REVIEW

Metabolic syndrome, obesity and kidney stones

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Abstract

Objectives: To give a comprehensive and focused overview on the current knowledge of the causal relations of metabolic syndrome and/or central obesity with kidney stone formation.

Methods: Previous reports were reviewed using PubMed, with a strict focus on the keywords (single or combinations thereof): urolithiasis, nephrolithiasis, kidney stones, obesity, metabolic syndrome, bariatric surgery, calcium oxalate stones, hyperoxaluria, insulin resistance, uric acid stones, acid–base metabolism.

Results: Obesity (a body mass index, BMI, of > 30 kg/m²) affects 10–27% of men and up to 38% of women in European countries. Worldwide, > 300 million people are estimated to be obese. Epidemiologically, a greater BMI, greater weight, larger waist circumference and major weight gain are independently associated with an increased risk of renal stone formation, both for calcium oxalate and uric acid stone disease.

Conclusions: There are two distinct metabolic conditions accounting for kidney stone formation in patients with metabolic syndrome/central obesity. (i) Abdominal obesity predisposes to insulin resistance, which at the renal level causes reduced urinary ammonium excretion and thus a low urinary pH; the consequence is a greater risk of uric acid stone formation. (ii) Bariatric surgery, the only intervention that facilitates significant weight loss in morbidly obese people, carries a greater risk of calcium oxalate nephrolithiasis. The underlying pathophysiological mechanisms are profound enteric hyperoxaluria due to intestinal binding of calcium by malabsorbed fatty acids, and severe hypocitraturia due to soft or watery stools, which lead to chronic bicarbonate losses and intracellular metabolic acidosis.

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Introduction

Obesity, i.e. a body mass index (BMI) of >30 kg/m², has become an epidemic condition around the world, and affects 10–27% of men and up to 38% of women in European countries [1,2]. In the USA the percentage of obese adults increased from 15% in 1995 to 24% in 2005 [1]. Of the adult population of the USA >5% are considered morbidly obese, defined as having a BMI of ≥40 kg/m² [3]. Worldwide, over 300 million people are estimated to be obese [1].

Epidemiological studies suggest that a greater BMI, greater body weight, larger waist circumference and major weight gain are independently associated with a greater risk of renal stone formation [4]. Among nearly 6000 renal stone-formers those with a body weight of >120 kg had significantly higher urinary excretion rates of calcium, oxalate and uric acid (UA), all established risk factors for nephrolithiasis, than those of <100 kg [5]. However, in a study of >2000 male and female stone-formers and >1000 male and female healthy controls from the Health Professionals Follow-Up Study and the Nurses Health Studies I and II [6] the positive association between BMI and urinary calcium disappeared after adjusting for urinary sodium level (i.e. salt consumption) and for urinary phosphate (i.e. an index of protein consumption). Furthermore, urinary supersaturation of calcium oxalate (CaOx), the main driving force for the most prevalent CaOx stone formation, was not related to BMI [6].

However, the same large database showed that urinary pH was inversely related to BMI, i.e. more obese people have lower urinary pH values [6]. A very similar finding was obtained when plotting urinary pH against body weight in nearly 5000 kidney-stone formers from the two main stone centres in the USA [7]. Because urinary supersaturation of UA progressively increases with decreasing urinary pH [8], it is not surprising that a direct relationship between urinary UA supersaturation to BMI was found by Taylor and Curhan [6]. Thus the greater incidences of renal stones in more recent years in the USA [9] and Europe [10] might primarilly be caused by a specific increase in UA nephrolithiasis in increasing numbers of obese people [6]. Indeed, Daudon et al. [11] showed that the prevalence of UA stone disease both in men and in women progressively increased with increasing BMI, which is not the case for the prevalence of CaOx and calcium phosphate stone formers (Fig. 1).

Abdominal (central) obesity is the key feature of the so-called metabolic syndrome, as defined in Box 1 [12,13].

Box 1

The definition of the metabolic syndrome according to the International Diabetes Federation, 2005. Adapted from Alberti et al. [12].

Central (abdominal) obesity that is ethnicity-specific (Europeans, waist circumference, men >94 cm, women >80 cm; USA, waist circumference, men >102 cm, women >88 cm, according to the Adult Treatment Panel III 2001 definition likely to be used [13]).

Plus two of the following criteria:

1) Arterial hypertension: systolic >130 mmHg
diastolic >85 mmHg
or treatment for diagnosed hypertension

1) Triglycerides >1.7 mmol/L or specific treatment
2) Low HDL cholesterol
<1.30 mmol/L (women)
<1.00 mmol/L (men)
or specific treatment

1) Plasma glucose >5.6 mmol/L or previously diagnosed type 2 diabetes.

This cluster of cardiovascular risk factors in obese people, increasingly common around the world, affected 27% of the American population in 2000 [14]. According to the epidemiological trial NHANES III, traits of the metabolic syndrome are significantly associated with a self-reported history of kidney stones; with no traits of the metabolic syndrome the prevalence of kidney stones was 3%, and increased to 7.5% with three traits and to 9.8% with five traits, respectively [14]. Lately, similar findings were obtained in a cross-sectional analysis from Korea, where kidney stones were diagnosed by ultrasonography or CT. Among 34,895 screened individuals the prevalence of stones progressively increased with the number of metabolic syndrome components [15]. The multivariate adjusted odds ratio for kidney stones was highest for individuals with hypertension (1.47, 95% CI 1.25–1.71), and higher than for those with the whole metabolic syndrome (1.25, 95% CI 1.03–1.50) [15]. Other significant risk factors for kidney stones were increases in age and waist circumference, as well as male gender, but not serum triglyceride or high-density lipoprotein (HDL) cholesterol levels [15].

The aim of the present review was to show that the global increase in the prevalence of obesity and meta-
bolic syndrome might soon be followed by an epidemic of kidney stone disease, mainly through two pathophysiological mechanisms, i.e. (i) an increased prevalence of UA stone formation due to increasingly low urinary pH values (‘undue urine acidity’), and (ii) an increased prevalence of CaOx stones due to hyperoxaluria/hypocitraturia after bariatric surgery.

Metabolic syndrome, low urinary pH and UA stone formation

Pathophysiology

When the urinary pH is low, UA is primarily present as poorly soluble undissociated UA (solubility 0.54 mmol/L) [8]. Therefore, even at normal urinary UA excretion rates, abundant UA crystallisation with subsequent stone formation can occur. Indeed, clinical experience shows that UA stone formation is mainly caused by a low urinary pH (‘undue urine acidity’) but not by hyperuricosuria [8]. As such abnormally low urinary pH values are often associated with primary gout, it was initially thought that idiopathic UA nephrolithiasis might be a manifestation of primary gout [16]. Two independent studies subsequently showed that the reason for a low urinary pH in most normo-uricosuric UA stone formers was a reduced renal ammonium excretion [17,18]. Furthermore, the increase in urinary ammonium excretion after acid loading in UA stone formers was five to seven times lower than in ‘common’ calcium stone formers or healthy controls [18].

UA stones, metabolic syndrome and insulin resistance

As mentioned above, Maalouf et al. [7] studied almost 5000 stone patients from two main centres in the USA and found an inverse correlation between urinary pH and body weight. Most recently, Otsuki et al. [19] not only confirmed these findings but showed that lower fasting urinary pH values were significantly related to increases in waist circumference, fasting blood glucose level, glycosylated haemoglobin A1c and serum triglycerides, as well as decreases in HDL cholesterol. Thus there were significant associations of urinary pH with all traits of the metabolic syndrome except mean blood pressure [19].

Earlier Sakhaee et al. [18] showed that a third of pure UA stone-formers, but none of the calcium stone-formers or healthy controls, were diabetic. Abate et al. [20] later directly assessed insulin sensitivity in humans by measuring the glucose-disposal rate (a surrogate for insulin sensitivity) during a euglycemic hyperinsulinaemic clamp procedure, as originally described previously [21], in 55 healthy controls and 13 selected pure UA stone-formers. As shown in Fig. 2A the glucose-disposal rate was significantly higher in healthy controls than in UA stone-formers, thus UA stone-formers showed increased insulin resistance. A further important finding of this study was that, compared with healthy controls, lower urinary pH values in UA stone-formers were associated with a significantly lower ratio of urinary ammonium to net acid excretion (Fig. 2B) [20]. Moreover, urinary pH values were positively related to insulin sensitivity in the 55 healthy controls, i.e. a higher urinary pH was associated with higher insulin sensitivity. However, the lower urinary pH values in the 13 UA stone-formers tended to cluster in the area of higher insulin resistance [20].

Similar findings were also obtained by Otsuki et al. [19] who showed that progressively lower fasting urinary pH values were not only correlated with greater waist circumferences, but also with increases in insulin resistance. Thus abdominal obesity appears to indicate insulin resistance [22] on the one hand and is directly linked to a low urinary pH (‘undue urine acidity’) on the other in patients with metabolic syndrome and UA stone dis-
ease. As noted by Otsuki et al. [19], a lower urinary pH was also associated with higher serum urea nitrogen levels, which might reflect a higher intake of protein. Indeed, in young adults, a diet-induced acid load has been shown to be the primary determinant of the potential renal acid load, whereas body surface area is a better estimate of urinary organic anion excretion [23].

Conclusion

Fig. 3 summarises the most likely pathophysiology of UA stone formation in patients with the metabolic syndrome.

Renal tubular insulin resistance

\[ \text{↓ renal ammoniagenesis} \]
\[ \text{↓ ammonium ion excretion} \]
\[ \text{↑ free H}^+ \text{ ions in tubular lumen} \]
\[ \text{↓↓ urine pH} \]
\[ \text{↑ uric acid stone formation} \]

Figure 3 The most likely pathophysiology of UA stone formation in patients with metabolic syndrome.

Refer to the document for further details.
The renal complications of bariatric surgery

Previously the potential renal complications of bariatric surgery have had little attention. A first small study reported hyperoxaluria, nephrolithiasis and oxalate nephropathy as serious complications of the RYGB procedure [27], and subsequent independent reports emphasised that one major complication of modern bariatric surgery might be hyperoxaluric CaOx nephrolithiasis. In a retrospective study Asplin et al. [28] reported that compared with normal controls and “routine” kidney-stone formers, 132 patients with nephrolithiasis after bariatric surgery excreted more than twice the amount of urinary oxalate. A smaller study from the Mayo Clinic [24] showed that increasingly many patients developed CaOx stones within a mean of 2.9 years after RYGB surgery. A small cross-sectional analysis of patients from the same cohort before and 12 months after a RYGB showed that hyperoxaluria and substantial increases in urinary CaOx supersaturation occurred in more than half of the previously normo-oxaluric patients [24].

The pathophysiology of hyperoxaluria after malabsorptive bariatric surgery

The pathophysiology of hyperoxaluria after RYGB is not completely understood. Two possibilities have been discussed [24,28]. First, RYGB might induce a functional short bowel syndrome with an enteric hyperoxaluric state secondary to increased fatty acid, bile salt and oxalate delivery to the intact colon, similar to what can be found in Crohn’s disease and after a jejuno-ileal bypass [31].

As ingested calcium binds to unabsorbed fatty acids (“calcium soaps”), dietary oxalates reach the colon uncomplexed by calcium and are then absorbed. From this well-known mechanism, it could be hypothesised that a longer common channel after RYGB surgery might predispose to more significant fat malabsorption and thus hyperoxaluria. Previous studies in inflammatory bowel disease appear to confirm this hypothesis, as the degree of hyperoxaluria corresponds with the degree of steatorrhoea [31].

Second, alterations in the intestinal flora after RYGB could play a role. Oxalobacter formigenes, normally part of the human intestinal microflora, can metabolise oxalate as an energy source, and normal colonisation with O. formigenes protects against increases in oxalate absorption and excretion into urine [32]. Indeed, decreased intestinal colonisation with oxalate-degrading bacteria was reported in patients who had undergone jeuno-ileal bypass surgery [33]. Whether or not RYGB surgery also alters colonisation with O. formigenes is currently unknown.

In conclusion RYGB surgery can predispose to hyperoxaluric CaOx nephrolithiasis, primarily in the monohydrate form. The most likely cause of hyperoxaluria is gastrointestinal hyperabsorption of oxalate due to reduced intestinal precipitation by dietary calcium, i.e. enteric hyperoxaluria. Consequently, an increase in calcium intake to 4–6 g/day, ingested with meals, is expected to reduce oxalate absorption and hyperoxaluria, as shown by the teaching case (Box 2).

Box 2 Teaching case
CaOx nephrolithiasis after RYBG surgery

In 1999, a 53-year-old female healthcare administrator received a adjustable gastric band to treat morbid obesity (body weight 113 kg, height 166 cm, BMI 41 kg/m²). Three years later she underwent a RYGB procedure due to intolerance of the gastric banding. In the following years she had several surgical procedures for postoperative internal abdominal hernias. By the end of 2009, 7 years after RYGB surgery, she had left-sided renal colic and ESWL was required for a left-sided kidney stone. At the beginning of 2010 a residual stone in the left kidney was again treated by ESWL. Stone analysis by X-ray diffraction showed 80% CaOx monohydrate and 20% CaOx dihydrate. She had a metabolic evaluation; the results of the 24-h urine measurements (Table 1) showed severe hyperoxaluria and profound hypocitraturia.

The patient was put on a calcium-rich diet (4–6 g/day, ingested with meals) to precipitate sufficient oxalate within the gastrointestinal tract and thereby avoid hyperabsorption of oxalate. In addition, she was treated with alkali in the form of potassium citrate (2 × 30 mmol/day). After repeated interventions to optimise the dietary and medical treatment, the 24-h urine collection 1.5 years later showed normal urinary citrate levels and only minimally elevated urinary oxalate excretion (Table 1). The patient remained stone-free.

The pathophysiology of hypocitraturia after malabsorptive bariatric surgery

As shown by the teaching case (Box 2), malabsorptive states such as the classic short-bowel syndrome, Crohn’s...
RYGB surgery is associated with chronic bicarbonate losses and the development of intracellular metabolic acidosis, the latter being a well-known cause of hypocitraturia.

**Overall conclusion**

Based on present knowledge, RYGB surgery predisposes to hyperoxaluric and hypocitraturic CaOx nephrolithiasis. This appears to occur by two simultaneous pathophysiological effects; (i) RYGB induces an enteric hyperoxaluric state due to fat malabsorption and binding of calcium to unabsorbed fatty acids which allows for hyperabsorption of oxalates unbound by the missing free calcium; and (ii) the continuous passage of soft or watery stools after malabsorptive procedures such as RYGB surgery is associated with chronic bicarbonate losses which induce intracellular metabolic acidosis, a well-known cause of hypocitraturia.

**Conflict of interest**

The author has no conflict of interest to declare.

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None.

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