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Influence of body size on urinary stone composition in men and women

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Abstract A larger body size has been shown to be associated with increased excretion of urinary lithogenic solutes, and an increased risk of nephrolithiasis has been reported in overweight patients. However, the type of stones produced in these subjects has not been ascertained. Based on a large series of calculi, we examined the relationship between body size and the composition of stones, in order to assess which type of stone is predominantly favoured by overweight. Among 18,845 consecutive calculi referred to our laboratory, 2,100 came from adults with recorded body height and weight. Excluding calculi from patients with diabetes mellitus, as well as struvite and cystine stones, the study material consisted of 1,931 calcium or uric acid calculi. All calculi were analysed by infrared spectroscopy and categorized according to their main component. Body mass index (BMI) values were stratified as normal BMI (<25 kg/m^2), overweight (BMI 25–29.9) or obese (BMI≥30). Overall, 27.1% of male and 19.6% of female stone formers were overweight, and 8.4 and 13.5% were obese, respectively. In males, the proportion of calcium stones was lower in overweight and obese groups than in normal BMI group, whereas the proportion of uric acid stones gradually increased with BMI, from 7.1% in normal BMI to 28.7% in obese subjects ($P<0.0001$). The same was true in females, with a proportion of uric acid stones rising from 6.1% in normal BMI to 17.1% in obese patients ($P=0.003$). In addition, the proportion of uric acid stones markedly rose with age in both genders ($P<0.0001$). The average BMI value was significantly higher in uric acid stone formers aged <60 years than in all other groups, whereas it did not differ from other groups in those aged ≥60 years. Stepwise regression analysis identified BMI and age as significant, independent covariates associated with the risk of uric acid stones. Our data provide evidence that overweight is associated with a high proportion of uric acid stones in patients less than 60 years of age, whereas beyond this limit, advancing age is the main risk factor.

Keywords Body mass index · Overweight · Obesity · Nephrolithiasis · Uric acid

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Introduction

The prevalence of nephrolithiasis has been relentlessly increasing over the past half-century [1–3], in parallel with marked changes in dietary habits in all affluent societies [4]. Simultaneously, another untoward consequence of the changes in Western diet was the epidemic progression of obesity in all industrialized countries over the past decades [5–7]. This temporal coincidence in the prevalence of overweight and nephrolithiasis led to the suspicion that overweight might be a risk factor for the formation of renal stones. In support of this hypothesis, a larger body size was shown to be associated with an increased prevalence and incidence of kidney stone disease in both genders in two large-scale epidemiological studies [8, 9]; however, these studies did not disclose the type of stones. In other studies, obesity was associated with a higher urinary excretion of lithogenic solutes, including calcium, oxalate and uric acid, all factors potentially favouring calcium oxalate (CaOx) stone formation [10–13]. On the other hand, it was recently shown that urinary pH has a strong, graded inverse association with body weight in patients with urinary stones [14]. Because a low urine pH is the major risk factor for uric acid (UA) stone formation [15], overweight may thus also favour UA nephrolithiasis. As a matter of fact, the prevalence of UA stones was reported to be higher in obese stone formers than in lean subjects [16] and, reciprocally, body size was found to be significantly higher in patients with idiopathic UA nephrolithiasis than in calcium stone formers [17, 18].

Thus, it may be that overweight may just as well favour UA as CaOx stone formation. However, until now, the influence of body size on the chemical type of stones formed had not been evaluated. In a previous study, we reported the influence of age and gender on urinary stone composition and showed that the proportion of UA stones increased with age in both genders [19]. In the present study, we examined the influence of body size, as reflected by the body mass index (BMI), on the distribution of stone components in a large series of consecutive calculi referred to our laboratory over the recent period.

Materials and methods

From January 1, 1997 to December 31, 2003, 18,845 consecutive calculi from patients aged ≥15 years (13,165 males, 5,680 females) were referred for analysis to Laboratoire CRISTAL. We included in the study only calculi from patients for whom information on both body weight and height was available. There were 2,100 calculi from patients for whom anthropometric determinations had been provided, thus allowing us to calculate BMI. These 2,100 patients did not differ from the 16,745 other patients without available BMI in terms of age (47.8 ± 14.3 vs. 47.6 ± 12.7, NS), sex ratio (M/F 2.31 vs. 2.32) and stone component distribution (calcium stones 89.8 vs. 91.2%, NS; UA stones 10.2 vs. 9.8%; NS). In particular, the distribution of the main components of calcium stones was comparable in the two groups, whether considering CaOx monohydrate (50.3 vs. 50.9%) or dihydrate (24.5 vs. 24.1%) or calcium phosphate (15.0 vs. 15.2%). We excluded from the analysis 83 calculi from patients with diabetes mellitus, because diabetes by itself may influence stone composition as suggested by recent studies [20, 21], and 86 struvite and cystine calculi, because they are secondary to specific causes not known to be influenced by body size. Finally, the study material comprised calculi from 1,931 non-diabetic adult stone-forming patients (1,370 males, 561 females).

Each stone was analysed according to our previously published protocol [22, 23]. In short, morphological examination of both surface and section of calculi was followed by sequential Fourier transform infrared (FTIR) spectroscopic analysis, with quantification of the various stone components. Calculi were classified into four categories based on their main component (i.e. accounting for 50% or more of the stone content): calcium oxalates, with distinction between CaOx monohydrate (or whewellite, Ww) and CaOx dihydrate (or weddellite, Wd), calcium phosphates (CaP) including carbapatite and brushite and UA (including anhydrous and dihydrate forms).

Body mass index was calculated by dividing the weight (in kilograms) by the square of the height (in meters). Individual BMI values were stratified into three categories, the highest two corresponding to the World Health Organization definitions of overweight (BMI 25–29.9) and obesity (BMI≥30). Patients with a BMI < 25 were taken as the reference, normal BMI group. Distribution of BMI in the present series of stone formers was compared with the data on BMI distribution in the general French population known by a nation-wide inquiry conducted in the year 2000, i.e. in the middle of our study period [24].

Statistical analysis

Results are presented as means ± SEM. Categorical comparisons were performed using the Chi^2 test. Multiple logistic regression analysis was used to evaluate the relative risk, estimated by the odds ratio of BMI and age on the occurrence of the various types of stones in both genders.

Results

Prevalence of overweight in stone formers

Overall, 672 (34.8%) patients had a BMI≥25, including 24.9% overweight and 9.9% obese. The proportion of overweight was higher in males than in females (27.1 vs. 19.6%, $P < 0.001$), whereas the proportion of obesity was higher in females than in males (13.5 vs. 8.4%, $P < 0.001$). As a result, the global proportion of stone formers with a BMI≥25 was similar in males and females, at 35.5 and 33.1% ($P = 0.33$), respectively. However, the proportion of patients with a BMI≥25 was significantly higher in UA than in calcium stone formers (54.3 vs. 33.4%, $P < 0.001$).

In 26,982 subjects representative of the French general population in the year 2000 [24], the overall proportion of subjects with a BMI≥25 was 39%, a figure close to the average value observed over the 7-year period, 1997–2003, in our series. The proportion of overweight subjects was the highest in males whereas obesity was more frequent in females, as was also observed in our patients.

Distribution of stones with respect to BMI

The distribution of the four types of stones within the three classes of BMI differed between men and women.

In male stone formers (Table 1), calcium-containing stones accounted for 89.9% of the total series of 1,370 stones. As compared with the normal BMI group, the global proportion of calcium stones was lower in the overweight group (88.7 vs. 92.9%, $P = 0.011$) and even more so in the obese group (71.3 vs. 92.9%, $P < 0.0001$).

Table 1 Distribution of the various types of calculi from 1,370 men with respect to BMI

Type of stones	< 25 (n = 884)	25–29.9 (n = 371)	≥30 (n = 115)	P value (overall Chi^2)
Whewellite (n = 687)	446 (50.4)	194 (52.3)	47 (40.9)	0.096
Weddellite (n = 409)	275 (31.1)	109 (29.4)	25 (21.7)	0.16
Total calcium oxalate (n = 1,096)	721 (81.5)	303 (81.7)	72 (62.6)	< 0.0001
Carbapatite (n = 106)	75 (8.5)	23 (6.2)	8 (7.0)	0.36
Brushite (n = 30)	25 (2.8)	3 (0.8)	2 (1.7)	0.078
Total calcium phosphate (n = 136)	100 (11.3)	26 (7.0)	10 (8.7)	0.059
Total calcium stones (n = 1,232)	821 (92.9)	329 (88.7)	82 (71.3)	< 0.0001
Uric acid stones (n = 138)	63 (7.1)	42 (11.3)	33 (28.7)	< 0.0001

The proportion of Ww stones did not differ between normal BMI and overweight groups, but was marginally lower in the obese group (40.9 vs. 50.4%, $P = 0.053$). The proportion of Wd stones was significantly lower in the obese group than in the normal BMI group ($P = 0.039$). The proportion of CaP stones, either carbapatite or brushite, was the highest in lean subjects. In contrast, the proportion of UA stones markedly increased with BMI, from 7.1% in normal BMI to 11.3% in overweight and 28.7% in obese men (overall Chi^2, $P < 0.0001$).

In female stone formers (Table 2), calcium-containing stones accounted for 91.1% of the total series of 561 stones, a global proportion similar to that observed in males. The proportion of calcium-containing stones decreased from the normal BMI to the overweight group (93.9 to 87.3%; $P = 0.02$) and to the obese group (82.9%, $P < 0.002$). Among calcium stones, the distribution of Ww and Wd stones did not vary significantly with BMI, whereas the proportion of CaP stones, either carbapatite or brushite, was significantly lower in the obese group as compared to the other two BMI groups ($P < 0.05$). Of note, carbapatite stones were three times more frequent in females than in males, whereas a male preponderance was observed in brushite stones. As in males, the proportion of UA stones markedly increased with BMI, rising from 6.1% in the normal BMI group to 12.7% in overweight and 17.1% in obese groups (overall Chi^2, $P = 0.003$). Finally, in both males and females, only the proportion of UA stones rose with BMI, with this effect more marked in males.

Combined influence of BMI and age

Because our previous study had shown an increasing proportion of UA stones with ageing [19], we further analysed the respective influence of body size and age on the distribution of stone components. In the whole series of stone formers, the BMI was slightly lower in patients aged < 40 years, whereas there was no difference between the 40–59.9 and ≥60 year groups, both in males and females (Table 3). This essentially reflects the findings in patients with calcium stones who account for the largest part of patients. In contrast, BMI was markedly higher in UA stone formers aged < 40 years and 40–59.9 years as compared to older ones, both in males and females. However, a decrease in BMI was observed in old subjects, i.e. subjects aged 65 years or more, in both calcium and UA stone formers, as in the general population (Fig. 1).

Multivariate analysis

Stepwise logistic regression analysis examined the respective influence of age, gender and BMI on the various types of stones. For Ww stones, age was the only factor selected, not gender nor BMI. For Wd stones, both gender and age, and not BMI, were the significant risk factors. In contrast, for CaP stones, gender, BMI and age (in decreasing order) were significant risk factors. For UA stones, BMI and age were identified as significant risk factors. The relative risk of having, or not having, UA stones was further examined by logistic regression with age and BMI as continuous variables (Table 4). In the whole series, both BMI and age were significant, independent variables associated with UA stones and the same was true for patients aged < 60 years with the BMI having the most marked influence. In contrast, in patients aged ≥60 years, age became the most important factor.

Table 2 Distribution of the various types of calculi from 561 women with respect to BMI

Type of stones	< 25 (n = 375)	25–29.9 (n = 110)	≥30 (n = 76)	P value (overall Chi^2)
Whewellite (n = 279)	184 (49.1)	57 (51.2)	38 (50.0)	0.87
Weddellite (n = 75)	56 (14.9)	8 (7.3)	11 (14.5)	0.11
Total calcium oxalate (n = 354)	240 (64.0)	65 (59.1)	49 (64.5)	0.62
Carbapatite (n = 146)	104 (27.7)	29 (26.4)	13 (17.1)	0.16
Brushite (n = 11)	8 (2.1)	2 (1.8)	1 (1.3)	0.89
Calcium phosphate (n = 157)	112 (29.9)	31 (28.2)	14 (18.4)	0.128
Total calcium stones (n = 511)	352 (93.9)	96 (87.3)	63 (82.9)	0.0027
Uric acid stones (n = 50)	23 (6.1)	14 (12.7)	13 (17.1)	0.0027

Table 3 Distribution of BMI with respect to the various types of calculi and age classes in both sexes

	< 40 years ($n=640$)	40–59.9 years ($n=870$)	≥60 years ($n=421$)	P value (40–59.9 vs. ≥60)	P value (overall Chi^2)
Whole series					
Males ($n=1,370$)	24.3 ± 0.2 (458)	25.5 ± 0.1 (620)	25.3 ± 0.2 (292)	NS	< 0.001
Females ($n=561$)	24.2 ± 0.4 (182)	24.9 ± 0.3 (250)	24.9 ± 0.4 (129)	NS	0.29
Calcium stones					
Males ($n=1,232$)	24.2 ± 0.1 (449)	25.2 ± 0.1 (563)	25.2 ± 0.1 (220)	NS	< 0.0001
Females ($n=511$)	24.1 ± 0.4 (179)	24.5 ± 0.3 (227)	25.2 ± 0.5 (105)	NS	0.18
Uric acid stones					
Males ($n=138$)	31.9 ± 1.5 (9)	28.8 ± 0.6 (57)	25.6 ± 0.5 (72)	< 0.0001	< 0.0001
Females ($n=50$)	32.1 ± 3.3 (3)	28.3 ± 1.2 (23)	23.9 ± 1.2 (24)	0.009	< 0.0001

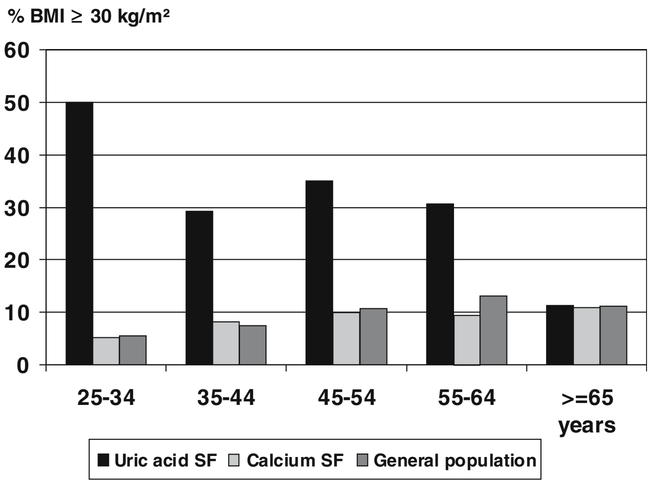

Fig. 1 Proportion of obese subjects (BMI≥30 kg/m^2) with respect to age in uric acid and calcium stone formers (SF) and in the French general population

Discussion

The aim of the present study was to examine the association between body weight and the composition of stones in nephrolithiasis patients, with the hypothesis that overweight may favour UA rather than CaOx stone formation. Our findings confirm this hypothesis by showing that BMI in excess of 25 kg/m^2 is associated with an increased proportion of UA stones, and not of calcium-containing stones. In addition, they show that the influence of body weight on the risk of UA stones is especially apparent in patients aged less than 60 years, whereas beyond this limit increasing age is the predominant factor.

Table 4 Logistic regression analysis of factors associated with uric acid stones

Variables	Odds ratios (95% CI)	P value
Whole series ($n=1,931$)		
BMI^a	1.09 (1.08–1.10)	< 0.0001
Age^b	1.04 (1.03–1.05)	< 0.0001
Aged < 60 years ($n=1,510$)		
BMI^a	1.11 (1.10–1.12)	< 0.0001
Age^b	1.02 (1.00–1.04)	0.005
Aged ≥60 years ($n=421$)		
Age^b	1.05 (1.01–1.08)	< 0.001
BMI	1.044 (0.995–1.095)	0.07

^{a}Per 1 kg/m^2 BMI
^{b}Per 1 year of age

The hypothesis of a possible relationship between excess weight and stone formation was suggested by the temporal parallelism between the rising incidence of obesity and of urolithiasis in the recent decades in Western countries. However, studies examining whether a larger body size is associated with an increased risk of stone formation gave inconclusive results.

Several epidemiological studies concluded to an association between the body size and nephrolithiasis. Based on two large cohorts in the USA (the Nurse's Health Study I, or NHS I, and the Health Professionals Follow-up Study, or HPFS), Curhan et al. [8] found the prevalence of a stone history and the incidence of stone episodes to be directly associated with BMI, the magnitude of the association being greater among women; however, the type of stones was not known. In a subsequent study by the same group [9], obesity at baseline and weight gain during follow-up were both associated with the risk of incident stone episodes, the magnitude of the effect of BMI again being greater in women than in men, but the type of stones was not defined. Among 527 CaOx stone formers evaluated by Siener et al. [13], a BMI≥25 was found in as many as 59.2% of male and 43.9% of female patients, but the prevalence of obesity in the German population over the same period was not given.

Studies based on case–control methodology gave conflicting results. Earlier ones found no difference in body weight between the calcium stone formers and controls. More recently, Nishio et al. [25] reported a higher mean BMI in male Japanese calcium stone formers than in controls, but the difference was apparent only in the third and sixth decades of life. Serio and Fraioli [26] reported the proportion of subjects with a BMI > 25 to be higher among male and female stone formers than in the general Italian population, but the type of stones was not given. Hall et al. [27] found a significantly higher BMI in 1,179 stone-forming women aged ≥50 years than in their age-matched non-stone-forming counterparts, without precision as to the type of stones. In another study in the USA by Curhan et al. [28], the mean body weight of prevalent stone formers as compared to age-matched controls was also found to be higher among older women (NHS I cohort), but lower in younger women (NHS II cohort) and in men (HPFS cohort).

In the present series, a BMI value ≥25 was found in nearly 35% of stone formers, a figure close to the proportion of 39% observed in the nation-wide OBEPI study in the French general population [24]. The overall proportion of obese subjects (≥30) was slightly higher in our stone formers than in the OBEPI study (9.9 vs. 8.8%), but no formal statistical comparison can be made because the studied populations were not identical. Of note, there was a tendency towards lower BMI values in oldest subjects (aged 65 years or more) in the general population as well as in our series of stone formers as shown in Fig. 1.

Studies evaluating metabolic risk factors possibly associated with the risk of CaOx stone formation in overweight patients similarly led to conflicting conclusions. The common hypothesis was that overweight patients, due to high food intake, may have a higher urinary excretion of lithogenic solutes, especially oxalate, calcium and uric acid. Powell et al. [11] reported increased urinary concentrations of sodium, uric acid, sulphate and phosphate in obese stone formers of both genders and of oxalate in males only. In the study of Ekeruo et al. [16], obese stone formers had higher calcium, uric acid, oxalate and sulphate urinary excretion than their non-obese counterparts. In their cohort of 527 CaOx stone formers, Siener et al. [13] observed a higher daily urinary excretion of sodium, calcium, phosphate, sulphate and uric acid in both men and women with a BMI≥25, and of oxalate in women only. However, in another study by the same group [12], the mean BMI value was similar in patients with or without hyperoxaluria, and multiple logistic regression analysis showed no association between BMI and urinary oxalate excretion. Conversely, Lemann et al. [10] found body size to be the major determinant of urinary oxalate excretion among healthy adults in both genders. Thus, there is no consensus as to the association of body size with urinary oxalate excretion and the risk of CaOx stone formation.

In contrast, there are convincing arguments to suggest a role of obesity in favouring the formation of UA stones, the major risk factors of which are a low urine pH and hyperuricosuria [15, 29–31]. Maalouf et al. [14] recently showed that urinary pH has a strong, inverse association with body weight, so that overweight patients appear to be at risk of the formation of acidic urine. Accordingly, urinary pH was significantly lower in obese than in non-obese stone formers and UA was found in calculi as many as 63% of the former, as compared to 11% in the study of Ekeruo et al. [16]. Reciprocally, BMI was markedly higher in patients with idiopathic uric acid nephrolithiasis than in hyperuricosuric CaOx stone formers and in control subjects [15, 32]. The same was observed in our patients in whom the proportion of obese subjects was strikingly higher in UA than in calcium stone formers.

A common pathophysiological mechanism, i.e. insulin resistance, was recently proposed to explain the relationships between obesity and uric acid nephrolithiasis [18, 33]. Indeed, the low urinary pH characteristic of idiopathic UA stone formers has been shown by Sakhaee et al. [18] to be associated with a decreased ammonium excretion, which itself may be a renal manifestation of insulin resistance, as recently shown by Abate et al. [33] in overweight patients with recurrent UA nephrolithiasis. Thus, it results that overweight patients are likely to be at a high risk of forming UA stones. Confirming this hypothesis, our data provide evidence of the major influence of an increasing BMI on the risk of forming uric acid stones, as the proportion of uric acid stones was nearly two times higher in overweight and nearly four times higher in obese patients than in lean patients in both genders. In addition, they point out a not yet reported finding, i.e. that influence of overweight is apparent mainly in patients under 60–65 years of age, whereas an increasing age is the major factor in older persons. Because decreased ammonium excretion resulting in a lower urinary pH is frequent in the elderly [34, 35], age-associated defective urinary acidification may be the major contributing factor in older subjects. Indeed, prevalence of insulin resistance also increases with age [6] and may at least in part be related to an age-associated decline in mitochondrial function [36]. A combination in variable proportions of these factors may explain why the proportion of UA stones increases in older subjects even in the absence of overweight.

Finally, we suggest as a unifying hypothesis that insulin resistance, a frequent metabolic consequence of obesity, may be the link between overweight, production of acidic urine and formation of UA stones in overweight patients. In addition, the increasing prevalence of insulin resistance with ageing could explain the formation of UA stones in older subjects irrespective of body weight.

On a practical point of view, our data suggest that overweight/obese subjects are at particular risk of UA nephrolithiasis. They should be screened for the presence of silent, asymptomatic stones and risk factors for UA stone formation, namely urine pH and uricosuria. From a broader perspective, overweight/obese subjects with diagnosed UA nephrolithiasis should be especially screened for components of the metabolic syndrome, in accordance with current recommendations [37]. Similar recommendations may be applicable to older subjects with UA nephrolithiasis.

A limitation of our study is that it was only based on the analysis of a series of stones from patients with known body height and weight. Therefore, we could not determine whether, or not, the global incidence of nephrolithiasis was higher in overweight than in normal-sized subjects. However, even if we cannot exclude that the incidence of CaOx stone increases with increasing BMI, our data provide clear evidence that there is a shift towards UA stone production in overweight/obese subjects. Another limitation is that we had no information as to the serum and urinary biochemistry of patients, so that we could not analyse the relationship between BMI and lithogenic factors in the various types of stones. Further studies are needed to evaluate urinary pH, ammonium excretion and glucose tolerance together with all lithogenic parameters in calcium and UA stone formers in a wide range of BMI and age.

In conclusion, our results indicate that overweight and obesity are electively associated with an increased proportion of uric acid stones, and not of calcium oxalate or phosphate stones, and that the influence of a larger body size on the formation of UA stones is mainly apparent in subjects aged < 60 years. In older subjects, frequency of UA stones increases even in the absence of overweight. Such findings may have clinical relevance. They suggest that evaluation of overweight stone formers should not be limited to risk factors of calcium oxalate stone formation, but also be oriented to search for risk factors of uric acid nephrolithiasis, especially in middle-aged adults. Reciprocally, overweight subjects with UA nephrolithiasis should be evaluated for the presence of the metabolic syndrome.

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