Published in final edited form as:
Surg Obes Relat Dis. 2019 June 01; 15(6): 1020–1023. doi:10.1016/j.soard.2019.04.001.

Comment on: Metabolic surgery improves renal injury independent of weight loss: a meta-analysis

William P. Martin[a], **Prof Carel W. le Roux**[a,b]

[a]Diabetes Complications Research Centre, Conway Institute, School of Medicine, University College Dublin, Ireland [b]Division of Investigative Science, Imperial College London, UK

Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease and significantly elevates cardiovascular disease risk [1]. Persons with DKD accounted for 45.4% and 38.2% of incident and prevalent cases of end-stage renal disease in the United States in 2015, respectively [2]. Current management of DKD focuses on control of hyperglycemia and hypertension along with renin-angiotensin-aldosterone system blockade to minimise proteinuria. The most notable recent advances in DKD care include sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 agonists which reduce glycosylated hemoglobin (A1C), blood pressure, body weight, cardiovascular mortality, and nephropathy progression [3]. Despite this, existing therapies for DKD slow the rate of renal functional decline rather than reversing it.

Excess visceral adiposity accentuates podocyte dysfunction and increases albuminuria in individuals with type 2 diabetes mellitus (T2D) [4]. In turn, excess leakage of albumin precipitates tubular injury, which further increases renal inflammation leading to progressive DKD [5]. This is particularly true for patients with obesity in whom only suboptimal weight loss can usually be achieved. A novel approach to DKD management is to augment treatment response through intentional weight loss. Metabolic surgery can halt the progression of and reverse pathological manifestations of rodent DKD [6]. Metabolic surgery reduced the incidence of albuminuria (urinary albumin excretion ≥30mg/24 hours) by 63% up to 15 years postoperatively and the incidence of end-stage renal disease by 73% over median 18-year follow-up in the Swedish Obesity Study (SOS) cohort [7, 8]. Insulin resistance predicts a higher risk of nephropathy progression in the setting of diabetes [9]; accordingly, individuals with hyperinsulinaemia and severely increased albuminuria derived the greatest renoprotective benefit from metabolic surgery in the SOS cohort [8]. Similarly, metabolic surgery improved eGFR and albuminuria at 7 years postoperatively in those with moderate, high, and very high baseline chronic kidney disease risk in the Longitudinal Assessment of Bariatric Surgery-2 study cohort [10]. The current systematic review and meta-analysis investigates the relationship between improvements in body-mass index (BMI), glycemic control, and systolic blood pressure with reductions in proteinuria after

Correspondence to: Carel W. le Roux.

*Corresponding author: Prof. Carel W. le Roux, Diabetes Complications Research Centre, Conway Institute, School of Medicine, University College Dublin, Ireland. carel.leroux@ucd.ie.

Europe PMC Funders Author Manuscripts

metabolic surgery, and therefore interrogates the relative importance of weight loss-dependent and –independent mechanisms to the anti-proteinuric effect of metabolic surgery.

The authors performed a systematic review and meta-analysis examining changes in albuminuria after metabolic surgery in persons with T2D, and their correlation with changes in A1C, BMI, and systolic blood pressure. Albuminuria was assessed using the urine albumin:creatinine ratio or 24-hour urine albumin excretion rate. The correlation between changes in A1C and BMI after metabolic surgery was also assessed. The authors identified 15 suitable studies of mixed study design (5 retrospective cohort studies, 8 prospective cohort studies, 1 prospective case-control study, and 1 randomised controlled trial). Thirteen of the fifteen studies were single-arm surgical intervention studies, while two included studies (1 prospective cases-control study and 1 randomised controlled trial) also had a medically treated control group. Ten, four, three, and two studies assessed the impact of Roux-en-Y gastric bypass surgery, sleeve gastrectomy, ileal interposition plus sleeve gastrectomy, and laparoscopic adjustable banding, respectively.

Mean age, BMI, and diabetes duration were 48.2±4.5 years, 41.4±7.0 kg/m^2, and 8.7±2.5 years in surgically treated patients, respectively. No difference in age, BMI, and diabetes duration was observed between surgically treated patients and the 2 medically treated control groups. Remission of T2D and albuminuria was achieved in 58.4% and 56.6% of individuals in included single-arm metabolic surgery intervention studies, respectively. Mean reductions in BMI, A1C, urine albumin:creatinine ratio, and 24-hour urine albumin excretion rate in surgically treated individuals were -10.2kg/m^2, -2.1%, -27.4mg/g, and -52.2mg/24hours, respectively. No relationship between change in urinary albumin excretion and changes in BMI, A1C, and systolic blood pressure after metabolic surgery were identified; similarly, no relationship between change in A1C and BMI was identified. Reductions in albuminuria after metabolic surgery thus appear to occur independently of improvements in body weight, glycemic control, and systolic blood pressure.

Albuminuria is an important determinant of DKD progression. However, in the current era of aggressive blood pressure control and widespread use of inhibitors of the renin-angiotensin-aldosterone system, non-albuminuric DKD is increasingly recognised [11]. Thus, remission of albuminuria may not necessarily reflect remission of DKD – there is no evidence to suggest that metabolic surgery results in remission of all of the renal manifestations of diabetes. Assessment of kidney function is important in this context; the absence of measured glomerular filtration rate is a limitation of the studies included in this meta-analysis.

Sexual dimorphism in relation to DKD outcomes is recognised, with hormone-dependent changes in the renin-angiotensin-aldosterone system and nitric oxide pathways posited as the main contributing factors [12]. Males with T2D are at higher risk of DKD onset and progression compared with females [13]. The inability to assess for gender interaction between changes in albuminuria, A1C, blood pressure, and BMI after bariatric surgery is therefore a limitation of the present study. Additionally, the 15 studies included were not enriched for individuals with DKD given the relatively young age and short diabetes duration of included individuals; this may have reduced the effect size and partly account for

the absence of a relationship between postoperative improvements in BMI, A1C, and systolic blood pressure with reductions in albuminuria. Equally, muscle mass decreases after metabolic surgery and urinary creatinine excretion decreases by approximately -14.3% at 1 year postoperatively [14]. Lower urinary creatinine excretion may artificially elevate the urine albumin:creatinine ratio, and thus postoperative changes in muscle mass may have biased the results of the current meta-analysis somewhat.

The findings of the present study are stimulating and provide a strong rationale to identify weight loss-independent mediators of proteinuria reduction after metabolic surgery in individuals with T2D. Mechanistic studies have elucidated that changes in leptin, adiponectin, and glucagon-like peptide-1 signalling, enhanced natriuresis, reduced systemic and intra-renal inflammation, gut microbiota shifts, and improved high-density lipoprotein functionality are central to cardiovascular and renal protection after metabolic surgery [15]. Identification of the interplay between these mechanisms and their impact on components of the glomerular filtration barrier, whose disruption leads to progressive proteinuria in DKD [16], could lead to the development of novel therapies which exploit an enhanced understanding of the cellular pathway responses of kidney cells to metabolic surgery.

Metabolic surgery has traditionally been investigated as a means of achieving remission of T2D in individuals with severe obesity (BMI ≥35 kg/m^2). However, the utility of metabolic surgery in decreasing the incidence and severity of microvascular complications of T2D, particularly DKD, is increasingly recognised [17]. The current findings suggest that preoperative body weight and the degree of postoperative weight loss are not the primary determinants of metabolic benefit and renoprotection after metabolic surgery, and support ongoing endeavours to define the role of metabolic surgery in the DKD treatment algorithm such as the Microvascular Outcomes after Metabolic Surgery (MOMS) trial in which individuals with T2D, modest obesity (BMI 30-34.9 kg/m^2), and albuminuria have been randomised to either Roux-en-Y gastric bypass surgery plus medical therapy or medical therapy alone [18].

It is imperative that diabetologists and nephrologists harness the potential efficacy of metabolic surgery to slow the progression of DKD. The current study provides compelling evidence that the renoprotective benefits of metabolic surgery are not simply due to improvements in conventional risk factors for DKD progression (BMI, glycemic and blood pressure control), and indeed distinct mechanisms must exist which independently exert anti-proteinuric effects after metabolic surgery [15]. As an example, enhanced glucagon-like peptide-1 signalling is observed after Roux-en-Y gastric bypass surgery while administration of liraglutide slows the progression of DKD [19]. Further elucidation of these mechanisms is central to the translation of metabolic surgery as a treatment for DKD, and to the development of medications which mimic aspects of the post-metabolic surgery milieu to slow the progression of DKD.

References

[1]. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. Journal of the American Society of Nephrology: JASN. 2013; 24:302–8. [PubMed: 23362314]

[2]. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2018; 71:A7. [PubMed: 29477157]

[3]. Cherney DZI, Bakris GL. Novel therapies for diabetic kidney disease. Kidney Int Suppl. 2018; 8:18–25.

[4]. Sharma K. The link between obesity and albuminuria: adiponectin and podocyte dysfunction. Kidney international. 2009; 76:145–8. [PubMed: 19404275]

[5]. Pagtalunan ME, Miller PL, Jumping-Eagle S, Nelson RG, Myers BD, Rennke HG, et al. Podocyte loss and progressive glomerular injury in type II diabetes. The Journal of clinical investigation. 1997; 99:342–8. [PubMed: 9006003]

[6]. Neff KJ, Elliott JA, Corteville C, Abegg K, Boza C, Lutz TA, et al. Effect of Roux-en-Y gastric bypass and diet-induced weight loss on diabetic kidney disease in the Zucker diabetic fatty rat. Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery. 2017; 13:21–7. [PubMed: 27665150]

[7]. Carlsson LM, Romeo S, Jacobson P, Burza MA, Maglio C, Sjoholm K, et al. The incidence of albuminuria after bariatric surgery and usual care in Swedish Obese Subjects (SOS): a prospective controlled intervention trial. International journal of obesity. 2015; 39:169–75. [PubMed: 24798033]

[8]. Shulman A, Peltonen M, Sjostrom CD, Andersson-Assarsson JC, Taube M, Sjoholm K, et al. Incidence of end-stage renal disease following bariatric surgery in the Swedish Obese Subjects Study. International journal of obesity. 2018; 42:964–73. [PubMed: 29568103]

[9]. Ahlqvist E, Storm P, Karajamaki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. The lancet Diabetes & endocrinology. 2018; 6:361–9. [PubMed: 29503172]

[10]. Friedman AN, Wahed AS, Wang J, Courcoulas AP, Dakin G, Hinojosa MW, et al. Effect of Bariatric Surgery on CKD Risk. Journal of the American Society of Nephrology: JASN. 2018; 29:1289–300. [PubMed: 29335242]

[11]. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease. Clinical Journal of the American Society of Nephrology. 2017; 12:2032. [PubMed: 28522654]

[12]. Clotet S, Riera M, Pascual J, Soler MJ. RAS and sex differences in diabetic nephropathy. American journal of physiology Renal physiology. 2016; 310:F945–f57. [PubMed: 26962103]

[13]. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Archives of internal medicine. 1998; 158:998–1004. [PubMed: 9588433]

[14]. Navarro-Diaz M, Serra A, Romero R, Bonet J, Bayes B, Homs M, et al. Effect of drastic weight loss after bariatric surgery on renal parameters in extremely obese patients: long-term follow-up. Journal of the American Society of Nephrology: JASN. 2006; 17:S213–7. [PubMed: 17130264]

[15]. Martin WP, Docherty NG, Le Roux CW. Impact of bariatric surgery on cardiovascular and renal complications of diabetes: a focus on clinical outcomes and putative mechanisms. Expert review of endocrinology & metabolism. 2018; 13:251–62. [PubMed: 30231777]

[16]. Fissell WH, Miner JH. What Is the Glomerular Ultrafiltration Barrier? Journal of the American Society of Nephrology. 2018; 29:2262. [PubMed: 30030419]

[17]. O'Brien R, Johnson E, Haneuse S, Coleman KJ, O'Connor PJ, Fisher DP, et al. Microvascular Outcomes in Patients With Diabetes After Bariatric Surgery Versus Usual Care: A Matched Cohort Study. Annals of internal medicine. 2018; 169:300–10. [PubMed: 30083761]

[18]. Cohen RV, Pereira TV, Aboud CM, Caravatto PPdP, Petry TBZ, Correa JLL, et al. Microvascular Outcomes after Metabolic Surgery (MOMS) in patients with type 2 diabetes mellitus and class I obesity: rationale and design for a randomised controlled trial. BMJ Open. 2017; 7

[19]. Mann JFE, Orsted DD, Brown-Frandsen K, Marso SP, Poulter NR, Rasmussen S, et al. Liraglutide and Renal Outcomes in Type 2 Diabetes. The New England journal of medicine. 2017; 377:839–48. [PubMed: 28854085]