Diabesity and microvascular disease: the impact of weight loss

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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.

Br J Diabetes 2024;24(1):6-12
https://doi.org/10.15277/bjd.2024.438

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.[1] 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.

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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.[2] 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.[2] 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

Study	Total no. of participants	Study design	Key results
Neuropathy			
Callaghan *et al* [2] 2018	4,002	Cross-sectional population-based study	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)
Callaghan *et al* [3] 2016	155	Cross-sectional observational study Obese (n = 102) vs. lean (n = 53)	Prevalence of neuropathy was 3.8% in lean controls vs. 11.1% in non-diabetic obese participants ($p \leq 0.01$). Waist circumference was associated with neuropathy (OR 1.24 [95% CI 1.00–1.55])
Hanewinckel *et al* [4] 2016	1,256	Prospective population-based cohort study	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 3.38]), 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
Azmi *et al* [5] 2021	46	Prospective comparative study. Twenty-six obese people without diabetes compared to 20 controls	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
Retinopathy			
Zhang *et al* [6] 2001	319	Retrospective analysis of DCCT primary prevention cohort, 153 participants with $HbA_{1c} \leq 6.89\%$ compared against 166 participants with $HbA_{1c} \geq 9.49\%$.	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 HbA_{1c} and longer duration of participation in the study
Henricsson *et al* [7] 2003	627	Prospective observational study of people between 15-34 years of age with incident diabetes mellitus	High BMI and HbA_{1c} 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
Chao *et al* [8] 2007	4,344	Population-based cross-sectional study	Presence of retinopathy in patients without diabetes was independently associated with BMI >30 kg/m^2 (OR 1.3 [95% CI 1.0–1.7])
Gray *et al* [9] 2015	14,657	Retrospective study using data from Medicare Current Beneficiary Service and Medicare claims	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
Van Leiden *et al* [10] 2002	626	Retrospective population-based study	BMI >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
Dirani *et al* [11] 2011	492	Prospective observational study	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 = 0.013)
Nephropathy			
Ejerblad *et al* [12] 2006	1,924	Population-based case control study of 926 patients with chronic renal failure and 998 controls	Overweight (BMI $\geq$25 kg/m^2) at age 20 was associated with a significant three-fold excess risk for CRF, relative to BMI <25. Obesity (BMI $\geq$30) among men and severe obesity (BMI $\geq$35) among women anytime during lifetime was linked to three- to four-fold increases in risk
Peters *et al* [13] 2009	738	Cohort study (148 obese people compared against 589 non-obese controls)	Examination of the relation between age and GFR failed to reveal any adverse effect of obesity on age-related decline in renal function
Iseki *et al* [14] 2004	100,753	Cross-sectional observational study from a registry of patients in Okinawa, Japan	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
Gelber *et al* [15] 2005	11,104	Prospective observational study	Overweight and obesity (BMI > 26.6 kg/m^2) associated with higher odds of CKD (eGFR < 60 mL/min); OR 1.45 [95% CI 1.19–1.76], p<0.001. Increased CKD risk with BMI change > 10%
Vivante *et al* [19] 2012	1,194,704	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	Obesity increased the risk of diabetic and non-diabetic ESRD (HR 19.37 [95% CI 14.13–26.55] 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)
Hsu *et al* [20] 2009	177,550	Population-based study from integrated healthcare delivery system in the US; 842 cases of ESRD	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
Munkhaugen *et al* [21] 2009	74,986	Retrospective observational study	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 > 30 and >35 kg/m^2 (HR 2.66 [95% CI 1.28–5.53] and HR 5.94 [95% CI 1.94–18.20], respectively
Chandie Shaw *et al* [22] 2007	205	Cross-sectional observational study in persons without diabetes	Central adiposity (increased WHR) increased risk of developing microalbuminuria and macroalbuminuria
Kramer *et al* [23] 2005	5,897	Cross-sectional observational study	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

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; HbA_{1c}, glycated haemoglobin; RR, 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.[3] 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.[4] The association with peripheral neuropathy was stronger with more components of metabolic syndrome.[4] 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.[5]

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.[6-11] 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).[6] The study found that despite good glycaemic control, with glycated haemoglobin A1c (HbA_{1c}) of <53 mmol/mol (7%), 10% of participants developed diabetic retinopathy. In contrast, in patients with an HbA_{1c} >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.[6] 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.[7]

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/m^2) and an increased prevalence of retinopathy in a cross-sectional analysis of people without diabetes.[8] 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.[9] The Hoorn study also found a positive trend between diabetic retinopathy and increasing BMI in patients both with and without known diabetes].[10] Additionally, Dirani *et al* demonstrated that a BMI >30 kg/m^2 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.[11] 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,[12] while others suggest otherwise.[13] However, a substantial body of evidence supports the notion that obesity is associated with worse renal outcomes, including end-stage renal disease (ESRD),[14] chronic kidney disease (CKD),[15] renal stones,[16] renal cancer,[17] and post-transplant graft rejection.[18]

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 three and seven times more likely, respectively, to develop all-cause ESRD compared to those with normal BMI in patients with and without diabetes.[19] Moreover, the risk of diabetic ESRD was 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.[20] 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/m^2). However, the risk of ESRD doubled with a BMI above 30 kg/m^2 and increased six-fold with a BMI above 35 kg/m^2.[21] 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/m^2, 12.1% in BMI 25–30 kg/m^2 and 27.2% in BMI >30 kg/m^2). Similar results were noted in normoglycaemic individuals of South Asian descent, where adiposity was an independent predictor of albuminuria.[22]

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.[15,23] 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.

The impact of weight loss

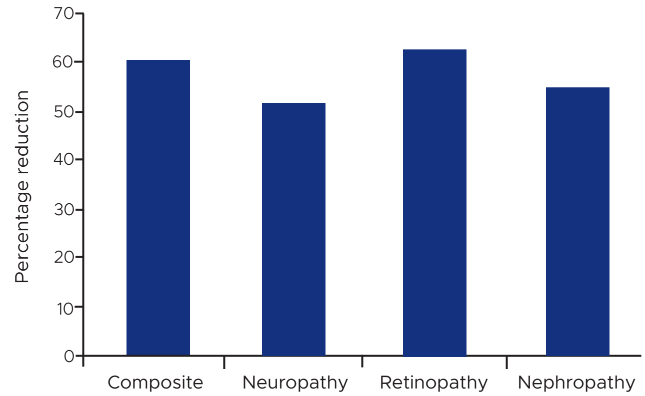
When considering the demonstrated relationship between obesity and microvascular disease, it is plausible that weight reduction might have favourable effects. Many studies analysing associations between microvascular disease and weight loss have been short term, and it is therefore difficult to assess 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 pharmacologically-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.

Figure 1. Reduction in incidence of microvascular disease following bariatric surgery



Derived from data published in O'Brien *et al*. [34]

Compared to a control cohort, patients who underwent bariatric surgery had a marked reduction in the incidence of microvascular disease. Composite measure indicates overall summation of all microvascular complications. There were more than 50% reductions in the incidence of all microvascular disease markers.

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

Study	Total no. of participants	Study design	Key results
Coleman *et al* [33] 2016	4,683	Retrospective observational cohort study in patients with diabetes	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])
O'Brien [34] 2018	15,083	Retrospective matched cohort study; 4,024 surgical cohort vs 11,059 non-surgical.	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])
Carlsson *et al* [35] 2015	3,108	Prospective multi-centre case-controlled cohort study; 1,498 surgical patients vs 1,610 controls	SOS study cohort. Bariatric surgery was associated with reduced incidence of albuminuria compared with usual obesity care (adjusted HR 0.37; p<0.001)
Miras *et al* [36] 2015	95	Prospective case-controlled cohort study; 70 patients with T2DM undergoing surgery vs. 25 medically treated	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
Adam *et al* [37] 2021	26	Prospective observational cohort study using detailed microvascular disease parameter phenotyping	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
Reynolds *et al* [38] 2023	127	Prospective cohort study; 79 patients completed follow-up	After bariatric surgery, IENFD improved (proximal thigh, +3.4 ± 7.8, p<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
Merlotti *et al* [39] 2017	2,966 (total number in meta-analysis)	Meta-analysis of seven studies assessing diabetic retinopathy	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
Li *et al* [42] 2016	Different renal microvascular parameters leading to differential numbers per cohort of outcome	Systematic review and meta-analysis assessing renal outcomes	Statistically significant reduction in hyperfiltration, albuminuria and proteinuria after bariatric surgery
Scheurlen *et al* [43] 2019	876 patients (15 studies)	Systematic review and meta-analysis	Weight loss and glycaemia-independent improvements in DKD (uACR or albuminuria) following bariatric surgery
Friedman *et al* [44] 2018	2,144	Prospective multi-centre observational cohort study following patients up for up to 7 years after bariatric surgery	Improvement in CKD risk was seen after bariatric surgery including up to 7 years post-operatively. Most improvement in those with higher baseline risk; <10% of patients had increase in CKD risk after bariatric surgery

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; IENFD, 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;[38] 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 m^2).[39,40]

In patients without diabetes mellitus we previously demonstrated that, compared to a control cohort, patients with obesity had impairment of a range of clinical and corneal nerve morphological markers of peripheral neuropathy, including non-structural proteins (NSP), vibration perception threshold (VPT), warm temperature perception (WPT), deep breathing heart rate variability (DB-HRV), peroneal and sural nerve amplitudes, corneal nerve fibre density (CNFD), corneal nerve branch density (CNBD) and corneal nerve fibre length (CNFL). 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.[41-43] 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

Key message

- Obesity is an independent risk factor for microvascular disease
- Weight loss interventions are key in preventing microvascular complications, especially in people with diabetes mellitus
- Weight loss interventions can also help delay progression of or reverse early microvascular complications of diabetes mellitus

CKD and eGFR improvement (associated with weight loss) after bariatric surgery, with a number needed to treat of 4.[35,44] 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.[42] 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 neuropathy and nephropathy, improvements in retinopathy after bariatric surgery are less encouraging. 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.[1,39] 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.
Funding None

References

1. Bashir B, Iqbal Z, Adam S, *et al.* Microvascular complications of diabetes and obesity – role of bariatric surgery. *Obes Rev* 2023; **24**(10) :e13602. Epub ahead of print. https://doi.org/10.1111/obr.13602
2. Callaghan BC, Gao L, Li Y, *et al*. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. *Ann Clinical Translational Neurology* 2018;**5**(4): 397-405. https://doi.org/10.1002/acn3.531
3. Callaghan BC, Xia R, Reynolds E, *et al*. Association between metabolic syndrome components and polyneuropathy in an obese population. *JAMA Neurol* 2016;**73**(12):1468-76. https://doi.org/10.1001/jamaneurol.2016.3745
4. Hanewinckel R, Drenthen J, Ligthart S, *et al.* Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: a prospective population-based cohort study. *J Neurol Neurosurg Psychiatry* 2016;**87**(12):1336–42. https://doi.org/10.1136/jnnp-2016-314171
5. Azmi S, Ferdousi M, Liu Y, *et al*. Bariatric surgery leads to an improvement in small nerve fibre damage in subjects with obesity. *Int Journal Obesity Lond* 2021;**45**(3):631-8. https://doi.org/10.1038/s41366-020-00727-96.
6. Zhang L, Krzentowski G, Albert A, *et al*. Risk of developing retinopathy in Diabetes Control and Complications Trial type 1 diabetic patients with good or poor metabolic control. *Diabetes Care* 2001;**24**(7):1275-9. https://doi.org/10.2337/diacare.24.7.1275
7. Henricsson M, Nyström L, Blohmé G, *et al*. The incidence of retinopathy 10 years after diagnosis in young adult people with diabetes: results from the nationwide population-based Diabetes Incidence Study in Sweden. *Diabetes Care* 2003;**26**(2):349-54. https://doi.org/10.2337/diacare.26.2.349
8. Chao JR, Lai MY, Azen SP, *et al*. Retinopathy in persons without diabetes: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci* 2007;**48**(9):4019-25. https://doi.org/10.1167/iovs.07-0206
9. Gray N, Picone G, Sloan F, *et al.* The relationship between BMI and onset of diabetes mellitus and its complications. *South Med J* 2015; **108**(1):29-36. https://doi.org/10.14423/SMJ000000000000214
10. van Leiden HA, Dekker JM, Moll AC, *et al.* Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn Study. *Diabetes Care* 2002;**25**(8):1320-5. https://doi.org/10.2337/diacare.25.8.1320
11. Dirani M, Xie J, Fenwick E, *et al*. Are obesity and anthropometry risk factors for diabetic retinopathy? The Diabetes Management Project. *Invest Ophthalmol Vis Sci* 2011;**52**(7):4416-21. https://doi.org/10.1167/iovs.11-7208
12. Ejerblad E, Fored CM, Lindblad P, *et al*. Obesity and risk for chronic renal failure. *J Am Soc Nephrol* 2006;**17**(6):1695-702. https://doi.org/10.1681/ASN.2005060638
13. Peters AM, Ciapryna MB, Bowles PF, *et al*. Obesity does not accelerate the decline in glomerular filtration rate associated with advancing age. *Int J Obesity (Lond)* 2009;**33**(3):379–81. https://doi.org/10.1038/ijo.2009.6
14. Iseki K, Ikemiya Y, Kinjo K, *et al*. Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Internat* 2004;**65**(5):1870–6. https://doi.org/10.1111/j.1523-1755.2004.00582.x
15. Gelber RP, Kurth T, Kausz AT, *et al*. Association between body mass index and CKD in apparently healthy men. *Am Journal Kidney Diseases* 2005;**46**(5):871–80. https://doi.org/10.1053/j.ajkd.2005.08.015
16. Taylor EN, Stampfer MJ, Curhan GC. Obesity, weight gain, and the risk of kidney stones. *JAMA* 2005;**293**(4):455–62. https://doi.org/10.1001/jama.293.4.455
17. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncology* 2005l;**23**(21):4742–54. https://doi.org/10.1200/JCO.2005.11.726

18. van Dijk BA, Schouten LJ, Kiemeney LA, *et al*. Relation of height, body mass, energy intake, and physical activity to risk of renal cell carcinoma: results from the Netherlands Cohort Study. *Am J Epidemiol* 2004; **160**(12): 1159-67. https://doi.org/10.1093/aje/kwh344
19. Vivante A, Golan E, Tzur D, *et al*. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. *Arch Int Med* 2012; **172**(21):1644–50. https://doi.org/10.1001/2013.jamainternmed.85
20. Hsu CY, Iribarren C, McCulloch CE, *et al*. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Int Med* 2009;**169**(4):342–50. https://doi.org/10.1001/archinternmed.2008.605
21. Munkhaugen J, Lydersen S, Widerøe TE, *et al*. Prehypertension, obesity, and risk of kidney disease: 20-year follow-up of the HUNT I study in Norway. *Am J Kidney Dis* 2009;**54**(4):638–46. https://doi.org/10.1053/j.ajkd.2009.03.023
22. Chandie Shaw PK, Berger SP, Mallat M, *et al*. Central obesity is an independent risk factor for albuminuria in nondiabetic South Asian subjects. *Diabetes Care* 2007;**30**(7):1840–4. https://doi.org/10.2337/dc07-0028
23. Kramer H, Luke A, Bidani A, *et al*. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. *Am J Kidney Diseases* 2005;**46**(4):587-94. https://doi.org/10.1053/j.ajkd.2005.06.007
24. Polemiti E, Baudry J, Kuxhaus O, *et al*. BMI and BMI change following incident type 2 diabetes and risk of microvascular and macrovascular complications: the EPIC-Potsdam study. *Diabetology* 2021;**64**(4):814-25. https://doi.org/10.1007/s00125-020-05362-7
25. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **380**(24): 2295-2306. https://doi.org/10.1056/NEJMoa1811744
26. Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al*. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**(15): 1436-46. https://doi.org/10.1056/NEJMoa2024816
27. Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2016; **374**(11):1094. https://doi.org/10.1056/NEJMc1600827
28. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**(7):644-57. https://doi.org/10.1056/NEJMoa1611925
29. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**(4):347-57. https://doi.org/10.1056/NEJMoa1812389
30. Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375**(19):1834-44. https://doi.org/10.1056/NEJMoa1607141
31. Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; **375**(4):311-22. https://doi.org/10.1056/NEJMoa1603827
32. Bosch C, Carriazo S, Soler MJ, *et al*. Tirzepatide and prevention of chronic kidney disease. *Clin Kidney J* 2022;**16**(5):797–808. https://doi.org/10.1093/ckj/sfac274
33. Coleman KJ, Haneuse S, Johnson E, *et al*. Long-term microvascular disease outcomes in patients with type 2 diabetes after bariatric surgery: evidence for the legacy effect of surgery. *Diabetes Care* 2016;**39**(8):1400-07. https://doi.org/10.2337/dc16-0194
34. O'Brien R, Johnson E, Haneuse S, *et al*. Microvascular outcomes in patients with diabetes after bariatric surgery versus usual care: a matched cohort study. *Ann Intern Med* 2018;**169**(5):300-10. https://doi.org/10.7326/M17-2823
35. Carlsson LM, Romeo S, Jacobson P, *et al*. The incidence of albuminuria after bariatric surgery and usual care in Swedish Obese Subjects (SOS): a prospective controlled intervention trial. *Int J Obes* 2015;**39**(1):169–75. https://doi.org/10.1038/ijo.2014.72
36. Miras AD, Chuah LL, Khalil N, *et al*. Type 2 diabetes mellitus and microvascular complications 1 year after Roux-en-Y gastric bypass: a case-control study. *Diabetologia* 2015;**58**(7):1443-7. https://doi.org/10.1007/s00125-015-3595-7
37. Adam S, Azmi S, Ho JH, *et al*. Improvements in diabetic neuropathy and nephropathy after bariatric surgery: a prospective cohort study. *Obesity Surgery* 2021;**31**(2):554-63. https://doi.org/10.1007/s11695-020-05052-8
38. Reynolds EL, Watanabe M, Banerjee M, *et al*. The effect of surgical weight loss on diabetes complications in individuals with class II/III obesity. *Diabetologia* 2023;**66**(7):1192-1207. https://doi.org/10.1007/s00125-023-05899-3
39. Merlotti C, Ceriani V, Morabito A, *et al*. Bariatric surgery and diabetic retinopathy: a systematic review and meta-analysis of controlled clinical studies. *Obes Rev* 2017;**18**(3):309–16. https://doi.org/10.1111/obr.12490
40. Adam S, Ho JH, Syed AA, *et al*. Response to letter to the Editor concerning: Adam S *et al*. Improvements in diabetic neuropathy and nephropathy after bariatric surgery: a prospective cohort study. *Obesity Surgery* 2022;**32**(10):3460-2. https://doi.org/10.1007/s11695-021-05818-8
41. Docherty NG, le Roux CW. Bariatric surgery for the treatment of chronic kidney disease in obesity and type 2 diabetes mellitus. *Nature reviews Nephrology* 2020;**16**(12):709-20. https://doi.org/10.1038/s41581-020-0323-4
42. Li K, Zou J, Ye Z, *et al*. Effects of bariatric surgery on renal function in obese patients: a systematic review and meta analysis. *PLoS One* 2016;**11**(10):e0163907 https://doi.org/10.1371/journal.pone.0163907
43. Scheurlen KM, Probst P, Kopf S, *et al*. Metabolic surgery improves renal injury independent of weight loss: a meta-analysis. *Surgery Obesity Related Dis* 2019;**15**(6):1006-20. https://doi.org/10.1016/j.soard.2019.03.013
44. Friedman AN, Wahed AS, Wang J, *et al*. Effect of bariatric surgery on CKD risk. *J Am Soc Nephrol* 2018;**29**(4):1289-300. https://doi.org/10.1681/ASN-2017060707