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ORIGINAL PAPER

# Metabolic diagnosis in stone formers in relation to body mass index

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**Abstract** It is known that several metabolic abnormalities that favor stone formation have a strong dependence on environmental and nutritional factors. The incidence and prevalence of kidney stone is increasing while there has been a parallel growth in the overweight/obesity rate, and epidemiologic studies have shown a significant association between overweight/obesity and increased nephrolithiasis risk. The aim of this study was to assess if metabolic abnormalities observed in stone patients differ in relation to their BMI. We evaluated 817 renal stone formers (459 men and 358 woman) in an outpatient setting. They were all studied with a standard protocol (two 24 h urine collections and serum parameters) and classified according to their BMI in normal, overweight and obese and according to age in <50 or >50 year old. In the whole population we found that 58.7% were either overweight or obese: 39.4% ($n = 322$) were OW and 19.3% ($n = 158$) were OB. The proportion of overweight was significantly higher among men than women. In women of all ages regardless of BMI, hypercalciuria was the most prevalent diagnosis. Hyperuricosuria increased its prevalence significantly only in overweight and obese women <50 years of age ($p < 0.01$). Hypercalciuria was the predominant diagnosis in normal weight men of both age groups. Hyperuricosuria was the most frequent abnormality in overweight and obese men followed by gouty diathesis and both increased their prevalence significantly from normal weight to obesity and in both age groups ($p < 0.05$ and $<0.01$). We conclude that the only abnormalities that increased their prevalence significantly with increasing BMI were hyperuricosuria and gouty diathesis, the first one in men of all ages and women under 50 years of age, while the second one only in men.

**Keywords** Kidney stones · Metabolic abnormalities · BMI · Overweight · Obesity

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## Introduction

In the last decades, the incidence and prevalence of kidney stone in the western countries has increased [1], while there has been a parallel growth in the overweight (OW)/obesity (OB) rate [2, 3]. Epidemiologic studies have also shown a significant association between nephrolithiasis and obesity [4–6] and that weight gain increases the risk of kidney stone formation, greater in women than in men [7].

Some studies in stone patients have shown that obesity is associated with an increased urinary excretion of calcium, oxalate and uric acid, thereby increasing the risk for calcium-containing kidney stones [8–10] while in the another study overweight/obesity produced a significant increase in the urinary excretion of oxalate and uric acid but no change in urinary calcium [7]. In this study a significant decrease in urinary pH was observed with increasing body mass index

(BMI) but only in men, increasing the risk of uric acid stones. We have also observed that in male stone patients with OW/OB and older age, low urine pH was their main pathogenic factor for uric acid stone formation [11]. From another point of view, Daudon et al. [12] has examined the relationship between body size and stone composition, in order to assess which type of stone is predominantly favored by overweight/obesity. He showed that uric acid stones prevalence gradually increased with BMI in both genders, but to a greater extent in males than females.

However, there are a few data regarding which metabolic abnormalities are seen in stone patients with increasing body weight. Ekeruo et al. [13] observed that the most frequent metabolic abnormalities among obese stone formers were hypercalciuria, gouty diathesis, hypocitraturia and hyperuricosuria. In this work the authors compared obese patients with (BMI > 30) with non-obese patients including both normal and overweight.

Thus, the aim of our study was to assess if the increase in body mass index (overweight and obesity) favors a particular kind of metabolic abnormality in stone patients and if this is influenced by sex and age.

## Materials and methods

### Study population

We retrospectively evaluated the medical records of 817 consecutive renal stone formers (459 men and 358 women) that were referred to our outpatient stone clinic for their metabolic risk factor evaluation. None of these patients had received treatment (either medical or surgical) before they were studied. The population was divided in those under or over 50 years of age and by sex. The reason for choosing 50 years as the turning point for age was that some studies have shown that around that age there is a change in the type of renal calculi seen in stone formers [14]. They were classified according to their BMI (kg/m$^2$) in normal (BMI < 24.9), overweight (BMI $\geq$ 25 and $\leq$ 29.9) and obese (BMI $\geq$ 30). Patients with cystinuria and primary hyperparathyroidism were excluded. Stone composition analysis was available in 263 patients.

### Study protocol

All the patients were studied with a standard protocol that included two 24 h urine collections and determination of serum parameters while taking their usual diet. After collection, urine samples were refrigerated for measurements of total volume, creatinine, sodium, potassium, calcium, phosphorus, uric acid, oxalate, citrate and urea. Fasting venous blood samples were obtained before breakfast for electrolytes, creatinine, urea nitrogen, calcium, phosphorus and uric acid. Urinary sediment and pH were determined in the 2-h fasting sample. The patients were studied at least 1 month after an episode of renal colic and they should have a negative urine culture. Urine was kept refrigerated during collection. No preservatives were added.

Patients were considered as having idiopathic hypercalciuria (IH) if the urinary calcium excretion was more than 4 mg/kg/day (0.1 mmol/kg/day) or more than 220 mg/24 h in women or 300 mg/24 h in men, with normal serum calcium; hyperuricosuria (HU) a uric acid excretion >700 mg/24 h (4.13 mmol/24 h) for women, and >800 mg/24 h (4.72 mmol/24 h) for men; hypocitraturia (HCIT) as urinary citrate excretion <350 mg/24 h (1.8 mmol/24 h); hypomagnesuria (HMG), a magnesium excretion <70 mg/day, and hyperoxaluria (HOX), an oxalate excretion >45 mg/day. Gouty diathesis (GD) or "unduly acidic urine pH" (UAUpH) was defined as urine pH < 5.5 in at least two occasions separated by at least 1 h on the same day. Low urine volume (LUV) was defined as a urine volume <1,000 ml/24 h.

### Methods

Serum calcium was measured by ISE methodology with the Synchron CX3 Delta automated analyzer (Beckman, Beckman Instruments, Inc. Brea, California, USA); the same methodology was used for urinary calcium determination (done in an acidified aliquot). Coefficient of variation was 1.3% at 8 mg/dl and 1.5% at 14 mg/dl. Serum and urine creatinine were measured by a Jaffe kinetic method using CCX spectrum automated analyzer (Abbott Laboratories, USA). Serum coefficient of variation was 7% at 0.8 mg/dl and 1.8% at 4.2 mg/dl. Urine CV was 2.9% at 43 mg/dl and 3% at 87 mg/dl. Phosphate was measured by UV (molybdate) using CCX Spectrum automated analyzer (Abbott Laboratories, USA). Urine CV was 2.9% at 43 mg/dl and 3% at 87 mg/dl and serum CV was 6.5% at 2.4 mg/dl and 2.8% at 4.5 mg/dl. Sodium and potassium were measured by Synchron CX3 autoanalyzer. Uric acid (done in an alkalinized aliquot to prevent precipitation) was analyzed using uricase method. (CV 5% at 2.7 mg, 3% at 7.0 mg and 3% at 10 mg). Urinary citrate was determined enzymatically [19] using reagents from Sigma-Aldrich Corp. (St. Louis, Missouri, USA). Oxalate (done in an acidified aliquot) was determined enzymatically (Trinity Biotech, Bray Co., Wicklow, Ireland). Urinary pH was measured with a pH electrode in the second urine of the morning immediately post-voiding. The mean of the two urine samples was used in calculations. We did not calculate the relative super saturation values or analyze urinary acidification defects.

**Table 1** Classification of patients of both sexes according to BMI

| BMI | Males ($n = 459$) | Females ($n = 358$) | All Patients ($n = 817$) |
|---|---|---|---|
| Normal | 27.8% ($n = 128$) | 58.5% ($n = 209$) | 41.3% ($n = 337$) |
| Overweight (OW) | 52.2% ($n = 237$)* | 23.7% ($n = 85$) | 39.4% ($n = 322$) |
| Obesity (OB) | 20.5% ($n = 94$) | 17.8% ($n = 64$) | 19.3% ($n = 158$) |

* Males versus females $p < 0.001$

Statistical analysis

Statistical analysis was done using the test for differences between two percentages using Statistica software, Version 5.0 (Statsoft). The relationship between BMI, sex and age with the different metabolic diagnoses was assessed by logistic regression analysis considering the metabolic diagnoses as dependent variables and BMI, sex and age as independent variables. In both the cases a $p$ value $\leq 0.05$ was considered significant.

## Results

In the whole population, we found that 58.7% of the patients had overweight or obesity: 39.4% ($n = 322$) were OW and 19.3% ($n = 158$) OB. Table 1 shows the presence of overweight and obesity according to sex in stone formers. The proportion of overweight was significantly higher among men than women, while the rate of obesity was similar in both genders. Seven hundred and thirty-eight patients had only one metabolic diagnosis, while 79 patients had more than one.

In women under 50 years of age, independent of their BMI, idiopathic hypercalciuria (IH) was the most prevalent metabolic abnormality found (Table 2). There was a significant increase in HU as the BMI increased from normal to obese, and the rest of the metabolic diagnoses did not show significant changes.

In women over 50 years of age, we observed that IH, as seen in younger women and regardless of BMI, was the most prevalent diagnosis (Table 2). But unlike younger women, we did not find any significant change in other metabolic abnormalities with increasing BMI.

With respect to young men, we found that IH was the most frequent metabolic abnormality in those with normal BMI (40%), while in those with OW and OB, (31.7 HU and 48%) was the most frequent diagnosis, followed by IH and gouty diathesis (GD). Both HU and GD prevalence increased significantly with increasing BMI (Table 3).

With regard to men over 50 years of age, we noted that in those with normal BMI, like in younger men, IH was the first in frequency while in those patients with OW and OB, HU was the most prevalent diagnosis followed by GD and IH (Table 3). As in younger men, both HU and GD increased in frequency with increasing BMI, with the difference that this increase was significant only between N and OB subjects.

Although HOX increased with the rise of BMI particularly in men it was not statistically significant probably because of the small number of patients with this abnormality. The logistic regression analysis showed that there was a significant effect of BMI only on HU ($p < 0.01$) and GD ($p < 0.05$).

Stone analysis was available only in 263 patients (64 women under 50 years of age and in 33 older women; in 108 males under 50 years of age and in 58 older men) Table 4. We observed that calcium stones represented 90.6% in the patients with normal weight, 82.3% in overweight and 90.4% in the obese. On the other hand, uric acid stone frequency was 6.5% in the N, 19.3% in OW and

**Table 2** Diagnosis in women in relation to age and BMI

| | IH | HU | GD | HCIT | HMG | HOX |
|---|---|---|---|---|---|---|
| ≤50 years of age | | | | | | |
| N | 54% ($n = 92$) | 4.7% ($n = 8$) | 14.2% ($n = 24$) | 19% ($n = 33$) | 4.1% ($n = 7$) | 3.0% ($n = 5$) |
| OW | 54% ($n = 25$) | 17.4%* ($n = 8$) | 21.7% ($n = 10$) | 13% ($n = 6$) | 4.3% ($n = 2$) | 2.1% ($n = 1$) |
| OB | 57% ($n = 20$) | 22.8%** ($n = 8$) | 22.8% ($n = 8$) | 11.4% ($n = 4$) | 2.8% ($n = 1$) | 2.8% ($n = 1$) |
| >50 years of age | | | | | | |
| N | 45.0% ($n = 18$) | 7.5% ($n = 3$) | 20.0% ($n = 8$) | 15% ($n = 6$) | 7.5% ($n = 3$) | 5.0% ($n = 2$) |
| OW | 46.1% ($n = 18$) | 17.5% ($n = 7$) | 28.2% ($n = 11$) | 10.2% ($n = 4$) | 2.6% ($n = 1$) | 5.1% ($n = 2$) |
| OB | 48.2% ($n = 14$) | 10.3% ($n = 3$) | 24.1% ($n = 7$) | 13.8% ($n = 4$) | 3.4% ($n = 1$) | 7.0% ($n = 2$) |

*N* normal weight, *OW* overweight, *OB* obesity, *IH* idiopathic hypercalciuria, *HU* hyperuricosuria, *GD* gouty diathesis, *HCIT* hypocitraturia, *HMG* hipomanesuria, *HOX* hyperoxaluria

* N versus OW $p < 0.01$

** N versus OB $p < 0.01$

**Table 3** Diagnosis in men in relation to age and BMI

| | IH | HU | GD | HCIT | HMG | HOX |
|---|---|---|---|---|---|---|
| ≤50 years of age | | | | | | |
| N | 40% (*n* = 44) | 20% (*n* = 22) | 16.4% (*n* = 18) | 18.2% (*n* = 20) | 5.5% (*n* = 6) | 3.6% (*n* = 4) |
| OW | 27% (*n* = 40) | 31.7%* (*n* = 47) | 27%* (*n* = 40) | 10.8% (*n* = 16) | 3.3% (*n* = 5 ) | 4.7% (*n* = 7) |
| OB | 30% (*n* = 15) | 48%** (*n* = 24) | 44%** (*n* = 22) | 14% (*n* =7 ) | 2.0% (*n* = 1) | 8.2% (*n* = 4) |
| >50 years of age | | | | | | |
| N | 27.8% (*n* = 5) | 22.2% (*n* = 4) | 16.7% (*n* = 3) | 11% (*n* = 2) | 5.6% (*n* = 1) | 5.6% (*n* = 1) |
| OW | 28% (*n* = 25) | 36.0% (*n* = 32) | 32.5% (*n* = 29) | 5.6% (*n* = 5) | 1.1% (*n* = 1) | 9.0% (*n* = 8) |
| OB | 20.4% (*n* = 9) | 50.0%• (*n* = 22) | 47.7%• (*n* = 21) | 2.3% (*n* = 1) | 2.3% (*n* = 1) | 11.4% (*n* = 5) |

*N* normal weight, *OW* overweight, *OB* obesity, *IH* idiopathic hypercalciuria, *HU* hyperuricosuria, *GD* gouty diathesis, *HCIT* hypocitraturia, *HMG* hipomagnesuria, *HOX* hyperoxaluria

* N versus OW $p < 0.05$

• N versus OB $p < 0.05$

** N versus OB $p < 0.001$

**Table 4** Stone analysis in 263 patients

| (A) In the whole group | N | OW | OB |
|---|---|---|---|
| Ca Ox | 91 | 79 | 43 |
| Ca P | 3 | 2 | 1 |
| Uric acid | 7 | 16 | 5 |
| Ca Ox + Ca P | 3 | 1 | 2 |
| Ca Ox + uric acid | 0 | 4 | 1 |
| Phos/$NH_4$/Mg | 3 | 2 | 0 |
| Total | 107 | 104 | 52 |

| (B) According to sex | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | N | OW | OB | N | OW | OB |
| Ca Ox | 42 | 66 | 27 | 49 | 13 | 16 |
| Ca P | 0 | 0 | 0 | 3 | 2 | 1 |
| Uric acid | 6 | 16 | 4 | 1 | 0 | 1 |
| Ca Ox + Ca P | 1 | 1 | 0 | 2 | 0 | 2 |
| Ca Ox + uric acid | 0 | 1 | 1 | 0 | 3 | 0 |
| Phos/$NH_4$/Mg | 1 | 0 | 0 | 2 | 2 | 0 |
| Total | 50 | 84 | 32 | 57 | 20 | 20 |

*N* normal weight, *OW* overweight, *OB* obesity

11.5% in OB. The difference in uric acid stones frequency between patients with normal weight (7/107; 6.5%) and those with overweight/obesity (26/156; 16.6%) was statistically significant ($p = 0.03$).

According to gender, in men we found that calcium stones represented 80.5% in N, 81.4% in OW and 87.5% in OB. Uric acid stones in men had a frequency of 12.5, 20.9 and 15.2% in N, OW and OB, respectively. In women, calcium stone frequency was 91.5% in N, 88.9% in OW and 95% in OB, while uric acid stones were observed in 1.7, 11.1 and 5% in N, OW and OB, respectively. Thus there was an increase in uric acid stones in overweight/obese men but not in women.

## Discussion

The evaluation of BMI in our stone patients showed that 58.7% were overweight or obese. The proportion of OW patients was significantly higher in males than females, independent of age. There are a few studies that have assessed the prevalence of OW/OB in nephrolithiasis patients. Among them is the study by Siener et al. [9], they observed that in 527 calcium oxalate stone formers 54.5% presented OW or OB. Overweight was also significantly more frequent in men than in women. Unlike the stone formers in the present study the rate of obesity was lower in both genders (10.4% in women; 9.6% in men). In France, Daudon et al. observed [12] a prevalence of OW/OB of 34.8% in 672 stone patients, which is less than what we observed in our population. Like in the present study the proportion of OW was higher in males than females (27.1 vs. 19.6%) but different from our results the prevalence of obesity was higher in women than men (13.5 vs. 8.4%). In USA, Ekeruo et al. [13], who only assessed the prevalence of obesity in 1021 patients with nephrolitiasis found that 140 (14%) were obese; this was somewhat lower than what we have found.

In recent years, several studies have shown that weight gain increases the urinary excretion of promoters of the crystallization in stone patients [7–9, 15], but little is known if the metabolic diagnoses differ in relation to BMI. Our study found that in stone patients, some abnormalities increased their prevalence as BMI goes up. One of them was hyperuricosuria that rose in prevalence with the increase in body weight in both sexes. In men this increase was independent of age, whereas in women, it occurred only in those <50 years old, although this could be due to the small number of older women in the sample. An exaggerated ingestion of a diet rich in animal protein characteristic of the daily diet of our country may probably explain this results in this OW/OB patients.

Gouty diathesis or unduly acidic urine pH, as it would be better called, was the other diagnosis that increased its frequency with the increase in BMI but it was observed only in men. Several studies [15, 16] have shown the inverse relation between urinary pH and body weight in stone patients. Maalouf et al. [16] retrieved data from 4,883 patients with nephrolithiasis who underwent ambulatory evaluation. Patients were divided in increasing sextiles of body weight, and urinary pH was adjusted for urinary creatinine and for age. They found that urinary pH had a strong, graded inverse association with body weight. Urinary creatinine and age were both found to be significant covariates of urinary pH, while gender was not a significant independent variable after adjustment for urinary creatinine. Obesity may sometimes cause uric acid nephrolithiasis by producing excessive acid urine due to insulin resistance. Normally insulin stimulates ammoniagenesis [17] and increases Na+/H+ exchange activity in the renal proximal tubule segments [18]. Type 2 diabetes is a risk factor for nephrolithiasis in particular uric acid stones. The main risk factor for uric acid nephrolithiasis in type 2 diabetes patients is a low urine pH. Cameron et al. [19] studied three groups of patients: those with type 2 diabetes but not stone formers; non-diabetic patients who were uric acid stone formers, and normal volunteers. Patients with type 2 diabetes and UASF had lower 24-h urine pH than normals and urine pH inversely correlated with both body weight. Finally Abate et al. [20] studied 55 healthy non-stone-formers with a large range of BMI and 13 patients with recurrent uric acid nephrolithiasis. They underwent hyperinsulinemic euglycemic clamp and 24-h urinary studies. For the non-stone former population, low insulin sensitivity significantly correlated with low 24-h urinary pH and patients with recurrent uric acid nephrolithiasis they were found to be severely insulin resistant. Thus low urinary pH can be considered as a new marker of insulin resistance.

With respect to the female population of this study, we did not find a decrease in urinary pH with increasing body weight. Other authors such as Nouvenne et al. [21] have also not observed significant changes in urinary pH with the increase of BMI in 420 lithiasic women and in 290 healthy control women.

We observed that hypercalciuria was the most frequent diagnosis in women independent of the body weight and unlike other authors [13] it did not increase with the rise in BMI. We could not assess if old women were receiving any type of antiresorptive medication that could affect calcium excretion. In male stone patients hypercalciuria was the most frequent diagnosis only in those with normal weight.

On the other hand, Ekerou et al. [13] were the first to assess the difference in the diagnoses with changes in body weight, but considered only between obese (BMI > 30) and non-obese patients. They found in 83 obese stone patients that GD was significantly most frequent (54%) compared to the non-obese patients (18%) and HU was also significantly prevalent in the OB group (43%) compared to the non-obese patients (20%). They also found a significant increase in hyperoxaluria in the obese stone patients. Several years ago Lemann et al. [22] showed that even in normal subjects urinary oxalate excretion increases with body size. In our study, we also observed a trend to increase in this metabolic diagnosis in both groups of men, but it was not significant. In the study by Ekerou et al. [13], although they did not separate by gender, they found that hypercalciuria was significantly more frequent in the obese patients (59 vs. 48%). The stone analysis of our study has one important limitation: it was only done in 263 of 817 patients. Despite this limitation, the analysis of renal stones showed that calcium oxalate stones predominate in all weight stratums. Calcium oxalate, calcium phosphate and mixed calcium oxalate + calcium phosphate stone frequency were similar in the three BMI groups. However, pure uric acid stones or mixed with calcium oxalate were significantly increased in overweight/obese patients compared with normal weight patients (6.5 vs. 16.6%; $p = 0.03$). As expected, the differences were attributable to men, as they had more frequently hyperuricosuria and gouty diathesis with increasing weight.

We conclude that the most important findings of our study are that Hyperuricosuria and Unduly acidic urine pH or gouty diathesis were the only abnormalities that increased their prevalence significantly with increasing BMI. Hyperuricosuria increased its prevalence significantly in both sexes except in women over 50 years of age, while gouty diathesis increased significantly only in men. We also observed that idiopathic hypercalciuria was the most frequent abnormality observed in women independent of weight and age and significantly more frequent than in males. Hyperoxaluria and gouty diathesis were significantly more frequent in men.

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