

Bariatric surgery as urate-lowering therapy in severe obesity

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Gout represents a metabolically driven inflammatory arthropathy, which could be substantially influenced by adiposity and lifestyle risk factors. As such, influenced by the trends in lifestyle factors associated with Westernisation,^{1,2} gout prevalence has increased in the last few decades worldwide (eg, 3.9% of US adults (8.3 million) in 2007–2008³).⁴ The disease burden of gout has been further complicated by a high level of cardiovascular (CV)–metabolic comorbidities (eg, hypertension in 74%; obesity in 53%⁵) and their sequelae (eg, increased future risk of myocardial infarction and premature death^{6,7}).

Among many known modifiable risk factors for hyperuricaemia and gout, obesity is one of the strongest, as observed in many prospective cohort studies.^{8–12} To date, few medical interventions, except bariatric surgery, have been effective in the treatment of obesity. Indeed, studies have shown that bariatric surgery not only induces substantial weight loss but also greatly improves key obesity-related CV–metabolic abnormalities and outcomes,^{13–15} including blood pressure, glucose, insulin, triglycerides, high-density lipoprotein (HDL)-cholesterol, serum uric acid (SUA) levels¹⁶ and overall mortality.¹⁷

In their timely study, Dalbeth *et al*¹⁸ sought to examine the potential pathogenetic and clinical relevance of the urate-lowering benefits of bariatric surgery. Over 1 year of prospective follow-up of 60 individuals with severe obesity (body mass index (BMI) ≥ 35 kg/m²) and type 2 diabetes, bariatric surgery led to a weight reduction of 34 kg, and proportions of those with SUA levels higher than the urate saturation point and the usual urate-lowering therapy (ULT) target (SUA=0.36 mmol/L)¹⁹ declined by 37% and 41%, respectively. Among the 12 gout patients included in this study, the proportion of SUA above 0.36 mmol/L declined from 83% (10/12) at baseline to 33% (4/12) 1 year after surgery; the corresponding

proportion of ULT use also declined from 75% (9/12) to 33% (4/12). Despite its relatively small sample size, these findings provide additional evidence for the urate-lowering benefits of bariatric surgery among obese diabetic patients, and also raise several conceptual and practical issues relevant to the topic.

CAN WEIGHT LOSS INDUCE A CLINICALLY MEANINGFUL URATE REDUCTION?

Despite some sceptical views on the relevant role of weight loss in the management of hyperuricaemia and gout, the study by Dalbeth *et al* provides evidence that considerable weight loss can reduce SUA levels in a pathogenetically and clinically meaningful way. This is consistent with the findings from previous studies.^{13, 15, 20–24} For example, in the Swedish Obese Subjects Study (total N=4047), bariatric surgery decreased SUA levels by 14% at 2 years (n=1845) and 8% at 10 years (n=641) compared with their control groups.¹³ Furthermore, bariatric surgery was associated with 78% and 51% lower odds of hyperuricaemia at 2 years and 10 years after the surgery, respectively.¹³ In a dietary intervention (as opposed to bariatric surgery) study by Dessein and colleagues, 13 *non-diabetic gout* patients (mean BMI=30.5 kg/m²) received a low-calorie diet over 16 weeks²⁴ and achieved a weight loss of 7.7 kg, a SUA reduction of 0.1 mmol/L (from 0.57 to 0.47 mmol/L), and even a reduction in the frequency of monthly gout attacks from 2.1 to 0.6 (p=0.002). Similarly, an analysis based on a lifestyle intervention trial showed that compared with no weight change, the odds of achieving SUA levels of 0.36 mmol/L for a weight loss of 1–4.9, 5–9.9 and ≥ 10 kg were 1.43, 2.17 and 3.90, respectively.²³ The corresponding ORs of achieving SUA levels of 0.42 mmol/L were 1.30, 1.86 and 3.66. Consistent findings were observed in a Japanese dietary intervention study.¹⁵

Dalbeth *et al*'s study was limited to those with diabetes. This is noteworthy because the impact of weight loss on SUA may vary by presence of diabetes, as diabetes and hyperglycaemia are associated with SUA levels lower than in non-diabetic individuals, likely due to the uricosuric effect of glycosuria.^{25–28} For example, a large prospective

cohort study (n=10 000) showed that, compared with normal individuals, the prevalence of hyperuricaemia was 63% lower in men with type 2 diabetes.²⁸ This finding can also explain the higher baseline SUA levels in the non-diabetic gout patients (0.57 mmol/L) of Dessein *et al*'s intervention study²⁴ compared with that seen in the diabetic gout patients (0.41 mmol/L) of Dalbeth *et al*'s study,¹⁸ despite the considerably higher baseline BMI levels in the latter (30.5 vs 48.5 kg/m²). Furthermore, the underlying mechanism could also explain the discrepancy in the impact of dietary intervention components of the two studies.^{18, 24} Regardless, as discussed above, among the 12 gout patients with diabetes, the bariatric surgery resulted in a SUA reduction of 0.08 mmol/L from the study baseline. This would mean that the large weight loss of 34.0 kg from bariatric surgery overcame the presumed loss of the uricosuric effects of glycosuria. Correspondingly, it was noteworthy that the level of SUA reduction associated with a weight loss of 34.0 kg by bariatric surgery among these diabetic patients¹⁸ was similar to (or possibly smaller than) that achieved by a weight reduction of 7.7 kg among non-diabetic patients.²⁴ Therefore, the SUA impact of this level of weight reduction could be substantially larger among those without diabetes.²⁴

POTENTIAL MECHANISMS UNDERLYING THE URATE-LOWERING EFFECTS

Weight loss is thought to decrease SUA levels primarily by increasing renal excretion of urate and in part by decreasing urate production.^{27, 29–31} For example, a previous intervention study found that fractional excretion of uric acid was substantially lower among obese individuals compared with normal controls at baseline (4–5% vs 11–12%, respectively).¹⁵ Furthermore, urinary urate excretions were also lower in obese subjects than in controls, suggesting that hyperuricaemia in obese individuals was primarily attributed to impaired renal clearance of uric acid. Importantly, weight loss intervention by diet and exercise resulted in the normalisation of fractional excretion of uric acid among these obese individuals.¹⁵ Although not addressed in the study by Dalbeth *et al*, this is likely through declining insulin resistance and insulin levels, which are associated with reduced renal urate excretion and hyperuricaemia.^{32–34} Notably, previous bariatric surgery studies have found a substantial decline in insulin levels and insulin resistance.^{16, 35}

Using linear regression models, Dalbeth *et al* included potential predictors,

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regardless of temporal ordering, and found that baseline SUA levels, diuretic cessation, glomerular filtration rate (GFR) improvement and sex independently predicted SUA change after bariatric surgery. While this approach might serve a predictive purpose, the causal mechanistic implications of these findings appear limited. This is because these variables represent different time points in causal pathways and thus their effect estimates for potential causal impacts are not directly comparable.³⁶ For example, sex and baseline SUA levels should not be mediators in the causal pathway between bariatric surgery and SUA reduction as these variables occur temporally preceding bariatric surgery, whereas the obvious decline in the use of thiazide (from 43% to 7%) is a likely consequence of bariatric surgery, and its effect represents part of the impact of bariatric surgery on SUA levels. Furthermore, the final model failed to find a significant association with weight reduction, which does not appear to make biological sense. Yet, this is expected because the model simultaneously adjusted for downstream mediators such as diuretic use and GFR improvement. To date, various analytic approaches have been developed to partition the total effect of a particular risk factor into plausible causal pathways and to quantify the magnitude of impact of each causal pathway. Employing these methods would clarify the underlying biological mechanisms and quantify the magnitudes of their mediation effects, which in turn can help understand the pathogenetic pathways and potentially improve gout care.

THE BENEFITS OF WEIGHT LOSS WITH REGARD TO COMORBIDITIES OF GOUT

Beyond urate-lowering benefits in obese hyperuricaemic or gout patients, weight loss improves CV-metabolic-renal abnormalities associated with obesity,^{24 37 38} and bariatric surgery may improve survival.¹⁷ For example, Dessein's dietary intervention study showed significant improvements in total cholesterol, total cholesterol/HDL-C ratio and triglyceride levels.²⁴ Similarly, the bariatric surgery-induced weight loss in Dalbeth *et al*'s study was accompanied by an improvement in fasting glucose, HbA1c, GFR, triglycerides and blood pressure. These multiple benefits have been documented by randomised controlled trials (RCTs) that compared bariatric surgery with medical therapy among obese patients with uncontrolled diabetes.^{37 38} For example, an RCT of patients with severe obesity and uncontrolled

diabetes showed that at 2 years diabetes remission had occurred in no patients in the medical therapy group versus 75–95% in the bariatric surgery group.³⁸ Furthermore, total cholesterol, triglycerides and HDL cholesterol levels normalised in 27.3%, 0% and 11.1% of patients in the medical therapy group compared with 100%, 86–92.3% and 73–100% in the bariatric surgery group, respectively. Another RCT of obese patients with uncontrolled diabetes showed that insulin use was 38% at 12 months in the medical therapy group compared with 4–8% in the bariatric surgery group.³⁷ These multiple CV-metabolic-renal benefits are highly relevant in the holistic management of gout patients as they often have these comorbidities and are at an increased risk of developing related sequelae. Notably, potential CV-metabolic-renal benefits from pharmacological ULT options in gout patients remains largely unknown to date.

In conclusion, despite the lack of a control group and likely underestimation of impact size related to glycosuria-induced uricosuria of diabetic patients,^{25–27} this prospective cohort study adds evidence that bariatric surgery can lead to clinically meaningful SUA target levels and cessation of ULT among gout patients with severe obesity. While the sole purpose of controlling gout would likely not justify bariatric surgery among obese gout patients, if such a surgery is conducted in otherwise indicated patients with gout, it would be reasonable to seek opportunities to withdraw ULT with a proper follow-up plan. Furthermore, the multiple comorbidity and potential survival benefits of this approach and other weight loss measures should be appropriately appreciated in determining their comparative effectiveness with other available ULT options.

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