AJKD
Original Investigation

Influence of Dietary Protein on Glomerular Filtration Before and After Bariatric Surgery: A Cohort Study

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Background: Obesity-associated elevations in glomerular filtration rate (GFR) are common and may play a role in the development of kidney disease, so identifying the underlying mechanism is important. We therefore studied whether reductions in dietary protein intake, which is known to modulate GFR, explain why GFR decreases after bariatric surgery–induced weight loss.

Study Design: Cohort study with participants as their own controls.

Setting & Participants: 8 severely obese patients with normal kidney function were recruited from bariatric surgery centers in Indianapolis, IN. All participants were placed on a fixed-protein (50-g/d) diet for 1 week before and after a minimum of a 20-kg weight loss by bariatric surgery and were followed up closely by dieticians for adherence.

Predictor: Ad lib versus low-protein diet before versus after bariatric surgery.

Outcome: Measured GFR, using repeated-measures analysis, was used to estimate the independent effects of diet and surgery.

Measurement: GFR was measured using plasma iohexol clearance.

Results: A median of 32.9 (range, 19.5-54.4) kg was lost between the first presurgery visit and first post-surgery visit. Dietetic evaluations and urinary urea excretion confirmed that patients generally adhered to the study diet. GFRs on an ad lib diet were significantly higher before compared to after surgery (GFR medians were 144 (range, 114-178) and 107 (range, 85-147) mL/min, respectively; $P = 0.01$). Although bariatric surgery (−26 mL/min; $P = 0.005$) and dietary sodium intake (+7.5 mL/min per 100 mg of dietary sodium; $P = 0.001$) both influenced GFR, consuming a low-protein diet did not ($P = 0.7$).

Limitations: Small sample size; mostly white women; possible lack of generalizability.

Conclusions: The decrease in GFR observed after bariatric surgery is explained at least in part by the effects of surgery and/or dietary sodium intake, but not by low dietary protein consumption.
Am J Kidney Dis. 63(4):598-603.

INDEX WORDS: Obesity; bariatric surgery; glomerular filtration rate; glomerular hyperfiltration; protein; diet; kidney; renal function; weight reduction.

The global obesity crisis shows little sign of relenting.[1] This has major implications for the field of nephrology in as much as obesity has been linked in a variety of experimental and observational settings to the development and progression of chronic kidney disease.[2-6] A variety of putative mechanisms have been postulated to account for the obesity–chronic kidney disease link. Among them are supranormal elevations in glomerular filtration rate (GFR; so-called glomerular hyperfiltration), a frequent finding in obese individuals that in certain settings may lead to intraglomerular and systemic hypertension and ultimately kidney injury.[7,8]

The mechanisms underlying glomerular hyperfiltration are not fully understood, though a relative afferent (vs efferent) vasodilation of the glomerular arteriole has been implicated.[9] Although this process may be linked to the influence of excess adiposity by, for example, upregulation of the renin-aldosterone axis and tubuloglomerular feedback,[10] an alternative explanation involves the effects of dietary intake. High-protein diets consumed in the short or long term also are known to induce glomerular hyperfiltration,[11-14] and it is notable that obese persons consume more protein than do lean individuals.[15] Other nutrients, such as dietary sodium, also may influence renal hemodynamics.[16]

Weight reduction has been demonstrated to reverse the elevations in GFR[17] and also protect against kidney disease.[18] Whether the reduction in GFR is attributable to shrinking adipose mass, a decrease in dietary protein consumption, or other factors that occur in parallel with weight loss are unknown.

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Received July 24, 2013. Accepted in revised form November 6, 2013. Originally published online January 2, 2014.

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0272-6386/$36.00
http://dx.doi.org/10.1053/j.ajkd.2013.11.012

Elucidating the mechanisms involved in glomerular hyperfiltration may help in developing strategies to reduce obesity-associated kidney injury. Thus, we performed an experiment to test the hypothesis that reductions in GFR observed after bariatric surgery are explained by lower postsurgical dietary protein consumption.

METHODS

Participants

Most participants in this study were part of a larger project that examined the relationship between GFR, obesity, and weight reduction.[19-21] Obese individuals were recruited from bariatric surgery clinics and public advertisements in the Indianapolis, IN, area between 2004 and 2011. The relevant institutional review boards (study no. 0309-03) approved the protocol (ClinicalTrials.gov study number: NCT00244790), and all patients gave written informed consent after reviewing a written summary of the plan. The study adhered to the Declaration of Helsinki. A data safety and monitoring board oversaw the study. Inclusion criteria included age 18 years or older, ability to give informed consent, body mass index $\geq 30\ kg/m^2$, and planned bariatric surgery. Exclusion criteria included pregnancy, iodine allergy, diagnosis of diabetes mellitus, use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, serum creatinine level >1.3 mg/dL for women and >1.5 mg/dL for men, and dialysis dependency. Pregnancy was excluded by a urine pregnancy test on the day of study.

Dietary Intervention

The intervention was designed to study participants on a low-protein dietary intervention before and after bariatric surgery. All studies were performed in the Indiana University General Clinical Research Center in a fasting state. Participants were studied prior to surgery while consuming an ad lib diet. They then were provided with 7 days' worth of a low-protein diet that consisted of 50 g of animal protein and 4 g of sodium daily and isocaloric dietary content calculated using standard equations. The study diet was low in protein because of the expectation that individuals would spontaneously lower their protein consumption after surgery. After 1 week of following the study diet, each participant returned to the research center to be studied again. An identical protocol was performed after bariatric surgery. The postsurgery low-protein diet was the same as the presurgery diet with the exception of sodium content, which was decreased to 2 g daily, and caloric intake, which was set at 800 kcal daily. These changes were made to make the diet palatable and tolerable in light of the dietary restrictions that bariatric surgery imposed. Thus, times 1 and 2 occurred 1 week apart following an ad lib and low-protein diet, respectively, prior to bariatric surgery. Times 3 and 4 occurred 1 week apart following an ad lib and low-protein diet, respectively, after bariatric surgery. Of note, postsurgery visits were performed after a minimum of 20 kg was lost, an amount that was believed to be sufficient to see significant GFR changes based on our preliminary analyses. An Indiana University General Clinical Research Center dietitian using the University of Minnesota's Nutrition Data System for Research nutrient calculation software (www.ncc.umn.edu) developed the study diet while tailoring it as much as possible to the participant's dietary tastes. Meals were prepared and frozen in disposable containers that subsequently could be microwaved or heated in ovens at home. Individuals were carefully instructed to limit their dietary intake during the study period to study meals only and return any unfinished meals at the end of the study week. Dieticians contacted participants by telephone during the study intervention period to assess dietary adherence and help resolve any diet-related problems. They also estimated dietary nonadherence at the end of the study by quantifying any unfinished meals (patients were asked to bring in all unfinished meals) and performing a 24-hour dietary recall interview.

Measurements

GFR was calculated from plasma iohexol (Omnipaque-300; GE Healthcare) clearance. Plasma was isolated and stored at −80°C until measured by capillary electrophoresis using a Model 2050 CE instrument (Beckman Instruments), as previously reported,[19] or high-performance liquid chromatography (Agilent 1100) with UV detection. Individual iohexol clearances (in milliliters per minute) were estimated using standard noncompartmental methods with iohexol clearance equivalent to dose divided by the area under the plasma concentration-time curve from time zero through infinity. In cases in which only 2 plasma concentrations were available per individual, population pharmacokinetic methods were used as previously described.[20] Body mass index and body surface area[22] were calculated during each visit from measured weight and height while wearing a hospital gown and no shoes. The average of 2 blood pressures obtained while seated and separated by a 5-minute interval was used. Serum creatinine was measured using the Roche/Hitachi Creatinine Plus enzymatic assay (Roche Diagnostics) calibrated to an isotope-dilution mass spectrometry method. Measurements of 24-hour urine creatinine, sodium, potassium, and urea were performed using standard laboratory techniques. One gram of urinary urea excretion was considered to be the equivalent of 6.25 g of dietary protein.[23]

Statistical Methods

The study's primary aim was to determine the effect of weight reduction on GFR after controlling for dietary protein consumption, the working hypothesis being that the reduction in GFR observed after weight loss would disappear if protein intake was fixed. Participant demographic information and baseline characteristics were summarized by median and range or frequency for continuous and categorical variables, respectively. Changes in variables were measured using Wilcoxon signed rank test because the normality assumption was violated. In order to test effects of a low-protein diet on changes in GFR while controlling for bariatric surgery and urine sodium level, we used a repeated-measures analysis of covariance model. All statistical tests were performed at a 2-sided 5% significant level using the IBM SPSS Statistics 20 software package or SAS, version 9.3 (SAS Institute Inc), and R statistical software, version 2.15 (R Foundation for Statistical Computing).

RESULTS

Sixteen persons were enrolled for the study, but 8 did not complete the study protocol for various reasons (withdrew consent, 4; pregnant, 1; and nonadherent to diet, 3). Individuals who dropped out were similar to the 8 obese participants in terms of age (median, 44 [range, 22-51] years), sex (75% women), and race (75% white). The remaining 8 severely obese participants primarily were white and female with fasting glucose and blood pressure levels that were in the normal range or at most mildly elevated (Table 1). Serum creatinine levels also were normal. All participants underwent Roux-en-Y gastric bypass except one, who underwent a vertical sleeve gastrectomy. A median of 32.9 (range, 19.5-54.4) kg was lost between the first presurgery visit and first