Potential surgical treatment of the microvascular complications of diabetes

Karl John Neff, Carel W le Roux

Type 2 diabetes is associated with a high rate of microvascular complications (diabetic nephropathy, retinopathy and neuropathy). Current treatment for these diseases includes ACE inhibitors and intensive glycaemic control, but despite their widespread use there is a subgroup of people with obesity and diabetes in whom microvascular disease continues to progress, resulting in renal failure, blindness and crippling diabetic neuropathy. Recent randomised controlled trials have shown bariatric surgery to be more effective than intensive medical treatment in improving glycaemic and metabolic control in people with obesity and diabetes. As hyperglycaemia is the major risk factor for microvascular complications, it is possible that bariatric surgery could improve renal, retinal and neurological diabetic outcomes. However, there are few data on the effect of bariatric surgery on these diabetic complications. This article reviews the literature on microvascular outcomes after bariatric surgery, suggests future research directions and highlights potential therapeutic opportunities in diabetic kidney disease.

Type 2 diabetes is associated with microvascular complications (diabetic nephropathy, retinopathy and neuropathy), which can be present from diagnosis (Harris et al, 1992). The frequency of these complications increases over time, with up to 80% of people with diabetes diagnosed with microvascular disease by the time they have lived 20 years with the condition (Harris et al, 1992). These diseases can deteriorate despite the use of intensive glycaemic control, antihypertensive therapy and agents that block the renin–angiotensin axis, such as angiotensin-converting-enzyme (ACE) inhibitors (Araki et al, 2005; Hemmingsen et al, 2011).

Bariatric surgery can effectively reduce weight and improve glycaemic control and hypertension (Sovik et al, 2011; Schauer et al, 2012; Sjöström et al, 2012). The bariatric surgical procedures most commonly used are Roux-en-Y gastric bypass, adjustable gastric banding and vertical sleeve gastrectomy (Buchwald and Oien, 2009). Biliopancreatic diversion, with or without duodenal switch, is a less commonly performed procedure (Smith et al, 2011a). All these procedures are associated with weight loss and remission of diabetes (Buchwald and Oien, 2009; Kashyap et al, 2010; Pournaras et al, 2010). Bariatric surgery can also have socio-economic and psychological benefits, including improvement in mood, self-esteem, mobility and employment (Papamargaritis et al, 2010).

In contrast to non-surgical weight loss methods, bariatric surgery can produce sustained weight loss for up to 20 years postoperatively (Sjöström et al, 2012). Recently, bariatric surgery has been proven to be more effective at improving glycaemic and metabolic control, and thereby reducing the risk of microvascular disease, than intensive medical therapy alone (Mingrone et al, 2012; Schauer et al, 2012). These improvements in microvascular risk factors, such as hyperglycaemia and hypertension, can persist in the long term. This would be expected to produce significant benefits in terms of the risk of microvascular disease.

Despite this, the effect of bariatric surgery on

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Article points

1. Bariatric surgery has proved more effective than intensive medical treatment in improving glycaemic and metabolic control in people with obesity and diabetes in recent randomised controlled trials.
2. Since hyperglycaemia is the major risk factor for microvascular complications, it is possible that bariatric surgery could improve renal, retinal and neurological diabetic outcomes.
3. This article reviews the literature on microvascular outcomes after bariatric surgery, suggests future research directions and highlights potential therapeutic opportunities in diabetic kidney disease.

Key words

- Bariatric surgery
- Microvascular complications
- Obesity
- Type 2 diabetes

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1. There is increasing recognition that bariatric surgery may protect people with diabetes from diabetic kidney disease (DKD) and retinopathy.
2. Albuminuria, the earliest sign of DKD, is reduced by bariatric surgery, with reduced excretion on 24-hour urine collections for up to 24 months following gastric bypass.
3. In people with newly diagnosed type 2 diabetes, bariatric surgery preserves renal function, as measured by the estimated glomerular filtration rate, to a greater extent than medical treatment alone.

microvascular complications has only recently become a focus of investigation. There is increasing recognition that bariatric surgery may protect people with diabetes from diabetic kidney disease (DKD) and retinopathy.

This article reviews the evidence for the effects of bariatric surgery on the microvascular complications of diabetes, including neuropathy. Particular attention is paid to the evidence in cohorts with established microvascular disease, and future directions for research are suggested.

Diabetic kidney disease

DKD is the most frequent cause of end-stage renal disease (ESRD) in the developed world (Collins et al, 2012). Obesity is also associated with chronic kidney disease (Chagnac et al, 2000; Bosma et al, 2004; Wang et al, 2008; Kramer et al, 2009). Weight loss interventions, including bariatric surgery, can effectively reduce weight and markers of renal disease such as proteinuria (Navaneethan et al, 2009). Some of this effect may be due to remission of type 2 diabetes and hypertension following bariatric surgery (Buchwald and Oien, 2009; Meijer et al, 2011; Fenske et al, 2013). However, other mechanisms, including improvements in renal inflammation, may also contribute (Rao, 2012; Fenske et al, 2013).

Renal outcomes after bariatric surgery in people with renal disease have only recently been investigated (Agrawal et al, 2008; Hofsø et al, 2010; Miras et al, 2012; Navaneethan et al, 2010; Amor et al, 2013; Fenske et al, 2013). The earliest sign of DKD is albuminuria, as tested on 24-hour urine collections or on spot urine samples using the albumin:creatinine ratio. Albuminuria is reduced by bariatric surgery, with reduced excretion on 24-hour urine collections for up to 24 months following gastric bypass (Navarro-Diaz et al, 2006; Serra et al, 2006; Agrawal et al, 2008).

Bariatric surgery produces reductions in the urinary albumin–creatinine ratio in those with preoperative microalbuminuria (Agrawal et al, 2008; Afshinnia et al, 2010; Heneghan et al, 2012). This can result in remission of DKD (as defined by microalbuminuria) (Heneghan et al, 2012). The remission rate associated with medical treatment does not exceed 18% over 5 years, whereas after surgery it can be as high as 60% over 5 years (Newman et al, 2005; Afshinnia et al, 2010; Heneghan et al, 2012).

In those without DKD, bariatric surgery may have a preventive role as it can prevent the development of microalbuminuria (Heneghan et al, 2012). When compared with medical therapy alone, bariatric surgery can reduce the incidence of microalbuminuria by more than 80% (Iaconelli et al, 2011). This effect is reported up to 10 years, and is seen in tandem with weight loss, durable remission of diabetes and improved blood pressure control (Iaconelli et al, 2011). Bariatric surgery preserves renal function, as measured by the estimated glomerular filtration rate (eGFR), in people with newly diagnosed type 2 diabetes to a greater extent than medical treatment alone (Iaconelli et al, 2011).

In patients with established renal impairment, bariatric surgery may help to improve renal function. In a study that included people with stage 3 renal disease (eGFR 30–60 mL/min/1.73m^2) and those with normal renal function, both groups showed improvements in eGFR. The subgroup with stage 3 disease demonstrated an increase in eGFR from 49 to 67 mL/min/1.73m^2 (Hou et al, 2012). Those with stages 3 to 5 renal disease (eGFR <60 mL/min/1.73m^2) are not often included in bariatric surgery studies (Navarro-Diaz et al, 2006; Navaneethan et al, 2009; Iaconelli et al, 2011; Getty et al, 2012). This may be due to concern that individuals with reduced renal function may have increased perioperative mortality (Nguyen et al, 2011; Turgeon et al, 2012). While this remains to be proven, caution must be taken with this group, and a specialist multidisciplinary approach utilised when considering bariatric surgery.

However, the potential to use bariatric surgery as a "bridging" treatment in end-stage DKD is exciting. Currently, while it is suggested that obesity should not specifically exclude candidates from renal transplantation per se, several national guidelines recommend BMI limits that can exclude many obese people from renal transplant (Kasiske et al, 2001; Heemann et al, 2011). These recommendations are based on data suggesting that higher BMIs are associated with higher rates of surgical complications and delayed graft function post-transplant (Lentine et al, 2012). Renal transplant services are seeing increasing numbers of obese candidates presenting for evaluation; this population therefore remains vulnerable as they may not be able to access a transplant list.

Case series have reported successful gastric bypass in nine pre-transplant candidates on dialysis (Alexander et al, 2004; Alexander and Goodman, 2007). These individuals all went on to have successful renal transplantation after their bariatric surgery (Alexander et al, 2004; Alexander and Goodman, 2007). The bariatric surgery was associated with sustained weight loss over 5 years, improved glucose homeostasis and greater blood pressure control (Alexander et al, 2004; Alexander and Goodman, 2007). This resulted in maintenance of graft function, and was not associated with any increase in perioperative mortality.

Other data are less positive. Individual case reports of gastric banding in renal transplant recipients, and in those awaiting transplant, report a higher rate of postoperative complications (Lentine et al, 2012). These cases were completed without increased mortality. Data on 29 people awaiting renal transplantation who subsequently underwent bariatric surgery report a higher complication rate and mortality rate than expected (Modanlou et al, 2009). There was also a high rate of complications in a cohort of 87 transplant recipients who underwent gastric bypass after transplantation (Modanlou et al, 2009; Smith et al, 2011b).

While these results are concerning, these data were obtained before 2004 and include only open procedures (Modanlou et al, 2009). Currently the laparoscopic approach is more commonly used, and is associated with less morbidity than the open approach (Reoch et al, 2011). There has been considerable refinement of preoperative assessment and perioperative care since these studies were completed.

This illustrates the need for new data to accurately quantify any risk that might currently exist. Prospective controlled data on the use of bariatric surgery in ESRD is particularly important in order to clarify the risks and potential benefits in this population, as many are denied renal transplantation based on their BMI. The risk of obese cohorts waiting for transplant on dialysis needs to be balanced with the risks of bariatric surgery.

For now, bariatric surgery must be considered as having significant risk in people with ESRD awaiting renal transplant. This needs to be understood in the context of the limited evidence base, comprising case reports and observational data. Further study in this area is urgently needed to inform best practice.

Diabetic retinopathy

There are fewer studies investigating the effect of bariatric surgery on diabetic retinopathy. The studies that have been done suggest that retinopathy rates are low after bariatric surgery (Johnson et al, 2013). It also appears that the risk of microvascular disease, including retinopathy, can be reduced by 80%, and the risk reduction can persist up to 10 years postoperatively (Johnson et al, 2013).

Data from studies that include some form of retinal disease score show that most people with diabetes and pre-existing retinopathy either remain stable or improve, with full regression to normal in some of those with early retinopathy (Miras et al, 2012; Varadhan et al, 2012). In those without retinopathy, bariatric surgery can prevent the development of disease (Miras et al, 2012; Varadhan et al, 2012). In case series following patients over 14 years, bariatric surgery was found to protect people with diabetes from blindness, although more specific data on retinal grading were not available (Pories et al, 1995).

In their retrospective cohort study of almost 16 000 patients, Johnson et al (2013) found that less than 1% of the bariatric surgery group had progressed to end-stage retinopathy, in keeping with earlier data (Pories et al, 1995). However, this study had too few patients with retinopathy to make a definitive comment on the outcomes postoperatively, other than that bariatric surgery did not worsen outcomes in the medium to long term, which is very reassuring.

Improvements in the diabetic milieu and resultant reductions in endothelial stress within the retinal arteries are likely to be the major factors responsible for improved retinal outcomes (Lammert et al, 2012; Miras et al, 2012). However, as there are no mechanistic data specifically within a bariatric cohort, the mechanisms that might explain improvements in retinopathy remain to be determined.

The paucity of data investigating retinal outcomes

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2. It also appears that the risk of microvascular disease, including retinopathy, can be reduced by 80%, and the risk reduction can persist up to 10 years postoperatively.
3. Studies that include some form of retinal disease score find that most people with diabetes and pre-existing retinopathy either remain stable or improve after bariatric surgery, with full regression to normal in some of those with early retinopathy.
4. Improvements in the diabetic milieu and resultant reductions in endothelial stress within the retinal arteries are likely to be the major factors responsible for improved retinal outcomes.

Page points

1. The effects of bariatric surgery on glycaemic control would be expected to contribute to reductions in microvascular complications.
2. The improved blood pressure after bariatric surgery would also be likely to be beneficial in microvascular disease.
3. There are data suggesting improvements in renal outcomes after bariatric surgery, but further study is needed to determine its effect on diabetic kidney disease.
4. There are few data on the effect of bariatric surgery on retinal or diabetic neurological disease; the existing evidence base is essentially limited to retrospective or observational data, although these generally indicate benefit.

after bariatric surgery needs to be addressed. Given the improved glycaemic and blood pressure outcomes after bariatric surgery, it would be expected that surgery could prevent retinopathy in those with diabetes. It may also facilitate regression in early disease. However, this needs to be determined in prospective controlled studies adequately powered to examine retinal disease. The development of a retinopathy registry based on the National Bariatric Surgery Registry would be of use in evaluating outcomes nationally. For now the data suggest benefit, and are certainly reassuring in that retinopathy does not worsen in case control and cohort data up to almost 15 years postoperatively.

Peripheral neuropathy

Neurological outcomes have been investigated even less frequently than retinopathy in bariatric cohorts. The available data on a cohort of 47 people with diabetes and pre-existing neuropathy showed that gastric bypass improved self-reported neuropathic symptomatology in approximately 50% of recipients (Schauer et al, 2003). Symptoms remained stable in 39% and worsened in 7%. Data were not available in the remainder of participants.

The dearth of data specific to diabetic neuropathy is partially explained by the increased incidence of micronutrient deficiency-related neuropathy, which approaches 16% per year following bariatric surgery (Thaisetthawatkul et al, 2004). These neuropathies are most often related to deficiencies in vitamins B, D and E and copper (Koffman et al, 2006). This could potentially obscure diabetic disease, or could confound any potential examination of the effect of surgery on diabetic neuropathy. There are no data to indicate whether pre-existing diabetes or diabetic neuropathy predisposes to any additional micronutrient deficiency-related neuropathy. The most consistently established risk factors for neuropathy following bariatric surgery are non-compliance with micronutrient supplementation and excessive alcohol use (Koffman et al, 2006; Juhasz-Pocsine et al, 2007).

For these reasons, conclusions on the effects on diabetic neuropathy after bariatric surgery cannot be drawn at this stage. Prospective study on people with pre-existing diabetic neuropathy, with objective and subjective validated measurements of neuropathy, would be the first step. After bariatric surgery, people with diabetes are at high risk of micronutrient deficiency and should be counselled as to this risk, as it can precipitate non-diabetic neuropathy. The effect of surgery specifically on diabetic neuropathy remains to be determined.

Conclusions

While bariatric surgery is not a first-line therapy for people with diabetes, recent data from randomised controlled trials have shown that it can be an effective treatment in a subgroup with obesity-associated type 2 diabetes (Mingrone et al, 2012; Schauer et al, 2012). It is more effective than intensive medical treatment in these cohorts. It should therefore be considered a glycaemic therapy and not a weight loss procedure in people with obesity and type 2 diabetes. With improvements in the use of laparoscopic techniques, bariatric surgery is a safe and efficacious option, which can be life changing in those with obesity and diabetes that is refractory to medical treatment.

The effects on glycaemic control would be expected to contribute to reductions in microvascular complications. The improved blood pressure after bariatric surgery would also be likely to be beneficial in microvascular disease. While there are data suggesting improvements in renal outcomes, further study is needed to determine the effect of bariatric surgery on DKD. There is a paucity of data on the effect of bariatric surgery on retinal or diabetic neurological disease. The existing evidence base is essentially limited to retrospective or observational data, although these generally indicate benefit. Firm conclusions cannot be drawn without prospective controlled data specifically designed to investigate neurological or retinal outcomes. The use of bariatric surgery in this context needs to be a research priority. ■

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