Diabesity and microvascular disease: the impact of weight loss

SIRAJ FARID,1 BILAL BASHIR,2,3 ADEEL HAMAD,1 SHAISHAV DHAGE,1,2 JAN HOONG HO,1 HANDREAN SORAN,2,3 SAFWAAN ADAM1,2

Abstract
There is increasing evidence that obesity is an independent risk factor for the development of microvascular disease. Addressing modifiable risk factors such as obesity may help prevent and even reverse microvascular complications, including neuropathy, nephropathy and retinopathy.

In this review article, we examine the evidence for the impact of obesity on microvascular disease, as well as the effects of weight loss in individuals with and without type 2 diabetes mellitus (T2DM). Numerous studies have shown obesity to be an independent risk factor for neuropathy and nephropathy in patients with and without T2DM but the association between obesity and retinopathy is less clear. Addressing obesity through weight loss strategies can have beneficial outcomes. Although evidence for medical weight management is limited due to the lack of longitudinal data, there is growing recognition of the positive impact of surgical weight management. Recent studies have shown bariatric surgery to be protective against diabetic neuropathy despite previous concerns from older studies. Similarly, several studies have demonstrated improvements in renal measures after bariatric surgery. Improvements in retinopathy, however, have been less encouraging, with further research required to fully understand the impact of obesity. Overall, managing obesity and implementing weight loss through bariatric surgery has positive outcomes for reducing the burden of microvascular disease.

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Key words: microvascular, diabetes, pbesity

Introduction
Microvascular disease carries significant morbidity and mortality, and represents amongst the most serious complications of obesity and type 2 diabetes mellitus (T2DM). The chronic elevation of blood glucose damages the small blood vessels that supply organs and tissues, which most commonly manifests as neuropathy, nephropathy and retinopathy, all of which have significant impact on both quality of life and life expectancy. One of the important modifiable risk factors implicated in microvascular disease is obesity, which is increasingly recognised in patients both with and without T2DM. However, it is difficult to segregate and study the impact of obesity and hyperglycaemia on microvascular disease since their co-existence is not uncommon. It is imperative that modifiable elements are addressed to prevent and potentially reverse microvascular complications. In this review article, we aim to share some of the evidence pertaining to the risk conferred by obesity and the subsequent impact of weight loss on microvascular disease in people both with and without T2DM.

Methods
Databases including PubMed, MEDLINE and Web of Science were used to locate studies on obesity, diabetic microvascular disease and bariatric surgery. Search terms used included “Obesity”, “Diabetes”, “Nephropathy”, “Neuropathy”, “Retinopathy”, “Weight loss”, “Bariatric Surgery”. The search was conducted in two parts: first to understand the impact of obesity on microvascular disease and then to review the impact of bariatric surgery on microvascular parameters.

Obesity and microvascular disease parameters
The relationship between obesity and microvascular disease parameters is summarised in Table 1.

Peripheral neuropathy
Peripheral neuropathy is an established microvascular complication of diabetes; examining the evidence suggests that obesity is an independent risk factor (with or without a history of diabetes mellitus). A large population-based study showed that although hyperglycaemia had the strongest association with peripheral neuropathy, obesity was an important metabolic determinant. In this study, patients without T2DM had a higher risk of distal symmetrical neuropathy in the presence of components of the metabolic syndrome such as obesity. Similarly, in patients with diabetes the risk of peripheral neuropathy is compounded by obesity. These findings support similar observations in a large prospective cohort study where central obesity, high triglycerides and low HDL-cholesterol were found to be
Table 1. The relationship between obesity and microvascular disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of participants</th>
<th>Study design</th>
<th>Key results</th>
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<tbody>
<tr>
<td><strong>Neuropathy</strong></td>
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<tr>
<td>Callaghan et al ^1,2</td>
<td>4,002</td>
<td>Cross-sectional population-based study</td>
<td>Hyperglycaemia and obesity increased the risk of developing peripheral neuropathy (OR 2.60 [95% CI 1.77–3.80] and OR 1.09 [95% CI 1.02–1.18], respectively)</td>
</tr>
<tr>
<td>Callaghan et al ^3</td>
<td>155</td>
<td>Cross-sectional observational study Obese (n = 102) vs. lean (n = 53)</td>
<td>Prevalence of neuropathy was 3% in lean controls vs. 11.1% in non-diabetic obese participants (p &lt; 0.01). Waist circumference was associated with neuropathy (OR 1.24 [95% CI 1.00–1.55])</td>
</tr>
<tr>
<td>Hanewinkel et al ^4</td>
<td>1,256</td>
<td>Prospective population-based cohort study</td>
<td>Diabetes was associated with polyneuropathy (OR 3.01 [95% CI 1.60 to 5.65]), MetS was associated with polyneuropathy (OR 1.92 [95% CI 1.09 to 3.88]), with higher risk with increasing number of MetS components. Elevated WC (OR 2.84 [95% CI 1.35–5.99]) and raised triglycerides (OR 2.01 [95% CI 1.11–3.62]) increased risk of polyneuropathy. Findings for WC and triglycerides also show increased risk in persons without diabetes</td>
</tr>
<tr>
<td>Azmi et al ^5</td>
<td>46</td>
<td>Prospective comparative study Twenty-six obese people without diabetes compared to 20 controls</td>
<td>Obesity was associated with measures of neuropathy, specifically a higher NSP, VPT and WT and lower CT and DB HRV, peroneal and sural nerve amplitudes</td>
</tr>
<tr>
<td><strong>Retinopathy</strong></td>
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<tr>
<td>Zhang et al ^1</td>
<td>319</td>
<td>Retrospective analysis of DCCT primary prevention cohort, 153 participants with HbA1c &lt;6.89% compared against 166 participants with HbA1c &gt;9.49%</td>
<td>High BMI increased the odds of developing retinopathy (OR 1.11 [95% CI 1.01–1.24]). Other risk factors associated with retinopathy included higher baseline HbA1c and longer duration of participation in the study</td>
</tr>
<tr>
<td>Henriksson et al ^2</td>
<td>627</td>
<td>Prospective observational study of people between 15-34 years of age with incident diabetes mellitus</td>
<td>High BMI and HbA1c reduced the time to develop DR (RR 1.11 [95% CI 1.04–1.18] and RR 1.7 [95% CI 1.43–1.93], respectively)</td>
</tr>
<tr>
<td>Chao et al ^3</td>
<td>4,344</td>
<td>Population-based cross-sectional study</td>
<td>Presence of retinopathy in patients without diabetes was independently associated with BMI &gt; 30 kg/m^2 (OR 1.3 [95% CI 1.0–1.7])</td>
</tr>
<tr>
<td>Gray et al ^4</td>
<td>14,657</td>
<td>Retrospective study using data from Medicare Current Beneficiary Service and Medicare claims</td>
<td>Increased risk of ocular complications of diabetes mellitus for both men and women when stratified according to gender and BMI; risk increased progressively with higher BMI, especially for men</td>
</tr>
<tr>
<td>Van Leiden et al ^5</td>
<td>626</td>
<td>Retrospective population-based study</td>
<td>BMI &gt;28.4 kg/m^2 increased risk of RP (OR 3.52, 1.05–11.8) in people with diabetes. Raised BMI was not reported as a statistically significant risk factor for retinopathy in individuals without diabetes</td>
</tr>
<tr>
<td>Dirani et al ^6</td>
<td>492</td>
<td>Prospective observational study</td>
<td>Raised BMI (adjusted OR 1.06), NC and WC increased the risk of developing any form of DR. Presence of obesity increased risk of proliferative diabetic retinopathy (OR 6.52 [95% CI 1.49–28.6], p = 0.03)</td>
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<td><strong>Nephropathy</strong></td>
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<td></td>
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<tr>
<td>Ejeblad et al ^7</td>
<td>1,924</td>
<td>Population-based case control study of 926 patients with chronic renal failure and 998 controls</td>
<td>Overweight (BMI ≥25 kg/m^2) at age 20 was associated with a significant three-fold excess risk for ORF, relative to BMI &lt;25. Obesity (BMI ≥25) among men and severe obesity (BMI &gt;35) among women during lifetime was linked to three- to four-fold increases in risk</td>
</tr>
<tr>
<td>Peters et al ^8</td>
<td>738</td>
<td>Cohort study (146 obese people compared against 589 non-obese controls)</td>
<td>Examination of the relation between age and GFR failed to reveal any adverse effect of obesity on age-related decline in renal function</td>
</tr>
<tr>
<td>Iskéi et al ^9</td>
<td>100,753</td>
<td>Cross-sectional observational study of a registry of patients in Okinawa, Japan</td>
<td>BMI was associated with an increased risk of the development of ESRD in men (OR 1.27) but not women in the general population in Okinawa</td>
</tr>
<tr>
<td>Gelber et al ^10</td>
<td>11,104</td>
<td>Prospective observational study</td>
<td>Overweight and obesity (BMI &gt; 26.6 kg/m^2) associated with higher odds of CKD (eGFR &lt; 60 mL/min); OR 1.45 [95% CI 1.19–1.76], p&lt;0.001. Increased CKD risk with BMI change &gt; 10%</td>
</tr>
<tr>
<td>Vivante et al ^11</td>
<td>1,194,704</td>
<td>Retrospective observational study from military recruitment linked to Israeli ESRD registry data in which 874 patients developed incident ESRD in the 30-year study period</td>
<td>Obesity increased the risk of diabetic and non-diabetic ESRD (HR 1.37 [95% CI 1.13–2.65]) and HR 3.41 [95% CI 2.42–4.79], respectively) Overweight and obesity increased risk of all-cause ESRD (HR 3.0 [95% CI 2.5–3.6] and HR 6.89 [95% CI 5.52–8.80], respectively)</td>
</tr>
<tr>
<td>Hsu et al ^12</td>
<td>177,550</td>
<td>Population-based study from integrated healthcare delivery system in the US, 842 cases of ESRD</td>
<td>Increase in weight correlated with the development of renal failure (HR 4.39 [95% CI 3.38–5.70]) for Class 2 and 3 obesity. HR 3.11 [95% CI 2.51–3.84] for Class 1 obesity, and HR 1.65 [95% CI 1.39–1.97] for overweight</td>
</tr>
<tr>
<td>Munkhaugen et al ^13</td>
<td>74,986</td>
<td>Retrospective observational study</td>
<td>Pre-hypertensive participants were not at increased risk of ESRD if they were not obese; however, the risk was two and six times higher with BMI &gt; 30 and &gt;35 kg/m^2 (HR 2.66 [95% CI 1.28–5.53] and HR 5.94 [95% CI 1.94–18.20], respectively)</td>
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<tr>
<td>Chandle Shaw et al ^14</td>
<td>205</td>
<td>Cross-sectional observational study in persons without diabetes</td>
<td>Central adiposity (increased WHR) increased risk of developing macroalbuminuria and macroalbuminuria</td>
</tr>
<tr>
<td>Kramer et al ^15</td>
<td>5,897</td>
<td>Cross-sectional observational study</td>
<td>After adjustment for all covariates, both baseline overweight (OR 1.21 [95% CI 1.05–1.41]) and obesity (OR 1.40 [95% CI 1.20–1.63]) were associated with increased odds of incident CKD at year 5</td>
</tr>
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</table>

Summary of studies examining risk of microvascular disease (sub-stratified into neuropathy, retinopathy and nephropathy. OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; WC, waist circumference; NSP, neuropathy symptom profile; VPT, vibration perception threshold; WT, warm temperature threshold; CT, cold temperature threshold; BMI, body mass index; HbA1c, glycated haemoglobin; IR, risk ratio; HR, hazard ratio; ESRD, end-stage renal disease; WHR, waist-to-hip ratio; CKD, chronic kidney disease; DCCT, The Diabetes Control and Complications Trial; NC, neck circumference; WC, waist circumference
independently associated with peripheral neuropathy in individuals with and without diabetes. In another population-based cohort study, Hanewinckel et al also concluded that increased waist circumference was a risk factor for the development of peripheral neuropathy, after controlling for age, sex and hyperglycaemia. The association with peripheral neuropathy was stronger with more components of metabolic syndrome. We previously assessed neuropathy markers in obese patients without diabetes compared to a control group and showed that participants with obesity had a significantly higher neuropathy symptom profile.

Retinopathy

Diabetic retinopathy

Although several studies have shown that elevated body mass index (BMI) and central obesity are risk factors for the development and progression of diabetic retinopathy, establishing direct causality remains a challenge. Revisiting data from the Diabetes Control and Complications Trial (DCCT) revealed an interesting finding regarding the impact of BMI on the progression of retinopathy in patients with both ideal and suboptimal glycaemic measures in type 1 diabetes mellitus (T1DM). The study found that despite good glycaemic control, with glycated haemoglobin A1c (HbA1c) of <53 mmol/mol (7%), 10% of participants developed diabetic retinopathy. In contrast, in patients with an HbA1c >75 mmol/mol (9%), 43% did not develop retinopathy. In addition to diabetes duration, BMI was found to have made a significant contribution to this paradoxical observation. There was further supporting evidence from the Diabetes Incidence Study in Sweden, which showed that higher BMI was associated with increased severity and a shortened time to onset of incident retinopathy.

Retinopathy in people without diabetes

Few studies have specifically examined the presence of retinopathy in obese persons without diabetes; most studies have focused on individuals with pre-existing diabetes and have employed statistical models to elucidate the independent effect of obesity on retinopathy. The Los Angeles Latino Eye Study found an independent association between higher BMI (>30 kg/m²) and an increased prevalence of retinopathy in a cross-sectional analysis of people without diabetes. Gray et al reported a positive associations between obesity, T2DM and retinopathy, with a progressive increase in the risk of retinopathy with higher BMI, based on data from the Medicare Current Beneficiary Survey. The Hoorn study also found a positive trend between diabetic retinopathy and increasing BMI in patients both with and without known diabetes. Additionally, Dirani et al demonstrated that a BMI >30 kg/m² was three and six times more likely to be associated with proliferative diabetic retinopathy respectively, with significant positive association also observed for greater waist and neck circumference and development of retinopathy. These findings support the role of obesity in the development of retinopathy, independent of glycaemic control. It is important, however, to note that other factors such as hypertension and dyslipidaemia (particularly hypertriglyceridaemia), being frequent accompaniments of obesity, may also contribute to the development and progression of retinopathy.

Nephropathy

As with neuropathy, there is increasing evidence to demonstrate the independent impact of obesity on adverse renal measures, both in those with and without diabetes mellitus. The relationship between obesity and the development of nephropathy in individuals with diabetes and hypertension has been contentious, on balance supporting adverse renal outcomes in people with “diabesity”. Some studies argue that obesity is an independent risk factor for the development or progression of nephropathy, while others suggest otherwise. However, a substantial body of evidence supports the notion that obesity is associated with worse renal outcomes, including end-stage renal disease (ESRD), chronic kidney disease (CKD), renal stones, renal cancer, and post-transplant graft rejection.

While ESRD and CKD are often used as a surrogate markers for nephropathy, it is important to consider the broader implications of obesity on renal health. In a large retrospective nationwide population-based analysis, Vivante et al examined the association between BMI and the risk of all-cause ESRD in a cohort of 1.2 million individuals over a 25-year follow-up period. The findings revealed that overweight and obese subjects were six and 19 times higher in overweight and obese subjects, respectively. Another study by Hsu et al which included 842 cases of ESRD demonstrated similar trends, with increasing risk of developing ESRD with increasing BMI. A 20-year follow-up study of the HUNT I cohort revealed that individuals with pre-hypertension were not at an increased risk of ESRD if they were not obese (BMI <30 kg/m²). However, the risk of ESRD doubled with a BMI above 30 kg/m² and increased six-fold with a BMI above 35 kg/m². While most studies have focused on incidence or progression of renal failure, early nephropathy was examined in two cross-sectional epidemiological studies in the UK; there was increasing prevalence of microalbuminuria with increasing BMI in subjects without diabetes (3.1% in BMI <25 kg/m², 12.1% in BMI 25–30 kg/m² and 27.2% in BMI >30 kg/m²). Similar results were noted in normoglycaemic individuals of South Asian descent, where adiposity was an independent predictor of albuminuria.

Several studies have utilised statistical modelling techniques to investigate the influence of obesity on the incidence and progression of CKD and ESRD, revealing an independent association between obesity and renal outcomes. These findings underscore the significant impact of obesity on renal health and the increased risks it poses for the development and progression of nephropathy. The evidence highlights the importance of addressing obesity as a modifiable risk factor in efforts to prevent and manage renal complications.

8
The impact of weight loss

When considering the demonstrated relationship between obesity and microvascular disease, it is plausible that weight reduction might have favourable effects. Many studies analysing associations between microvascular disease and weight loss have been short term, and it is therefore difficult to assess the long-term impact of weight loss intervention. Evaluation of the influence of weight loss may be best observed through longitudinal data analysis, and the EPIC-Potsdam study is an example where impact of lifestyle factors on various chronic disease outcomes, including microvascular disease, was assessed over a 12-year duration.24 In this study, patients with a higher BMI at the start of the study were found to be at higher risk of developing microvascular disease, and patients who gained weight from time of diagnosis were also more likely to develop microvascular disease. Conversely, the risk of incident microvascular disease was lower in patients who lost weight from time of diagnosis. The two classes of anti-diabetic medication most associated with weight loss were sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA).

Few studies have focused on the effect of these drugs on microvascular outcomes as there are limited data for the impact on neuropathy and retinopathy. Despite this, some large studies have shown the beneficial effects of SGLT2 inhibitors on nephropathy.25-29 Similarly, GLP-1 RA have also shown renal benefits.30,31 None of these studies showed a direct or independent relationship to pharmaco-logically-induced weight loss. However, these medications have a multimodal mechanism of action which includes weight loss and therefore it remains a possibility that this is conferring a mechanistic advantage. Secondary end-point analysis in the early tirzepatide (a combined glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist) trials have shown potential renoprotective effects of the drug although studies exclusively examining the impact of tirzepatide on microvascular disease are yet to be reported.32

The role of bariatric surgery

Bariatric surgery has been shown to reduce microvascular disease burden. The incidence of new microvascular disease after bariatric surgery has been shown to be markedly reduced across studies.33-35 Coleman et al examined long-term microvascular disease outcomes in patients with T2DM who underwent bariatric surgery. After surgery patients who experienced remission of their T2DM had a 29% lower risk of developing microvascular disease than those in whom diabetes persisted (post-surgical follow up period of up to seven years).33 The study also found that the beneficial effects of bariatric surgery persisted even in the event of relapses following surgery, therefore supporting the notion of a “legacy effect” of bariatric surgery in relation to microvascular disease prevention. Furthermore, O’Brien et al, using diagnostic medical record ‘read codes’, demonstrated in a large cohort that bariatric surgery markedly reduced the incidence of microvascular disease (similar post-operative follow-up period of up to seven years).34 We have summarised their findings by demonstrating percentage reduction in microvascular disease incidence risk (compared to usual medical care) in Figure 1. The findings were further corroborated in the Swedish Obese Subjects (SOS) cohort, where bariatric surgery reduced the incidence of microvascular disease (risk reduction 44%) and was especially marked in those with prediabetes.35 Smaller studies have also added granularity to those data and established that bariatric surgery may reverse early manifestations of microvascular complications.36 Table 2 contains a summary of studies demonstrating the impact of bariatric surgery on microvascular disease parameters and outcomes.

Impact of bariatric surgery on neuropathy

An increasing body of evidence shows the protective effects of bariatric surgery in patients with and without an underlying diagnosis of T2DM. In a prospective cohort study (n=26), our group investigated how bariatric surgery affects microvascular complications in patients with T2DM, using detailed phenotyping.37 Our cohort consisted of patients with a relatively recent diagnosis of T2DM who underwent bariatric surgery. The key finding was that there were improvements in corneal nerve morphology (using corneal confocal microscopy), which suggested early reversibility of subclinical disease after bariatric surgery. The improvement in corneal nerve fibre length was associated with a reduction in serum triglycerides. Although there was an improvement in glomerular hyperfiltration, another early microvascular pathological manifestation, the retinal parameters were unchanged. Our findings were corroborated by Reynolds et al who, in a larger cohort (n=79), showed that bariatric surgery improved...
Table 2. Selected studies highlighting the effect of bariatric surgery on microvascular parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>Total no. of participants</th>
<th>Study design</th>
<th>Key results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coleman et al 2016</td>
<td>4,683</td>
<td>Retrospective observational cohort study in patients with diabetes</td>
<td>Covariate-adjusted analyses showed that patients who experienced T2DM remission had 29% lower risk of incident microvascular disease compared with patients who never remitted (HR 0.71 [95% CI 0.60-0.85])</td>
</tr>
<tr>
<td>O’Brien 2018</td>
<td>15,083</td>
<td>Retrospective matched cohort study; 4,024 surgical cohort vs 11,059 non-surgical</td>
<td>Bariatric surgery was associated with significantly lower risk for incident diabetic microvascular disease at 5 years (16.9% for surgical vs. 34.7% for non-surgical patients; adjusted HR 0.41 [95% CI 0.34-0.48])</td>
</tr>
<tr>
<td>Carlsson et al 2015</td>
<td>3,108</td>
<td>Prospective multi-centre case-controlled cohort study; 1,498 surgical patients vs 1,610 controls</td>
<td>SOS study cohort. Bariatric surgery was associated with reduced incidence of albuminuria compared with usual obesity care (adjusted HR 0.37, p&lt;0.001)</td>
</tr>
<tr>
<td>Miras et al 2015</td>
<td>95</td>
<td>Prospective case-controlled cohort study; 70 patients with T2DM undergoing surgery vs. 25 medically treated</td>
<td>Urine ACR decreased significantly in the surgical group but increased in the medical group. There were no significant differences between the surgical and medical groups in terms of retinopathy</td>
</tr>
<tr>
<td>Adam et al 2017</td>
<td>26</td>
<td>Prospective observational cohort study using detailed microvascular disease parameter phenotyping</td>
<td>Bariatric surgery resulted in improvements in CNFD, CNBD and CNFL and glomerular hyperfiltration (eGFRcyst-creat) in obese people with T2DM. CNFL improvements associated with reduced triglycerides whilst hyperfiltration with systolic blood pressure and %EBMIL. There was no change in retinopathy or uACR at 12 months in this study with a small sample size</td>
</tr>
<tr>
<td>Reynolds et al 2023</td>
<td>127</td>
<td>Prospective cohort study; 79 patients completed follow-up and number in meta-analysis</td>
<td>After bariatric surgery, INENFD improved (proximal thigh, +3.4 ± 7.8, p&lt;0.01). CAN (E/I) ratio -0.01 ± 0.1, p=0.89) and retinopathy (deviation −0.2 ± 3.0, p=0.52) were stable</td>
</tr>
<tr>
<td>Merlotti et al 2017</td>
<td>2,966 (total number in meta-analysis)</td>
<td>Meta-analysis of seven studies assessing diabetic retinopathy</td>
<td>Incident cases of retinopathy were fewer with bariatric surgery than with medical treatment; change of retinopathy score (three studies) was not different, while only two studies (limited number met inclusion) showing progression or regression of retinopathy</td>
</tr>
<tr>
<td>Li et al 2016</td>
<td></td>
<td>Different renal microvascular parameters leading to differential numbers per cohort of outcome</td>
<td>Statistically significant reduction in hyperfiltration, albuminuria and proteinuria after bariatric surgery</td>
</tr>
<tr>
<td>Scheurlen et al 2019</td>
<td>876 patients (15 studies)</td>
<td>Systematic review and meta-analysis assessing renal outcomes</td>
<td>Weight loss and glycaemia-independent improvements in DKD (uACR or albuminuria) following bariatric surgery</td>
</tr>
<tr>
<td>Friedman et al 2018</td>
<td>2,144</td>
<td>Prospective multi-centre observational cohort study following patients up for up to 7 years after bariatric surgery</td>
<td>Improvement in CKD risk was seen after bariatric surgery including up to 7 years post-operatively. Most improvement in those with higher baseline risk; &lt;10% of patients had increase in CKD risk after bariatric surgery</td>
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</table>

Table 2 summarises microvascular (neuropathy, retinopathy and nephropathy) measures and outcomes in selected studies after bariatric surgery. T2DM, type 2 diabetes mellitus; HR, hazard ratio; CI, confidence interval; SOS, Swedish Obese Subjects Study; ACR, albumin:creatinine ratio; CNFD, corneal nerve fibre density; CNBD, corneal nerve branch density; CNFL, corneal nerve fibre length; eGFRcyst-creat, estimated glomerular filtration rate calculated using both creatinine and cystatin C; INENFD, intra-epidermal nerve fibre density; CAN, cardiovascular autonomic neuropathy; E/I, expiration/inspiration; uACR, urinary albumin:creatinine ratio; DKD, diabetic kidney disease; CKD, chronic kidney disease.

Intraepidermal nerve fibre density of the thigh, like our study, it showed reversal of neuropathic markers. The study also found subjective improvement in established neuropathy-related patient-reported outcome measures. The improvements in neuropathy markers were greater than in a matched cohort who underwent non-surgical weight management and, notably, the average amount of weight loss in the surgical cohort was 2.5 times greater. The authors also demonstrated stability in retinopathy although they did show a worsening of estimated glomerular filtration rate (eGFR) (from 98 to 94.6 ml/min per 1.73 m²). Subsequently, after bariatric surgery, there were improvements in corneal markers CNFD, CNBD and CNFL, in parallel with clinical improvement based on NSP. Similar to patients with diabetes, there was an association with improvement in corneal nerve morphology and reduction in serum triglycerides.

**Impact of bariatric surgery on nephropathy**

Several studies have demonstrated significant improvements in renal measures following bariatric surgery. Renal risk factor measures such as hyperfiltration exhibit a risk ratio and risk reduction of almost half, while albuminuria and proteinuria are both reduced to less than half and less than a third, respectively. Longitudinal studies, including the SOS study with a 10-year follow-up and the Longitudinal Assessment of Bariatric Surgery 2 study with a 7-year follow-up, have reported a much lower risk of progression to stage 4 and 5...
CKD and eGFR improvement (associated with weight loss) after bariatric surgery, with a number needed to treat of 4.3,34,41 In further support of the benefit of bariatric surgery on renal outcomes, we recently reviewed the findings of 26 studies: there were improvements in renal parameters in 25 of the 26 studies.1 Li et al also reported improvements in glomerular hyperfiltration (RR 0.46), albuminuria (RR 0.42) and proteinuria (RR 0.31) in a pooled meta-analysis of 30 studies.32 The potential mechanisms leading to improvement in renal parameters after bariatric surgery on nephropathy were elegantly reviewed by Docherty and Le Roux,41 who postulated that improvements in visceral fat mass, adipose tissue function, incretin effects, hyperinsulinaemia, insulin resistance, dyslipidaemia leptin levels and renin-angiotensin activity all contributed to the observed improvements in renal function.

Impact of bariatric surgery on retinopathy
In contrast with nephropathy and nephropathy, improvements in retinopathy after bariatric surgery are less convincing. Evidence from 11 studies suggests that the net effect of bariatric surgery is stability, with a possible tendency towards progression in those with advanced retinopathy.139 Similar to the established observation in pregnancy, a rapid reduction in hyperglycaemia can worsen pre-existing diabetic retinopathy, and patients need to be counselled and screened closely for that possibility.40

Conclusion
Obesity is an independent risk factor for diabetic and non-diabetic microvascular disease, particularly for nephropathy and neuropathy. The evidence pertaining to medical weight management is limited due to sparse longitudinal outcomes. In contrast, bariatric surgery has demonstrated consistent improvements and reductions in incidence of both nephropathy and neuropathy, in people with and without diabetes. Although multimodal metabolic risk factor reduction is key, weight loss is likely to contribute to positive outcomes.

Conflict of interest
The authors have no conflicts of interest to declare in relation to this work.

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References
Diabetes and microvascular disease: the impact of weight loss. Farid S et al


