The association of body mass index and quantitative 24-h urine metabolites in patients with Nephrolithiasis: a systematic review and dose-response meta-analysis

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The association of body mass index and quantitative 24-h urine metabolites in patients with Nephrolithiasis: a systematic review and dose-response meta-analysis

Abstract

Objective: The aim of the present study was to evaluate the impact of body mass index (BMI) on urinary excretion of different metabolites in patients with nephrolithiasis.

Methods: A systematic search of PubMed and Scopus was performed up to November 2018. The eligible studies based on inclusion/exclusion criteria were screened and their data were extracted. Finally, 91 articles were included for dose response analysis, of which, 14 articles were included in mean difference analysis using STATA software. Patients were dichotomized according to their BMI, i.e. normal weight patients with BMI<25 and overweight/obese patients with BMI≥25 kg/m^2.

Results: Our results indicated that normal weight stone forming patients excreted less calcium ($p<0.001$), uric acid ($p<0.001$), oxalate ($p<0.001$), sodium $p<0.001$), citrate ($p<0.001$) and magnesium ($p<0.001$), however, these patients also had a higher urinary pH ($p<0.001$). Furthermore, it was observed that there is a linear dose-response relationship between BMI and 24-h excretion of oxalate ($p_{linearity}<0.001$), uric acid ($p_{linearity} < 0.001$), sodium ($p_{linearity=} 0.002$), phosphate ($p_{linearity} = 0.006$), citrate ($p_{linearity} = 0.003$) and creatinine ($p_{linearity}=0.0006$), rspectively.

Conclusion: The findings from the present study highlight that the urinary excretion of both stone promoters and inhibitors are increased in overweight and obese stone forming patients, but urinary pH is lower in these patients. This evidence suggests a potentially influential role of pH and oxalate, and interactions between promoters and inhibitors, in stone formation.

Introduction

In recent decades, the prevalence and incidence of renal stone disease, or urolithiasis, has increased, globally (1). The prevalence of urolithiasis in US adult population rose significantly from 5.2% in 1988–1994 to 8.8% in 2000-2010 (2, 3). Attempts have been made to reduce the risk of renal stone production, as it can lead to the progression of chronic kidney disease and consequential renal function loss, in addition to imposing a high medical economic burden (4).

Concomitant to the rising renal stone incidence; the prevalence of overweight and obesity is increasing throughout the world, for example 30.5% in 2000 vs. 35.7% in 2010 of the US adult population were classified as overweight or obese (5). Furthermore, obesity is a well-established risk factor in the etiology of chronic medical conditions such as hypertension, hyperlipidemia, hypercholesterolemia, diabetes mellitus, chronic kidney disease, cardiovascular disease etc. (6, 7). Because of concurrent increase in obesity worldwide, it has been suggested that the observed increase in overall stone disease might conceivably be causal (8). Indeed, it has been reported that obesity and weight gain represent independent risk factors for incident stone formation; whilst it has also been demonstrated that increased BMI, larger waist size, and weight gain, are strongly correlated with an increased risk for episodes of stone formation (9). Furthermore, the median number of stone occurrences is significantly higher in men with BMI > 25 (10), in addition to many studies reporting an increased risk of renal stone in obese patients (9, 11, 12). A recent meta-analysis, which evaluated the effect of BMI and fatness on risk of kidney stone formation, indicated that the relative risk of developing a stone formation is 1.21 per 5 unit increase in BMI and 1.16 per 10 cm increment in waist circumference, respectively (13). With the current incremental rate of obesity, it is estimated that there more than 44% of adults will be obese in the US by 2030, which, independent of other risk factors, could account for 0.36% increase in urolithiasis prevalence and a $157 million increase in its annual cost (14).

The pathophysiology of the relationship between urolithiasis and obesity is not yet fully understood, however, abnormal urinary excretion of metabolites in overweight and obese patients is one of the most plausible mechanisms. Recent studies on metabolic factors influencing stone disease in obese patients have highlighted that obese stone-forming patients excrete higher urinary levels of sodium, calcium, uric acid, oxalate, citrate and phosphate, along with serum uric acid and creatinine (9). The risk of stone disease in obesity is inversely associated with urinary pH, and such an acidic urinary environment is a notable risk factor for both uric acid and calcium oxalate stones (15, 16). However, the literature base, to-date, is equivocal as to the association between body mass index and stone formation (10, 17-20), highlighting the need for a meta-analytical assessment, to provide empirical, consensual. Thus, the aim of the present study was to evaluate the impact of body mass index on urinary excretion of different metabolites in patients with nephrolithiasis

Methods

This meta-analysis was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (21). We systematically searched PubMed and Scopus in November 2018 in order to identify potentially eligible studies without language restriction. The search strategy was as follows: [Kidney Calculi OR Kidney stone OR Kidney calculus OR Urolithiasis OR Nephrolithiasis OR Urinary Calculi OR Urinary stone OR Urinary calculus OR Renal stone OR Renal calculi OR Renal calculus] AND [Obesity OR Abdominal obesity OR General obesity OR Central obesity OR Overweight OR Body Mass Index OR BMI OR Body Weight OR Body Weight Changes OR Adiposity OR Weight Gain OR Weight Loss OR Body Composition OR Waist Circumference OR Waist-Hip Ratio OR body size OR Fat mass OR Body fat OR Fatness OR Body fatness OR Abdominal fatness] AND [Urine OR 24-hour urine OR

24 hour urine OR (urine AND pH) OR (urine AND oxalate) OR (Urine AND Oxalic acid) OR (Urine AND creatinine) OR (Urine AND citrate) OR (Urine AND calcium) OR (Urine AND uric acid) OR (Urine AND volume) OR (Urine AND magnesium) OR (Urine AND sodium) OR (urine AND metabolite) OR (urine AND metabolic workup) OR (Urine AND metabolic abnormality)].

Two investigators screened the titles and abstracts of all searched studies separately, and articles assessing the association between BMI and excretion of urinary metabolites in stone forming patients were included for further screening.

Inclusion/Exclusion criteria

For an article to be included in dose-response analysis, all the below criteria had to be met: 1) the study was performed on stone forming adults, (2) patients' body size was measured and reported as body mass index (kg/m^2), (3) the mean/median level of at least one 24-h urine metabolite was mentioned. For analyzing the impact of BMI<25 kg/m^2 and BMI≥25 kg/m^2, respectively, on 24-h on urine composition, the study had to report urinary excretion of metabolites in 24 hours in different categories of BMI, in addition to the above criteria. Studies that were not in English, were conducted in pediatric patients, their full-text were not available online, or used the same database of urolithiasis patients, were excluded. The two investigators performed this selection process independently.

Quality of study

Study quality and level of evidence was assessed using the Newcastle Ottawa Scale, which is a validated scale to score the methodology of observational studies (22).

Data extraction

The required data were screened and extracted in an independent duplicate manner by two investigators using a predetermined electronic data extraction form, including the following

information: first author, year, study design, country of study or patients database, number of studied patients, mean/median and SD/IQR of BMI, age and sex of the patients, mean/median and SD/IQR of 24-h urinary metabolites (pH, volume, calcium, citrate, oxalate, calcium, creatinine, phosphate, uric acid, magnesium, potassium and sodium).

In case of a disagreement, the original article were screened again carefully by the two investigators and a discussion were conducted until a consensus was reached.

Statistical analysis

The STATA 12.0 (StataCorp LP) computer software was used to perform this meta-analysis. All units of urinary metabolites were unified prior to analysis. In order to compare mean difference of 24-h urine metabolites between BMI<25 and BMI>25 groups, weighted mean difference (WMD) between BMI<25 and BMI>25 groups was calculated, and the pooled estimates was obtained using random effect model due to the heterogeneous basis of the studies. Heterogeneity among studies was identified using the Chi-square test and I^2 value. To test dose-response relationships, fractional polynomial models were used and the model with the lowest deviance was considered as the best-fitting model. The dose-response relationship between BMI and urinary metabolites was also plotted for each outcome separately. Publication bias was detected by visual assessment of funnel plot and also by Egger's test.

Results

Study characteristics

Of 1356 articles, 91 articles (10, 16, 18, 19, 23-109) met the inclusion criteria for dose-response analysis, involving 37710 patients who underwent 24-hour urine chemistry analysis (**Figure 1**). Among these 91 articles, 14 studies compared the difference of 24-h urine metabolites in different

categories of patients' BMI and were included for mean difference analysis between BMI<25 kg/m^2 and BMI>25 kg/m^2. **Table 1** details the basic characteristics of these 14 articles including number of BMI categories, number of patients in each category, patient's age and stone type. All these 14 studies were cohort and their level of evidence was rated as level 3. The Newcastle Ottawa Scale gives the maximum nine stars for high quality studies. Based on this scale, all 14 studies were deducted one star due to no description for the assessment of the outcome, whilst even studies were deducted one more star because they did not control for stone type.

Main outcomes of mean difference analysis between BMI groups

Ten studies were included for analysis of 24-h urine volume and their meta-analysis showed that there was a significant difference between 24-h urine volume of groups with BMI<25 kg/m^2 and BMI≥25 kg/m^{2}groups (-42.249 ml; 95% CI -83.027 to -1.471, p= 0.042; I^2=27.9, p=0.188) (**Table 2**). The volume of 24-h urine in those with BMI<25 kg/m^2 was lower than people with BMI>25 kg/m^2 kg/m^2. Patients in BMI<25 kg/m^2 group indicated a higher pH of urine than patients with BMI≥25 (0.263, 95% CI 0.167 to 0.36, p<0.001; I^2=76.1, p<0.001) (**Table 2**). Compared to patients with BMI≥25 kg/m^2, those with BMI<25 kg/m^2 excreted less lithogenic urine metabolites, including calcium (-24.077 mg, 95% CI -31.752 to -16.401, p<0.001; I^2=58.8, p=0.007), uric acid (-79.322 mg, 95% CI -100.327 to -58.316, p<0.001; I^2=81.1, p<0.001), oxalate (-2.71 mg, 95% CI -3.727 to -1.694, p<0.001; I^2=58.8, p=0.007) and sodium (-30.284 mg, 95% CI -36.985 to -23.584, p<0.001; I^2 =73, p<0.001). The excretion of urine inhibitors including citrate (-49.354 mg, 95% CI -69.592 to -29.115, p<0.001; I^2 =64, p=0.001) and magnesium (-6.381 mg; 95% CI -0.875 to -2.887, p<0.001; I^2 =66, p=0.007) was also lower in BMI<25 kg/m^2 group compared with BMI≥25 kg/m^2 group (**Table 2**). In addition, the excretion of other 24-h urine metabolites, including creatinine (-245.499 mg, 95% CI -285.387 to -205.61, p<0.001; I^2=71.3, p<0.001), phosphate (-

158.627 mg, 95% CI -195.482 to -121.772, p<0.001; I^2 =75.3, p<0.001), potassium (-6.689 mg, 95% CI -9.565 to -3.814, p<0.001; I^2=79.7, p<0.001) and urea (-3.669 mg, 95% CI -4.363 to -2.975, p< 0.001; I^2=0, p=0.437), was lower in patients with BMI<25 kg/m^2 than patients with BMI≥25 kg/m^2 (**Table 2**).

Publication Bias

Visual exploration of funnel plots did not indicate publication bias (**Figure 2**). The funnel plots, which were obtained for urine pH, as it includes the most studies, suggested that there were no small study effects. Publication bias was also assessed using Egger's test and it showed no statistical evidence of small study effects (p=0.556).

Main outcomes of dose-response analysis between BMI and excretion of 24-h urine metabolites

When the outcomes were evaluated for dose-response relationships, it was found that the excretion of 24-h urine oxalate ($p_{linearity}$<0.001), uric acid ($p_{linearity}$ < 0.001), sodium ($p_{linearity=}$ 0.002), phosphate ($p_{linearity}$ = 0.006), citrate ($p_{linearity}$ = 0.003) and creatinine ($p_{linearity}$=0.0006) was elevated by increasing BMI in a linear fashion (**Figure 3**). In contrast, no evidence was obtained for a dose-response relationship between BMI and total daily urinary excretion of volume ($p_{linearity}$= 0.087), pH ($p_{linearity}$= 0.029), calcium ($p_{linearity}$=0.261), magnesium ($p_{linearity}$= 0.316), potassium ($p_{linearity}$ = 0.126), and urea ($p_{linearity}$ = 0.134), respectively.

Discussion

In our meta-analysis, for all 24-h urine metabolites that were analyzed separately, the number of patients with BMI≥25 kg/m^2 was greater than those with BMI<25 kg/m^2 ,indicating a higher prevalence of obesity in the studied population of stone formers. Our results also indicated that the

level of all 24-h urine metabolites and 24-urine volume was higher in overweight and obese stone forming patients, but these patients had lower urinary pH.

The formation of a renal stones is a combinative process in which the main phenomenon is the supersaturation of several compounds that can crystallize, forming solid concretions in the urine. The crystallization is influenced by various factors, including a lack of crystallization inhibitors (such as citrate and magnesium), the presence of crystallization promoters (for example calcium, oxalate and uric acid), and some morpho-anatomic characteristics (110). Regarding the level of 24-h urine metabolites in obese stone formers, it was previously demonstrated that the urinary excretion of sodium, calcium, uric acid, oxalate, phosphate and ammonium is higher in obese stone formers compared to normal weight patients (17, 20). Concordantly, our results indicated that the level of 24-h urine sodium, calcium, uric acid, oxalate, phosphate, urea and creatinine was higher in overweight and obese stone forming patients. In addition, our dose-response analysis showed that the relationship between urinary excretion of oxalate, sodium, uric acid, phosphate and creatinine with BMI was linear.

In the present study, we observed that the level of 24-h urinary magnesium and citrate was higher in obese patients; while 24-h urine volume was also significantly greater in BMI≥25 kg/m^2 group. The findings of previous studies for urinary excretion of citrate, magnesium and 24-h volume are contradictory; indeed, some studies have suggested no difference for these parameters between obese and normal weight patients, whereas many others have proposed an increase of these parameters in obese patients (17, 19, 20, 111). Although the increases in urinary metabolites might simply be explained by the greater volume, some studies have suggested that urine osmolality is also higher in obese patients, which results in more concentrated urine (17). However, it should be

also considered that in a large population, as in the present meta-analysis, even small differences could account for statistical significance.

Our findings revealed a negative correlation between urinary pH and BMI, although the relationship was not linear. Many studies have suggested that acidic urine is a notable risk factor for formation of both uric acid and calcium oxalate stones (15, 107). The causal pathway for obesity to result in more acidic urine is currently under investigation. Tentatively, obesity is associated with insulin resistance and hyperinsulinemia, where the former might conceivably increase hydrogen ions released in the urine and consequential stone formation through activation of Na^+/H^+ exchange and ammoniagenesis (112). Furthermore, because of the acidic nature of uric acid, higher urinary excretion of uric acid in obese stone formers exacerbates lower urine pH and contributes to uric acid stone formation (107).

Regarding the increased risk of calcium oxalate stone formation in obese patients; although our results show higher excretion of both urinary lithogenic factors and inhibitors in the obese individuals, it is necessary to mention a few points in this regard. Firstly, the simultaneous elevation of urinary lithogenic risk factors can have an additive effect on stone formation. For example, according to some studies, high concentrations of oxalate (even transient hyperoxaluria) is toxic to renal tubular cells (113). Subsequently, oxalate-induced injury to renal tubular epithelial cells promotes adherence of the calcium oxalate crystals (114). Secondly, it has been suggested that changes in urinary oxalate exerts a greater influence on calcium oxalate supersaturation than proportional changes in calcium (115, 116). Indeed, it has been reported that at high urinary calcium concentrations, the saturation of calcium oxalate reached a plateau that did not exceed the theoretic formation product of calcium oxalate, whereas high oxalate concentrations did, thereby increasing the risk of calcium oxalate crystal formation (117). Thirdly, despite elevation of urinary

inhibitors, it appears that the urinary level of inhibitors is still not adequate to be able to overcome the lithogenic factors. Therefore, the interaction between lithogenic and inhibitory compounds in a complex biological fluid, such as urine (when a growing crystal is present), is of utmost importance.

There were some limitations in our study that must be addressed. First, there was high heterogeneity for nearly all of the studied urinary metabolites. Second, we could not perform subgroup analysis for different types of kidney stone, since most of the included studies were conducted on a mixed population of patients with different types of kidney stones, however, according to the mechanisms proposed for formation of kidney stone, the changes in the type of urinary metabolite is an important factor in the formation of different stones. Third, the super saturation of each urinary metabolite is notable in the evaluation of kidney stone formation, but it was not assessed in the included studies. Finally, there were diabetic and hypertensive stone forming patients among the studied population which might have influenced the excretion of urinary metabolites, however, subgroup analysis was not possible as the findings in these patients were not reported separately.

Conclusion

The present study highlights that overweight and obesity increase the urinary excretion of both stone promoters (calcium, sodium, oxalate and uric acid) and inhibitors (citrate and magnesium), but the prevalence of kidney stones is still higher in overweight/obese patients. Therefore, the higher risk of kidney stone formation in obese individuals might be due to the higher potential of some urinary factors on stone formation such as pH and oxalate or interaction between promoters and inhibitors, but detailed mechanistic enquiries must be performed. .

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