Is Bariatric Surgery an Effective Treatment for Type II Diabetic Kidney Disease?

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Abstract
Type II diabetic kidney disease is devastating to patients and society alike. This review will evaluate bariatric surgery as a treatment for diabetic kidney disease primarily through its ability to induce and maintain regression of type II diabetes. The review begins by outlining the global challenge of diabetic kidney disease, its link to obesity, and the comparative benefits of bariatric surgery on weight and type II diabetes. It then surveys comprehensively the relevant literature, which reports that although bariatric surgery is associated with reductions in albuminuria, its effect on harder clinical end points like progression of diabetic kidney disease is not known. The review also includes a critical assessment of the risks and costs of bariatric surgery and concludes by acknowledging the major knowledge gaps in the field and providing research strategies to overcome them. Until these knowledge gaps are filled, clinicians will be forced to rely on their own subjective judgment in determining the benefit-risk ratio of bariatric surgery for patients with diabetic kidney disease.

Introduction
Type II diabetic kidney disease (DKD) presents a challenge for nephrologists in light of its high prevalence (1), its pronounced adverse effects on clinical outcomes, and its enormous effect on health care costs and resources. Unfortunately, current treatment options for DKD, which are primarily pharmacologic in nature, have only modest effects on its progression (1) and are associated with costs and side effects that often limit their use.

An alternative and less recognized approach to treating DKD involves weight reduction. Because obesity is believed to be intimately linked to the development of diabetes, reversing obesity through weight loss may in theory be an effective tool not only in slowing disease progression but curing it altogether. Of all of the weight reduction strategies available, bariatric surgery is by far the most effective and sustained and has even been shown in some patients to induce remission of diabetes. However, the weight loss approach to treating type II DKD is understudied by nephrologists (2).

This article will critically analyze the available literature to determine if bariatric surgery is an effective treatment for DKD. It will also address any knowledge gaps and practical issues that need to be addressed before adopting bariatric surgery as a mainstream treatment. Although weight loss may have potentially salutary effects on kidney health that are independent of its effects on diabetes (3), this topic is beyond the scope of this article and will not be addressed.

The Challenge of DKD
Type II DKD is believed to be the leading global cause of kidney failure (4). In the United States, it accounts for more than one of every two new cases of ESRD (5), with several other countries having even higher rates (5). The presence of DKD confers a markedly increased risk of cardiovascular events and death. Patients with diabetes and CKD have a 31% 10-year incidence of all-cause mortality and 20% incidence of cardiovascular mortality (6). These rates are far higher than the corresponding rates for patients with nondiabetic CKD, which itself is a high-risk group. DKD also accounts for a greatly disproportionate portion of health care dollars, totaling many billions annually (7).

Treatment options for DKD revolve around control of dysglycemia and BP (the latter preferably by inhibition of the renin-angiotensin-aldosterone axis). However, the evidence to support these interventions is mixed (2). In fact, the standard approach has failed to stem the rising prevalence of DKD, despite its use in growing numbers of patients with type II diabetes (1). Recent attempts to identify alternative drug therapies for DKD have also failed (8). There is, therefore, an immediate need to consider alternative approaches to prevent the development and progression of DKD.

Obesity and the Development of DKD
Although the precise pathophysiology of DKD is not fully understood, it seems that excess weight is a key factor in the development of type II diabetes. In the majority of patients, weight gain precedes and is strongly predictive of type II diabetes (9,10). This is elegantly depicted in a Centers for Disease Control survey of the United States population between 1994 and 2013 that found the prevalence of diabetes lagging very closely behind that of obesity (as defined...
by body mass index [BMI] of $\geq 30$ kg/m$^2$) (10). The presence of type II diabetes is, in turn, by definition a necessary requirement for the development of DKD. The converse of these observations is likely also true. Weight reduction has the potential to induce remission of type II diabetes (see below), and correction of the diabetic milieu is expected to induce regression of DKD. The latter point was suggested by findings in eight patients with type I diabetic nephropathy who underwent pancreas transplantation with subsequent resolution of their diabetes. Kidney biopsies 10 years later showed reversal of their diabetic kidney lesions (11). This example supports the concept that the essential ingredient in curing DKD is inducing remission of diabetes, regardless of how it is done. As will be discussed, in overweight or obese patients with type II diabetes large weight reduction can sometimes accomplish this goal.

The facts above raise the possibility that by inducing regression or remission of type II diabetes weight reduction may represent an alternative approach to treat DKD. Although the precise numbers of patients with DKD suffering from excess adiposity are not known, obesity is very common in both the greater diabetes (approximately 90%) (12) and CKD (approximately 17%) (5) populations. Thus, a treatment strategy on the basis of weight reduction would likely be applicable to a large proportion of the population with DKD.

**Comparative Effect of Bariatric Surgery on Weight and Remission of Diabetes**

Weight reduction can be achieved by nonsurgical interventions (pharmacotherapy and dietary and lifestyle changes) or with what has become an increasingly accepted option, bariatric surgery. According to the American Society for Metabolic and Bariatric Surgery (ASMBS), approximately 179,000 bariatric procedures were carried out in the United States in 2013 in patients who were likely to have met standard qualifying criteria: BMI $\geq 40$; BMI $\geq 35$ and at least two obesity–related comorbidities (including type II diabetes); and inability to achieve a healthy sustained weight loss despite efforts to do so. The term bariatric surgery actually encompasses several specific procedures as shown in Figure 1. According to the ASMBS, sleeve gastrectomy and Roux-en-Y gastric bypass are currently the two most commonly performed (42% and 34%, respectively).

Of all of the available weight loss strategies, bariatric surgery unquestionably offers the most intensive and durable results. A meta-analysis including 11 clinical trials that randomized obese participants to bariatric surgery versus nonsurgical treatment for weight reduction with at least 6 months of follow-up found that patients in the surgery arm lost significantly more weight (mean difference, 26 kg; $P<0.001$) and that the difference was more pronounced in heavier patients (i.e., BMI $>40$ kg/m$^2$; mean difference, 31 kg) (13). This finding is consistent in the medical literature and should not be surprising, in part because nonsurgical weight reduction methods offer, on average, only modest weight reduction. This fact was shown in the seminal National Institutes of Health (NIH)-sponsored multicenter randomized trial Action for Health in Diabetes (Look AHEAD), which was designed to compare the effects of an intensive lifestyle intervention versus standard education and support (control arm) on weight and clinical outcomes in 5145 overweight or obese patients with type II diabetes. By year 10 of follow-up, mean weight loss was 6% (approximately 6 kg) in the intervention group and 3.5% in controls (14). Of note, 6% mean weight loss is likely to represent the upper end of what can be achieved by lifestyle interventions, because weight loss may be more challenging outside the auspices of a clinical trial. Similarly, pharmacotherapy for obesity offers similarly modest average weight loss results (15) with added safety concerns (16).

How do nonsurgical and surgical strategies compare in terms of inducing remission of type II diabetes? The fact that an intensive lifestyle intervention for weight loss has only minimal influence on diabetes was shown conclusively in Look AHEAD (17). In that study, partial and complete remission of diabetes were defined as transitioning to a prediabetes level of glycemia (fasting plasma glucose of 100–126 mg/dl and hemoglobin A1c [HbA1c] of 5.7%–6.5%) or full normalization of glucose levels (fasting plasma glucose $<100$ mg/dl and HbA1c $<5.7%$), respectively, when off of diabetes medications. After 1 year (the point of peak weight loss), only 11.5% of participants in the intervention group had a partial or complete remission of diabetes. This fell to 7.3% in year 4, with only 3.5% having a complete remission.

In contrast, two separate meta-analyses of randomized controlled trials and/or nonrandomized observational studies in patients with type II diabetes found that bariatric surgery was much more effective in inducing remission of diabetes compared with nonsurgical therapy (odds ratio, 14.1 [95% confidence interval, 6.7 to 29.9] [18]; relative risk, 22.1 [95% confidence interval, 3.2 to 154.3] [13]). A limitation of these findings was related to differences in the definition of remission, making it more difficult to objectively compare interventions.

The largest such randomized trial, very recently published and not included in the meta-analyses above (19), compared intensive lifestyle and medical management without and with a gastric bypass in 120 obese patients with type II diabetes. Over a 24-month follow-up period, the gastric bypass group lost 17% more of their baseline weight than the nonsurgical group. At 24 months, 42% of patients in the surgery group had partial remission (HbA1c $\leq 6.5\%$ off of diabetes medications) of diabetes, and 25% had full remission (HbA1c $\leq 6.0\%$ off of diabetes medications) compared with 0% and 0%, respectively, in the nonsurgical group. Of note, Ikramuddin et al. (19) used the American Diabetes Association definition for remission. An even more recently published randomized trial of 61 obese participants with longer follow-up (36 months) echoed these findings (20). The results of these studies suggest that if there is any possibility of treating DKD through remitting the underlying diabetes by weight loss, bariatric surgery is by far the most effective such strategy available. Interestingly, even before these data were published, the American Diabetes Association recommended bariatric surgery for patients who had type II diabetes that could not be controlled by nonsurgical methods (21).

Of note, the individual bariatric procedures (Figure 1) differ in terms of their effects. The greatest amount and durability of weight lost as well as degree of remission of
diabetes occur with the (infrequently used) biliopancreatic diversion with duodenal switch followed, in order, by the Roux-en-Y gastric bypass, sleeve gastrectomy, and gastric banding (22). One finding common to all bariatric surgeries is that, over time and on average, patients regain some of the weight that they initially lost. For example, in one prominent study that included over 4000 patients undergoing bariatric surgery, change in weight at 1 and 10 years postsurgery was \(-38\%\) and \(-25\%\), respectively, in the gastric bypass group, and \(-21\%\) and \(-13\%\), respectively, in gastric banding patients.

How Does Bariatric Surgery Remit Diabetes?

The mechanisms(s) underlying bariatric surgery’s powerful effects on weight and metabolic parameters,
including regression of diabetes, are important to under-
stand, because they might lead to newer, less invasive
therapies for DKD. The traditional view has been that
the effects are a direct result of mechanical or anatomic
changes associated with the surgical procedure itself.
Hence, bariatric surgery procedures were previously cate-
gorized into restrictive and malabsorptive categories. A
growing body of research now finds this perspective to
be outdated. Ongoing investigations are now beginning
to piece together a much more complex picture that in-
volves postsurgical changes leading to adaptations in the
gut that are modulated by its own hormonal and nervous
systems interacting with gut microbia, bile acids, and
nutrient delivery (23).

Effect of Bariatric Surgery on DKD

There are several reasons why bariatric surgery may
have the potential to ameliorate DKD. First and foremost,
postsurgical regression of diabetes is expected to retard or
possibly even reverse the still incompletely understood
mechanisms through which chronic dysglycemia damages
the kidney. In addition, putative risk factors for kidney
disease, like hypertension, hyperinsulinemia and insulin
resistance, dyslipidemia, and glomerular hyperfiltration,
are also improved after surgery (20,24–27). However, the
literature in this area is presently too handicapped by
limitations—small sample sizes, relatively short–term follow-
up periods, lack of control groups, and inclusion of patients
identified as having DKD solely on the basis of elevations in
albuminuria or proteinuria—to tease out how, if at all, bari-
iatric surgery improves DKD.

The literature describing the effects of bariatric surgery
on renal parameters in patients with type II diabetes or
obese patients undergoing bariatric surgery is shown in Table 1. The fact that all of the
reports were published within the past 10 years attests to growing interest in this topic. The most consistent finding is that albuminuria and proteinuria levels fall after sur-
gery, with most studies also showing a reduction in serum creatinine. Although these findings seem to be salutary on
the surface, their implications are uncertain, because they
may simply be reflecting changes in renal physiology un-
related to the pathophysiology of DKD. For example, the
reduction in proteinuria and albuminuria could be caused by
lower glomerular filtration that is commonly seen after
bariatric surgery (26). Whether this represents a protective
effect against DKD is not known (28). Similarly, the ob-
erved improvement (i.e., drop) in serum creatinine is most
likely caused by loss of lean body mass (and subsequent
reduced generation of creatinine) that coincides with large
weight loss rather than a clear effect on glomerular filtra-
tion (26).

What is notable about the literature in this area is the lack
of data on whether bariatric surgery influences major
clinical end points, like progression of DKD, development
of ESRD, or other major outcomes, like hospitalization and
death.

Bariatric Surgery to Treat DKD: Epidemiologic Data

No population–based epidemiologic surveys exist of pa-
ients with DKD undergoing bariatric surgery. Studies of
bariatric surgery in the broader CKD population, which
includes patients on dialysis and patients with kidney
transplants are, therefore, the next best available source
of information.

From 2002 to 2011, 1114 patients on dialysis and 395
patients with kidney transplants ages 20 years old and
older who were insured by Medicare underwent bariatric
surgery (5). Approximately 60% of the surgeries were gas-
tric bypasses, with gastric banding making up almost all of
the remaining surgeries; 42% of the patients had diabetes,
and of these, 81% had a BMI of ≥35 kg/m². After surgery,
the mean BMI dropped from 44 kg/m² to around 35 kg/m²
at 18 months, where it remained. Thus, bariatric surgery
seems to be highly effective in inducing large weight loss in patients with CKD. Whether it improves kidney
function or other major end points in such patients is
still unknown.

Risks and Costs of Bariatric Surgery for DKD

Any serious consideration of using bariatric surgery to
treat DKD must account for the associated risks and costs.
As in the previous section, studies in the CKD populace
will be used to assess such risks because of the lack of data
on patients with CKD.

Bariatric surgery carries with it a 30-day perioperative
mortality risk of about 0.1%–0.2% (29,30), with a 3-year all–
cause mortality rate of 0.9% (30). Patients with stages II–V
CKD have a similar 30-day mortality rate (31), although a
higher rate (1.3%) has been reported in patients with ESRD
(5). Longer–term all–cause mortality rates for patients
with CKD are not available whereas for patients with ESRD the
probabilities of overall survival at 1 and 3 years were 90%
and 79%, respectively, between 2002 and 2011 (5). Of note,
the presence of DKD alone is associated with a striking
10-year mortality rate of ≥50% (6), with the rate increasing
even further (66%) after dialysis is started. Notwithstanding
the limited available data, it is therefore not implausi-
ble to expect that the longevity benefits of treating DKD
with bariatric surgery could outweigh the mortality risks
associated with surgery.

Bariatric surgery is also associated with complications
that are directly related (bleeding, stomal stenosis, leaks,
wound healing, etc.) or unrelated (malnutrition, sepsis,
thromboembolism, etc.) to the procedure itself. Complica-
tion and reoperation rates after bariatric surgery are 17%
and 7%, respectively, in the general population (29). Inter-
estingly, one large observational study found little, if any,
relative increase in 30-day complications in patients with
CKD (32). This conflicts with previous reports that the
presents of preoperative kidney impairment and diabetes
are associated with higher morbidity and mortality after
major abdominal surgery (33) and a greater risk of AKI after
bariatric surgery, respectively (34). Postoperative kidney
stone formation is also a concern, particularly with proce-
dures (Roux-en-Y gastric bypass and biliopancreatic diver-
sion with duodenal switch) that affect oxalate and citrate
excretion (35–37). A more severe manifestation of this process
is oxalate nephropathy, which has even been associated with
rapid progression to ESRD (38). All of these risks, including
worsening of underlying DKD, must be considered when
referring patients for bariatric surgery.
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Type of Bariatric Surgery</th>
<th>No. of Subjects (with Type II Diabetes)</th>
<th>Follow-Up Period (mo)</th>
<th>Remission of Type II Diabetes, %</th>
<th>Effect on GFR Markers</th>
<th>Effect on Albuminuria/Proteinuria</th>
<th>Effect on Clinical End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case reports</td>
<td>RYGB</td>
<td>1 (100%)</td>
<td>26</td>
<td>N/A</td>
<td>↓ sCr (1.4→1.2)</td>
<td>↓ Proteinuria (6.3→0.07 g/d)</td>
<td>N/A</td>
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<td></td>
<td>RYGB</td>
<td>1 (100%)</td>
<td>3</td>
<td>100</td>
<td>↓ sCr (4.3→4.0)</td>
<td>↓ Proteinuria (5.9→0.8 g/d)</td>
<td>N/A</td>
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<td></td>
<td>RYGB</td>
<td>1 (100%)</td>
<td>12</td>
<td>100</td>
<td>N/A</td>
<td>↓ Albuminuria (&lt;2 mg/24 h)</td>
<td>N/A</td>
</tr>
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<td></td>
<td>RYGB, LAGB</td>
<td>2 (50%)</td>
<td>17–19</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>Renal function recovered, dialysis stopped</td>
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<tr>
<td>Cohorts</td>
<td>RYGB</td>
<td>9 (56%)</td>
<td>24–48</td>
<td>N/A</td>
<td>Average sCr for two patients with diabetic nephropathy increased over time (approximately 1.8→2.7)</td>
<td>N/A</td>
<td>N/A</td>
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<td></td>
<td>RYGB</td>
<td>94 (34%)</td>
<td>12 (mean)</td>
<td>N/A</td>
<td>No change in sCr</td>
<td>↓ Albuminuria (17→6 mg/g)</td>
<td>N/A</td>
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<td></td>
<td>Not specified</td>
<td>25 (72%)</td>
<td>12–24</td>
<td>N/A</td>
<td>↓ sCr (1.4→1.2), increase in eGFR (48→62)</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td>RYGB, others</td>
<td>15 (100%)</td>
<td>6</td>
<td>N/A</td>
<td>↓ sCr (0.8→0.6), no change in cystatin C</td>
<td>↓ Albuminuria (65→39 mg/g)</td>
<td>N/A</td>
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<td></td>
<td>RYGB</td>
<td>35 (54%)</td>
<td>12</td>
<td>84</td>
<td>↓ 15% in 24-h CrCl, sCr, cystatin C</td>
<td>No change</td>
<td>N/A</td>
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<td></td>
<td>BPD</td>
<td>22 (100%)</td>
<td>120</td>
<td>100</td>
<td>No change in sCr, eGFR, MA: 32%→0%</td>
<td>N/A</td>
<td>N/A</td>
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<td></td>
<td>RYGB</td>
<td>56 (68%)</td>
<td>6–24+</td>
<td>N/A</td>
<td>↓ sCr (1.4→1.2) in mild DKD, ↑ in moderate DKD (2.2→2.7)</td>
<td>N/A</td>
<td>N/A</td>
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<td></td>
<td>RYGB, SG, LAGB</td>
<td>52 (100%)</td>
<td>60–92</td>
<td>44</td>
<td>No change in sCr</td>
<td>↓ Albuminuria by 58% regression</td>
<td>N/A</td>
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<td></td>
<td>LAGB</td>
<td>23 (100%)</td>
<td>30 (mean)</td>
<td>N/A</td>
<td>N/A</td>
<td>↓ Albuminuria (67→15 mg/g)</td>
<td>N/A</td>
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<tr>
<td></td>
<td>RYGB</td>
<td>131 (100%)</td>
<td>60–108</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Predicated 5-yr risk of developing nephropathy (57) (12→6.6%)</td>
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<tr>
<td></td>
<td>RYGB, SG</td>
<td>97 (100%)</td>
<td>36</td>
<td>28</td>
<td>↓ sCr (0.7→0.6)</td>
<td>↓ MA by 70%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>SG</td>
<td>5 (20%)</td>
<td>12</td>
<td>N/A</td>
<td>No change in sCr, cystatin C, eGFR (compared with control group)</td>
<td>No change in proteinuria (compared with control group)</td>
<td></td>
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</tbody>
</table>
Cost is another important consideration. Bariatric surgery costs approximately $15,000–$30,000 depending on the specific procedure and in the absence of rare but severe complications (39). This compares favorably to the long-term costs of progressive DKD (40), particularly if ESRD develops, where the annual cost is approximately $70,000–$90,000 (5). The key to cost savings would be to limit the bariatric option to higher-risk individuals at risk of progression.

**Areas of Uncertainty**

A number of important questions need to be addressed before recommending bariatric surgery as a treatment for DKD. First, does bariatric surgery actually slow progression of DKD? If so, which patients with DKD should be targeted for such an approach? Which bariatric procedure offers the best renoprotective effects? Are kidney-related benefits proportional to the weight lost? What effect does weight reaccumulation have on remission of DKD? Is actual remission required to treat DKD, or can more modest improvements suffice? What are the rates of complications and mortality after bariatric surgery in patients with DKD, and are these risks outweighed by the kidney–related and other benefits? What additional benefits, such as improvements in dialysis access placement or transplantation wait–listing rates, can bariatric surgery offer?

Answering these questions will be challenging. A recent NIH symposium on long-term outcomes in bariatric surgery (41) reviewed, in detail, the major hurdles in conducting well powered, randomized, controlled bariatric surgery trials, specifically with regard to recruitment, sample size, and length of follow-up. Given the current funding environment, it was felt that alternative research strategies, including large observational studies using existing or prospective databases, should be considered. This may be especially relevant when considering the extended length of time that it could take to reverse DKD (11). The authors of this article and associated collaborators are currently working on just such a strategy.

**Conclusions**

DKD is devastating to individuals and society. By inducing regression or remission of type II diabetes, bariatric surgery may also have the capability to effectively treat DKD. Small, short–term studies of bariatric surgery in patients with type II diabetes and DKD suggest a renoprotective effect primarily as reflected by a reduction in albuminuria, but effects on harder, more clinically relevant outcomes are lacking. The field is, therefore, ripe for clinical studies designed to elucidate the kidney-related benefits of bariatric surgery.

**Disclosures**

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