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Bariatric Surgery and Kidney Disease Outcomes in Severely Obese Youth

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Abstract

Bariatric surgery, an emerging treatment for severely obese youth with and without T2D, provides marked improvement in insulin resistance, beta-cell function, and central adiposity. Further, preliminary data suggest that bariatric surgery also results in significant improvement in markers of obesity-related nephropathy and DKD, beyond that which can be achieved with current medical interventions. Yet, the mechanisms whereby bariatric surgery attenuates kidney disease remain unclear. This review summarizes the data on the effects of bariatric surgery on obesity-related nephropathy and DKD in youth with and without T2D, in addition to potential mechanisms underlying the nephroprotective effects of weight loss surgery and how these may differ in Roux-en-Y gastric bypass vs. vertical sleeve gastrectomy. Finally, we discuss potential future non-surgical therapies to mitigate kidney disease.

Introduction:

Severe obesity now affects 4–6% of youth in the United States and predicts poor health outcomes, including increased risk of chronic kidney disease (CKD) and premature death (1). Obesity is one of the strongest risk factors for incident CKD in adults and obesity-related nephropathy is increasingly recognized in youth. The increasing prevalence of

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Conflicts of interest

PB has acted as a consultant for Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi, Novo Nordisk and Horizon Pharma. PB serves on a clinical development board for Boehringer Ingelheim and the advisory board of XORTX. DHvR has acted as a consultant and received honoraria from Boehringer Ingelheim and Eli Lilly, Merck, Novo Nordisk, and Sanofi and has received research operating funds from AstraZeneca, Boehringer Ingelheim-Eli Lilly Diabetes Alliance, MSD, and Novo Nordisk.

obesity also has implications for lifetime risk for type 2 diabetes (T2D), cardiovascular disease and premature death (1). In fact, the prevalence of youth-onset type 2 diabetes (Y-T2D) is increasing in parallel with the rise in obesity in the United States, and world-wide (2, 3). Y-T2D now represents a substantial percentage of new cases of diabetes in children and adolescents, ranging from 14% in non-Hispanic Whites to 86% in American Indians (2–4). Almost 40% of people with diabetes will develop diabetic kidney disease (DKD) (5), and 50% of Y-T2D will develop early DKD during young adulthood (6–9). Compared to adult-onset T2D, Y-T2D has a more aggressive phenotype with a greater degree of insulin resistance (IR), mitochondrial dysfunction, and higher prevalence of DKD, increasing the risk for early mortality and arguing for dedicated studies in youth (2, 10, 11). Despite the high prevalence and gravity of DKD and obesity-related nephropathy, Y-T2D is characterized by a suboptimal response to currently approved medical therapies, and major challenges in adherence and management. Although major therapeutic advances have been made in diabetes care for adults with T2D, the only FDA approved medications as of June 2019 for youth-onset T2D were metformin and insulin, with the recent addition of GLP-1 receptor agonist. Further, the recently completed Restoring Insulin Secretion (RISE) study, where youth and adult participants were randomly assigned to receive either 12 months of metformin or 3 months of insulin glargine followed by 9 months of metformin, early insulin glargine and metformin both failed to improve β -cell function in Y-T2D (12, 13). Moreover, RISE demonstrated that IR and insulin secretion were markedly higher in Y-T2D in comparison to adults, calling for novel approaches to Y-T2D (12, 13).

Metabolic bariatric surgery is now increasingly recognized as an accepted treatment option for severe obesity in youth that has beneficial effects on long-term obesity-related comorbidities, including kidney disease (14, 15). However, the mechanisms whereby bariatric surgery confers kidney protection remains incompletely understood. Although metabolic bariatric surgery is most commonly performed in later adulthood, data indicate that the longstanding effects of severe obesity from adolescence to adulthood increase the likelihood of complications including hypertension, nephropathy and cardiovascular disease (16).

Accordingly, this review will summarize existing data on the effects of metabolic bariatric surgery on obesity-related nephropathy and DKD in adolescents and adults with and without T2D, in addition to potential mechanisms underlying the nephroprotective effects of weight loss surgery and how these may differ in Roux-en-Y gastric bypass (RYGB) vs. vertical sleeve gastrectomy (VSG). Finally, we discuss promising future non-surgical strategies to mimic the nephroprotective effects mediated by metabolic bariatric surgery for people who are deemed unfit for surgery or lack insurance coverage.

Obesity-related nephropathy and DKD in children

The epidemic of obesity witnessed in recent decades has been paralleled by an increase in kidney disease, with the incidence of end-stage kidney disease (ESKD) nearly quadrupling from 1980–2000 (17). Recent estimates indicate that 24–33% of all kidney disease in the United States is related to obesity (18). Although quantifying the contribution of childhood obesity and obesity-related Y-T2D to the overall burden of ESKD in adulthood is

challenging, recent evidence suggests these conditions in childhood carry significant risk of poor kidney outcomes. A recent analysis investigated early kidney disease in participants in the Teen-LABS cohort, a prospective observational study of 242 adolescents ages 13–19 who underwent bariatric surgery. Preoperatively, 17% had elevated albuminuria and 3% had impaired GFR (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m²), indicating an alarmingly high prevalence of preexisting kidney damage in adolescents with severe obesity (19). Another study investigated biomarkers of tubular kidney injury in 22 severely obese adolescents without clinical evidence of kidney disease (i.e., normoalbuminuria and preserved eGFR). Urinary biomarkers, including NGAL, KIM-1, and IL-18, were increased compared with lean participants, indicating the presence of subclinical kidney injury in severe obesity (20). To investigate long-term outcomes of childhood obesity, Vivante et al. investigated the association of obesity at age 17 with ESKD in 1.2 million adolescents followed for an average of 25 years. Obesity was associated with a 6-fold increased risk of developing ESKD and a 19-fold risk of ESKD related to DKD (21). Therefore, severe obesity in childhood confers substantial risk for early kidney disease and progression to ESKD in adulthood.

Y-T2D frequently complicates childhood obesity, and children with this condition represent a particularly vulnerable population for adverse outcomes. Compared to type 1 diabetes (T1D), children and young adults with Y-T2D have significantly higher long-term risk of developing CVD and ESKD (22, 23). Moreover, Y-T2D is associated with increased renal disease and mortality compared with adult-onset T2D (2). The prevalence of DKD in youth with T2D, defined as elevated albuminuria, has been reported to range from 28% to 40% within 0–5 years of diagnosis in single center studies (23–26). The prevalence and trajectory of DKD in Y-T2D has been investigated in two large multicenter studies in children: the SEARCH for Diabetes in Youth study (hereafter, the SEARCH study) and the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study. The SEARCH study enrolled 272 Y-T2D from 5 US sites and investigated renal outcomes over 7.9 years. DKD was present in 19.9% of those with T2D compared to only 5.8% in T1D (10). The TODAY study enrolled 669 adolescents at 15 centers across the US with T2D in a randomized trial to investigate the effect of medical management strategies on diabetes outcomes. In this study, microalbuminuria was present in 6.3% at baseline and increased to 16.6% at the end of the trial (average follow-up 3.9 years) (11). The participants of the TODAY clinical trial were enrolled in two longitudinal observational follow-up studies, TODAY 2 Phase 1 and TODAY 2 Phase 2, which sought to detail the rates of complications in Y-T2D as they transition to young adulthood. Data from Today 2 Phase 2 demonstrated that the 12-year cumulative incidence of elevated albuminuria was 40% in Y-T2D, and 48% for hyperfiltration (27). Finally, in an observational study of 242 youth with T2D in Manitoba, Canada, 6.7% developed ESKD at a mean follow-up of 9 years (28). Genetic factors of First Nations youth may, however, contribute to the higher risk than that which has been observed in more diverse cohorts. The rapid rise of kidney disease in this population is alarming, and these data indicate that a significant proportion of Y-T2D have existing DKD that will progress to ESKD in adulthood.

Bariatric surgery to treat obesity-related kidney disease and DKD in children

Considering the limited efficacy of lifestyle and pharmacologic interventions to treat severe obesity and obesity-related T2D, bariatric surgery has become an increasingly accepted treatment option for severely obese adolescents (29, 30). Bariatric surgical procedures most commonly performed include VSG, RYGB, and adjustable gastric banding. All three procedures have proven efficacy and are becoming increasingly used for adolescents with severe obesity and obesity-related comorbidities (1). Short-term outcomes have been excellent, including 25–35% weight loss following surgery and improvement in many obesity-related comorbidities, such as insulin resistance, dyslipidemia, and hypertension (31–37). Moreover, bariatric surgery in adolescents with obesity and T2D has resulted in improved glycemic control and sustained remission compared to medical management (38, 39). Accordingly, evidence-based best practice guidelines for pediatric/adolescent weight loss surgery recommend that adolescents with severe obesity and comorbid conditions should be strongly considered for weight loss surgery (40). Kidney disease, however, was not mentioned in these guidelines as a selection criterion for bariatric surgery, but mounting adolescent data would support inclusion of kidney disease as a comorbidity that should justify consideration of surgery, as we outline below.

In adult literature, consistent improvements in albuminuria and GFR following bariatric surgery has been reported (14, 41, 42). We recently performed a three-year longitudinal study of the Teen-LABS cohort to investigate kidney outcomes in youth following bariatric surgery (15). Similar to adult data, improvement in albuminuria and GFR was observed in those with pre-operative kidney impairment. In participants with a preoperative eGFR < 90 ml/min/1.73m², eGFR improved from a mean of 76 ml/min/1.73m² to 102 ml/min/1.73m² at three years follow up. Similarly, in those with elevated albuminuria at baseline (albumin-to-creatinine ratio [ACR] ≥ 30mg/g), the median ACR decreased from 74 mg/g to 17 mg/g. GFR and albuminuria remained stable in those without any evidence of pre-operative kidney disease. To investigate the effect of bariatric surgery on DKD, we recently investigated and compared 5-year kidney outcomes in adolescents with severe obesity and Y-T2D in the Teen-LABS and TODAY studies. Elevated albuminuria was present in 21% of TODAY participants receiving medical management at baseline and increased to 43% at 5 years. Conversely, albuminuria decreased from 27% of Teen-LABS participants prior to surgery to 5% at 5 years follow-up. TODAY participants had a 27-fold higher odds of DKD at 5 years compared to Teen-LABS participants in adjusted analyses (43). Additionally, a recent combined analysis of Longitudinal Assessment of Bariatric Surgery (LABS) adults and Teen Longitudinal Assessment of Bariatric Surgery (Teen-LABS) adolescents showed that adolescents experienced earlier remission of DKD than adults in response to bariatric surgery (44). These data indicate that bariatric surgery improves kidney outcomes in youth with severe obesity youth, including those with T2D. Bariatric surgery should therefore be strongly considered as a treatment option for adolescents with severe obesity and evidence of early kidney disease. However, it is important to underscore that Teen-LABS and LABS studies almost exclusively employed RYGB whereas VSG is now the procedure of choice in youth. Accordingly, there is an urgent need for studies defining the renal effects of VSG.

Potential mechanisms of nephroprotection with bariatric surgery

It is unclear how metabolic bariatric surgery effects the dramatic attenuation of kidney disease in those with obesity and T2D. Proposed mechanisms of action include improvements renal energetics, hemodynamic stress (hyperfiltration), and improvements in metabolic factors such as insulin sensitivity, reversal of inflammation, lipid metabolism, and other hormonal changes associated with weight loss (45–50). In the paragraphs below, the potential nephroprotective effects of these proposed mechanisms will be discussed.

A. Improvement in renal hemodynamic function

Elevated GFR, or hyperfiltration, is perhaps the earliest manifestation of kidney disease in obesity and Y-T2D. Hyperfiltration is thought to represent a precursor to single-nephron increases in glomerular pressure, which eventually leads to podocyte injury, proteinuria, and glomerulosclerosis (51). Hyperfiltration at the histologic level is evident by increased glomerular size, podocyte hypertrophy, and in severe cases perihilar glomerular sclerosis (52, 53). The exact cause of hyperfiltration in obesity and Y-T2D is uncertain, but may relate to increased sodium retention, sympathetic activation, or upregulation of the renin-angiotensin-aldosterone system (RAAS) (54). Insulin resistance also predicts hyperfiltration in Y-T2D (55). Several studies have demonstrated that hyperfiltration improves following bariatric surgery and weight loss, indicating that this phenotype of early kidney disease may be a reversible physiologic adaptation (56–59). Therefore, bariatric surgery may reverse progressive increases in intraglomerular pressure by improving the putative mechanisms of hyperfiltration. As hyperfiltration is associated with the development of proteinuria (51), reversal of maladaptive intraglomerular hemodynamics may partially explain the regression of albuminuria in adolescents who undergo bariatric surgery.

B. Improvement in metabolic and lipid factors

Obesity is characterized by aberrant accumulation of fatty acids and their metabolites in non-adipose tissues such as the liver, heart, skeletal muscle, and kidneys. This results in various lipotoxic effects that are believed to contribute to inflammation and insulin resistance, (60) both of which are causally related to kidney disease (61). Data also suggest that lipotoxic effects directly mediate chronic kidney injury in obesity and metabolic syndrome. Intracellular accumulation of saturated fatty acids, most specifically palmitic acid, causes injury to both glomerular and tubular epithelial cells (62, 63). This may occur via production of reactive oxygen species and subsequent mitochondrial damage, which in turn leads to impaired fatty oxidation and further increase in fatty acid accumulation (64, 65). Obesity is also associated with increased production and accumulation sphingolipids, including ceramides and sphingomyelin species, which are composed of a sphingosine and fatty acid (66). Sphingolipids have recently been shown to mediate glomerular changes observed in diabetes, including mesangial hypertrophy and glomerular fibrosis (67, 68).

Improvement in lipid metabolism may be a mechanism of improved kidney outcomes following bariatric surgery. Improvement in clinical lipid parameters, including decreased total cholesterol and increased HDL, have consistently been observed following bariatric surgery (69). Recent studies have also demonstrated decreased levels of the nephrotoxic

lipid species mentioned above. Fatty acid profiles are improved 1 year following bariatric surgery, with decreased saturated fatty acids and increased levels of anti-atherogenic polyunsaturated fatty acids (70, 71). Interestingly, in the immediate months following bariatric surgery, a transient increase in serum fatty acids has been observed, which may represent augmented lipolysis and mobilization of fatty acids from adipose tissue and other organs (72–74). Improvement in sphingolipid profiles, specifically in people undergoing RYGB and biliopancreatic diversion procedures (BPD), has also been observed 3–6 months post operatively (75–77). In a recent analysis of urinary sphingolipids in adolescents undergoing bariatric surgery, we reported that almost all species investigated were significantly elevated preoperatively and improved 1 year postoperatively (78). Collectively, these studies suggest that improvement in lipotoxic fatty acids and other lipid metabolites may at least partially mediate the nephroprotective effects of bariatric surgery,

In addition to reduced levels of potentially nephrotoxic lipid species following bariatric surgery, improved adipocyte function *per se* may also exert nephroprotective effects. Obesity is a state of adipokine dysregulation, or adiposopathy, which is defined as pathologic adipose tissue that promotes functional disturbances in susceptible individuals. Recently, adiposopathy has been directly implicated as a cause of kidney injury in obesity (79, 80). Altered levels of fat-derived adipokines, including leptin and adiponectin, has been associated with initiation and progression of CKD (79, 80). In murine models of obesity, decreased adiponectin levels cause increased proteinuria, podocyte dysfunction, and interstitial fibrosis (81, 82). High leptin levels that are present in obesity may directly affect kidney function by stimulating glomerular cell proliferation (83) and mesangial cell hypertrophy (84). Several studies have shown that this adipocyte dysregulation improves following bariatric surgery, with resultant increases in adiponectin and decreases in leptin levels (85–87). These metabolic effects may have a directly beneficial effect in reversing kidney injury that occurs in obesity and Y-T2D.

C. Improvement in renal energetics

Albeit speculative, the net effect of the renal hemodynamic and metabolic changes would likely be improved substrate utilization and adenosine triphosphate generation, which when coupled with reduced renal energy expenditure from attenuated hyperfiltration, glucosuria and sodium reabsorption could collectively mitigate renal hypoxia risk.

The initial metabolic and molecular derangements underlying the development of early DKD are poorly understood. Renal hypoxia, potentially stemming from a mismatch between increased renal energy demand and impaired substrate utilization, is emerging as a unifying early pathway in the development of DKD and a potential therapeutic target (88–91) (Figure 1). T2D is characterized by mechanisms that 1) *increase renal ATP consumption*, including elevated glomerular filtration rate (GFR, i.e. hyperfiltration), effective renal plasma flow (ERPF) and filtered Na^+ load, and 2) *decrease ATP generation*, including insulin resistance and mitochondrial dysfunction (Fig. 1). Insulin resistance shifts renal fuel utilization towards free fatty acid oxidation, which has a low ATP yield per O_2 consumed (92, 93). Further, insulin resistance limits ATP synthesis by inhibiting AMP-kinase (AMPK) (94, 95), and is associated with mTOR complex 1 (mTORC1) hyperactivation which results in

mitochondrial dysfunction (96, 97) and reduced electron transport chain efficiency (98). It has been hypothesized that the imbalance between renal hypermetabolism and impaired substrate utilization leads to increased renal O₂ consumption, since the majority of ATP produced in the kidneys is through aerobic metabolism (99). The high O₂ demand ultimately leads to renal hypoxia, to which a diabetic kidney may be unable to adapt due to an impaired hypoxia-inducible factor (HIF) system (88–90). Bariatric surgery may correct the metabolic mismatch (Figure 2). Bariatric surgery improves insulin resistance (45) and provides remission of T2D in 86% of youth (100). Further, bariatric surgery is associated with greater attenuation of hyperfiltration and albuminuria than standard medical therapy (43). Accordingly, bariatric surgery, while not the ideal treatment for all Y-T2D, may be the ideal model to enhance our understanding of the potential metabolic imbalance between renal energy expenditure and substrate utilization underlying early DKD.

Roux-en-Y gastric bypass vs. vertical sleeve gastrectomy

VSG and RYGB represent the most common bariatric procedures today, and likely have distinct metabolic effects. RYGB appears to exert a more pronounced effect on gastrointestinal hormonal secretions (101). Recent data indicate that kidney outcomes may also be differentially affected depending on the type of bariatric surgery. Using propensity score matching, Imam et al. compared kidney outcomes between patients receiving RYGB and VSG. Over a 3-year follow-up period, patients who underwent RYGB experienced a 6.6 ml/min/1.73m² improvement in eGFR compared to those who underwent VSG (42). Similarly, in the Teen-LABS cohort, we demonstrated that RYGB, compared to VSG, was associated with 7.0 ml/min/1.73m² improvement in eGFR following surgery (15). Both analyses were adjusted for clinically important covariates, including BMI and baseline eGFR, indicating an independent beneficial effect in those undergoing RYGB. While the cause of comparatively improved kidney function following RYGB is not known with certainty, differential changes in lipid profiles may offer a plausible explanation. Specifically, RYGB has been shown to have a much more pronounced effect in reducing levels of potentially nephrotoxic lipid species compared to VSG. In two recent studies investigating the effect bariatric surgery on lipidomic profiles, patients receiving RYGB experienced an overall marked reduction in serum sphingolipids, including many ceramides and sphingomyelin species, compared to those undergoing VSG (75, 76). Moreover, decreases in these lipids following RYGB were associated with decreases in body weight and increased insulin sensitivity (76). Improved levels of nephrotoxic sphingolipids may similarly contribute to the renoprotective effects of RYGB, though future studies are needed to investigate this.

Potential non-surgical interventions to mimic effects of bariatric surgery

Although data demonstrate a marked attenuation of obesity-related nephropathy and DKD in response to bariatric surgery, the potential risks associated with metabolic bariatric surgery needs to be emphasized. Complications of metabolic bariatric surgery are described in detail elsewhere (38), but include the risk of repeat surgery, dietary deficiencies, potential negative effects on bone health, offspring, as well as mental health. Clinical adverse events previously reported in participants in Teen-LABS show that 23% experienced complications that

required subsequent operation and/or readmission that were related or possibly related (e.g., cholecystectomy for gallstones) to their prior bariatric surgery (38). However, RYGB, the surgery done predominantly in Teen-LABS, appears to have more complications than the currently preferred VSG procedure. We do not yet know the extent of complications observed with VSG in severely obese adolescents with T2D. Additionally, bariatric surgery incurs a substantial initial cost and may not be available to all due to inequitable insurance coverage. Accordingly, there is a critical need to better understand the molecular and metabolic mechanisms of nephroprotection underlying bariatric surgery to uncover novel targetable pathways for the development of novel non-surgical therapeutic targets.

Non-surgical strategies might be most effective if they simultaneously address both sides of the mismatch equation, i.e. *ATP consumption* and *ATP generation* (Figure 3). A promising example includes combining agents that may lower *renal ATP consumption* [e.g. SGLT2 inhibitors (88) or vasopressin receptor blockers (102)] with interventions to improve *ATP generation* [e.g. mitochondrial peptides and bioavailable-small molecule activators of AMPK and mTORC1 inhibitors (95, 97, 103, 104)]. Even small enhancements in fuel utilization minute to minute may translate into large improvements in kidney function and ultimately clinical outcomes. Hypoxia-adaptability is also a promising therapeutic target. The HIF system induces cell-type specific gene expression changes to promote cell survival in response to hypoxia, including increased erythropoietin (EPO) production in the kidney. Data also suggest that EPO has direct renoprotective effects beyond improving hematocrit and oxygen carrying capacity. For example, EPO has been shown to prevent podocyte injury (105, 106), improve endothelial function and attenuate albuminuria (107). Further, it is hypothesized that activation of HIF system and increased EPO may explain some of the cardio-renal benefits of SGLT2 inhibitors. Indeed, a mediation analysis of the EMPA-REG OUTCOME trial found that change in hematocrit explained 51.8% of the effect of empagliflozin versus placebo on the risk of cardiovascular death (108). HIFs can also be directly increased by Prolyl Hydroxylase (PH) inhibitors which prevent degradation of these proteins. PH inhibitors are novel drug agents, which are designed to increase erythropoietin production and phase 3 trials are underway to evaluate their role in treatment of anemia of CKD (#NCT02876835 (109–111)). If changes in HIF1 α expression in response to bariatric surgery relate to nephroprotection, PH inhibitors may be promising agent to repurpose to impede DKD in Y-T2D.

Conclusions and Future Directions:

Obesity-related nephropathy is increasingly recognized as one of the leading causes of CKD, and over 40% of people with diabetes will develop DKD during their lifetime which continues to be the leading cause of renal failure (5). Bariatric surgery is now increasingly recognized as a treatment option for severely obese youth with and without T2D, and data suggest that bariatric surgery mitigates DKD risk to a greater extent than what is observed with standard medical therapy (14, 15). Additionally, less invasive surgical procedures are now available including VSG which may have a superior safety profile to RYGB, but it remains unclear whether it exerts similar nephroprotective effects. Accordingly, studies comprehensively profiling the renal effects of VSG is needed for severely obese youth with and without T2D. Furthermore, studies with bariatric surgery may provide the ideal model to

better understand the metabolic and molecular pathophysiology underlying early DKD which is needed to combat this accelerating public health problem. Precision medicine and an integrated biological approach to obesity-related nephropathy and DKD integrating rigorous physiology procedures, biomarker discovery and tissue-based morphometrics, metabolomics and transcriptomics are likely needed to achieve this objective. Such technologies offer a platform to deeply investigate potential molecular mechanisms activated by bariatric surgery and define innovative non-surgical interventional targets to impede early DKD and obesity-related nephropathy.

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Figure 1.
Renal energetics dysfunction underlying DKD

Figure 2.
Potential Mechanisms for Improvement in Kidney Disease after Bariatric Surgery

Figure 3.
Potential non-surgical strategies