Comment on: Impact of serum uric acid on renal function after bariatric surgery: a retrospective study

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Obesity is an independent risk factor for renal functional decline in people with chronic kidney disease and is highly prevalent amongst people with the leading cause of chronic kidney disease, diabetic kidney disease [1]. Intentional weight loss strategies hold promise as a means of arresting progressive renal functional decline in diabetic kidney disease [2]. Optimisation of renal outcomes after metabolic surgery centres on blood pressure and glycaemic control as well as addressing proteinuria. The role of uric acid-lowering in this setting is controversial. Purines (adenine, guanine) from nucleic acids (RNA, DNA) are metabolised to xanthine and hypoxanthine, and subsequently converted to uric acid by xanthine oxidase [3]. Uric acid is a nitrogenous waste product which is excreted via the urine. Epidemiologic studies highlight a relationship between hyperuricemia and renal functional decline, proteinuria, and cardiovascular disease [4]. Whether serum uric acid plays a causal role in chronic kidney disease progression or is simply a biomarker of kidney function remains a controversial question which is currently being addressed by placebo-controlled, randomised controlled studies such as the PERL study in which people with diabetic kidney disease and hyperuricemia are randomised to uric acid-lowering therapy or placebo [5]. The current study adds to the observational evidence implicating uric acid as a marker of adverse renal outcomes and, importantly, is the first study to examine this phenomenon in patients with and without baseline chronic kidney disease after metabolic surgery.

The authors performed a single-centre retrospective review to investigate the relationship between serum uric acid and renal parameters (creatinine and CKD-EPI$_{creatinine}$ eGFR) in n=252 Asian patients before and 12 months after metabolic surgery. Uric acid-lowering therapy was prescribed for symptomatic gout but not for asymptomatic hyperuricemia. Mean age and body-mass index (BMI) were 40.5 ± 11.2 years and 39.0 ± 5.5 kg/m^2, respectively, while 55.2% of the study cohort were female. Diabetes was present in 62 (24.6%) people at baseline. Renal function was normal (eGFR 90-124.9 mL/min/BSA) in 176 (69.8%) patients at baseline, while 76 (30.2%) individuals had impaired renal function (eGFR <90 mL/min/ BSA). Individuals with baseline eGFR 125 mL/min/BSA (indicative of glomerular

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hyperfiltration) and with end-stage renal disease were excluded. The majority of participants (n=233, 92.5%) underwent laparoscopic sleeve gastrectomy.

Significant improvements in metabolic parameters including BMI, glycaemic control, and lipid indices were observed at 12 months. Serum creatinine values increased in those with normal baseline kidney function (0.71 ± 0.12 vs. 0.75 ± 0.16 mg/dL, p=0.004) and remained stable (1.0 ± 0.4 vs. 1.0 ± 0.3 mg/dL, p=0.344) in those with impaired renal function despite significant reductions in BMI (>10 kg/m^2) in both subgroups. Prevalence of hyperuricemia (defined as serum uric acid >7.0 mg/dL) decreased from 40.4% at baseline to 22.2% at 12-month follow-up. Serum uric acid significantly decreased at 12 months in those with normal kidney function at baseline (6.6 ± 1.7 vs. 5.7 ± 1.5 mg/dL, p<0.001) but did not decrease in those with kidney disease (6.9 ± 1.7 vs. 6.6 ± 1.6 mg/dL, p=0.255). In those with impaired renal function, but not those with normal kidney function, serum uric acid negatively associated with eGFR at 12 months by Pearson correlation (r=-0.417, p=0.005). This relationship persisted after adjustment for age, gender, and surgery type as well as postoperative changes in glycaemia, plasma insulin, and BMI by multivariable regression. Plasma insulin also negatively associated with eGFR at 12 months in those with impaired kidney function by multivariable regression, consistent with emerging evidence on the damaging effects of persistent hyperinsulinemia on kidney function [6].

The absence of data on medication usage at baseline and follow-up in the study cohort is an important caveat, and may serve as a confounder in the different trajectories of serum uric acid observed after metabolic surgery. Metabolic surgery improves blood pressure control with requirement for fewer antihypertensive medications [7]. Metabolic surgery also reduced the incidence of albuminuria by 63% over median 10-year follow-up in the Swedish Obese Subjects study [8]. Blood pressure and proteinuria are important modifiable risk factors of chronic kidney disease progression which are effectively targeted through renin-angiotensin-aldosterone system (RAAS) inhibition in clinical practice [9].

Therefore, the absence of blood pressure and proteinuria data are notable limitations with respect to interpreting renal outcomes after metabolic surgery in the current study. While the authors have controlled for many determinants of renal outcomes, the potential for confounding remains; prospective studies examining relationships between serum uric acid and renal function trajectories should control for blood pressure, proteinuria, and medications including xanthine oxidase inhibitors. Additionally, serum creatinine-based estimates of kidney function are unreliable in the setting of significant loss of lean muscle mass after metabolic surgery. Reductions in baseline serum creatinine of 10.17% and 9.0% at 12- and 24-month follow-up after gastric bypass surgery were reported by Navarro-Diaz et al [10]. The absence of reductions in serum creatinine despite significant weight loss at 12 months in the current study is noteworthy, and could influence the observed relationships between serum uric acid and renal function trajectories. Prospective studies should use both serum creatinine and cystatin C to estimate kidney function after metabolic surgery to resolve such discrepancies, although measurement of glomerular filtration rate would be preferable [11].

The Swedish Obese Subjects study and the Longitudinal Assessment of Bariatric Surgery have highlighted that metabolic surgery reduces the incidence of proteinuria and chronic kidney disease progression over extended follow-up [12, 13]. The renoprotective effect of metabolic surgery is partly attributable to improvements in blood pressure and metabolic parameters. However, reductions in albuminuria after metabolic surgery occur independently of improvements in body weight, glycaemia, and blood pressure [14]. Weight loss-independent mediators of the renoprotective effects of metabolic surgery include changes in leptin, adiponectin, and glucagon-like peptide-1 signalling, enhanced natriuresis, and reduced systemic and intrarenal inflammation [2]. Further weight-independent renoprotective mechanisms of metabolic surgery are sought.

Angiotensin-II increases proximal tubular apical membrane Na^+-H^+ antiporter activity, which creates a pH gradient that promotes a parallel increase in uric acid$^-$-OH$^-$ exchange that drives proximal tubular uric acid reabsorption [15]. The current study raises the possibility that reduced RAAS activation after metabolic surgery reduces proximal tubular reabsorption of uric acid to reduce hyperuricemia and improve renal outcomes. Indeed, pooled estimates from 5 randomised controlled studies of uric acid-lowering therapy in patients with chronic kidney disease highlighted a mean difference in eGFR of 3.9 mL/min/BSA in favour of xanthine oxidase inhibitors suggesting that uric acid may play a primary pathogenic role in chronic kidney disease progression [16]. Increased uricosuria as a consequence of untreated hyperuricemia may induce a renal epithelial inflammatory response and ultimately cause uric acid nephrolithiasis which obstructs renal tubular flow [17]. Additionally, animal and human studies suggest that uric acid may cause glomerular hypertension by stimulating the proliferation of arteriolar vascular smooth muscle cells and disrupting glomerular hemodynamics [18, 19].

Nevertheless, without adequately powered, placebo-controlled studies, concrete causal inferences regarding the renoprotective benefits of uric-acid lowering therapy cannot be drawn. Uric acid is filtered by the glomerulus and subsequently handled entirely in the proximal tubule by 3 processes: reabsorption of filtered uric acid, tubular secretion of uric acid, and post-secretory reabsorption of secreted uric acid in the early, mid, and late proximal tubules, respectively [20]. The net effect is urinary excretion of 6-12% of the filtered uric acid load. Hyperuricemia complicating chronic kidney disease occurs at least partly due to a disruption of renal handling of uric acid. Therefore, uric acid may serve as a biomarker of kidney function rather than a pathogenic mediator of progressive renal functional decline.

Whether a primary pathogenic insult to the kidney or a marker of another injurious stimulus to the kidney (or both), persistent hyperuricemia after metabolic surgery in people with kidney disease appears to identify a subgroup of patients at higher risk for adverse renal outcomes. Hyperuricemia in this setting may reflect suboptimal treatment response and persistent angiotensin-II activity driving proximal tubular uric acid reabsorption. A prospective observational study of individuals with baseline chronic kidney disease and persistent post-metabolic surgery hyperuricemia with longer-term follow-up for renal and cardiovascular disease outcomes is warranted. Ultimately, however, the current study highlights the need for a placebo-controlled randomised controlled trial of uric-acid

lowering therapy in those with baseline chronic kidney disease and persistent asymptomatic hyperuricemia after metabolic surgery. Febuxostat (nonpurine xanthine oxidase inhibitor) and Allopurinol (purine base analogue xanthine oxidase inhibitor) are the mainstay of uric acid-lowering therapy in the outpatient setting. Compared with Allopurinol, Febuxostat has greater hypouricemic activity and requires less dosage adjustment in renal impairment [21]. However, in a recent randomised controlled trial of Allopurinol versus Febuxostat in patients with gout and cardiovascular disease (mean BMI 33.5 ± 7.0 kg/m^2, chronic kidney disease stages 1-3), Febuxostat increased all-cause and cardiovascular mortality [22].

Thus, questions persist regarding the pathogenic role of uric acid in chronic kidney disease and the optimal uric acid-lowering therapy in this setting. Nevertheless, ongoing elucidation of weight-independent renoprotective mechanisms of metabolic surgery and identification of strategies to optimise renal outcomes in the postoperative setting are needed to optimise the translation of metabolic surgery as a treatment for chronic kidney disease and to counter the increasing prevalence of obesity and diabetes-related renal diseases.

Acknowledgments

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