Review Article

Chronic kidney disease and metabolic surgery in Asia

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Abstract: The incidence of metabolic disease is steadily rising in Asia. Obese patients with and without metabolic disease are both at risk of chronic kidney impairment and subsequent renal failure, a disease with significant mortality and morbidity. With metabolic surgery proven to be effective for diabetes remission, there has been recent interest in the efficacy of metabolic surgery for prevention or thwarting renal disease progression in obese patients. Metabolic surgery with its resultant malabsorption syndromes, may in fact put one at higher risk of acute renal impairment post operatively due to nephrolithiasis. We examine the recent evidence in the medical literature for the benefits and risks of bariatric surgery in patients with renal impairment. Recent evidence both from Asian and Western patients suggest that glomerular filtration capability and proteinuria improve post bariatric surgery, especially in patients undergoing Roux-en-Y gastric bypass. There is still a lack of literature pertaining to the efficacy of metabolic surgery in the improvement of renal function in Asian patients subgroups especially in those who undergo other procedures apart from RYGB and those who undergo bariatric surgery prior to or after renal transplant.

Keywords: Bariatric surgery; chronic renal insufficiency; renal impairment; hyperfiltration; gastric bypass

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Introduction

The incidence of metabolic disease is steadily rising in Asia. The diagnosis of Metabolic Syndrome, in the unified American Heart Association (AHA) and International Diabetes Foundation (IDF) definition, is defined as the presence 3 out of the 5 following risk factors: elevated waist circumference, raised triglycerides, reduced high density lipoprotein cholesterol, hypertension and raised fasting plasma glucose (1). The prevalence of metabolic disease in Asia was reported to be 10–15% in most regions (2), with some areas such as India (3) and the Middle East approaching the trends seen in the United States. Given the promising results in diabetes remission demonstrated by metabolic surgery (4-6), the pick-up rate of bariatric surgery has increased tremendously in Asia over the past few years.

CKD and obesity

Although the incidence of obesity in Asia is not as high as in the west, Asians are at greater cardiovascular risks compared to Caucasians with similar body mass indices (BMI) (2,7). Studies have demonstrated that the average age of diabetes onset in Asians was 10 years earlier than their Caucasian counterparts (8); the average age of Asian patients with diabetic nephropathy was also found to be earlier than Caucasians (9). Furthermore, Asians were also more likely to develop diabetes and pre-diabetes at any given BMI compared to Caucasians and normal weight Asians had a higher prevalence of DM compared to obese counterparts in the west (8). The rate of decline in renal function was observed to be more rapid in Asian patients with diabetic nephropathy compared to Caucasians, especially so in those with proteinuria (10).

The indication for bariatric surgery for Asians is a BMI of 37.5 kg/m^2 without co-morbidities and 32.5 kg/m^2 in patients with hyperglycaemia that is not adequately controlled despite optimal medical treatment (11), the presence of metabolic syndrome or other cardiovascular risk factors. Chronic kidney disease (CKD) strictly is not an indication for bariatric surgery but obesity is a major risk factor for essential hypertension and diabetes mellitus. Both conditions, when chronic predispose to CKD. In a retrospective review of 320,000 patients who underwent health screening, it was found that higher baseline BMI was a significant risk factor for the development of end stage renal disease even after adjustment for blood pressure and diabetes mellitus (12). Patients with class III obesity were 7 times as likely to develop ESRD compared to those with normal BMI (12). In a Chinese cohort followed up for 5 years, Cao *et al.* found that the incidence of CKD linearly increased with higher BMI regardless of the presence or absence of metabolic syndrome (13). Compared to patients with normal weight, obese patients without metabolic syndrome were 2.39 times as likely to develop kidney impairment compared to 2.77 times if they were diagnosed with metabolic syndrome. Increased BMI was an independent risk factor for CKD and only 26.1% of this increased risk of CKD was explained by metabolic syndrome (13). Similarly, in a Korean cohort, Chang *et al.* demonstrated that the risk of CKD was raised even in metabolically healthy obese individuals and obese patients were 3.6 times as likely to develop CKD in compared to patients with normal weight after adjustment of metabolic risk factors (14).

Staging of CKD

CKD is a heterogeneous disease with a wide range of spectrum of presentations. In the earliest of stage of chronic kidney impairment, glomerular hyper filtration occurs as a result of increased renal plasma flow secondary to renal vasodilatation (15) likely as a result of renin- aldosterone pathway activation due to sodium reabsorption (16). Obese patients with CKD were also more likely to have hypertension which result in a higher transcapillary hydraulic pressure which in tandem with a vasodilated afferent arteriole leads to increased glomerular filtration (15). Controversy exists on the threshold value for defining glomerular hyperfiltration with most studies defining it as glomerular filtration rate of >125 mL/min (17).

Following glomerular hyperfiltration, focal segmental glomerulonephrosclerosis (FSGS) often sets in resulting in microalbuminuria and proteinuria. The severity of albuminuria is measured often using 24-hour urine albumin levels and urine albumin to creatinine (uACR) and urine protein to creatinine (UPCR) ratios. Chronic glomulonephrosclerosis because of obesity and hypertension, together with diabetic nephropathy from long standing diabetic microvascular complications eventually leads to reduction of renal plasma flow, renal hypertension and glomerular hypofiltration syndromes. The MDRD and CKD and epidemiology equation (CKD-EPI) formula is expressed indexed to body surface area, which is disproportionately affected by fat mass in obese patients (18). Hence, in obese patients, controversy exists on the best way to measure kidney function. The estimation of glomerular filtration rate using the CKD-EPI formula and indexation of GFR using ideal body weight provides a better estimate of glomerular filtration function (18) than indexation of GFR using real body weight. Recent literature suggests that the CKD-epidemiology collaboration (CKI-EPI) formula may be the preferred formula for estimation of the eGFR in morbid obesity (19).

In the classification of severity of CKD, stage 1 CKD is defined as having normal or increased GFR (>90 mL/min/1.73 m^2), stage 2 as GFR of 60–89 mL/min /1.73 m^2, stage 3 as GFR of 30–59 mL/min/1.73 m^2, stage 4 as GFR of 15–30 mL/min/1.73 m^2 and stage 5 as end stage renal failure (20). To better prognosticate outcomes, the guidelines recommend analysing GFR together with severity of proteinuria using protein excretion rate and/or uACR ratio (20).

Safety of bariatric surgery in CKD and dialysis dependent patients

Although end stage renal failure itself represents a high-risk co-morbidity and contraindication for major surgical procedures, it has been reported that bariatric surgery is safe in dialysis patients (21) and renal transplant candidates (22). Saleh *et al.* reported an increasing trend of overall complications with worsening GFR which was statistically significant in patients undergoing RYGB with mortality increasing two fold in patients with CKD stage 4 and 5 compared to patients with CKD stage 1 and 2 (23). In a series of 22 patients on renal dialysis, 2 patients had early major complications and 4 had late complications which required surgical or endoscopic intervention. There was 1 mortality 45 days after laparoscopic gastric bypass which

was presumed to be due to line sepsis and not directly related to surgery (22). At the time of last follow up, 18 out of the original 22 patients had achieved sufficient weight loss and suitable for renal transplant (22). The authors conclude that bariatric surgery is safe for dialysis patients, albeit at a higher risk profile and may facilitate placement of obese patients on dialysis onto renal transplant waiting lists. There is a paucity of data in the safety of Asian patients with chronic kidney impairment undergoing bariatric surgery but the safety profiles of Asian patients undergoing metabolic surgery should not be dissimilar compared to Caucasian patients.

CKD and metabolic surgery

Following the success of metabolic surgery in diabetes remission, there has been considerable interest in the efficacy of metabolic surgery in the reversal or even remission of kidney impairment and proteinuria. In several large volume metabolic surgery units worldwide, there have been reports of improved renal function after bariatric surgery. Earlier studies reported improvement of serum creatinine in 76.6% of patients with renal impairment after bariatric surgery (24). Hyper-filtration, the feature of early renal impairment as earlier discussed as well as microalbuminuria resolved in nearly 50% of patients with kidney impairment who underwent bariatric surgery (25).

Prior studies have demonstrated the exponential relationship between the risk of poorer renal function (26) and graft loss after renal transplant and pre-operative BMI, with patients with BMI >36 kg/m^2 30% more likely to suffer renal graft loss compared to those with BMI between 24–26 kg/m^2 (27). Laparoscopic sleeve gastrectomy has shown to be an effective method to help renal transplant candidate lose weight so that they can be put on transplant waiting lists (28). Patients who have undergone renal transplant are at risk of weight gain partly as a side effect of immunosuppression regimes. Bariatric surgery in post renal transplant patients has been shown to be safe (29), and may even improve urine proteinuria and serum creatinine which may have a beneficial long term effect on graft survival (30).

On the other hand, it has also been reported that metabolic surgery may cause a transient worsening of kidney function by rhabdomyolysis and nephrolithiasis (31). Male gender, premorbid hypertension, higher APACHE II scores, blood transfusions (32), higher BMI (33) and history of diabetes (34) were reported to predispose patients to developing acute renal impairment post bariatric surgery. A shorter operative duration would help reduce the incidence of rhabdomyolysis after surgery. Obesity is a risk factor for nephrolithiasis and increasing body size has been shown to be associated with increased urinary urate and oxalate (35), resulting in nephrolithiasis and renal impairment secondary to urinary outflow obstruction. In rat models who underwent RYGB, high levels of lymphocytes were found in the renal medulla and their kidneys were plagued by tubular atrophy, basement membrane thickening and glomerulosclerosis (36). It has been postulated that the underlying mechanism causing nephrolithiasis in patients post RYGB is due to increased enteric absorption of oxalate. Fat malabsorption post RYGB results in a reduction of calcium ions that are free to bind free oxalate ions and this leads to increased oxalate absorption in the gut (37). Oxalate is filtered at the glomerulus and secreted by the proximal tubules, an excess of oxalate leads to nephrolithiasis. Hence, renal function should be closely monitored in patients who have undergone extensive bypasses with a short absorptive limb as they are at risk of renal impairment secondary to fat malabsorption.

There is limited data on how kidney function is affected by post bariatric surgery body composition changes in Asian patients. In a Taiwanese cohort of 233 patients, majority of whom underwent laparoscopic gastric bypass surgery, improvement of GFR as estimated by the MDRD formula from 146.4±17.1 to 133.9±25.7 mL/min was observed in the hyperfiltration group (baseline GFR >125 mL/min) 1 year after surgery (38). Improvement in GFR was observed in patients with stage 2 and stage 3 CKD. The authors also observed a trend towards reduction of albuminuria after surgery with reduction of 26.2% of patients with macro-albuminuria pre-surgery to 18.0% post-surgery.

In our series of 68 obese patients who underwent bariatric surgery, we observed improvement in renal function in both subgroups of patients with eGFR (estimated by the CKD-EPI formula) more than 90 mL/min and those with eGFR less than 90 mL/min. In patients with eGFR <90 mL/min, the mean serum creatinine decreased from 110 to 96 μmol/L with an improvement of median eGFR from 69 to 79 mL/min. In the eGFR> 90mL/min subgroup, there was an improvement of glomerular hyperfiltration as demonstrated by a decline of absolute GFR from 143 to 122 mL/min (P<0.001) (39). Overall, a significant improvement was also observed in renal function as measured by absolute GFR and Lean weight adjusted Cockcroft-Gault formulae. In our series, changes in absolute GFR was linearly associated with loss of fat mass

(95% CI: 0.221–0.712), percentage excess weight loss (95% CI: 0.227–0.421), and change in body surface area (95% CI: 0.317–0.816) (39). This seems to suggest that changes in body composition post bariatric surgery has profound effects on renal function, as measured by the glomerular filtration rate.

In patients with stage III (microalbuminuria 30–299 mg/day) and stage IV (>300 mg/day) diabetic nephropathy, Zhang *et al.* demonstrated that overall remission of diabetic nephropathy was 58.3% at 1 year prospective follow up post laparoscopic roux- en- y gastric bypass (40). In patients with stage III DN, albuminuria decreased from mean of 83.7±59.1 to 18.9±14.7 mg 1 year post gastric bypass.

Albuminuria was halved from a mean of 1,052 to 513 mg in stage IV DN patients. On multivariate regression analysis, pre-operative systolic blood pressure, lower serum creatinine and lower albumin/creatinine ratio predicted for DN remission but not gender, age or duration of diabetes. Pre-operative albumin-creatinine ratio less than 126 mg predicted for DN remission.

Similar results were also reported in a Korean unit, with significant improvements in uACR and UPCR ratios. The Korean study offers interesting perspectives; they demonstrated that even in patients without diabetes mellitus, urinary albumin to creatinine ratio and eGFR improved after Roux-en-Y gastric bypass (41). This suggests that the presence of other mechanisms beyond that of improving glycaemic control and DM remission which improves the filtrating capabilities of the kidney glomeruli. Furthermore, the authors did not observe an improvement of urine ACR, urine PCR and eGFR in patients who underwent sleeve gastrectomy. However, the authors conclude that it may have been due to the small number of patients undergoing sleeve gastrectomy in this study and the high percentages of weight loss failure (45.7%) in these patients.

The improvement of renal function after bariatric surgery is likely to be multifactorial. Bariatric surgery results in better glycaemia control, normalized systolic blood pressure and an increase in the anti-inflammatory cytokine adiponectin (42) which ameliorates on going glomerular inflammation. The reduction of leptin levels after bariatric surgery decreases proinflammatory cytokines including IL-6, TNF-α and TGF-β, reducing the injurious effects of these cytokines on the kidney (43). Furthermore, the loss of visceral fat, reduction of intra-abdominal pressure may also aid in normalization of renal plasma flow and subsequent improvement of kidney function (44).

Conclusions

The prevalence of CKD and obesity in Asia are both increasing. Obesity itself represents a significant risk factor for eventual renal impairment even in the absence of other metabolic risk factors such as uncontrolled diabetes and hypertension. Like western populations, bariatric surgery has been shown to improve glomerular filtration rates and reduce proteinuria in obese patients who undergo metabolic surgery and improvement of kidney function is more likely in patients with early renal impairment. Currently, it is not known if improvement of kidney function will be sustained post bariatric surgery as only short term (1 year follow up data) has been published. There are limited studies from the Asian literature on the safety outcomes of bariatric surgery in patients with end stage renal failure awaiting transplant and their outcomes after bariatric surgery and transplantation. Given the popularity of sleeve gastrectomy in recent years, the renal outcomes of obese patients undergoing sleeve gastrectomy area also eagerly awaited.

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Footnote

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