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Impact of intentional weight loss on diabetic kidney disease

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Abstract

Type 2 diabetes mellitus (T2DM) and obesity constitute interwoven pandemics challenging healthcare systems in developed countries, where diabetic kidney disease (DKD) is the most common cause of end-stage renal disease. Obesity accelerates renal functional decline in people with T2DM. Intentional weight loss (IWL) strategies in this population hold promise as a means of arresting DKD progression. In the present paper, we summarize the impact of IWL strategies (stratified by lifestyle intervention, medications, and metabolic surgery) on renal outcomes in obese people with DKD. We reviewed the Medline, EMBASE and Cochrane databases for relevant randomized control trials and observational studies published between August 1, 2018 and April 15, 2019. We found that IWL improves renal outcomes in the setting of DKD and obesity. Rate of progression of DKD slows with IWL, but varying outcome measures among studies makes direct comparison difficult. Furthermore, established means of estimating renal function are imperfect owing to loss of lean muscle mass with IWL strategies. The choice of optimal IWL strategy needs to be individualized; future work should establish the comparative efficacy of IWL strategies in obese people with DKD to better inform such decisions.

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Author Contributions

All authors contributed to the conception of the manuscript title and content. J. A. H. and W. P. M. the manuscript. N. G. D. and C. W. leR. critically reviewed the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Conflict Of Interest

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Keywords

albuminuria; bariatric surgery; biomarkers; diabetic kidney disease; obesity; type 2 diabetes mellitus; weight loss

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1 Introduction

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease in developed countries and significantly elevates cardiovascular disease risk. At least 40% of individuals with type 2 diabetes mellitus (T2DM) complicated by obesity develop DKD, and 30% of those progress to end-stage renal disease. Current best medical therapy for DKD emphasizes intensive glycaemic and blood pressure control as well as renin-angiotensin-aldosterone system (RAAS) blockade, slowing the rate of renal functional decline rather than reversing it.[1]

Although advances in the treatment of DKD have been made over the past decade, most notably the identification of renoprotective properties of sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor analogues (GLP-1RAs), challenges persist for obese people. Amongst individuals with adult-onset diabetes, those with severe insulin-resistant diabetes characterized by insulin resistance and high body mass index have a higher risk of DKD (hazard ratio 2.89) and end-stage renal disease (hazard ratio 4.89) compared with those with mild age-related diabetes, despite similar glycaemic control.[2] This provides a rationale to pursue novel approaches to the treatment of DKD, particularly to address hyper-insulinaemia and to augment treatment response through intentional weight loss (IWL).

2 Methods

We searched the Medline, EMBASE and Cochrane databases for publications in the period between August 1, 2018 and April 15, 2019. We included randomized controlled trials (RCTs) and observational studies reporting on renal variables (estimated glomerular filtration rate [eGFR], albuminuria, urinary albumin to creatinine ratio [UACR], serum creatinine, or a composite renal outcome) amongst obese individuals with T2DM undergoing an IWL intervention. IWL interventions were stratified as lifestyle (dietary/exercise counselling), medication, or metabolic surgery.

A total of 12 studies (seven RCTs, five observational studies) were included based on the following “PICO” (Population, Intervention, Control, Outcome) framework: Population: adults aged ≥18 years, with a clinically assigned diagnosis of T2DM and DKD; Intervention: IWL in the form of dietary and lifestyle intervention, pharmacotherapy or metabolic surgery; Control: adults with T2DM and DKD not exposed to IWL interventions; and Outcomes: markers of renal function in T2DM and DKD, as well as emerging adverse events associated with weight loss interventions.

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3 Results

3.1 Lifestyle intervention

The Look-AHEAD RCT compared intensive lifestyle intervention (ILI), consisting of diet and exercise plans, with diabetes support and education (DSE) in people with obesity and T2DM. Greater weight loss was achieved in the ILI arm (mean one-year weight loss of 8.6% in the ILI arm vs 0.7% in the DSE arm).Very-high-risk chronic kidney disease (CKD) occurred less frequently in those assigned to the ILI arm: 0.63%, versus 0.91% in the DSE arm.[3]

Two observational studies examined the role of dietary intervention and renal outcomes in people with CKD. Friedman et al[4] established six people with obesity, T2DM, eGFR <30 mL/min/1.73m^2 or albuminuria >30 mg/d on an 800 kcal/d ketogenic very-low-calorie diet for 3 months. A median weight loss of 14 kg was observed over 12 weeks. Serum creatinine declined by 12%, with cystatin C trending in the same direction; however, albuminuria did not change significantly.[4] A Japanese research group used a low-calorie formula diet (25–30 kcal/kg and 0.8 g/kg protein for at least 3 months). A mean weight loss of 6 kg was achieved at 4 weeks, with serum creatinine decreasing from 172.4 ± 57.5 to 130.8 ± 46.9 μmol/L at 4 weeks over the same timeframe.[5]

3.2 Medical therapy

The SCALE Diabetes trial randomized 846 individuals with obesity and T2DM to once-daily liraglutide 3 mg, once-daily liraglutide1.8 mg, or once-daily placebo.[6] The percentage weight loss of baseline body weight at 56 weeks was 6%, 4.7% and 2% in the liraglutide 3 mg, liraglutide 1.8 mg, and placebo arms, respectively. Liraglutide 3 mg also had the greatest impact on albuminuria; UACR decreased by 18.4%, 10.8% and 2.3% in the liraglutide 3 mg arm, liraglutide 1.8 mg and placebo arms, respectively. [6] The LIRA-RENAL and LEADER RCTs also highlighted that liraglutide slowed the onset and progression of DKD.[7,8]

De Lucas et al[9] assessed the effect of liraglutide 1.8 mg (with or without other diabetes medications) on glycaemic control and renal function over 12 months in people with obesity and T2DM with CKD stage 3B.[9] The mean weight loss was 5.7 kg and glycated haemoglobin levels declined by 1.45%. eGFR increased by a mean of 6 mL/min/1.73 m^2 along with reductions in UACR.

The SGLT2 inhibitors reduce the rate of eGFR decline and the onset and persistence of albuminuria in people with T2DM independently of their impact on glycaemic control, blood pressure, and weight loss. The CREDENCE RCT assessed the impact of canagliflozin versus placebo in people with T2DM and CKD stages 2 and 3 established on a stable dose of an RAAS inhibitor.[10] The median UACR at baseline was 927 mg/g. Baseline body mass index in CREDENCE was 31.2 kg/m^2, with modest median weight loss of 1.2 kg achieved.[10] Enhanced natriuresis appears to be a mechanistic link between the renoprotective properties of SGLT2 inhibitors and GLP-1RAs; increased distal tubular sodium delivery activates tubuloglomerular feedback, which reduces glomerular hypertension and confers long-term renoprotection. Indeed, endogenous GLP-1 secretion

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and urinary sodium excretion increases after Roux-en-Y gastric bypass (RYGB) surgery and may also activate tubuloglomerular feedback in a similar fashion.

3.3 Metabolic surgery

Changes in albuminuria (UACR ≥3 mg/mmol) at 5-year follow-up have been reported by two RCTs of metabolic surgery.[11,12] Mingrone et al[11] randomized individuals to RYGB, biliopancreatic diversion with duodenal switch, or intensive medical therapy (IMT). In each of the study arms, 16%, 11% and 27% of individuals had albuminuria at baseline, respectively. At 5-year follow-up, 0% in the RYGB and biliopancreatic diversion with duodenal switch arms had albuminuria, while albuminuria persisted in 27% of the IMT arm.[11] Baseline rates of albuminuria were higher in STAMPEDE than in the RCT conducted by Mingrone et al (34%, 24% and 20% in the RYGB, vertical sleeve gastrectomy [VSG], and IMT arms, respectively).[12] Albuminuria decreased in the surgical arms at 5-year follow-up (19% in RYGB and 11% in VSG arms, respectively), while 22% of the IMT arm continued to experience albuminuria.[11] Thus, approximately 50% of people undergoing metabolic surgery benefitted from remission of albuminuria at 5-year follow-up.

The median percentage eGFR reductions in STAMPEDE at 5-year follow-up were 8%, 6% and 1% in the RYGB, VSG and IMT arms, respectively.[11] While these eGFR reductions may be partly explained by loss of lean muscle mass postoperatively, when considered with albuminuria reductions at 5-year follow-up in the surgical arms, decreased eGFR may represent remission of glomerular hyperfiltration after RYGB/VSG and subsequent long-term renoprotection.

A total of 2458 individuals were recruited to the observational Longitudinal Assessment of Bariatric Surgery (LABS-2) study,[13] of whom 71% underwent RYGB, 25% underwent laparoscopic-adjustable gastric banding, and 5% had other bariatric surgical procedures. At baseline 33% had diabetes and 9% had abnormal kidney function.[13] CKD risk category improved for the majority of participants up to 7 years postoperatively, particularly in those with baseline moderate and high CKD risk.[13]

The longitudinal Swedish Obese Subjects (SOS) trial compared bariatric surgery to usual care in 4047 individuals,[14] of whom 2037 received usual care and 2010 underwent metabolic surgery, including gastric banding, vertical banded gastroplasty or RYGB. All three types of surgery were associated with a lower incidence of albuminuria after 10 years compared with usual care, with RYGB surgery conferring the greatest reductions in albuminuria.[14] Risk of end-stage renal disease was lowered by ~70% over median 18-year follow-up in the SOS cohort.[14] Tables S1 and S2 summarize RCTs and observational studies of IWL interventions in people with obesity and T2DM, respectively.

4 Discussion

Lifestyle interventions improve renal outcomes in the short to medium term in people with obesity and T2DM, but lack evidence over longer durations. Recent additions to the T2DM medication algorithm, particularly GLP-1RAs and SGLT2 inhibitors, should slow the rate of progression of DKD and reduce associated cardiovascular morbidity once adopted

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into mainstream clinical practice. Despite this, DKD will remain a progressive disease for many, and strategies to arrest its progression entirely are urgently needed. Reduced risk of albuminuria and end-stage renal disease endorse metabolic surgery as an effective IWL intervention with long-term renoprotective benefits, although high-level RCT evidence investigating renal outcomes in people with obesity and T2DM undergoing metabolic surgery is currently lacking.

Obesity and diabetes are systemic diseases that cause simultaneous cardiac and renal end-organ damage to result in type V cardiorenal syndrome. Cardiovascular disease is the leading cause of death in patients with DKD. It is increasingly recognized that epigenetic changes induced by hyperglycaemia in cardiac and kidney cells may perpetuate ongoing functional loss in these organs, a finding in support of the “metabolic memory” effect whereby cardiac and renal end-organ damage accrues despite intensification of previously poor glycaemic control. Aberrant GLP-1 signalling plays an important role in renal and cardiac disease progression in diabetes, and enhanced GLP-1 signalling after RYGB surgery appears to be central to weight-loss-independent benefits in cardiac and renal function observed postoperatively. Indeed, Sardu et al examined outcomes in patients with diabetes and heart failure receiving cardiac resynchronization therapy and treated with conventional hypoglycaemic drugs versus those treated with GLP-1RAs, and found symptom burden (New York Heart Association class) and arrhythmia prevalence to be reduced among the latter.[15]

Inflammation accompanying obesity also contributes to cardiac and renal disease progression in people with DKD. Plasma soluble tumour necrosis factor receptor (sTNFR)1 and sTNFR2 levels predict risk of end-stage renal disease independently of conventional clinical variables in people with T2DM.[16] Levels of intrarenal inflammation, as manifested by urinary biomarkers, decline after metabolic surgery.[17] Sirtuin 6 (SIRT6) plays a key role in cardiac damage in the dysmetabolic climate engendered by obesity. A recent Italian study demonstrated the role of SIRT6 in the inflammatory pathway of subcutaneous abdominal fat in obese prediabetic individuals, and showed that its expression was regulated by metformin therapy.[18] Reductions in adipose tissue and systemic inflammation after metabolic surgery appear to confer beneficial cardiac and renal end-organ effects in people with diabetes. Three RCTs are underway to assess the potential renal benefits of metabolic surgery in those with obesity and T2DM and will help to better define the role of metabolic surgery in the DKD treatment algorithm: Prevention and Treatment of Diabetes Complications with Gastric Surgery or Intensive Medicines (PRODIGIES, NCT01974544),[19] Metabolic Outcomes after Microvascular Surgery (MOMS),[20] and IMPROVE-T2D.[21]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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