The effect of bariatric surgery on renal function and disease: a focus on outcomes and inflammation

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ABSTRACT

Renal dysfunction and disease, including hyperfiltration, proteinuria and hypofiltration, are commonly associated with obesity. Diabetic kidney disease is also common in obese cohorts. Weight loss interventions, including bariatric surgery, can effectively reduce weight and improve renal outcomes. Some of this effect may be due to the remission of Type 2 diabetes and hypertension. However, other mechanisms, including the resolution of inflammatory processes, may also contribute. The effect of bariatric surgery on renal function has only recently become a focus of particular investigation. In this study, we will review the effects of bariatric surgery on obesity-associated kidney disease. We will discuss the pitfalls in assessing renal function in obese cohorts and will examine the effect of bariatric surgery on renal function and urinary protein excretion using different mechanisms. We will give particular attention to the evidence for bariatric surgery in cohorts with established renal disease and suggest future directions. In particular, we will outline the evidence for inflammation as an important therapeutic target, and the emerging medical therapies being considered to exploit this target in obesity- and diabetes-related kidney disease.

INTRODUCTION

Renal dysfunction and disease is common in obese cohorts [1–5]. Obesity is associated with a decline in renal function over time [5]. The spectrum of renal dysfunction in obesity includes hyperfiltration, proteinuria and eventually hypofiltration [6, 7]. Obesity is also a key risk factor for diabetic kidney disease (DKD), which is the most frequent cause of end-stage kidney disease (ESRD) in the developed world [8].

Obese patients have a high rate of renal hyperfiltration, which correlates with increasing body mass index (BMI) and is also associated with chronic kidney disease (CKD) [1–4]. Within an obese cohort, it is not clear that greater degrees of obesity, or increasing weight, add risk [9]. However, the increased risk derived from obesity is independent of other obesity-associated risk factors, such as diabetes and hypertension [3, 4].

Weight loss interventions, including bariatric surgery, can effectively reduce weight and renal protein excretion and redmediate both hyperfiltration and CKD [10]. Some of this effect may be due to the remission of Type 2 diabetes and hypertension following bariatric surgery [11–13]. However, other mechanisms, including improvements in the inflammatory process, may also contribute [13, 14].

The effect of bariatric surgery on renal function and CKD has only recently become a focus of particular investigation, and the available data remain sparse [13, 15–19]. In this study, we review the effects of bariatric surgery on obesity-associated kidney disease and DKD. We will discuss the potential mechanisms responsible for these effects, with a focus on the effect of bariatric surgery on inflammation. Finally, we will discuss future directions, and the upcoming areas of interest in obesity- and diabetes-associated kidney disease research, including anti-inflammatory therapies in DKD. In order to
prepare the study, we undertook a literature review on PubMed using terms including ‘renal outcomes’, ‘bariatric surgery’, ‘obesity’ and ‘renal function’.

**REVIEW**

**Measuring renal function in the obese population**

Before considering the effect of bariatric surgery on renal outcomes, it is important to consider the potential pitfalls associated with calculating estimated glomerular filtration rates (eGFR) in the obese population. Currently, the two main methods of measuring eGFR in obese cohorts include the Modified Diet for Renal Disease (MDRD) equation and Cockcroft-Gault equation (CGE), which incorporate body surface area and weight, respectively.

The CGE can overestimate GFR in obese groups when compared with creatinine clearance measurements from 24-h urine collections [20]. MDRD is more accurate in obese groups with an eGFR of >60 mL/min, compared with the CGE in a cross-sectional study using $^{125}$I-iodothalate clearance as a gold standard [21]. However, in observational data, the median difference can be as little as 6 mL/min with an inter-quartile range of 15 mL/min, and MDRD can still overestimate renal function in those with eGFRs >60 mL/min [22].

The Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) has recently been proposed and in obese cohorts, this is as accurate as MDRD [21, 23]. Including lean body weight with the CGE or body surface area in MDRD or CKD-EPI can improve accuracy [24]. It has been suggested that a modified CGE based on lean body mass is the most accurate calculation of eGFR in the obese population (Cockcroft-Gault lean body weight, CG-LBW) [25]. However, at present, none of these equations provides an accurate estimate of GFR in obese cohorts, especially at GFR levels >60 mL/min, and this is likely to be problematic in patients with large changes in weight [20, 24].

**Bariatric surgery and renal outcomes: the potential benefits**

The bariatric surgical procedures most commonly available to treat obesity include Roux-en-Y gastric bypass (RYGB), adjustable gastric banding (AGB) and vertical sleeve gastrectomy [12]. Biliopancreatic diversion, with or without duodenal switch (BPD and BPD-DS), is a less commonly performed procedure [26]. All are associated with weight loss and the remission of diabetes [12, 27, 28]. As well as these commonly understood effects, bariatric surgery can have additional effects on physical, psychological and socio-economic outcomes, which are well described [29]. The potential benefits in renal outcomes are now being appreciated and can be evaluated by their effect on serum and urine markers of GFR, proteinuria and renal histological appearances.

**Renal function by serum and urine measurements**

The significant reduction in body weight and lean body mass after bariatric surgery results in a decrease in serum creatinine, which can be mistakenly interpreted as an improvement in renal function [13]. Many studies of the effect of bariatric surgery on renal function have been in cohorts with hyperfiltration. When creatinine clearance is measured on a 24-h urine collection without correcting for body surface area, RYGB reduces GFR from a baseline consistent with hyperfiltration (140 mL/min) to normal ranges (120 mL/min) within 12 months [30]. Similar effects are reported in other prospective data [9, 31]. These changes in GFR can occur as early as 6 months and correlate with the degree of weight loss [20, 32]. However, after the first post-operative year, there is no further improvement, with creatinine clearance remaining stable at 24 months of follow-up in prospective studies [30].

RYGB does not appear to alter eGFR in patients with normal function when measured 1 year post-operatively by CG-LBW [9]. However, while the mean eGFR did not change, fewer were classified as hyperfiltrating or as having CKD post-operatively, which represents an improvement in renal function [9]. In total, 13% of this cohort had hyperfiltration pre-operatively, and this was reduced to 10% at 1 year post-operatively. In addition, 3% of the cohort with hypofiltration demonstrated improved eGFR by CG-LBW at 1 year post-operatively [9].

In case-controlled data over a 10-year period, BPD preserves renal function in patients with newly diagnosed Type 2 diabetes [33]. This cohort maintained an eGFR between 70 and 80 mL/min/1.73 m$^2$, while a medically treated control group had a continuous decline in eGFR to ~40 mL/min/1.73 m$^2$ over 10 years [33]. This may be related to all of the patients undergoing BPD achieving remission of their diabetes, as well as improved blood pressure control and improved inflammation.

Other prospective data in a cohort of 233 found that those within the normal eGFR range at the onset of the study had small increases in eGFR from 81 to 99 mL/min at 1 year post-operatively [31]. This study also included patients with Stage 3 renal disease group, and this sub-group demonstrated an increase in eGFR from 49 to 67 mL/min [31]. Approximately 45% of the cohort within this study had either hyperfiltration or CKD, although these data are limited by the inherent inaccuracy of GFR estimation as described previously.

Patients with Stages 3–5 CKD (eGFR <60 mL/min) are not often included in bariatric surgery studies [10, 30, 33]. Their exclusion from studies may be due to the perception that patients with CKD may be at increased operative mortality after surgery [34, 35]. Currently, this may dissuade many from selecting candidates with Stages 3–5 CKD for bariatric surgery.

Therefore, the evidence base for bariatric surgery in CKD at this level is sparse, and mainly based on observational or case-control data [10]. Table 1 outlines the findings of the major studies. The available data suggest that patients with Stage 3 CKD (eGFR 30–60 mL/min) can derive benefit with improvements in eGFR after bariatric surgery [31, 36, 37]. The improvements in eGFR can even be greater at Stage 3 CKD when compared with those with Stage 1 or 2 disease [37]. In established CKD, the improvements in blood pressure and glycaemia associated with bariatric surgery can at least prevent progressive loss of eGFR [33, 38].
These emerging data would suggest that the thinking on CKD and bariatric surgery needs to be re-examined. The data on bariatric surgery in patients with severe renal disease described in case series suggest that patients with ESRD can have successful RYGB and AGB without significant post-operative complications [39–42]. In some cases, bariatric surgery

Table 1. Renal function changes by serum and urine measurements: key studies

<table>
<thead>
<tr>
<th>Study author [reference]</th>
<th>Number of participants</th>
<th>Study design</th>
<th>Study duration</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro-Diaz et al. [30]</td>
<td>102</td>
<td>Prospective controlled study of cohort undergoing gastric bypass</td>
<td>24 months</td>
<td>1: CCL (mL/min) 2: Proteinuria (g/24 h) 3: Albuminuria (mg/24 h)</td>
<td>1: Reduced from mean 140 mL/min to 118 mL/min (P = 0.001) 2: No change 3: Reduced from mean 14 mg/24 h to 13 mg/24 h (P = 0.006)</td>
</tr>
<tr>
<td>Luaces et al. [9]</td>
<td>61</td>
<td>Prospective study of cohort undergoing bariatric surgery (mainly gastric bypass)</td>
<td>12 months</td>
<td>1: eGFR by CG-LBW 2: Percentage of participants with eGFR &gt;120 mL/min 3: Percentage of participants with eGFR &lt;60 mL/min</td>
<td>1: No change 2: 14.8% pre-operatively — improved in 9.8% at 12 months 3: Impaired in 8.3% pre-operatively and improved in 3.3% at 12 months</td>
</tr>
<tr>
<td>Getty et al. [20]</td>
<td>37</td>
<td>Prospective study of cohort undergoing gastric bypass</td>
<td>6 months</td>
<td>1: eGFR by MDRD 2: CCL</td>
<td>1: Mean increased from 92 mL/min/1.73 m² to 105 mL/min/1.73 m² 2: Improved in correlation with weight loss</td>
</tr>
<tr>
<td>Saliba et al. [32]</td>
<td>35</td>
<td>Prospective study of cohort undergoing gastric bypass</td>
<td>12 months</td>
<td>1: eGFR by CCL 2: Urinary cystatin C to creatinine ratio</td>
<td>1: Reduced by 15% in diabetic sub-group and 21% in non-diabetic sub-group (P &lt; 0.05) 2: Increased in diabetic sub-group only (P &lt; 0.05)</td>
</tr>
<tr>
<td>Iaconelli et al. [33]</td>
<td>50</td>
<td>Case-controlled study of cohort undergoing BPD or medical treatment</td>
<td>10 years</td>
<td>eGFR by MDRD</td>
<td>Stable at between 70 and 80 mL/min/1.73 m² in the BPD group and chronic decline over 10 years to Stage 3 CKD in the medical group</td>
</tr>
<tr>
<td>Jose et al. [37]</td>
<td>25</td>
<td>Retrospective analysis of cohort before and after BPD</td>
<td>4 years</td>
<td>eGFR by MDRD</td>
<td>Improved from 87 to 97 mL/min/m² with the greatest improvement in a sub (N = 7) with eGFR &lt;60 mL/min/m²</td>
</tr>
</tbody>
</table>

BPD, biliopancreatic diversion; CCL, creatinine clearance measured in a 24-h urine collection; CG, Cockroft-Gault formula; CG-LBW, Cockroft-Gault lean body weight formula; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease formula.
has resulted in the recovery of renal function in dialysis-dependent patients [43, 44]. However, caution is still needed given the limitations of the evidence base. Further prospective long-term studies are needed. Randomized controlled studies of bariatric surgery compared with non-surgical weight loss or medical management with primary renal outcome measures such as measured GFR are not available, but would be immensely useful.

**Proteinuria.** Most studies on the effect of bariatric surgery on proteinuria include cohorts with either normoalbuminuria, microalbuminuria or both [10]. This means that sub-group analyses are often needed to determine the effect of bariatric surgery on proteinuria [45]. On meta-analysis of these data, weight loss is correlated with reduced proteinuria [45]. None of these studies includes patients with nephrotic range proteinuria [45].

Proteinuria and albuminuria on 24-h urine collections are both reduced at 12 months following RYGB [18, 30, 46]. Albuminuria continues to improve at 24 months of follow-up [30]. Bariatric surgery can improve the urinary albumin-creatinine ratio in those with pre-surgical microalbuminuria and can result in remission of microalbuminuria [18, 45, 47]. In diabetic groups, the remission rate of microalbuminuria can approach 60% at a 5-year follow-up [47]. This compares to an expected remission rate of 18% in cohorts with Type 2 diabetes [48].

In cases of ‘normoalbuminuria’, there is no decrease in protein excretion between 4 weeks and 6 months after bariatric surgery [16, 32, 49]. However, in this group, bariatric surgery prevents the development of microalbuminuria [47]. When compared with medical therapy alone, bariatric surgery can reduce the incidence of microalbuminuria by over 80% [33]. This effect is reported up to 10 years in case-controlled data and is seen in tandem with weight loss, durable remission of diabetes and improved blood pressure control [33].

The mechanisms of effect in reducing proteinuria are multiple, but include improved blood pressure and improved glucose homeostasis [16, 33, 45]. However, the improvements also correlate with weight loss, and it is possible that reduced inflammation associated with weight loss contributes a beneficial effect [13, 45]. If this is the case, then there may be an opportunity to exploit this mechanism using therapy to modulate the pro-inflammatory state. Therefore, further focused study on immune mechanisms underlying the improvements in proteinuria after bariatric surgery should be a priority within this field of research.

**Histological data.** There are few data on renal histological changes in bariatric surgery recipients, but animal data have suggested that RYGB can lead to degenerative changes, consistent with an acute nephritis in diet-induced obesity Sprague-Dawley rats [50]. However, this study was critically limited as they did not measure renal function in their animal model [50]. Available histological data in humans are mainly limited to case reports or case series. In these data, the histological appearances of obesity-associated kidney disease improve after bariatric surgery, with associated improvements in renal function [43, 44].

**Bariatric surgery: a bridge to transplantation in obese cohorts with end-stage renal disease**

Currently, several national guidelines suggest that when possible, body weight should be reduced to a non-obese category before renal transplantation [51]. It is recognized that obesity should not specifically exclude candidates from renal transplantation per se [51, 52]. However, higher body mass indices are associated with higher rates of surgical complications and higher rates of delayed graft function [53]. This presents challenges to renal transplant services, which are seeing increasing numbers of obese candidates presenting for evaluation [53].

One solution that has gained interest is the use of bariatric surgery as a ‘bridging’ procedure for those with obesity and CKD awaiting transplantation. Case series have reported successful RYGB in nine pre-transplant candidates on dialysis, with successful post-RYGB renal transplantation [39, 40]. The mean excess weight loss was 70% at 5 years post-RYGB and was associated with improved glucose homeostasis and blood pressure control [39, 40]. This was achieved without peri-operative mortality or graft loss.

There are individual case reports of AGB in renal transplant recipients, and in those awaiting transplant [53]. These cases were completed without mortality, but with a higher rate of reported complication [53]. US data on 29 patients awaiting a renal transplant who subsequently underwent bariatric surgery while on the waiting list report a higher complication rate and mortality rate than expected [54]. There was also a high rate of morbidity in a cohort of 87 transplant recipients who underwent RYGB after transplantation [54]. The total 30-day mortality rate in both cohorts was 3.5%, which exceeds the current expected rate of 0.3% [54, 55].

While this is concerning, these data are from before 2004 and include only open procedures [54]. Currently, the laparoscopic approach is more commonly used and is associated with less morbidity than the open approach [56]. This illustrates the need for prospective controlled data on the use of bariatric surgery in ESRD to clarify the risks and benefits in this population. For now, bariatric surgery must be considered as having significant risk in those with ESRD awaiting renal transplant. This needs to be understood in the context of the limited evidence base comprising case reports and observational data. The risk of obese cohorts waiting for transplant on dialysis needs to be balanced with that of bariatric surgery. Further study in this area is urgently needed to inform best practice.

**Bariatric surgery and renal outcomes: the potential pitfalls**

Despite the data suggesting a potentially beneficial role for bariatric surgery in those with CKD, there are also pitfalls to consider. Nephrolithiasis is common after bariatric surgery [57]. The incidence rate varies but can be as high as 3% after bariatric surgery [57, 58]. In those affected, the rate of recurrent nephrolithiasis is over 30% [58]. Hyperoxaluria is the
major cause of nephrolithiasis after bariatric surgery and increased hyperoxaluria is maintained for at least 2 years post-operatively in prospective data [57–60].

This is of concern as it can result in oxalate nephropathy and CKD [59, 61, 62]. In those with pre-existing CKD, the addition of oxalate injury can precipitate further renal impairment and even renal failure requiring renal replacement therapy [62]. In renal allograft recipients, this can be catastrophic, and two cases of individuals who developed acute kidney injury secondary to oxalate nephropathy have been reported [63]. One of these cases required on-going dialysis [63]. However, in both cases, there were multiple other factors to explain graft failure and hyperoxaluria other than the history of bariatric surgery [63]. The two cases were 7 and 27 years post-surgery at the time of kidney injury [63].

The risk of nephrolithiasis after the second year of bariatric surgery is unknown [64]. Similarly, the incidence of CKD or ESRD related to hyperoxaluria has not been quantified in this cohort [64]. The available data are mainly from case reports or case series [61, 62]. While it is true that hyperoxaluria persists, and even increases over time post-operatively, other pro-nephrolithiasis factors such as the relative supersaturation of calcium oxalate normalize over time [59, 60].

Therefore, more data are needed to determine the real risk of hyperoxaluria and associated renal damage in the current bariatric population. For now, this cohort needs to be considered as high risk for nephrolithiasis and managed accordingly. The risks of nephrolithiasis may be mitigated by simple fluid supplementation measures and adequate intake of calcium [65]. However, this is based on retrospective observational data and is yet to be proven [65].

Another potential pitfall in the acute post-operative phase is rhabdomyolysis. Rhabdomyolysis is common in open bariatric surgery when diagnosed by serum creatinine kinase levels greater than five times the upper limit of normal [66, 67]. This is best described in open RYGB because patients are more immobile and given their high BMI they put long-term pressure on several of the major muscle groups [66, 67]. The duration of surgery is a possible contributor to kidney injury theoretically, although this has not been proven. Rhabdomyolysis is associated with acute kidney injury in case reports, but this is not the case in prospective cohort studies [66, 67]. Despite this discrepancy, the risk of rhabdomyolysis needs to be anticipated in bariatric surgery candidates and should be carefully screened for.

Renal disease and inflammation: the effect of bariatric surgery

The mechanisms for the improvement in renal function are not fully understood. Bariatric surgery reduces weight and improves hypertension and hyperglycaemia, which can explain some of the effect on eGFR [20, 30, 36]. Advanced glycation end products and oxidative stress are altered by changes in blood pressure and glucose homeostasis, and are important mechanisms in the pathogenesis of DKD [68]. However, the role of inflammation is increasingly recognized to be key to the process of kidney disease in obese cohorts, with and without diabetes [13, 19, 69].

Chronic low-grade inflammation is commonly associated with obesity. C-reactive protein (CRP) correlates with the development of DKD [14, 70]. Bariatric surgery can reduce CRP and remediate the pro-inflammatory chemokine and cytokine milieu by reducing the levels of pro-inflammatory molecules, while enhancing anti-inflammatory chemokine and cytokine production [14, 71, 72]. However, these data are from cohort studies, and the randomized studies’ results need confirmation [14].

The use of cytokines like tumour necrosis factor alpha or interleukins in monitoring the changes in inflammation after bariatric surgery remains controversial [14, 71–74]. The difficulty arises as there can be a tissue-specific relationship between cytokines and chemokines, and the improvements in these measurements seen after surgery can be multi-factorial, leading to distortion of the data [73–76]. To best determine the effect of bariatric surgery on the inflammatory process within an organ system, the studies need to be focused on a particular disease process with pre-defined outcome measures.

There are particular cytokines that can be correlated with the development of renal disease [77]. Monocyte-chemoattractant protein-1 (MCP-1), also known as CC-chemokine ligand 2 (CCL2), is one that is strongly associated with renal disease in both obesity and diabetic nephropathy [78, 79]. It is possible that MCP-1 causes renal damage via macrophage accumulation and renal inflammation [79]. Blockade of the MCP-1 pathway delays the development of renal disease in diabetic animal models, and is associated with improved cell function in human in vitro studies [80–82].

Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine involved in the activation of macrophages and the recruitment of macrophages to the site of inflammation. Increased MIF expression has been detected in some subtypes of glomerulonephritis in patients [83]. Treatment with anti-MIF antibodies has been shown to reduce the production of pro-inflammatory cytokines, including interleukin 1, and the severity of experimental models of glomerulonephritis [84]. Raised serum concentrations of MIF have been detected in obese patients [85].

Improvements in renal inflammation following bariatric surgery are associated with that in renal function [13, 49, 86]. The amelioration in inflammation has been best described in RYGB, SG and AGB, with data finding comparable effects in these three modalities [13, 49]. The improvement in urinary MCP-1/creatinine ratio at 4 weeks is similar after AGB, RYGB and SG, although RYGB has additional effects in reducing chemokine-ligand 18 (CCL-18) [49]. These effects continue with further substantial reductions in pro-inflammatory chemokine and cytokine profiles by 12 months [49].

The bariatric surgery-induced reductions in MCP-1 are associated with improvements in renal function [13, 49, 86]. Some of this change is a result of weight loss, as changes in the levels of MCP-1 correlate with the degree of post-operative weight loss [13, 49]. Other undetermined mechanisms also act in addition to weight loss to reduce MCP-1-related inflammation. After RYGB, MCP-1 is reduced to levels lower than that of lean controls, inferring that the relationship between MCP-1 improvements and weight or fat mass may not be as simple as it seems [87].
One explanation for this may be the role of macrophages in obesity-associated inflammation. Macrophages are a key component of the inflammatory process in CKD, including DKD, and can mediate several central inflammatory pathways [88]. They are major producers of MCP-1 in adipose tissue [75]. Macrophages can present as pro-inflammatory (‘classically activated’; designated M1) or anti-inflammatory phenotypes (‘pro-repair’; designated M2 and related subsets). A change from anti-inflammatory to pro-inflammatory macrophage phenotypes could advance existing renal disease and is likely to be an initiating event in CKD in obesity [88, 89].

The reduction in inflammatory infiltrate in renal disease [95]. This gut hormone mediates regulation of macrophage aggregation and inflammation. Inhibition of pro-inflammatory macrophage infiltration in rodent renal models is associated with reduced fibrosis, lower grades of renal disease and down-regulation of transforming growth factor beta [90, 91]. Bariatric surgery in mice can reduce the infiltration of pro-inflammatory macrophages, with consequent down-regulation of several major pro-inflammatory pathways [75]. Similarly, transfection of an anti-inflammatory macrophage phenotype can reduce renal disease in rodent models, whereas transfection of a pro-inflammatory macrophage accelerates renal injury [92]. In this model, macrophages were isolated from BALB/c mice and stimulated with lipopolysaccharide to induce an M1 macrophage phenotype, or treated with interleukins 4 and 13 to induce an M2 phenotype. The treated macrophages were then infused into an adriamycin-induced CKD mouse model [92]. Those infused with M2 macrophages have less-severe histological and functional diseases when compared with the M1-treated animals [92].

**Gut hormones and remediating inflammation in obesity: new frontiers**

Now that inflammation is recognized as an important therapeutic target in obesity-associated CKD and DKD, the challenge is to identify any therapeutic opportunities that can improve outcomes in the affected population [93]. Bariatric surgery can reduce inflammation and improve renal function in humans, and may become a new treatment strategy for those with renal impairment and obesity [13]. However, before this can be recommended, the use of bariatric surgery in this cohort needs to be further investigated.

Bariatric surgery is not suitable for all and several recent observations have suggested that the raised endogenous gut hormones may be central mediators of the anti-inflammatory effects of RYGB [16]. In prospective studies, albuminuria decreased to a greater extent after RYGB when compared with AGB and SG at 6 months post-operatively, despite comparable amounts of weight loss [16]. RYGB, AGB and SG are associated with weight loss and the remission of diabetes, but RYGB is most consistently associated with improved gut hormone secretion post-operatively [12, 27, 28].

Gut hormones are increasingly associated with reduction of inflammation in obese cohorts losing weight [94, 95]. In kidney disease, this occurs, at least in part, through T-cell mediated regulation of macrophage aggregation and inflammation, with reductions in pro-inflammatory activity [94–96]. The reduction in inflammation correlates with improved histological appearances in renal disease [95]. This gut hormone effect on inflammation appears to be independent of changes in glycaemia [95, 97, 98].

The effect of bariatric surgery augmented that gut hormone responses or exogenous glucagon-like-peptide-1 (GLP-1) analogues in psoriasis have shown particularly impressive results [94, 99, 100]. The anti-inflammatory effect has been shown to act through the T-cell population, and therefore could regulate macrophage activity, which is a major immunological component of renal inflammation and disease progression in DKD [101].

Dipeptidyl peptidase 4 inhibitors (DPP4i) inhibit the degradation of gut hormones, resulting in greater serum levels of peptides like GLP-1 [102–104]. This class of medication is being investigated for use in those with DKD. In observational data, the use of the DPP4i sitagliptin is associated with reduced rates of albuminuria [102]. Human study has shown that DPP4i, similar to GLP-1 analogues, can move the macrophage immunophenotype from pro-inflammatory to anti-inflammatory, with associated improvements in the inflammatory cytokine and chemokine profiles in vitro [105]. In clinical trials, reductions in pro-inflammatory interleukins can be produced with DPP4i [106].

In animal models of Type 2 diabetes and DKD, sitagliptin can reduce renal inflammation as assessed histologically, and can improve serum renal indices and delay the histological progression of kidney disease [104]. This is in the context of a significant change in glucose homoeostasis [104]. It can also prevent the development of a pro-inflammatory immunophenotype in diet-induced obesity [107]. Other animal data have identified improved renal endothelial vascular responses and reduced blood pressure, which may play a role in improved renal function in DPP4i [108, 109].

Moving forward, we need to investigate the role of gut hormones in remediating inflammation in renal disease specifically. Further study is needed in humans, with a system-specific focus and measurement of changes in fat mass, blood pressure, glucose homeostasis, inflammation (by CRP and system-specific cytokines and chemokines) and immunophenotype. We must then define the mechanisms of the effects seen in GLP-1 analogue therapy and DPP4i. If proven to have an anti-inflammatory effect, then the gut hormones or DPP4i could be explored as anti-inflammatory therapy in obesity-associated CKD and DKD, opening up a new horizon in the prevention and treatment of these diseases.

**CONCLUSION**

Bariatric surgery improves renal function in those with hyperfiltration. It may also improve renal outcomes in patients with established CKD. However, it should be remembered that renal impairment has also been associated with increased operative mortality in surgical subjects in observational data. Therefore, more studies are needed to fully define the safety and benefits of bariatric surgery in this group.

The improvements in CKD are achieved through improvements in blood pressure, glycaemia, dyslipidaemia and inflammation. Inflammation is a key component in this mechanism.
It seems likely that the enhanced gut hormone response following bariatric surgery improves gut hormone regulation of the inflammatory response.

The existing evidence base is essentially limited to retrospective or observational data, and the findings need to be tested prospectively in longer-term studies. The reports, to date, are encouraging, as they suggest that DKD can be improved or prevented by bariatric surgery, in the context of reduced weight, improved blood pressure and improved glycemic control [29–35]. The use of bariatric surgery in CKD and DKD needs to be a research priority. Robust prospective studies, ideally with randomized control groups allocated to best medical care, need to be completed.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the contents of this paper have not been previously published.

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Effects of weight loss on renal function in obese CKD patients: a systematic review

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ABSTRACT

Obesity is an independent risk factor for the development and progression of chronic kidney disease (CKD). We conducted a systematic review to assess the benefits of intentional weight loss in obese subjects with altered glomerular filtration rate (GFR), proteinuria or albuminuria. MEDLINE, EMBASE and CENTRAL databases were searched for articles reporting longitudinal data on the effect of weight loss on renal parameters in obese patients with altered kidney function. Thirty-one (2013 subjects) were included. In the 13 studies where weight loss was achieved by bariatric surgery,