Bariatric surgery and renal function: a precarious balance between benefit and harm

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Abstract

Medical treatment of obesity and lifestyle modification have limited effectiveness in treating it in morbidly obese individuals. Importantly, bariatric surgery is regarded as the only therapy that is effective in maintaining significant weight loss in morbidly obese individuals. Despite the fact that bariatric surgery-induced weight loss is associated with a significant decrease in morbidity and mortality and improvement in renal function, bariatric surgery has recently been shown to be associated with a significant risk of nephrolithiasis. The main risk factor for nephrolithiasis is increased excretion of urinary oxalate. In this review, we discuss the association between bariatric surgery, an increased risk of renal stone formation and oxalate nephropathy.

Keywords: bariatric surgery; obesity; oxalate nephropathy; renal stone

Introduction

It is widely accepted that obesity is associated with a marked increase in morbidity and mortality [1], but it is now evident that obesity is associated with a marked increase in risk of renal diseases and it is also regarded as a modifiable risk factor for renal diseases [2]. The clustering of insulin resistance, dysglycaemia, dyslipidaemia, hypertension and central obesity represent the major features of metabolic syndrome [3]. This cluster of factors may share a common aetiology which is a risk factor not only for cardiovascular disease but also for renal disease [4]. Importantly, obesity per se is an independent risk factor for the development of end-stage renal disease (ESRD) as well as diabetes and hypertension [5]. Morbid obesity has been shown to be associated with nephrotic syndrome, and it has been reported that proteinuria and segmental glomerulosclerosis can be present in obese patients even in the absence of diabetes [6]. In addition, a large-scale study including 6818 renal biopsies from 1986 to 2000 revealed a 10-fold increase in renal lesions, such as glomerulomegaly and focal segmental glomerulosclerosis, which were associated with obesity [7]. An increased frequency of obesity-related glomerulopathy occurs in parallel with an increased prevalence of obesity within the general population [7]. Interestingly, Brenner et al. have also suggested that there is an association between poor fetal and infant growth and reduced nephron endowment, hypertension and chronic kidney disease (CKD) [8]. Barker and Hales originally proposed that the thrifty phenotype hypothesis is based on the epidemiological associations between poor fetal and infant nutrition and growth. This early insult is thought to predispose to subsequent development of type 2 diabetes in adult life, producing permanent changes in glucose–insulin metabolism [9]. These events during fetal and infant life may lead to a decrease in nephron number [10]. This effect leads to an overall reduction in renal function, altering glomerular structure, fibrosis and decreasing renal reserve [11]. Ultimately, these changes may predispose to hypertrophy of other nephrons, hyperfiltration and proteinuria. In addition, reduction in nephron number is associated with hyperactivation of the renin–angiotensin system, fluid and electrolyte imbalance and hypertension [12]. Importantly, a permanently reduced nephron number is essential but not alone sufficient to mediate nutritionally induced CKD. An increase in body mass and associated insulin resistance in later life may increase the risk of hypertension and progressive renal disease in those individuals whose renal function is compromised because of impaired renal development in early life [13,14].

Several studies have shown that obesity is also associated with increased risk of renal stone formation [15–17]. However, once body mass index (BMI) is >30 kg/m², further increases in BMI do not significantly increase the risk of renal stone disease [18]. The association of renal stone formation with obesity may be due to increases in the intake of lithogenic substances such as calcium, oxalate and purine-rich foods. Of note, obesity is usually associated with insulin resistance that alters renal acid–base metabolism, resulting in a lower urine pH (caused by decreased ammonia production) and increased risk of uric acid stone disease. Lee et al. showed that obesity was significantly associated...
with an increase in risk of renal stone formation [19]. Obese stone formers excreted increased amounts of sodium, calcium and uric acid, while the urinary pH in a 24-h urine sample was decreased compared with non-obese stone formers. Obesity is known to be associated with an increase in risk of uric acid stone formation. Multivariate regression modelling stratified by stone incidence has shown that obesity is the only strong predictor of stone recurrence in first-time stone formers [19]. No association between obesity and stone recurrence has been detected in recurrent stone formers suggesting a different mechanism in this group of patients. Interestingly, weight loss has been shown to be associated with improvement in glomerular haemodynamics, insulin sensitivity and decreased urine albumin excretion [21]. It is plausible that weight loss can also adversely affect stone risk. Commonly used low-carbohydrate diets increase the risk of both calcium and uric acid stones. Importantly, bariatric surgery (in particular gastric bypass surgery) has been shown to frequently cause hyperoxaluria with increased risk of stone formation and even oxalate nephropathy [8].

Potential benefit of bariatric surgery on adipocytokines

Adiponectin is most abundant and adipose-specific adipocytokine is decreased with increasing fat mass, BMI and serum triglyceride [28]. Adiponectin is known to be anti-atherogenic, anti-inflammatory and anti-diabetogenic. A low adiponectin level is linked to insulin resistance, type 2 diabetes, atherosclerosis and acute coronary syndrome [29]. Bariatric surgery has been shown to ameliorate insulin resistance, improve the adiponectin level and decrease IL-18, CRP and TNF-α [30,31]. Interestingly, RYGB in five individuals with diabetes was associated with a decrease in CRP and leptin with no alteration in the level of adiponectin and TNF-α [32]. Therefore, it is plausible to suggest that bariatric surgery has the potential benefit of treating obesity and the associated low-grade inflammatory condition.

Types of procedure of bariatric surgery

Bariatric surgery procedures are divided into three categories [22]:

(i) Restrictive procedures: the main aim of this procedure is to restrict the amount of food the patient can eat. This is achieved by creating a small gastric pouch with a narrow outlet. The most common type of surgery is adjustable laparoscopic gastric banding. This procedure is the second most commonly performed bariatric procedure after the Roux-en-Y gastric bypass (RYGB).

(ii) Malabsorptive procedures: the main aim of this procedure is to bypass a segment of small intestine so that less food is absorbed (biliopancreatic diversion, biliopancreatic diversion with duodenal pouch). This procedure is technically demanding and is associated with many complications, and is not frequently performed.

(iii) Hybrid (RYGB) procedure: this procedure can be performed as open surgery or laparoscopically. The aim is to restrict food intake by creating a gastric pouch that limits absorption by bypassing the proximal intestine with a Roux limb. The standard Roux limb is 75–150 cm long and bypasses the distal stomach, duodenum and a short segment of the jejunum, resulting in malabsorption.

Potential renal benefit of bariatric surgery

One of the important immediate benefits of bariatric surgery before weight loss is an improvement in glucose tolerance [33]. Adams et al. have shown that gastric bypass surgery in 7925 obese individuals was associated with a significant reduction in long-term mortality (18 years after surgery), particularly decreasing deaths from diabetes, heart disease and cancer [34]. The prospective, controlled Swedish Obese Subjects study involved 4047 obese subjects. Of these subjects, 2010 underwent bariatric surgery and 2037 received conventional treatment. Bariatric surgery was associated with long-term weight loss and decreased overall mortality during an average of 10.9 years of follow-up [35]. Bariatric surgery is also associated with a significant improvement in dyslipidaemia, hypertension, urinary albumin excretion, markers of atherosclerosis and quality of life, all of which may have an impact on renal function [36–38].

Bariatric surgery has been shown to be associated with a significant improvement in all parameters of renal function. For instance, in a total of 25 patients with stage 3 CKD with glomerular filtration rate (GFR) 30–59 mL/min/1.73 m² and mean BMI at surgery was 49.8 kg/m², the mean GFR was 47.9 mL/min/1.73 m². With surgery, the BMI had decreased significantly to 38.4 kg/m² at the end of 6 months and to 34.5 kg/m² at the end of 12 months. The mean systolic blood pressure had decreased from 133±13 to 128±17 mmHg at the end of 12 months. The mean GFR at 6 months of follow-up had improved significantly to 56.6 and to 61.6 mL/min/1.73 m² at 12 months [39]. Interestingly, in one patient, gastric bypass surgery was associated with a significant improvement in focal glomerulosclerosis, and in another patient, recovery of renal function in a dialysis-dependent patient following gastric bypass surgery was reported [40]. Importantly, laparoscopic bariatric surgery has also been shown to be safe and effective to treat obesity in renal transplant patients [41]. Furthermore, bariatric sur-
gery in 61 obese individuals was associated with an improvement in blood pressure, GFR and albuminuria 2 years after the surgery [42]. In a series of 45 non-transplant patients with established renal disease who had undergone a gastric bypass, nine had resolution, improvement or stabilization of their kidney function. Two of these patients were already receiving, or were ready for, dialysis. Their average age at gastric bypass was 43.0±4.3 years, and their mean BMI was 48.9±1.9 kg/m². Of these nine patients, five had a primary diagnosis of focal segmental glomerulosclerosis, two had membranous glomerulonephritis and two had diabetic nephropathy. One patient had biopsy-proven membranous glomerulonephritis that completely resolved after 9 years of postoperative follow-up. The two dialysis patients were able to discontinue dialysis for 27 and 7 months, respectively. The remaining patients had stable renal function for 2–5 years postoperatively [43]. In a retrospective study of 94 obese adults who had RYGB surgery with a mean 12-month follow-up, a reduction in albuminuria was observed [44].

Interestingly, bariatric surgery is associated with a favourable impact on renal function in individuals with diabetes. Saliba et al. showed that RYGB is associated with an improvement in GFR in diabetic individuals but with worsening tubular function [45]. Furthermore, RYGB in diabetic individuals is associated with an improvement in albuminuria [36].

Taking all these factors into consideration, it seems that bariatric surgery markedly improves major risk factors for renal injury (type 2 diabetes, hypertension and dyslipidaemia) as well as parameters of renal function (GFR, urinary albumin excretion) (Figure 1). However, not all of the effects of bariatric surgery on the kidney are beneficial, and bariatric surgery is associated with a significant increase in risk of stone formation.

Matlaga et al. identified 4639 patients who underwent RYGB surgery and a control group of 4639 obese patients who did not have surgery in a 5-year period (2002–06) [46]. After RYGB surgery, 7.65% of patients were diagnosed with urolithiasis compared with 4.63% of obese patients in the control group. Subjects in the treatment cohort more commonly underwent shock wave lithotripsy [81 (1.75%) vs 19 (0.41%)] and ureteroscopy [98 (2.11%) vs 27 (0.58%)]. Logistic regression analysis showed that RYGB surgery was a significant predictor of urinary calculus [46]. In contrast, gastric banding in 201 individuals was not associated with an increased risk of renal stone disease or renal stone surgery during 5 years of follow-up [47]. Mole et al. described eight patients who underwent bariatric surgery and developed significant CKD due to oxalate nephropathy [48]. In three of these patients, the bypass surgery was reversed before the onset of ESRD. Several factors have been identified as causing nephrolithiasis after gastric bariatric surgery. Park et al. measured 24-h urinary collections in 45 patients after bariatric surgery over 2 years [49]. Their results suggested that bariatric surgery was associated with increased urinary oxalate and calcium oxalate supersaturation. Other important potential precipitating factors were a decreased urinary volume and decreased urinary citrate [49]. This finding was in accordance with the findings of Penniston et al. who studied 27 patients after gastric bypass surgery and another 12 patients after gastric banding [50]. Urinary oxalate level was higher and urinary citrate level lower after gastric bypass surgery, whilst urinary volume was equally reduced in both groups [50]. Importantly, calcium oxalate supersaturation was higher in the gastric banding group. There is general

Potential benefit of bariatric surgery

- Improved lipid profile
- Decreased need for antihypertensive medication
- Improved insulin sensitivity and glucose tolerance
- Improved parameters of renal function

Decrease mortality and morbidity

Improves quality of life

Fig. 1. Bariatric surgery has shown benefit in treating type 2 diabetes, hyperlipidaemia and obesity. Additionally, bariatric surgery decreases the need for antihypertensive medication with improvement in blood pressure.
agreement in the literature that hyperoxaluria is a characteristic feature of post-bariatric renal stones and is associated with a reduction in both citrate and urine volume [51–53]. Even in the individuals who did not develop calculi, it has been suggested that there was higher prevalence of hyperoxaluria [54].

It is possible that hyperoxaluria associated with bariatric surgery is linked to fat malabsorption leading to steatorrhoea. In normal individuals, calcium and oxalate within the lumen of the intestine combine to form insoluble calcium oxalate complexes that are excreted in the faeces. After bariatric surgery, excessive intraluminal fatty acids bind to calcium and leads to inhibition of the formation of calcium oxalate. Therefore, this leads to excess reabsorption of oxalate by intestinal mucosa and increases the risk of hyperoxaluria with subsequent increased risk of renal calculi formation [8,9].

**Bariatric surgery and oxalate nephropathy**

Oxalate nephropathy is one of the under-reported complications of bariatric surgery. It is characterized by tubular crystalline deposition of calcium oxalate leading to acute and CKD [8,9]. The main risk factor for calcium oxalate deposition is hyperoxaluria; however, the presence of fluid depletion and previous renal insufficiency could markedly increase the risk of renal failure. The prognosis of oxalate nephropathy after RYGB is poor and may lead to ESRD in the majority of patients. Oxalate nephropathy and CKD are among the most recognized complications of jejunoileal bypass surgery. Sinha et al. reported that in 60 patients who had bariatric surgery, two developed CKD due to biopsy-proven oxalate nephropathy [52]. Nelson et al. also reported two cases of oxalate nephropathy that led to ESRD, which necessitated dialysis [51]. Furthermore, Nasr et al. reported oxalate nephropathy after RYGB in 11 patients (eight patients with morbid obesity and three patients with gastric adenocarcinoma) [55]. However, the majority of these patients had diabetes and pre-existing renal insufficiency [55]. Their conclusion was that oxalate nephropathy is an under-recognized complication of RYGB, and patients with pre-existing renal disease may be at higher risk [55]. Importantly, there are no guidelines for the management of oxalate nephropathy after RYGB. Whether the reversal of bypass surgery leads to improvement in renal function is controversial and needs to be clarified with further research. Importantly, the need for renal biopsy should be considered in people whose renal function deteriorates after RYGB (Figure 2). Enteric hyperoxaluria is managed by decreasing the amount of oxalate available for absorption from the gastrointestinal tract. This can be achieved by restricting oral intake of oxalate and fat with appropriate dietary advice. In addition, administration of oral calcium can be recommended because calcium forms a complex with free oxalate and limits its absorption [56]. This strategy could be of potential use post-surgery because bariatric surgery is associated with vitamin D deficiency and hypocalcaemia [57]. Furthermore, risk of calcium oxalate precipitation may also be minimized by increasing fluid intake with good hydration. Further research is urgently needed in this area in order to establish evidence-based guidance for decreasing risk of urolithiasis after bariatric surgery.

**Conclusion**

Bariatric surgery for the treatment of obesity has become increasingly common. RYGB, the most common bariatric surgery procedure, results in significant hyperoxaluria and supersaturation of calcium oxalate as early as 3 months post-procedure. Therefore, RYGB surgery results in a higher incidence of renal lithiasis compared with gastric banding. Importantly, a rare complication of bariatric surgery may be oxalate nephropathy and ultimately CKD. Despite the fact that bariatric surgery is associated with a marked decrease in morbidity and mortality, further research is needed to determine the best means of treating renal complications associated with bariatric surgery.

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**References**


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What nephrologists need to know about antiphospholipid syndrome

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Abstract

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent arterial or venous thrombosis and/or pregnancy losses, in the presence of persistently elevated levels of antiphospholipid antibodies (aPL) and/or evidence of circulating lupus anticoagulant (LA). The kidney is a major target organ in both primary and secondary APS. With the expanding spectrum of renal diseases associated with APS, and the impact of APS in ESRD care, this subject is of increasing relevance to nephrologists. This review describes the various clinical manifestations and histological features of this syndrome, with reference to the kidney.

Keywords: anticardiolipin antibodies; antiphospholipid syndrome; lupus anticoagulants; nephropathy

Introduction

The antiphospholipid syndrome (APS) was first described by Hughes in the mid-1980s as a disorder of hypercoagulability in association with antiphospholipid antibodies (aPL), namely anticardiolipin antibodies (aCL) and/or circulating lupus anticoagulants (LA) [1]. It was in systemic lupus erythematosus (SLE) that this syndrome was first reported [2]; however, APS may occur, though less frequently, in the absence of associated autoimmune disease, the so-called primary APS [3]. In the past two decades, a variety of immunologically mediated thrombotic events related to almost every organ system has been identified as features of this syndrome. The diagnosis of definite APS is made when the patient fulfills one clinical (vascular thrombosis or pregnancy morbidity) and at least one laboratory [LA, aCL and/or anti-β2-glycoprotein-1 (anti-β2GP1) antibodies] criterion [4]. As the kidney represents a major target organ in both primary and secondary APS, some nephrologists are now challenging to include the nephropathy of APS in the classification criteria of definite APS [5–7].

Renal involvement in primary APS is typically caused by thrombosis occurring at any location within the renal vasculature, leading to diverse effects, depending on the size, type and site of the vessel involved. The renal manifestations of APS thus may include renal artery stenosis (RAS) and/or renovascular hypertension, renal infarction, APS nephropathy (APSN), renal vein thrombosis, and increased allograft vascular thrombosis [8–12]. The spectrum of renal lesions associated with primary APS has been more recently expanded to involve non-thrombotic conditions, such as glomerulonephritis [13]. It is unclear whether, in addition to thrombosis, other mechanisms could also contribute to the pathogenesis of APS-associated nephropathy. Furthermore, renal manifestations of APS may co-exist with other pathologies, especially proliferative lupus nephritis.

The true incidence of renal involvement in primary APS has not been well determined, in part because of the frequent occurrence of thrombocytopenia and systemic hypertension, discouraging renal biopsy. It has also been suggested that patients with APS may have a higher risk of developing biopsy-related complications, which could be challenging to manage.

Although the kidney represents a major target organ in APS, renal involvement in this syndrome was poorly recognized until recently. The objective of this review is to present the best available information related to the renal manifestations of APS. A summary of the treatment options will also be presented.