Kidney outcomes three years after bariatric surgery in severely obese adolescents

see commentary on page 279

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A significant number of severely obese adolescents undergoing bariatric surgery have evidence of early kidney damage. To determine if kidney injury is reversible following bariatric surgery, we investigated renal outcomes in the Teen-Longitudinal Assessment of Bariatric Surgery cohort, a prospective multicenter study of 242 severely obese adolescents undergoing bariatric surgery. Primary outcomes of urine albumin-to-creatinine ratio and cystatin C-based estimated glomerular filtration rate (eGFR) were evaluated preoperatively and up to 3 years following bariatric surgery. At surgery, mean age of participants was 17 years and median body mass index (BMI) was 51 kg/m^2. In those with decreased kidney function at baseline (eGFR under 90 mL/min/1.73m^2), mean eGFR significantly improved from 76 to 102 mL/min/1.73m^2 at three-year follow-up. Similarly, participants with albuminuria (albumin-to-creatinine ratio of 30 mg/g and more) at baseline demonstrated significant improvement following surgery: geometric mean of ACR was 74 mg/g at baseline and decreased to 17 mg/g at three years. Those with normal renal function and no albuminuria at baseline remained stable throughout the study period. Among individuals with a BMI of 40 kg/m^2 and more at follow-up, increased BMI was associated with significantly lower eGFR, while no association was observed in those with a BMI under 40 kg/m^2. In adjusted analysis, eGFR increased by 3.9 mL/min/1.73m^2 for each 10-unit loss of BMI. Early kidney abnormalities improved following bariatric surgery in adolescents with evidence of preoperative kidney disease. Thus, kidney disease should be considered as a selection criteria for bariatric surgery in severely obese adolescents who fail conventional weight management.

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Severe obesity, defined as a body mass index (BMI) > 120% of the 95th percentile or an absolute BMI ≥ 35 kg/m^2, is increasing and now affects 4% to 6% of US children and adolescents.[1–3] The American Heart Association recently issued a consensus statement to raise awareness of this growing problem and summarize available treatment options. Considering the limited effectiveness of lifestyle and pharmacologic interventions, use of bariatric surgery has been advocated for appropriately selected adolescents with severe obesity and obesity-related comorbidities.[4]

The obesity epidemic has been paralleled by a proportionate increase in chronic kidney disease (CKD).[5] Obesity now is recognized as an independent risk factor for CKD, with recent estimates indicating that 24% to 33% of all kidney disease could be related to obesity.[6] Obese children, moreover, have a significantly higher risk of developing CKD and end-stage renal disease in adulthood.[7,8] To estimate the prevalence of early kidney disease in severely obese adolescents, we recently conducted a baseline analysis of the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort. Teen-LABS is a prospective observational study of adolescent bariatric surgical patients that aims to understand the broad-ranging outcomes after bariatric surgery. We reported that a concerning number of severely obese adolescents undergoing bariatric surgery had evidence of early kidney disease at baseline before surgery: 17% had albuminuria and 3% had significantly decreased estimated glomerular filtration rate (eGFR).[9]

Despite promising results of bariatric surgery to improve obesity and obesity-related comorbidities,[10] little is known about the potential salutary effect of bariatric surgery on obesity-related kidney disease in adolescents. To determine if early kidney injury that is associated with severe obesity reverses after weight loss surgery, we analyzed kidney outcomes in the Teen-LABS cohort up to 3 years after bariatric surgery. We hypothesized that albuminuria and eGFR would improve postoperatively, with the greatest improvement occurring in those with the most severe kidney abnormalities before undergoing bariatric surgery.

RESULTS

Demographic and clinical characteristics

The mean age at surgery was 17.1 years. Of the 242 subjects, 75.6% were female and 64.9% were non-Hispanic white.

Procedures included Roux-en-Y gastric bypass (gastric bypass) in 66.5%, sleeve gastrectomy in 27.7%, and adjustable gastric band in 5.8%. Clinical characteristics of the cohort at baseline and at the 3-year follow-up evaluation are presented in Table 1. Significant improvements occurred in BMI and other cardiovascular risk factors after bariatric surgery. The median BMI decreased from 50.5 kg/m^2 at baseline to 36.2 kg/m^2 at the 3-year follow-up evaluation. Most of this change occurred during the first 6 months postoperatively, after which the median BMI was 38.0 kg/m^2. Significantly reduced ferritin levels and increases in transferrin levels were evident in the cohort. However, significant improvements were seen in the homeostasis model assessment of insulin resistance, C-reactive protein, and the percentage of participants with dyslipidemia, hypertension, and diabetes. The percentage of participants taking antihypertensive medications also decreased: 22% at baseline compared with 7% at the 3-year follow-up evaluation. Of those taking antihypertensive medications, 59% were taking angiotensin-converting enzyme inhibitors at baseline and 23% at the 3-year follow-up evaluation.

Estimated glomerular filtration rate

The mean (±SD) of cystatin C–based eGFR at baseline was 108 ± 27 ml/min per 1.73 m^2, and this increased by 6% to 115 ± 29 ml/min per 1.73 m^2 at 3 years after surgery ($P = 0.02$). In this severely obese cohort, a low eGFR (<90 ml/min per 1.73 m^2) was observed in 24.8% (59 of 238) at baseline and improved to 15.5% (29 of 187) at the 3-year follow-up evaluation ($P = 0.004$). An abnormally high eGFR (≥150 ml/min per 1.73 m^2) was present in 7.1% (17 of 238) at baseline and in 7.5% (14 of 187) at 3 years ($P = 0.83$).

The 3-year follow-up evaluation of eGFR stratified by baseline level of renal function (<90 vs. ≥90 ml/min per 1.73 m^2) is presented in Figure 1. The majority of improvement in renal function occurred in those with a baseline eGFR of <90 ml/min per 1.73 m^2, whose mean (±SD) eGFR was 76 ± 12 ml/min per 1.73 m^2. In this group, eGFR improved by 34% to 102 ± 28 ml/min per 1.73 m^2 at the 3-year follow-up evaluation ($P < 0.0001$). Improvement in renal function first was detected at the earliest postoperative visits (6–12 months postoperatively), and then remained stable throughout the remainder of the study period. Among the 7 subjects with a baseline eGFR of <60 ml/min per 1.73 m^2, eGFR improved from 52 ± 7 ml/min per 1.73 m^2 at baseline to 98 ± 32 ml/min per 1.73 m^2 at 1 year (n = 6; $P = 0.03$), 103 ± 38 ml/min per 1.73 m^2 at 2 years (n = 6; $P = 0.01$), and 94 ± 48 ml/min per 1.73 m^2 at 3 years (n = 5; $P = 0.08$) of follow-up evaluation. However, those with an eGFR ≥90 ml/min per 1.73 m^2 at baseline did not change significantly over time (118 ± 21 ml/min per 1.73 m^2 at baseline and 119 ± 28 ml/min per 1.73 m^2 at the 3-year follow-up evaluation; $P = 0.98$). A nonstatistically significant decrease in eGFR also was detected in the small subgroup (n = 17) with eGFR ≥150 ml/min per 1.73 m^2 at baseline, for whom the mean eGFR of 162 ± 16 ml/min per 1.73 m^2 decreased to an eGFR of 138 ± 32 ml/min per 1.73 m^2 at 3 years (n = 15; $P = 0.07$).

Albuminuria

Albuminuria was observed in 17.0% (39 of 230) of the cohort at baseline and decreased to 11.0% (19 of 173) at the 3-year follow-up evaluation ($P = 0.06$). Participants with albuminuria at baseline showed a significant improvement in the albumin-to-creatinine ratio (ACR): the geometric mean of the ACR was 74 mg/g (95% confidence interval, 45–121 mg/g) at baseline and decreased to 17 mg/g (95% confidence interval, 10–28 mg/g) at 3 years ($P < 0.0001$). Of these subjects, 69% experienced normalization of albuminuria at the 2-year follow-up evaluation, and 75% experienced resolution of albuminuria at the 3-year follow-up evaluation.

The 3-year follow-up evaluation of the ACR ratios stratified by baseline level of albuminuria is presented in Table 2. Preoperatively, 13.9% (32 subjects) had microalbuminuria and 3.0% (7 subjects) had macroalbuminuria. Among those with microalbuminuria, an 83% reduction in ACR was observed 1 year postoperatively ($P < 0.0001$). The 7 participants with macroalbuminuria at baseline also showed a remarkable improvement during the study period, 3 of whom had complete normalization of urinary protein at the 1-year follow-up evaluation ($P < 0.0001$). Among those with normal levels of urinary albumin at baseline, there was no significant change in the ACR at the 3-year follow-up evaluation, although 11 of these subjects (7.6%) developed incident microalbuminuria at 3 years.

Association of BMI with GFR during the study period

The relationship between BMI and eGFR was investigated at each study time point. At baseline, those with higher BMI values showed a lower eGFR; a strongly negative correlation was observed (r = -0.34; $P < 0.0001$). However, this inverse association between BMI and eGFR dissipated postoperatively, and was no longer significant by 2 years

Table 1 | Clinical characteristics at baseline and 3-year follow-up evaluation in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort

Variable	Baseline (N = 242)	3-year follow-up evaluation (N = 206)	*P* value
BMI, kg/m^2	50.5 (45.2, 58.3)	36.2 (30.2, 44.9)	<0.0001
Hypertension	104 (43.7%)	29 (15.3%)	<0.0001
Type 2 diabetes	30 (12.6%)	1 (0.6%)	<0.0001
Dyslipidemia	179 (75.2%)	54 (30.0%)	<0.0001
Transferrin, mg/dl	268 (244, 292)	313 (274, 352)	<0.0001
Ferritin, μg/l	37.0 (23.0, 66.0)	9.0 (5.0, 24.0)	<0.0001
Serum albumin, g/dl	4.1 (3.9, 4.4)	4.3 (4.1, 4.5)	<0.0001
HOMA-IR	5.91 (3.60, 9.98)	1.97 (1.20, 3.32)	<0.0001
hsCRP, mg/l	0.63 (0.30, 1.17)	0.09 (0.03, 0.32)	<0.0001
HbA1c	5.20 (5.00, 5.50)	5.1 (4.9, 5.3)	<0.0001

BMI, body mass index; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.
Data are presented as medians (25th, 75th percentile) or n (%). *P* values were generated from generalized linear mixed models analysis.

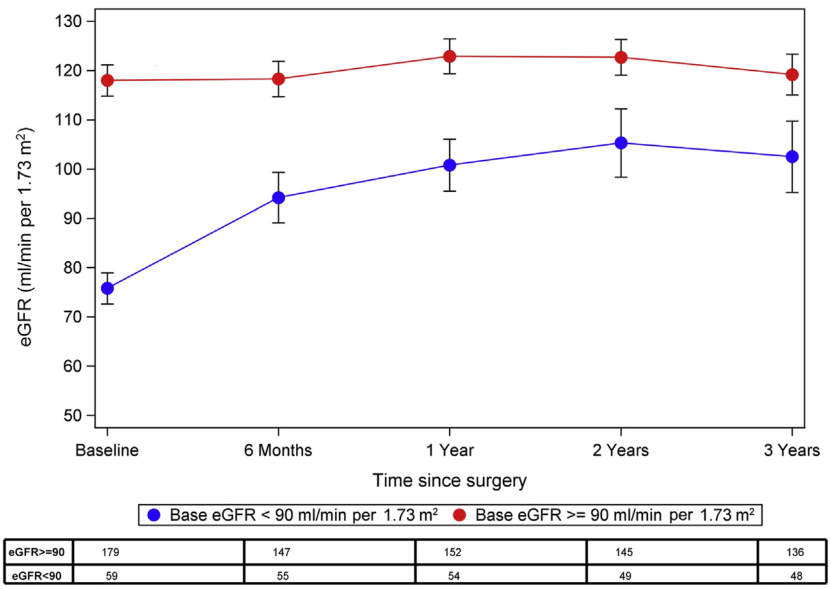

Figure 1 | Three-year follow-up evaluation of estimated glomerular filtration rate (eGFR) in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort. Least-squares means and 95% confidence intervals are presented at each time point using generalized linear mixed models analysis. Participants were stratified according to baseline kidney function. Base, baseline.

(r = -0.11; $P = 0.13$). To further investigate this finding, the association of BMI with eGFR was examined separately among those with BMI values of <40 kg/m^2 and ≥40 kg/m^2 at follow-up visits (Figure 2). Among subjects with a BMI <40 kg/m^2 at follow-up evaluation, no association of BMI with eGFR was observed. However, the negative association of BMI with eGFR persisted in those with a BMI ≥40 kg/m^2 during the follow-up period. Among these subjects with residual severe obesity postoperatively, a mean decrease of 7.0 ml/min per 1.73 m^2 in eGFR occurred for each 10-kg/m^2 increase greater than 40 kg/m^2 in BMI ($P = 0.0001$).

Multivariate analysis: predictors of eGFR and albuminuria at follow-up evaluation

Mixed-effects linear regression modeling was performed to investigate demographic and clinical variables associated with eGFR and ACR after weight loss surgery (Table 3). Regression models were adjusted for baseline eGFR and baseline ACR, as appropriate. After adjusting for significant covariates, eGFR increased by 3.9 ml/min per 1.73 m^2 for each 10-unit loss of BMI at follow-up evaluation ($P < 0.0001$). Higher serum albumin and transferrin levels at follow-up evaluation were associated with an increase in eGFR, whereas white race and male sex were associated with a decreased eGFR. An increased eGFR at follow-up evaluation also was observed after gastric bypass compared with sleeve gastrectomy. Although postoperative improvement in albuminuria was observed in participants with an increased ACR, weight loss was not associated linearly with ACR at follow-up evaluation ($P = 0.61$). Multivariate analysis indicated that female sex, hypertension at follow-up evaluation, and an increasing ferritin level at follow-up evaluation were associated with a worsening (increased) ACR.

DISCUSSION

We report kidney outcomes up to 3 years after bariatric surgery in the Teen-LABS cohort. Among participants with baseline kidney abnormalities, kidney function and

Table 2 | Three-year follow-up evaluation of proteinuria in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort

Baseline status	Baseline (N = 230)	6 months (N = 180)	1 year (N = 189)	2 years (n = 182)	3 years (N = 173)
Normal[a]	5.7 (3.7, 9.5) [n = 191]	6.0 (3.8, 13.0) [n = 145]	6.3 (4.1, 10.7) [n = 156]	5.7 (4.1, 10.7) [n = 149]	5.9 (4.1, 12.2) [n = 145]
Microalbuminuria[b]	58.9 (45.2, 176.9) [n = 32]	10.5 (4.7, 19.2) [n = 28]	11.2 (6.0, 19.1) [n = 26]	8.0 (6.4, 16.6) [n = 27]	10.2 (5.5, 14.0) [n = 23]
Macroabulminuria[b]	729 (533, 1677) [n = 7]	38.7 (4.8, 611.0) [n = 7]	80.7 (7.6, 245.1) [n = 7]	106.1 (30.4, 121.4) [n = 6]	67.5 (11.2, 173.8) [n = 5]

Data are presented as the geometric mean (95% confidence interval) of urine albumin (in milligrams) per gram of urine creatinine (the albumin-to-creatinine ratio). Participants were stratified according to their baseline level of albuminuria. n represents the number of participants at each time point.
[a]Baseline measurement was different from the 6-month and 12-month measurements ($P < 0.03$) (using a Tukey-Kramer adjustment to account for multiple comparisons).
[b]Baseline measurement was different from the 6-month, 1-year, 2-year, and 3-year measurements, all $P < 0.00001$ (using a Tukey-Kramer adjustment to account for multiple comparisons).

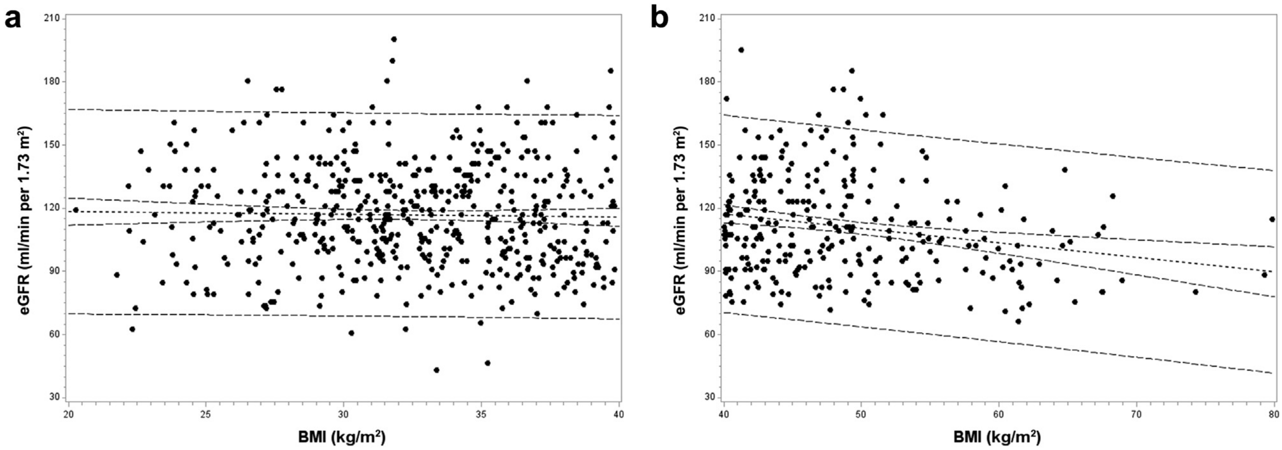

Figure 2 | Association of body mass index (BMI) with estimated glomerular filtration rate (eGFR) at follow-up evaluation in the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort. The association of BMI with eGFR was investigated separately according to BMI at follow-up evaluation. (**a**) BMI <40 kg/m^2 ($P = 0.41$), and (**b**) BMI ≥40 kg/m^2 ($P = 0.0001$).

albuminuria improved 6 to 12 months after bariatric surgery and remained stable for the duration of the study period. Equally important, in participants without evidence of preoperative kidney disease, kidney function and albuminuria remained stable throughout the follow-up period.

Proteinuria and decreased kidney function in obese subjects often indicates the presence of obesity-related glomerulopathy, which is characterized by increased glomerular size, increased mesangial matrix, and glomerular sclerosis.[11,12] This condition can portend a grave prognosis, with up to 50% progressing to end-stage renal disease within 10 years of diagnosis.[13] Therefore, vigilant screening of severely obese adolescents is needed to identify those with evidence of early kidney injury. In this cohort, 13 participants (5%) had evidence of significant kidney disease, defined by an ACR ≥300 mg/g (macroalbuminuria) or an eGFR <60 ml/min per 1.73 m^2 (CKD stage 3). These participants showed a marked reduction of albuminuria and an increase in eGFR after bariatric surgery. Similarly, those 63 (23%) participants with microalbuminuria or mildly reduced eGFR (<90 ml/min per 1.73 m^2) at baseline also improved after bariatric surgery. These findings suggest that surgical intervention may be an effective treatment to improve early kidney injury and prevent progression of obesity-related kidney disease.

Our results are consistent with previous adult studies that have shown improvement in albuminuria after bariatric surgery.[14–19] Improvements in serum creatinine and eGFR after bariatric surgery also have been observed in adults with decreased kidney function, although function has remained stable in those without baseline kidney disease.[20–22] Similar to adult studies, improvements in this adolescent cohort occurred mainly within a year of bariatric surgery.[18,22]

Hyperfiltration is a proposed mechanism of early kidney injury in obesity-related glomerulopathy that precedes the development of proteinuria and decreased kidney function.[23] We previously reported an increased prevalence of increased eGFR at baseline in the Teen-LABS cohort.[9] Interestingly, among the 17 participants with an increased eGFR at baseline (>150 ml/min per 1.73 m^2), a decreasing trend in eGFR was observed at the 3-year follow-up evaluation, although this should be interpreted with caution considering the small sample size. Previous studies in adults have reported similar changes in GFR after bariatric surgery,[16,18] suggesting that weight loss may improve obesity-induced hyperfiltration.

Table 3 | Multivariate analysis of 3-year outcomes

Predictors of eGFR			Predictors of ACR		
Variable	Increase in eGFR[a] (95% confidence intervals)	*P* value	Variable	Percentage increase in ACR (95% confidence intervals)	*P* value
BMI loss, per 10-kg/m^2 decrease	3.9 (2.4–5.4)	<0.0001	BMI loss, per 10-kg/m^2 decrease	2% (-6% to 10%)	0.61
Female sex, versus males	4.5 (1.5–7.5)	0.0003	Female sex, versus male	57% (41%–74%)	<0.0001
Nonwhite, versus white race	10.2 (7.5–12.9)	<0.0001	Hypertension, versus normotensive	38% (21%–56%)	<0.0001
Serum albumin, per 1-g/dl increase	6.2 (2.1–10.4)	0.003	Ferritin, per 10-μg/l increase	5% (3%–6%)	<0.0001
Transferrin, per 10-mg/dl increase	0.4 (0.1–0.6)	0.006			
Gastric bypass, versus sleeve gastrectomy[b]	7.0 (4.1–9.8)	<0.001			

ACR, albumin-to-creatinine ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate.
Models were adjusted for baseline eGFR or ACR ratio, as appropriate, and adjusted for study site (included as a random variable). All other variables included in the model are reported.
[a]eGFR was reported in ml/min per 1.73 m^2.
[b]Laparoscopic adjustable band included only 14 subjects and was not significantly different from sleeve gastrectomy (increase in eGFR of -0.2; $P = 0.96$).

We previously reported a strong association of increased BMI with lower eGFR at the baseline visit of Teen-LABS participants, with an adjusted 8 ml/min per 1.73 m^2 lower eGFR for every 10-kg/m^2 increase in baseline BMI. This finding prompted the important question of whether an intervention to reduce BMI would improve kidney function and/or dissociate the link between BMI and kidney function.[9] Indeed, these data optimistically suggest that bariatric surgery may prevent a progressive decrease in kidney function in severely obese adolescents with evidence of obesity-related kidney disease. Renal function improved significantly in participants with a low eGFR at baseline, and this improvement in eGFR at follow-up evaluation was associated directly with a reduction in BMI. However, a concerning facet of our study findings was that those with residual severe obesity likely still face residual risks. When the kidney outcome was examined separately among patients with persistent severe obesity at follow-up evaluation, evidence of a strong residual association between BMI and eGFR was present. Conversely, no relationship between BMI and eGFR was apparent in those who were no longer severely obese. It is not clear from these preliminary analyses what factors might mediate a continued association between residual severe obesity and renal dysfunction. However, a reasonable conclusion from the data is that there is plasticity in renal function that relates resolution of severe obesity with optimal kidney outcomes. Conversely, these data also prompt the physiologic hypothesis that factors that underlie obesity-related nephron damage, such as hyperfiltration and inflammation, may be reversed insufficiently in those who remain severely obese after bariatric surgery.

Our results indicate that demographic and clinical parameters other than BMI are related to albuminuria and kidney function after weight loss surgery. High serum transferrin and albumin levels were associated with increased eGFR at follow-up evaluation, associations that similarly have been observed in adults with moderate to advanced CKD.[24,25] It is speculated that higher albumin and transferrin levels may reflect improved nutritional status and increased protein intake, which are known to increase GFR.[26] Increased eGFR at follow-up evaluation also was observed after gastric bypass compared with sleeve gastrectomy, which may be related to recently described metabolic differences between these 2 procedures, with gastric bypass having more pronounced effects than the sleeve procedure.[27,28] Interestingly, non-Caucasian participants experienced a significantly greater improvement in eGFR over the study period compared with Caucasian participants. Racial variability exists in common causes of kidney disease, including diabetes and hypertension, and remains unexplained by modifiable risk factors.[29–32] It is possible that racial variability similarly can influence improvement in kidney function after bariatric surgery, and the relevance of this finding in our cohort warrants further evaluation. Increased albuminuria during the follow-up period was associated with female sex and increased ferritin. We previously reported similar associations at baseline in the Teen-LABS cohort.[9] Hypertensive participants also were more likely to have worsening albuminuria, which is of particular interest given the high prevalence of hypertension preoperatively. Taken together, these associations suggest that factors other than excess adiposity *per se* may be involved in the pathogenesis of obesity-related kidney disease. For example, metabolic risk factors and hypertension have been shown to modify the association of BMI with incident end-stage renal disease.[33] Future studies, however, are needed to establish a cause-and-effect relationship of potential mechanisms of obesity-related kidney disease.

This study had several strengths, including the relatively large sample size, standardized methods of data collection, and centralized and uniform laboratory analysis. The study protocol was designed to collect comprehensive data on long-term outcomes of bariatric surgery, including cardiovascular risk factors and kidney disease. Specifically, cystatin C was collected as part of the Teen-LABS protocol to optimize estimation of GFR in this unique, severely obese cohort. Cystatin C has shown superior performance in estimating GFR when compared with serum creatinine,[34] and creatinine-based estimations of GFR have performed inconsistently in obese patients.[35] Cystatin C also is less affected by demographic variables including age, sex, and race compared with serum creatinine.[36]

Nevertheless, several limitations of our study deserve mention. First, although cystatin C has been validated to provide an accurate estimation of kidney function,[37] we did not have a direct measurement of GFR. Some investigators have suggested cystatin C might slightly underestimate GFR in severely obese patients owing to an association with adiposity.[38] We cannot exclude that the performance of cystatin C–based eGFR was affected by body composition. However, eGFR remained unchanged in participants with normal renal function at baseline despite marked weight loss, suggesting that changes in body composition did not have a significant effect on GFR estimation. Serum cystatin C also can be affected mildly by factors other than renal function, which may affect GFR estimation. Gender variations in cystatin C have been reported, which may have accounted for the increased eGFR at follow-up evaluation among females, who comprised 76% of our study cohort.[36] Also, although we report outcomes for those who presented with eGFR values $\geq$150 ml/min per 1.73 m^2, there were limitations to using cystatin C–based estimates for assessment of hyperfiltration. Formal assessment of hyperfiltration requires direct GFR measurement with methods such as inulin clearance or a 24-hour urine collection, as has been performed by other investigators who showed improvement in hyperfiltration after bariatric surgery.[16,18] Second, the use of BMI as a marker of adipose tissue burden does not differentiate between fat and lean mass, or visceral and subcutaneous adiposity. Visceral adiposity in particular is a source of inflammatory cytokine secretion that has been implicated in the pathogenesis of obesity-related kidney disease.[5] Third, although the Teen-LABS study had relatively high retention rates, laboratory data were missing in 24% to 29% of the subjects at the 3-year follow-up evaluation. However, sensitivity analyses that imputed missing values were performed and supported our primary results. Finally, Teen-LABS was a prospective observational study and did not have a control arm, and our results should be interpreted in this context. Other treatment options, including caloric restriction and captopril, have been shown to decrease proteinuria in obese patients with kidney disease.[39,40] Future randomized controlled trials in patients with obesity-related kidney disease are needed to compare bariatric surgery with more conventional management strategies. However, nonsurgical treatment options in severely obese adolescents have shown only modest improvement in weight and cardiovascular risk factors, with poor long-term sustainability.[4]

In conclusion, we report 3-year kidney outcomes in a large cohort of adolescents undergoing bariatric surgery. Kidney function and albuminuria improved after weight loss surgery in those participants with evidence of preoperative kidney disease. Furthermore, BMI levels greater than 40 kg/m^2 at follow-up evaluation were associated with a progressive decrease in kidney function. These data support the addition of kidney dysfunction as a selection criterion for bariatric surgery in adolescents who reach a BMI of 40 kg/m^2 to optimize chances for reversal of severe obesity and kidney risks.

METHODS

Study population and design

The Teen-LABS study was developed as an ancillary study to the Longitudinal Assessment of Bariatric Surgery (LABS), a prospective observational study of adults undergoing bariatric surgery. The standardized methodology of the Teen-LABS study was patterned from the second phase of LABS, the goal of which was to evaluate the longer-term safety and efficacy of bariatric surgery as it relates to specific outcome domains, including kidney disease.[41] Briefly, 277 consecutive adolescents undergoing bariatric surgery at each of the 5 Teen-LABS participating centers were offered enrollment between March 2007 and December 2011. Clinical decision making was specified by center-specific patient care pathways. No attempt was made to standardize selection criteria for bariatric surgery, although all centers followed accepted guidelines for surgical treatment of obesity.[42] Baseline characteristics and obesity-related comorbidities of the Teen-LABS cohort have been described previously.[43] Thirty-five individuals either declined to participate or did not undergo surgery by the end of the enrollment period, leaving a final cohort of 242 subjects. During the 3-year follow-up period, 89.2% completed postoperative visits at 6 months, 90.1% at year 1, 89.3% at year 2, and 85.1% at year 3. Written informed consent was obtained from participants older than 18 years of age. For participants younger than age 18, written permission was obtained from caregivers and assent from the adolescent. The study protocol, assent/consent forms, and data and safety monitoring plans were approved by the institutional review board of each center.

Data collection and laboratory analysis

Data collection included demographic, anthropometric, and clinical variables to evaluate weight loss and cardiovascular, metabolic, and renal outcomes. Preoperative data were collected within 30 days of surgery, and follow-up data were obtained at 6 months and then annually after surgery. A Teen-LABS–certified clinical coordinator or surgical investigator followed standard definitions to determine the presence or absence of comorbid conditions using medical records, physical examination, interview, and laboratory values. Detailed descriptions of study definitions, including hypertension, diabetes, and dyslipidemia, have been published previously.[41] All laboratory assays were performed centrally at the Northwest Lipid Research Laboratories at the University of Washington (Seattle, WA). The homeostasis model assessment of insulin resistance was calculated by dividing the product of serum insulin (mU/ml) and glucose (mg/dl) by a factor of 405. The eGFR was calculated using the cystatin C–based Larsson *et al.*[44] formula (GFR $= 77.24 \times$ [cystatin C]$^{-1.2623}$) as recommended by the assay manufacturer (Dade Behring, Deerfield, IL) and as previously described. Proteinuria was assessed by the urine ACR. Microalbuminuria was defined as an ACR $\geq$30 mg/g and $<$300 mg/g; macroalbuminuria was defined as an ACR $\geq$300 mg/g.

Statistical analysis

Analysis was conducted using SAS, version 9.3 (SAS Institute, Cary, NC). Summary descriptive statistics were reported as frequencies (%) for the categoric variables and medians (25th percentile, 75th percentile) for continuous variables. The McNemar test was used to examine the change from baseline in the number of subjects with an increased ACR ratio and those with a reduced or abnormally high eGFR. Generalized linear mixed models were used to analyze eGFR and ACR after bariatric surgery to account for the repeated nature of the data and the within-subject correlation; both intercept and study center were specified as random effects and an autoregressive covariance structure was specified. Study subject was treated as a repeated measure and time (visit) was treated as categoric when specified in the model. A normal distribution and identity link function was used for continuous dependent variables and binomial distribution with logit link for binary dependent variables. Log transformation of ACR was performed to fulfill the assumptions of linear regression modeling. Multivariable analyses were conducted to identify predictors of eGFR and ACR at follow-up evaluation. The independent variable of interest in all of these models was BMI decrease; site identification was retained in all models as a random effect. The initial models included the baseline variables of age, sex, race (non-Hispanic white vs. all others), diagnosis of diabetes, surgery type, and the baseline value of the dependent variable (ACR or eGFR). Also included were the time-dependent variables of hypertension, dyslipidemia, transferrin, ferritin, serum albumin, homeostasis model assessment of insulin resistance, high-sensitivity CRP, and hemoglobin A1c. These variables were selected *a priori*. A backward elimination procedure was used to find the most parsimonious model with examination of the β coefficient of BMI decrease as variables were removed from the model. If the removal of a variable from the model changed the β coefficient for BMI decrease by more than 10%, the variable was retained in the model. Regression diagnostics were examined when the final model was determined. Least-square means and associated 95% confidence intervals were reported from the models. A Tukey-Kramer adjustment was used to adjust for multiple comparisons. Sensitivity analyses were performed using multiple imputation for missing covariates using SAS PROC MI and PROC MIANALYZE (SAS Institute, Cary, NC); the results did not alter any conclusions drawn from the results of the analyses. The critical value for statistical significance was set *a priori* at a P value of < 0.05.

Exploratory analysis of the association between BMI and eGFR was pursued, as in the baseline analysis of the Teen-LABS cohort in which we reported a significant association between BMI and eGFR.[9] In contrast to preoperative data, a similar linear association was not observed after surgery. To further explore the association of BMI with eGFR during follow-up visits, generalized additive models (SAS PROC GAM) and smoothing functions (SAS PROC TRANSREG) were used to examine spline functions and potential influential knots. Inflection points were observed at a BMI of 40 and 50 kg/m^2. The BMI of 40 kg/m^2 was examined further for a relationship with eGFR because this value is clinically meaningful and used in defining eligibility for bariatric surgery.[42]

DISCLOSURE

THI has received bariatric research grant funding from Ethicon Endosurgery, and has served as a consultant for Sanofi Corporation, NPS Pharma, Up To Date, and Independent Medical Expert Consulting Services, all unrelated to this project. All the other authors declared no competing interests.

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Teen-LABS is an ancillary study to the LABS study (U01 DK066557). The data collection methodology was patterned after LABS-1 and LABS-2, with modification as needed for the adolescent population. The Teen-LABS consortium gratefully acknowledges the expertise and guidance provided by the LABS consortium and Data Coordinating Center.

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