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Effect of being overweight on urinary metabolic risk factors for kidney stone formation

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ABSTRACT

Background. The prevalence and incidence of kidney stone disease have increased markedly during the past several decades, and studies have demonstrated that inappropriate dietary habits are leading to more obesity and overweight (OW) in children and adults, which may be important in stone formation. Obese and OW patients share most of the same risk factors for cardiovascular morbidity, while the impact of being OW, rather than obese, on urinary metabolic parameters of kidney stone formers (KSF) is less well known. The aims of this study were to investigate urinary metabolic parameters, stone composition and probability of stone formation (Psf) in OW KSF when compared with normal weight (NW) and obese KSF.

Methods. The kidney stone database for KSF attending a large metabolic stone clinic was investigated. Patients with a recorded BMI, confirmed diagnosis of kidney stone disease and full metabolic evaluation were divided into three categories: BMI ≤25.0 kg/m^2 (NW group), BMI 25–30 kg/m^2 (OW group) and BMI >30.0 kg/m^2 (obese group). Twenty-four hour urinary volume (U.Vol), pH (U.pH), calcium (U.Ca), oxalate (U.Ox), citrate (U.Cit), uric acid (U.UA), magnesium (U.Mg), sodium (U.Na) and potassium (U.K) excretions, along with stone composition and Psf, were then compared among the groups.

Results. A total of 2132 patients were studied, of whom 833 (39%) were NW, 863 (40.5%) were OW and 436 (20.5%) were obese. OW and obese KSF were older (mean age 43 ± 15 in NW, 48 ± 13 in OW and 50 ± 12 years in obese; P for trend <0.001), demonstrated increased female predominance and higher prevalence of diabetes, hypertension and gout. There were no statistically significant differences in U.Vol and U.Mg among the groups. However, significantly higher levels of U.Ca, U.Ox, U.Cit, by crude analysis, and U.UA (3.3 ± 1.1 versus 3.8 ± 1.2 versus 4.0 ± 1.2 mmol/L; P < 0.001 for trend), U.Na (151 ± 57 versus 165 ± 60 versus 184 ± 63 mmol/L; P < 0.001 for trend), and lower U.pH (6.3 ± 0.5 versus 6.1 ± 0.5 versus 6.0 ± 0.6; P < 0.001 for trend) by both crude and multivariate adjusted analysis models were demonstrated in OW and obese KSF. Stone composition data (N = 640) showed a significantly higher incidence of uric acid stones in OW and obese groups (P for trend < 0.001). In addition, higher Psf for CaOx, UA and CaOx/UA stone types were detected in OW and obese compared with NW KSF.

Conclusions. Similar to obese KSF, OW KSF show clear alterations in metabolic urinary profiles that are associated with increased overall risk of stone formation. This greater risk is primarily due to raised U.UA and U.Na, lower U.pH and higher prevalence of hypercalciuria, along with unchanged levels of the commonly measured urinary lithogenesis inhibitors. Moreover, our study established a higher incidence of uric acid, but not calcium, stones in OW KSF. Thus, appropriate evaluation and follow-up may be warranted even in OW patients who are at risk of increased stone formation. Whether modest weight loss in OW KSF will have a favourable impact on their metabolic urinary profiles and thereby diminish the risk of further stone formation needs exploring.

Keywords: BMI, diet, nephrolithiasis, oxalate, uric acid

INTRODUCTION

Several epidemiological studies have shown a positive association between incident stone risk and body mass index (BMI). Multiple risk factors have been proposed to explain this association and they include diet-dependent changes in urinary metabolic profile, altered renal acid–base metabolism and

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deficient ammonia production and excretion, which may all be linked to insulin resistance and impaired glucose metabolism [1]. Various urinary biochemical abnormalities have been recognized to increase the propensity for kidney stone formation in obese patients [2–6]. Lower urinary pH, together with greater urinary calcium, uric acid and oxalate excretions have been linked to obesity in kidney stone formers (KSF). Moreover, the impact of body fat distribution, along with total fat mass, appears to influence stone risk [7]. Both total body fat and trunk fat show an association with lower 24-h urinary pH, higher urinary uric acid and impaired urinary NH_4^+ excretion, whereas leg fat mass is not associated with urinary pH. Furthermore, a recent study demonstrated the independent association of low physical activity, higher caloric intake and BMI with increased risk of incident kidney stone development in a large cohort of post-menopausal women [8]. Although the association between overt obesity and a risk of kidney stone disease is clear, the impact of being overweight (OW), rather than obese, on urinary metabolic profiles has not been explored to the same extent. Moreover, the contribution of dietary factors and the potential effect of modest weight loss on the metabolic urinary profile of OW KSF are still unclear.

In the current study, we performed an analysis of prospectively collected demographic, clinical and dietary, and biochemical data of 2123 idiopathic calcium and uric acid KSF followed from 1995 to 2012 at the University College London Stone Clinic (University College and Royal Free Hospitals). The aims of the study were to investigate urinary metabolic parameters and stone composition, and to estimate the probability of stone formation (Psf) in OW KSF compared with normal weight (NW) and obese KSF. In addition, a contribution of dietary factors on the above-mentioned parameters was studied.

ORIGINAL ARTICLE

MATERIALS AND METHODS

Study population

The kidney stone database for the KSF attending the University College London Stone Clinic (University College and Royal Free Hospitals) from November 1995 to July 2012 was reviewed. Adult patients with a recorded BMI, confirmed diagnosis of kidney stone disease and full metabolic evaluation were divided into three categories: BMI $\leq$25.0 kg/m^2 (NW group), BMI 25–30 kg/m^2 (OW group) and BMI >30.0 kg/m^2 (obese group). Patients with stone types other than calcium or uric acid (for example, cystine stones, infection-related stones, drug-related stones or from patients with primary hyperoxaluria or distal RTA) were excluded from the analyses.

Study variables

Demographic and clinical characteristics were recorded for each individual at their first visit, including age, sex, body mass index (BMI), duration of stone disease, family history of kidney stones and history of urinary tract infections. Patients underwent a fasting blood sample for the determination of urea, creatinine, electrolytes, uric acid, bicarbonate and albumin, and a 24-h urine collection for measurement of 24 h urinary volume (U.Vol), pH (U.pH), calcium (U.Ca), oxalate (U.Ox), citrate (U.Cit), uric acid (U.UA), magnesium (U.Mg), sodium (U.Na) and potassium (U.K) excretions. Patients were also asked to fill out a food frequency questionnaire to investigate intakes of fluids, calcium, magnesium, phosphate, oxalate, animal protein, purine, fibre, sugar, sodium and potassium on their usual diet. For patients that spontaneously passed stones or who underwent surgery for kidney stones, biochemical stone analysis was performed. In addition, probability of stone formation (Psf), which is an index of the overall biochemical risk of forming stones consisting of uric acid, calcium oxalate, calcium phosphate or various combinations of these constituents, has been calculated for all patients. Generally, Psf discriminates well between stone-formers and normal subjects and predicts the likely severity of the disorder in a given individual as defined by the number of stone episodes per year experienced by the patient [9, 10].

Definitions of urinary metabolic abnormalities

Low urine volume was defined as urine volume <1 L/day. Hypercalciuria was defined as urine calcium excretion >7.5 mmol/day for men and 6.5 mmol/day for women. Hyperoxaluria was defined as urine oxalate excretion >0.5 mmol/day. Hyperuricosuria was defined as urine uric acid excretion >4.8 mmol/day for men and 4.5 mmol/day for women. Hypocitraturia was defined as urine citrate excretion < 1.52 mmol/day.

A stone was considered to be made of a single type (e.g. a 'pure' stone) if >95% of the stone weight was represented by a single constituent. In general, for a constituent to be considered in the stone composition it had to represent $\geq$5% of the stone weight.

Statistical analysis

Continuous variables were reported as both means with standard deviations, and medians with interquartile ranges. Between-sex differences were evaluated with the Wilcoxon rank sum test. Blood, 24-h urine and dietary data were trimmed at the 1st and 99th percentile to avoid an undue effect of extreme values.

Categorical variables were reported as counts and percent proportions and analysed for between-sex differences with the Fisher exact test and with the trend test for ordered variables.

Time trends for patient characteristics were evaluated with simple linear or logistic models with the patient characteristic of interest as the dependent variable and categorized year of visit as the predictor; the statistical significance of linear trends was checked using categorized year of visit as a continuous predictor. Stratifying the sample in quartiles of year of visit created categories of year of visit.

All the statistical analyses were performed with Stata version 12.1 (StataCorp, TX, USA).

RESULTS

A total of 2132 patients was studied, of whom 833 (39%) were NW, 863 (40.5%) were OW and 436 (20.5%) were obese.

Figure 1 presents the trends of BMI over time (1995–2012). A statistically significant and stepwise increase in average BMI

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(+0.14 kg/m^2 for the 2000–01 period, +0.97 kg/m^2 for the 2002–05 period, +1.16 kg/m^2 for the 2006–12 period compared with the 1995–99 period, P for trend <0.001) was observed over this time period.

The demographic and clinical characteristics of the population broken down by BMI categories are shown in Table 1. OW and obese KSF were older (mean age in years 43 ± 15 in NW, 48 ± 13 in OW, and 50 ± 12 in obese; P for trend <0.001), demonstrated a higher female preponderance and increased prevalence of diabetes, hypertension and gout (P for trend <0.001 for all the above variables). The prevalence of recurrent stone disease was 38% in NW, 61% in OW and 54% in obese KSF (P for trend <0.001). The median duration of kidney stone disease was not significantly longer in OW and obese KSF (P for trend = 0.04).

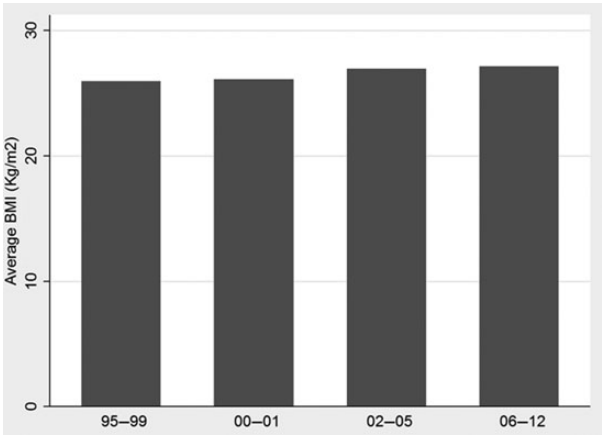

FIGURE 1: Trends of BMI of the study population over time—years 1995 to 2012. Statistically significant and stepwise increase in average BMI (+0.14 kg/m^2 for the 2000–01 period, +0.97 kg/m^2 for the 2002–05 period, +1.16 kg/m^2 for the 2006–12 period compared with the 1995–99 period, P-value for trend <0.001) was observed during this period of time.

Comparison of 24-h urine composition in patients stratified by categories of BMI is presented in Table 2. Both, crude and adjusted analyses are presented. Adjustment was performed for age, sex and all urinary parameters (mainly volume and creatinine excretion). Since diabetes and hypertension are well-recognized consequences of obesity and metabolic syndrome, adjustment for these confounders was not performed to avoid over adjustment. There were no statistically significant differences in U.Vol, and U.Mg among the groups. Significantly higher levels of U.Ca, U.Ox, U.Cit were detected by crude analyses only. However, significantly higher levels of U.UA (3.3 ± 1.1 versus 3.8 ± 1.2 versus 4.0 ± 1.2 mmol/L; P < 0.001 for trend), U.Na (151 ± 57 versus 165 ± 60 versus 184 ± 63 mmol/L; P < 0.001 for trend), U.K (69 ± 22 versus 72 ± 22 versus 72 ± 22, P = 0.01) and lower U.pH (6.3 ± 0.5 versus 6.1 ± 0.5 versus 6.0 ± 0.6; P < 0.001 for trend) were found

Table 1. Demographic and clinical characteristics of the population stratified by BMI categories

	Category of BMI			P for trend
	<25 kg/m^2 (n = 833)	25–29.9 kg/m^2 (n = 863)	≥30 kg/m^2 (n = 436)	
Age, years (mean ± SD)	43 ± 15	48 ± 13	50 ± 12	<0.001
Male sex (%)	63	78	70	<0.001
High blood pressure (%)	11	19	31	<0.001
Diabetes	3.1	7.9	14	<0.001
Gout	1.3	4.4	7.1	<0.001
Stone disease duration, years (median, range)	5 (0, 14)	5 (0, 17)	6 (0, 17)	0.68

Table 2. Twenty-four hour urine parameters of KSF stratified by categories of BMI and compared by crude and multivariate analysis

	Category of BMI			P-value for trend*
	<25 kg/m^2 (n = 668)	25–29.9 kg/m^2 (n = 719)	≥30 kg/m^2 (n = 357)	
Volume, L (mean ± SD)	2.0 ± 0.9	2.1 ± 0.8	2.0 ± 0.8	0.32 0.19
Creatinine, mmol (mean ± SD)	12 ± 3	14 ± 3	15 ± 4	<0.001 <0.001
Calcium, mmol (mean ± SD)	6.3 ± 3.0	6.7 ± 3.0	6.2 ± 3.1	0.02 0.09
Citrate, mmol (mean ± SD)	2.6 ± 1.4	2.7 ± 1.3	2.8 ± 1.5	0.02 0.90
Oxalate, mmol (mean ± SD)	0.35 ± 0.11	0.36 ± 0.10	0.38 ± 0.11	0.001 0.65
Uric acid, mmol (mean ± SD)	3.3 ± 1.1	3.8 ± 1.2	4.0 ± 1.2	<0.001 <0.001
Sodium, mmol (mean ± SD)	151 ± 57	165 ± 60	184 ± 63	<0.001 <0.001
Potassium, mmol (mean ± SD)	69 ± 22	72 ± 22	72 ± 22	0.02 0.01
Magnesium, mmol (mean ± SD)	4.1 ± 1.3	4.3 ± 1.3	4.1 ± 1.4	0.05 0.08
pH, U (mean ± SD)	6.3 ± 0.5	6.1 ± 0.5	6.0 ± 0.6	<0.001 <0.001

*For each variable, P for trend was calculated by both univariate (first value shown in the box) and adjusted analysis (second value shown). Adjusted models included age, sex and all the other urinary parameters.

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in OW and obese KSF in both crude and multivariate adjusted models. As expected, prevalence of the low urinary pH (<6) was more common in patients with hypocitraturia (42 versus 36%, P = 0.01) and this finding was similar for all BMI groups.

Crude and age- and sex-adjusted analyses of the prevalence of urinary metabolic abnormalities among the study groups are set out in Table 3. There were no statistically significant differences in the prevalence of low urine volume (7.0% versus 4.8% versus 4.9%, P = 0.87), hypocitraturia (25% versus 21% versus 21%, P = 0.06) and hyperoxaluria (6.8% versus 8.2% versus 11%, P = 0.07) among NW, OW and obese KSF, respectively. However, hyperuricosuria (9.3% versus 21% versus 27%, P < 0.001) and hypercalciuria (32% versus 39% versus 34%, P = 0.01) were significantly more prevalent between OW and obese patients. In addition, increased prevalence of higher Psf for CaOx, UA and CaOx/UA stone types was detected in OW and obese compared with NW KSF (Table 3).

Data on stone composition were available for 640 of the 2132 patients (30%) (Table 4). More than 60% of samples were stones composed of more than one constituent. The prevalence of calcium oxalate stones was slightly more than 50% in all BMI categories. However, calcium phosphate stones were significantly more prevalent in NW KSF, whereas the prevalence of uric acid stones was positively correlated with BMI (4.3 ± 18.9% versus 14 ± 34% versus 24 ± 41%, P for trend <0.001). There was no difference in the prevalence of calcium oxalate stones across the BMI groups (52 ± 39 versus 58 ± 39 versus 54 ± 41, P = 0.33).

No interaction by sex was detected in all of the above-mentioned analyses (24-h urine parameters and stone composition comparisons, P > 0.05 for all interactions).

Contribution of dietary parameters on urinary and stone composition was evaluated. The following dietary covariates were analysed: intake of fluid, calcium, magnesium, oxalate,

Table 3. Prevalence of urinary abnormalities and probability of stone formation (PsF) of KSF stratified by categories of BMI as detected by univariate and age- and sex-adjusted analysis

	Category of BMI			P-value for trend*
	<25 kg/m^2 (n = 668)	25–29.9 kg/m^2 (n = 719)	≥30 kg/m^2 (n = 357)	
Low volume (%)	7.3	5	5.3	0.11 0.66
Hypercalciuria (%)	32	39	34	0.02 0.01
Hypocitraturia (%)	23	20	20	0.27 0.03
Hyperuricosuria (%)	9.3	21	27	< 0.001 < 0.001
Hyperoxaluria (%)	6.9	8.8	10	0.14 0.18
High PSF CaOx (%)	42	45	47	0.26 0.05
High PSF CaPi (%)	68	56	45	< 0.001 < 0.001
High PSF UA (%)	1.8	3.3	9.5	< 0.001 0.001
High PSF CaOx/CaPi (%)	47	45	42	0.43 0.72
High PSF CaOx/UA (%)	2.8	5.1	11	< 0.001 0.001

*For each variable, P for trend was calculated by both univariate (first value shown) and age- and sex-adjusted analysis (second value shown).

Table 4. Stone composition of KSF stratified by categories of BMI

	Category of BMI			P-value for trend*
	<25 kg/m^2 (n = 236)	25–29.9 kg/m^2 (n = 271)	≥30 kg/m^2 (n = 133)	
Mixed stones (%)	69	67	61	0.27 0.86
Calcium oxalate, % (mean ± SD)	52 ± 39	58 ± 39	54 ± 41	0.19 0.33
Calcium phosphate, % (mean ± SD)	36 ± 35	24 ± 31	16 ± 23	<0.001 <0.001
Uric acid, % (mean ± SD)	4.3 ± 18.9	14 ± 34	24 ± 41	<0.001 <0.001

*For each variable, P for trend was calculated by both univariate (first value shown) and age- and sex-adjusted analysis (second value shown).

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animal protein and sodium. No statistically significant association was found between specific dietary components and urine metabolic parameters and stone composition.

DISCUSSION

The present study analysed a large data set of stone formers attending a metabolic stone clinic over almost two decades. OW was highly prevalent and actually represents the largest subgroup of this population. Not unexpectedly, gradual and significant increases in prevalence of diabetes, hypertension and gout were detected in OW and obese patients. Our study demonstrated multiple alterations in metabolic urinary profiles in OW KSF that are associated with increased overall risk of stone formation. These main risk factors appear to be due to raised urinary excretion of uric acid and sodium, higher prevalence of hypercalciuria and more acidic urine. Moreover, urinary volume, citrate and magnesium excretion were not influenced by higher BMI, leading to an imbalance between promoters and inhibitors of lithogenesis in the urine of even modestly obese KSF. Notably, our study demonstrated a significantly increased proportion of uric acid, but not calcium oxalate stones in the OW KSF. In addition, we established that OW KSF present with urinary metabolic parameters that are similar to those detected in overtly obese patients, while the prevalence and severity of biochemical alterations positively correlate with increasing BMI. Therefore, the same factors affect urinary lithogenic potential in OW KSF, putting these patients at considerable risk for recurrent stone formation.

Several previous studies have addressed the effect of obesity on urinary stone risk factors. Powell *et al.* [11] found higher excretion rates of calcium, oxalate and uric acid, and lower urine pH in obese KSF, along with higher urinary citrate excretion and urine volume. However, in this large study, obesity was defined as weight >120 kg in males and >100 kg in females. Therefore, the effect of modest overweight on urinary parameters cannot be determined. Subsequently, Taylor and Curhan [2] performed 24-h urine studies on subsets of three large cohort studies (NHS I and II and HPFS), including subjects with and without a history of kidney stone disease. In this study, each cohort was divided into quintiles of BMI. Similar to our findings, higher BMI positively correlated with higher urinary excretion rates of oxalate, sodium, uric acid and phosphorus, as well as a lower urine pH. Gender-related differences in urinary lithogenic parameters have been shown in several studies that investigated obese KSF. A study by Siener *et al.* [12] revealed a significant positive relationship between BMI and urinary uric acid, sodium, ammonium and phosphate excretion, and an inverse correlation between BMI and urinary pH in both men and women; whereas BMI was associated with urinary oxalate excretion only among women and with urinary calcium excretion only among men. Eisner *et al.* [13] reported increasing urine sodium and decreasing pH in men and increasing urine uric acid, sodium, and decreasing urine citrate in women.

Moreover, the contribution of dietary factors to the risk of kidney stone formation has been demonstrated by several studies. For example, consumption of a DASH-style diet rich in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein, has been reported to be associated with a marked decrease in the risk of incident kidney stones [14]. This positive effect appears to be mainly due to increasing urinary citrate excretion and urine volume [15]. In addition, the higher DASH scores are also associated with higher 24-h urinary excretions of potassium, magnesium, sulfate and phosphate, and higher urinary pH values due to the higher levels of alkali, potassium, magnesium and phosphorus that are consumed in fruits, vegetables and nuts. Furthermore, consumption of different beverages has been associated with a different incidence of kidney stones. Intake of sugar-sweetened soda and punch is associated with a higher risk of stone formation, whereas coffee, tea, beer, wine and orange juice are associated with a lower risk [16]. Despite these findings, our study failed to demonstrate any statistically significant associations between urine parameters and stone composition with the dietary covariates of intake of fluid, calcium, magnesium, oxalate, animal protein and sodium.

Although we could not demonstrate a significant association between dietary intakes and urinary metabolic abnormalities, higher excretion of urinary oxalate in OW patients has been detected by univariate analysis. While diet has been suggested to play a major role in idiopathic hyperoxaluria, studies have provided evidence that intestinal hyperabsorption of dietary oxalate, rather than the quantity of the ingested oxalate, is a major risk factor for hyperoxaluria [17, 18]. A significant relationship has been demonstrated between dietary intake of ascorbic acid, a precursor of oxalate, and urinary oxalate excretion in stone formers [19, 20]. However, controversy remains about whether the increased urinary oxalate is attributable to increased intestinal absorption of oxalate or to endogenous metabolism of absorbed ascorbate, or whether a high ascorbate intake is a marker for a high consumption of oxalate-rich fruits and vegetables. Moreover, an insufficient supply of calcium seems to play an important role. Obesity has been shown to be associated with an increased oxalate excretion, although the exact mechanism is still unclear [11]. Obesity-related alterations in the gut microbiome leading to decreased or lack of intestinal colonization by oxalate-degrading Oxalobacter formigenes can represent a possible pathological pathway resulting in increased intestinal oxalate absorption in OW KSF [21, 22]. However, there are no current studies specifically addressing this issue. In the present study, the link between nutritional status, as reflected by BMI, and hyperoxaluria was confirmed by univariate, but not multivariate analysis.

OW KSFs in our study showed increased prevalence of features of the 'metabolic syndrome': in addition to obesity, they present with a proportionally higher predominance of diabetes, hypertension and dyslipidaemia. Recent evidence suggests that the metabolic syndrome is associated with a significantly higher frequency of nephrolithiasis. Potential pathogenic links between the two conditions include metabolic factors that promote insulin resistance, as well as stone formation in urine, environmental factors such as diet, oxidative stress and inflammation and molecular changes affecting the

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transport of some analytes in urine [23]. Our study demonstrates that being even modestly overweight is associated with the metabolic syndrome and increased excretion of urinary lithogenic factors, and it supports the evidence that metabolic syndrome-related nephrolithiasis can be considered to be a multifactorial systemic disorder needing a multidisciplinary approach for its prevention and management.

While higher BMI is a surrogate marker of body fat mass, the role of body composition (lean mass and fat mass) on the urine metabolic profile is of some interest. Studies have provided evidence that lean mass seems to significantly influence urine composition, both in terms of lithogenesis promoters and inhibitors, while fat mass does not [24]. Moreover, both muscularity and adiposity (measured by BMI) seem to have a modest, but significant impact on urinary pH in young adults; however, fat mass did not affect urinary pH in the elderly [25]. In addition, the significance and magnitude of the 24-h urine chemistry abnormalities appear to differ by age and gender, a finding that also points towards the possibility that body composition, rather than just BMI, contributes to these alterations [26].

In our study, a large proportion of patients had biochemical stone analyses that clearly demonstrated that OW KSF, similar to obese patients, have a significantly higher prevalence of uric acid stones and a lower prevalence of calcium phosphate stones, a finding that is in keeping with patients having a more acid urine. Consistent with this are the Psf values calculated for the whole cohort that showed an increased risk for uric acid stone formation, along with a lesser risk for calcium phosphate stones. Generally, Psf represents an overall measure of the risk of forming five different types of stones, ranging from pure uric acid to calcium phosphate, including mixtures with urate and oxalate, and it calculates the risk of stone formation on a probability scale from 0 (improbable) to 1 (highly probable) [9, 10]. The technique combines small 'abnormalities' in urine biochemistry that by themselves are not outside the normal range, and so may not seem significant as an individual risk factor, although their particular combination can make the Psf value high because of the additive effect of small differences in measured parameters. In the recurrent KSFs, the higher the value of Psf, the greater is the severity of the disorder when defined by the average number of stone episodes experienced by a given patient per year over a long period of observation. Our study clearly demonstrated an association between OW and higher Psf for uric acid and calcium oxalate, which is consistent with the urinary metabolic abnormalities and stone composition (higher prevalence of hypercalciuria, hyperuricosuria and uric acid stones).

Our study has some limitations. First, it was based on observational data and we cannot rule out all known or unknown confounding factors to explain our results. Second, we evaluated only KSF without a control non-KSF group. Third, sources of potential error include over-collection or under-collection of 24-h urine specimens; although there is little reason to believe that participants with larger body size are more likely to provide inaccurate 24-h urine collections. Moreover, the observed relation between BMI and urinary creatinine excretion was as expected. However, our study does have the advantage that it investigated a large data set of UK stone formers with a high prevalence of overweight and obesity. We were also able to record dietary intake in a large subset of patients with biochemical stone analyses and calculated Psf values, and we could evaluate the relation between body size and urine composition.

In conclusion, our study focused on overweight (OW) KSF and demonstrated that even a slight increase in BMI is associated with multiple and marked differences in urine composition, and that these differences are similar to those found previously in obese patients. Our finding is of some importance, because of the increasing prevalence of OW and kidney stones in developed and developing countries, and that renal stone disease is emerging as a risk factor for both cardiovascular disease (CVD) and chronic kidney disease (CKD) [27, 28]. Therefore, appropriate evaluation and follow-up is warranted in OW and modestly obese patients, especially those with a history of KSF, due to their increased risk of forming kidney stones. Recommendation and adherence to a DASH-style diet may have a positive effect on urinary composition, as well as reducing CVD risk, and potentially CKD. However, whether modest weight loss in OW KSF will have a favourable impact on their metabolic urinary profiles and diminish their risk of further stone formation needs to be tested.

CONFLICT OF INTEREST STATEMENT

Authors declare that no financial conflict of interest exists and they have nothing to disclose. R.J.U. is currently on secondment as a Chief Scientist with AstraZeneca CVMD R&D, Molndal, Sweden.

REFERENCES

1. Asplin JR. Obesity and urolithiasis. Adv Chronic Kidney Dis 2009; 16: 11–20
2. Taylor EN, Curhan GC. Body size and 24-hour urine composition. Am J Kidney Dis 2006; 48: 905–915
3. Sarica K, Altay B, Erturhan S. Effect of being overweight on stone forming risk factors. Urology 2008; 71: 771–774; discussion 774–775
4. Negri AL, Spivacow FR, Del Valle EE *et al.* Role of overweight and obesity on the urinary excretion of promoters and inhibitors of stone formation in stone formers. Urol Res 2008; 36: 303–307
5. Maalouf NM, Cameron MA, Moe OW *et al.* Low urine pH: a novel feature of the metabolic syndrome. Clin J Am Soc Nephrol 2007; 2: 883–888
6. Sakhaee K, Capolongo G, Maalouf NM *et al.* Metabolic syndrome and the risk of calcium stones. Nephrol Dial Transplant 2012; 27: 3201–3209
7. Pigna F, Sakhaee K, Adams-Huet B *et al.* Body fat content and distribution and urinary risk factors for nephrolithiasis. Clin J Am Soc Nephrol 2014; 9: 159–165
8. Sorensen MD, Chi T, Shara NM *et al.* Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: a report from the Women's Health Initiative. J Am Soc Nephrol 2014; 25: 362–369
9. Robertson WG. A risk factor model of stone-formation. Front Biosci 2003; 8: s1330–s1338
10. Robertson WG, Peacock M, Heyburn PJ *et al.* Risk factors in calcium stone disease of the urinary tract. Br J Urol 1978; 50: 449–454
11. Powell CR, Stoller ML, Schwartz BF *et al.* Impact of body weight on urinary electrolytes in urinary stone formers. Urology 2000; 55: 825–830
12. Siener R, Glatz S, Nicolay C *et al.* The role of overweight and obesity in calcium oxalate stone formation. Obes Res 2004; 12: 106–113

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13. Eisner BH, Eisenberg ML, Stoller ML. Relationship between body mass index and quantitative 24-hour urine chemistries in patients with nephrolithiasis. Urology 2010; 75: 1289–1293
14. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. J Am Soc Nephrol 2009; 20: 2253–2259
15. Taylor EN, Stempfer J, Mount DB *et al.* DASH-style diet and 24-hour urine composition. Clin J Am Soc Nephrol 2010; 5: 2315–2322
16. Ferraro PM, Taylor EN, Gambaro G *et al.* Soda and other beverages and the risk of kidney stones. Clin J Am Soc Nephrol 2013; 8: 1389–1395
17. Hesse A, Schneeberger W, Engfeld S *et al.* Intestinal hyperabsorption of oxalate in calcium oxalate stone formers: application of a new test with [13C2]oxalate. J Am Soc Nephrol 1999; 10(Suppl): S329–S333
18. Siener R, Ebert D, Nicolay C *et al.* Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. Kidney Int 2003; 63: 1037–1043
19. Urivetzky M, Kessaris D, Smith AD. Ascorbic acid overdosing: a risk factor for calcium oxalate nephrolithiasis. J Urol 1992; 147: 1215–1218
20. Trinchieri A, Ostini F, Nespoli R *et al.* Hyperoxaluria in patients with idiopathic calcium nephrolithiasis. J Nephrol 1998; 11(Suppl. 1): 70–72
21. Siener R, Bangen U, Sidhu H *et al.* The role of Oxalobacter formigenes colonization in calcium oxalate stone disease. Kidney Int 2013; 83: 1144–1149
22. Moran CP, Shanahan F. Gut microbiota and obesity: role in aetiology and potential therapeutic target. Best Pract Res Clin Gastroenterol. 2014; 28: 585–597
23. Rendina D, De Filippo G, D'Elia L *et al.* Metabolic syndrome and nephrolithiasis: a systematic review and meta-analysis of the scientific evidence. J Nephrol 2014; 27: 371–376
24. Nouvenne A, Ticinesi A, Guerra A *et al.* Influence of lean and fat mass on bone mineral density and on urinary stone risk factors in healthy women. J Transl Med 2013; 11: 248
25. Remer T, Berkemeyer S, Rylander R *et al.* Muscularity and adiposity in addition to net acid excretion as predictors of 24-h urinary pH in young adults and elderly. Eur J Clin Nutr 2007; 61: 605–609
26. Curhan GC, Willett WC, Speizer FE *et al.* Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int 2001; 59: 2290–2298
27. Ferraro PM, Taylor EN, Eisner BH *et al.* History of kidney stones and the risk of coronary heart disease. JAMA 2013; 310: 408–415
28. Alexander RT, Hemmelgarn BR, Wiebe N *et al.* Alberta Kidney Disease Network. Kidney stones and cardiovascular events: a cohort study. Clin J Am Soc Nephrol 2014; 9: 506–512

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ORIGINAL ARTICLE

Prevalence and correlates of gout in a large cohort of patients with chronic kidney disease: the German Chronic Kidney Disease (GCKD) study

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ABSTRACT

Background. Reduced kidney function is a risk factor for hyperuricaemia and gout, but limited information on the burden of gout is available from studies of patients with chronic kidney disease (CKD). We therefore examined the prevalence and correlates of gout in the large prospective observational German Chronic Kidney Disease (GCKD) study.

Methods. Data from 5085 CKD patients aged 18–74 years with an estimated glomerular filtration rate (eGFR) of 30–<60 mL/min/1.73 m^2 or eGFR ≥60 and overt proteinuria at recruitment and non-missing values for self-reported gout, medications and urate measurements from a central laboratory were evaluated.

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