltration; however, whether this normalization in hyperfiltration translates into long-term renal benefits remains to be seen. Studies that assess the impact of medical interventions on glomerular hyperfiltration are lacking.

Patients who undergo weight loss might also lose muscle mass with a decrease in serum creatinine level (45). None of these studies explored the change in body composition with weight loss; therefore, the impact of loss of muscle mass on serum creatinine and renal function reported in these studies is unknown. This is important because the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault formulas are unreliable to estimate GFR in obese patients, and some of the included studies used these formulas to report renal function (46–48). Twenty-four-hour urinary studies are recommended to estimate creatinine clearance in obese patients with CKD. Some studies used 24-h urinary studies to estimate creatinine clearance, but some reported estimated GFR; therefore, we performed cumulative and subgroup analyses that did not show either decline or improvement in GFR with both methods of reporting.

Obesity is causally related to the development of high BP, diabetes, and hypercholesterolemia. Both BP reduction and lipid lowering reduce urinary protein excretion (49,50). We noted that weight reduction with diet and/or exercise was associated with improved SBP and lipid profile, but how much this improvement contributed to the reduction in proteinuria and stabilization/normalization of GFR could not be assessed from this analysis. Furthermore, given the smaller sample size, studies did not adjust for potential confounders such as the use of renoprotective medications and improvement in other important comorbid conditions, such as insulin resistance, which might independently influence the outcome measures studied.

The major strengths of our systematic review are the comprehensive search method, data review, and extraction by two reviewers. Like any other systematic review, this review is subject to publication bias even though we searched relevant conference proceedings to identify the studies. Other limitations of our meta-analysis include the suboptimal quality of the included studies and the presence of heterogeneity in the analysis. The included studies were of short duration and were not adequately powered to measure patient-centered outcomes such as progression of kidney disease (in terms of either doubling of serum creatinine or development of ESRD that warranted dialysis or transplantation) and mortality with intentional weight loss.

Most included studies enrolled patients with stages 1 through 3 CKD; therefore, these results may not be extrapolated to patients with more severe forms of kidney disease. One short-term study showed no relationship between amount of weight loss and the amount of reduction in proteinuria, whereas a long-term study showed contrary results. We could not assess whether the proteinuria and renal function differed on the basis of the amount of weight loss as a result of the lack

of adequate number of studies that reported the necessary details. We used the mean and SD of proteinuria (rather than geometric mean) from the included studies. Proteinuria, however, has a skewed distribution, which further limits the interpretation of this analysis.

Several questions merit investigation in this area. The most important is to study whether intentional weight loss with either bariatric surgery or diet and exercise affects renal function, the development of ESRD, and mortality in patients with preexisting kidney disease independent of its impact on diabetes, hypertension, and hyperlipidemia. This is important given the “obesity paradox” reported in dialysis patients: Obese patients live longer than patients who are nonobese. Furthermore, future studies should use consistent measures for assessing obesity and renal function given the limitations that are associated with the various measures that are used to assess BMI (51). Even before that, it may be prudent to study the impact of weight loss on inflammation, insulin resistance, and oxidative stress in patients with preexisting kidney disease, because these lie in the causal pathway for obesity and the development of kidney disease.

Conclusions

It seems that weight loss may offer renal benefits in addition to the cardiovascular benefits, thereby reducing both the cardiovascular and the CKD risks in these patients; however, the evidence supporting the role of intentional weight loss in patients with mild to moderate CKD to slow the progression of kidney disease is modest at best, and more research is needed in this area.

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Disclosures

None.

References

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM: Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 295: 1549–1555, 2006
2. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE: Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med* 351: 2694–2703, 2004
3. Yan LL, Daviglius ML, Liu K, Stamler J, Wang R, Pirzada A, Garside DB, Dyer AR, Van Horn L, Liao Y, Fries JF, Greenland P: Midlife body mass index and hospitalization and mortality in older age. *JAMA* 295: 190–198, 2006
4. Colditz GA, Willett WC, Rotnitzky A, Manson JE: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122: 481, 1995
5. Garrison RJ, Kannel WB, Stokes J 3rd, Castelli WP: Inci-

- dence and precursors of hypertension in young adults: The Framingham Offspring Study. *Prev Med* 16: 235–251, 1987
6. Wahba I, Mak R: Obesity and obesity-initiated metabolic syndrome: Mechanistic links to chronic kidney disease. *Clin J Am Soc Nephrol* 2: 550–562, 2007
 7. Wang Y, Chen X, Song Y, Caballero B, Cheskin LJ: Association between obesity and kidney disease: A systematic review and meta-analysis. *Kidney Int* 73: 19–33, 2008
 8. Hall JE, Crook ED, Jones DW, Wofford MR, Dubbert PM: Mechanisms of obesity-associated cardiovascular and renal disease. *Am J Med Sci* 324: 127–137, 2002
 9. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007
 10. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, de Zeeuw D, Shahinfar S, Toto R, Levey AS, AIPRD Study Group: Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition—A patient-level meta-analysis. *Ann Intern Med* 139: 244–252, 2003
 11. Jafar TH, Schmid CH, Landa M, Giatras I, Toto R, Remuzzi G, Maschio G, Brenner BM, Kamper A, Zucchelli P, Becker G, Himmelmann A, Bannister K, Landais P, Shahinfar S, de Jong PE, de Zeeuw D, Lau J, Levey AS: Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: A meta-analysis of patient-level data [published erratum appears in *Ann Intern Med* 137: 299, 2002]. *Ann Intern Med* 135: 73–87, 2001
 12. Praga M, Morales E: Obesity, proteinuria and progression of renal failure. *Curr Opin Nephrol Hypertens* 15: 481–486, 2006
 13. Hinojosa MW, Varela JE, Parikh D, Smith BR, Nguyen XM, Nguyen NT: National trends in use and outcome of laparoscopic adjustable gastric banding. *Surg Obes Relat Dis* 5: 150–155, 2009
 14. Kramer H, Tuttle KR, Leehey D, Luke A, Durazo-Arvizu R, Shoham D, Cooper R, Beddhu S: Obesity management in adults with CKD. *Am J Kidney Dis* 53: 151–165, 2009
 15. http://www.kidney.org/professionals/kdoqi/guidelines_ckd/p4_class_g1.htm. Accessed August 12, 2009
 16. National Heart, Lung, and Blood Institute: Obesity Education Initiative: Classification of Overweight and Obesity by BMI, Waist Circumference, and Associated Disease Risks. Available at: http://www.nhlbi.nih.gov/health/public/heart/obesity/lose_wt/bmi_dis.htm. Accessed May 9, 2009
 17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses, Ottawa, Ontario, Canada, Ottawa Health Research Institute. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed January 6, 2009
 18. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 7: 177–188, 1986
 19. Higgins J, Thompson S, Deeks J, Altman D: Measuring inconsistency in meta-analyses. *BMJ* 327: 557–560, 2003
 20. Morales E, Valero MA, León M, Hernández E, Praga M: Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. *Am J Kidney Dis* 41: 319–327, 2003
 21. Saiki A, Nagayama D, Ohhira M, Endoh K, Ohtsuka M, Koide N, Oyama T, Miyashita Y, Shirai K: Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. *Int J Obes (Lond)* 29: 1115–1120, 2005
 22. Solerte SB, Fioravanti M, Schifino N, Ferrari E: Effects of diet-therapy on urinary protein excretion albuminuria and renal haemodynamic function in obese diabetic patients with overt nephropathy. *Int J Obes* 13: 203–211, 1989
 23. Praga M, Hernández E, Andrés A, León M, Ruilope LM, Rodicio JL: Effects of body-weight loss and captopril treatment on proteinuria associated with obesity. *Nephron* 70: 35–41, 1995
 24. Cook S, MacLaughlin H, MacDougall IC: A structured weight management programme can achieve improved functional ability and significant weight loss in obese patients with chronic kidney disease. *Nephrol Dial Transplant* 23: 263–268, 2008
 25. Vasquez B, Flock EV, Savage PV, Nagulesparan M, Bennion LJ, Baird HR, Bennett PH: Sustained reduction of proteinuria in type 2 (non-insulin-dependent) diabetes following diet-induced reduction of hyperglycaemia. *Diabetologia* 26: 127–133, 1984
 26. Palomar R, Fernández-Fresnedo G, Domínguez-Diez A, López-Deogracias M, Olmedo F, Martín de Francisco AL, Sanz de Castro S, Casado Martín F, Gómez-Fleitas M, Arias M, Fernández-Escalante C: Effects of weight loss after biliopancreatic diversion on metabolism and cardiovascular profile. *Obes Surg* 15: 794–798, 2005
 27. Navarro-Díaz M, Serra A, Romero R, Bonet J, Bayés B, Homs M, Pérez N, Bonal J: Effect of drastic weight loss after bariatric surgery on renal parameters in extremely obese patients: Long-term follow-up. *J Am Soc Nephrol* 17[Suppl 3]: S213–S217, 2006
 28. Serra A, Granada ML, Romero R, Bayés B, Cantón A, Bonet J, Rull M, Alastrue A, Formiguera X: The effect of bariatric surgery on adipocytokines, renal parameters and other cardiovascular risk factors in severe and very severe obesity: 1-year follow up. *Clin Nutr* 25: 400–408, 2006
 29. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafer U, Ori Y: The effects of weight loss on renal function in patients with severe obesity. *J Am Soc Nephrol* 14: 1480–1486, 2003
 30. Agrawal V, Khan I, Rai B, Chengelis DL, Zalesin KC, Rocher LL, McCullough PA: The effect of weight loss after bariatric surgery on albuminuria. *Clin Nephrol* 70: 194–202, 2008
 31. Alexander JW, Goodman H: Gastric bypass in chronic renal failure and renal transplant. *Nutr Clin Pract* 22: 16–21, 2007
 32. Brochner-Mortensen J, Rickers H, Balslev I: Renal function and body composition before and after intestinal bypass operation in obese patients. *Scand J Clin Lab Invest* 40: 695–702, 1980
 33. Alexander JW, Goodman HR, Hawver LR, Cardi MA: Improvement and stabilization of chronic kidney disease after gastric bypass. *Surg Obes Relat Dis* 5: 237–241, 2009
 34. Kwan BC, Beddhu S: A story half untold: Adiposity, adipokines and outcomes in dialysis population. *Semin Dial* 20: 493–497, 2007
 35. Axelsson J, Stenvinkel P: Role of fat mass and adipokines in chronic kidney disease. *Curr Opin Nephrol Hypertens* 17: 25–31, 2008
 36. Hutley L, Prins JB: Fat as an endocrine organ: Relationship

- to the metabolic syndrome. *Am J Med Sci* 330: 280–289, 2005
37. de Ferranti S, Mozaffarian D: The perfect storm: Obesity, adipocyte dysfunction, and metabolic consequences. *Clin Chem* 54: 945–955, 2008
 38. Ramos LF, Shintani A, Ikizler TA, Himmelfarb J: Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. *J Am Soc Nephrol* 19: 593–599, 2008
 39. Maggard MA, Shugarman LR, Suttrop M, Maglione M, Sugerma HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG: Meta-analysis: Surgical treatment of obesity. *Ann Intern Med* 142: 547–559, 2005
 40. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrback K, Schoelles K: Bariatric surgery: A systematic review and meta-analysis [published erratum appears in *JAMA* 293: 1728, 2005]. *JAMA* 292: 1724–1737, 2004
 41. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, Eid GM, Mattar S, Ramanathan R, Barinas-Mitchel E, Rao RH, Kuller L, Kelley D: Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 238: 467–484, 2003
 42. Pereira JA, Lazarin MA, Pareja JC, de Souza A, Muscelli E: Insulin resistance in nondiabetic morbidly obese patients: Effect of bariatric surgery. *Obes Res* 11: 1495–1501, 2003
 43. Uzun H, Konukoglu D, Gelisgen R, Zengin K, Taskin M: Plasma protein carbonyl and thiol stress before and after laparoscopic gastric banding in morbidly obese patients. *Obes Surg* 17: 1367–1373, 2007
 44. Adams TD, Gress RE, Smith SC, Halverson RC, Simper SC, Rosamond WD, Lamonte MJ, Stroup AM, Hunt SC: Long-term mortality after gastric bypass surgery. *N Engl J Med* 357: 753–761, 2007
 45. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carlsson LM, Swedish Obese Subjects Study: Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 357: 741–748, 2007
 46. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP: Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 3: 348–354, 2008
 47. Geddes CC, Woo YM, Brady S: Glomerular filtration rate: What is the rationale and justification of normalizing GFR for body surface area? *Nephrol Dial Transplant* 23: 4–6, 2008
 48. Delanaye P, Rademecker RP, Rorive M, Depas G, Krzesinski JM: Indexing glomerular filtration rate for body surface area in obese patients is misleading: Concept and example. *Nephrol Dial Transplant* 20: 2024–2028, 2005
 49. Ruggenti P, Perna A, Ganeva M, Ene-Iordache B, Remuzzi G, BENEDICT Study Group: Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: A *post hoc* analysis of the BENEDICT trial. *J Am Soc Nephrol* 17: 3472–3481, 2006
 50. Navaneethan SD, Pansini F, Perkovic V, Johnson DW, Craig JC, Strippoli GF: HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2: CD007784, 2009
 51. Zoccali C: The obesity epidemics in ESRD: From wasting to waist? *Nephrol Dial Transplant* 24: 376–380, 2009