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ORIGINAL ARTICLE

Determinants of calcium and oxalate excretion in subjects with calcium nephrolithiasis: the role of metabolic syndrome traits

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Abstract

Background The association of metabolic syndrome (MetS) traits with urinary calcium (UCE) or oxalate excretion (UOE) is uncertain in calcium stone formers (CSFs). Our aim was to investigate this association in a large group of Caucasian CSFs.

Methods We retrospectively reviewed data of CSFs evaluated at our Kidney Stone Clinic from 1984 to 2015. Data on body mass index (BMI), MetS traits defined according to international consensus, family history of urolithiasis, anti-hypertensive treatments, calcemia, renal function, and 24-h urinary profile of lithogenic risk were collected. The association between MetS traits and UCE or UOE was tested with multivariate linear regression models accounting for a long list of potential confounders.

Results We included 3003 CSFs, aged 44 ± 14 years. The prevalence of hypertension, diabetes, overweight (BMI ≥ 25 kg/m^2) and dyslipidemia was 17, 2, 42 and 38%, respectively. Median values of UCE and UOE were 211 mg/24 h (IQR 143–296) and 28 mg/24 h (IQR 22–34), respectively. At a multivariate model, including age, sex, date of examination, drug treatments, family history, renal function, blood calcium and urinary factors as covariates, hypertension was a significant positive determinant of UCE (β ± SE 0.23 ± 0.07, p = 0.003), but overweight, dyslipidemia and diabetes were not. No MetS trait was significantly associated with UOE in multivariate models.

Conclusions In a large group of Caucasian CSFs, hypertension was the only MetS trait significantly associated with UCE, while no MetS trait was associated with oxalate excretion.

Keywords Hypertension · Diabetes · Obesity · Dyslipidemia · Hypercalciuria · Urolithiasis

Introduction

Metabolic syndrome (MetS) is significantly associated with a higher prevalence of nephrolithiasis [1]. In a large American population-based cross-sectional study, the odds of kidney stone disease significantly increased with the number of MetS traits, i.e. arterial hypertension, diabetes, dyslipidemia and abdominal obesity [2]. In stone formers (SFs), MetS traits are also significantly associated with a more complicated clinical course of nephrolithiasis [3].

Even if MetS influences a lower urinary pH in SFs, theoretically predisposing to uric acid stones, the most frequent stone composition remains calcium oxalate. Hypercalciuria, defined as calcium excretion ≥ 4 mg/kg/day or ≥ 250 mg/day in females and ≥ 300 mg/day in males, is the most frequent urinary metabolic risk factor of calcium nephrolithiasis [4], with a prevalence of 25–38% [5]. These definitions of high urinary calcium excretion (UCE) should be applied only under controlled dietary calcium intake [4], but are widely used in clinical practice even though no clear thresholds for risk of stone formation have been identified in subjects on a free diet [4, 5]. Urinary oxalate excretion (UOE) ≥ 20 mg/

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day is associated with an increased risk of calcium nephrolithiasis as well [6].

The influence of MetS traits on UCE and UOE in calcium SFs is not completely understood, since studies have focused on each trait in a separate way or have given conflicting results [7]. In 11,555 Japanese SFs, Kohjimoto et al. reported that, among MetS traits, hypertension and dyslipidemia were associated with hypercalciuria (UCE ≥ 4 mg/kg/day), while only dyslipidemia was associated with hyperoxaluria (UOE ≥ 45 mg/day) [3]. Sakhaee and colleagues, instead, showed that the association between MetS traits and UCE was not independent of covariates in smaller groups of American and Swiss SFs [8]. Finally, Taylor and Curhan demonstrated that overweight and diabetes, but not other MetS traits, were significant determinants of a high UOE in American adults with and without nephrolithiasis [9].

Thus, the aim of our retrospective study was to assess the possible association between MetS traits and UCE or UOE in a large group of Caucasian calcium SFs from Italy.

Methods

Study population

We considered for study inclusion all the SFs evaluated at the Kidney Stone Clinic of our University Hospital from 1984 to 2015. The clinical management and laboratory methods of urine analysis remained the same throughout this time period and were performed by the same skilled personnel, limiting possible information bias and missing data [10].

Included in the study were subjects with calcium stones who were 18 years or older at the time of the first renal colic and who underwent a complete clinical and laboratory evaluation with medical and pharmacologic history, physical examination, height, weight and blood pressure measurement, serum and 24-h urine analyses. The calcium composition of stones was assessed by the presence of one of the following: composition of passed stones with at least 80% calcium salts, radio-opaque retained stones at abdominal X-ray, calcium oxalate crystals in urine sediment.

Excluded were subjects with chronic kidney disease (creatinine clearance < 60 ml/min), secondary forms of calcium nephrolithiasis (such as hyperparathyroidism and intestinal diseases causing enteric hyperoxaluria), uric acid or radiotransparent calculi, mixed calculi (uric acid ≥ 20% in composition), recurrent urinary tract infections (UTIs) or struvite stones, urinary tract malformations or neurological diseases associated with voiding dysfunction. We also excluded patients with a past history of acute coronary syndrome or cerebrovascular accident, since the drug and lifestyle prescriptions given to these subjects could have affected MetS traits definition before the first visit to our center. Subjects taking calcium or alkali supplements, or with missing data on clinical records were excluded as well.

Data collection

The institutional electronic clinical record database was reviewed for participant selection. For each eligible SF, we collected data about age, sex, family history of stones, body mass index (BMI), presence of arterial hypertension, overweight, diabetes mellitus and dyslipidemia at the time of the baseline evaluation at our center. The use of antihypertensive, glucose-lowering and lipid-lowering agents was also considered.

Baseline laboratory data routinely assessed in our center were collected too. They included fasting serum calcium, cholesterol, triglycerides, glucose and creatinine, and full 24-h urinary profile of lithogenic risk (including pH, volume and excretion of calcium, oxalate, phosphate, uric acid, citrate, magnesium, potassium, sulfate, ammonium, sodium and creatinine). Twenty-four hour urine samples were collected while patients were on a free diet. Anti-hypertensive treatments known to affect calciuria, such as thiazide diuretics, vitamin D, and multivitamins were suspended 1 week before the collection. This management is in line with recommendations for metabolic diagnosis and medical prevention of urolithiasis by international consensus groups [11].

Urinary calcium, magnesium, potassium and sodium were determined by atomic absorption spectrophotometry; sulfate, phosphate and oxalate by ion chromatography; ammonium by the Berthelot colorimetric method; citrate by the citrate lyase method; uric acid by the uricase method and creatinine by the Jaffé method. All laboratory procedures regarding urine analyses were carried out by the same technician and remained consistent through the years [10]. Glomerular filtration rate (GFR) was estimated through the creatinine clearance formula.

MetS traits were defined according to international consensus statement [12]. Arterial hypertension was defined as the presence of elevated blood pressure (systolic > 135 mmHg, diastolic > 85 mmHg) on three repeated ambulatory measures taken during the baseline visit or as the presence of chronic antihypertensive drug treatment [12]. Since waist circumference data were available only in a minority of SFs, overweight was defined as BMI ≥ 25 kg/m^2. BMI was considered as a proxy of waist circumference since it is strongly correlated with this parameter in Caucasian subjects [13]. Dyslipidemia was defined as elevated fasting serum triglycerides (≥ 150 mg/dl) or reduced high-density lipoprotein (HDL) cholesterol (< 40 mg/dl in males and < 50 mg/dl in females) or active lipid-lowering treatment [12]. Diabetes mellitus was defined according to the presence of active glucose-lowering treatment [12].

Statistical analyses

Data were expressed as mean ± standard deviation for continuous variables with normal distribution, median and interquartile range (IQR) in the case of non-normally skewed distributions, or percentages for categorical variables. Clinical and laboratory variables were compared using Student's t, Mann–Whitney or Chi square tests as appropriate. Bonferroni test was applied for multiple comparisons among groups of SFs with different MetS traits (i.e. hypertension alone, overweight alone, dyslipidemia alone, obesity alone, more than one trait), taking the group without MetS traits as reference.

UCE and UOE were considered as outcome variables. In descriptive analyses, hypercalciuria was defined as UCE ≥ 4 mg/kg/24 h, even if some experts claim that this definition is not pathophysiologically rigorous in SFs on a free diet [4]. Similarly, hyperoxaluria was defined as UOE > 40 mg/day according to recent consensus [11, 14]. However, since some population-based studies have demonstrated that the risk of kidney stone formation is positively associated with UCE and UOE with no clear threshold effect [5, 6], UCE and UOE were also handled as continuous variables. Unadjusted Pearson correlation analysis was carried out as a preliminary analysis, to verify the correlation between MetS traits and UCE and UOE. Multivariate logistic regression analysis was then performed. To approximate normal distributions, log-transformed values for UCE and UOE were used in the multivariate analyses, and back-transformed for data presentation.

The association of MetS traits with UCE and UOE was verified through multivariate linear regression models. In these models, all MetS traits were considered, together with age and sex. Additional covariates for multivariate models were selected among factors that have been demonstrated in the scientific literature to significantly influence UCE and UOE in SFs or healthy subjects [4]. These factors included: urinary sodium, as a proxy of dietary salt intake; urinary ammonium and citrate, as significantly related to dietary acid load; urinary sulfate, as a proxy of animal protein intake influencing calcium excretion independently of acid load; urinary pH and volume; family history of stones; and GFR. Serum calcium and antihypertensive treatment were also included in multivariate models, since their effect on urinary calcium excretion could not be excluded. Finally, the date of patient evaluation was also included as a possible confounding factor, given the wide time span of enrolment and the demonstrated "secular trend" in lifestyle habits of SFs [10]. All statistical analyses were performed with SAS, version 9.1 (SAS Institute Inc., Cary, NC, USA). P values were considered as significant when < 0.05.

Results

General characteristics of the study population

The total number of eligible patients visited at our Stone Clinic was 4680. The number of SFs included in the study, according to inclusion and exclusion criteria, was 3003 (1710 M, 1293 F, mean age 44 ± 13 years). Calcium composition of stones was determined by stone analysis in 1526 cases (50.8%), and inferred by the presence of radio-opaque images in abdominal radiographs or calcium salt crystals in urinary sediment in 832 (27.7%) and 645 (21.5%) cases, respectively.

Among the SFs, 990 (32.9%) had no MetS traits, and thus were considered as the reference group for statistical analyses, and 1245 (41.4%) had one trait alone (112 hypertension, 558 overweight, 568 dyslipidemia, 7 diabetes). In 768 (25.7%) SFs, at least two MetS traits coexisted. The clinical and metabolic characteristics of these groups are reported in Table 1, which includes a within-group comparison of the characteristics with the Bonferroni test. Thus, the prevalence of hypertension, overweight, dyslipidemia and diabetes mellitus in the sample was 17.0% (511 patients), 41.5% (1247 patients), 38.3% (1149 patients) and 1.8% (55 patients), respectively.

MetS traits and UCE

The median value of UCE was 211 mg/24 h (IQR 143–296). Hypercalciuria (UCE ≥ 4 mg/kg/day) was present in 914 SFs (30.4%). The prevalence of hypercalciuria was 35.4% in SFs with no MetS traits, 43.7% in those with hypertension alone, 42.0% in those with dyslipidemia alone, 17.0% in SFs with overweight alone, 14.0% in those with diabetes alone, and 23.2% in SFs with more than one trait (Table 1; Fig. 1). Multiple comparisons did not show significant differences in prevalence of hypercalciuria within the considered groups. However, unadjusted Pearson correlation analysis, shown in Table 2, demonstrated a significant correlation between hypercalciuria and hypertension ($r = 0.03$, $p = 0.04$) and dyslipidemia ($r = 0.04$, $p = 0.02$).

At multivariate linear regression analysis, considering multiple potential confounding factors, hypertension was significantly and positively associated with UCE (β ± SE 0.23 ± 0.07, $p = 0.003$), while other MetS traits were not (Table 3). Other factors showing a significant association with UCE included age, date of the examination, family history of stones, GFR, active antihypertensive treatment, urinary pH, and excretion of sodium, sulfate, ammonium and citrate (Table 3).This association persisted also when subjects chronically taking thiazide diuretics as antihypertensive medication ($n = 112$) were excluded from the multivariate analysis ($p < 0.001$).

Table 1 General characteristics of the studied population of calcium SFs, categorized according to the number and type of metabolic syndrome traits

	Overall population (N = 3003)	No metabolic syndrome traits (N = 990) (1)	Arterial hypertension alone (N = 112) (2)	Overweight alone (N = 558) (3)	Dyslipidemia alone (N = 568) (4)	Diabetes mellitus alone (N = 7) (5)	> 1 metabolic syndrome trait (N = 768) (6)	p < 0.05 Bonferroni test
Age, years	44 ± 13	42 ± 15	40 ± 15	41 ± 15	50 ± 13	43 ± 17	47 ± 13	(1) vs. (4) vs. (6)
Females, %	43.1	50.8	48.2	26.0	53.3	28.5	35.9	(1) vs. (3) vs. (6)
Weight, kg	66.3 ± 12.1	62.9 ± 9.9	63.1 ± 10.4	81.7 ± 11.2	62.7 ± 9.7	61.0 ± 4.9	81.2 ± 14.0	(1) vs. (3) vs. (6)
Height, cm	168 ± 10	169 ± 9	167 ± 10	171 ± 9	169 ± 9	167 ± 5	169 ± 9	(1) vs. (3)
BMI, kg/m^2	23.6 ± 3.7	21.9 ± 2.1	22.5 ± 2.1	28.0 ± 2.5	21.9 ± 2.1	22.1 ± 2.2	28.2 ± 3.8	(1) vs. (3) vs. (6)
Family history of stones, n (%)	1261 (42.0)	438 (44.2)	52 (46.4)	247 (44.4)	226 (39.9)	2 (28.5)	296 (38.6)	–
Blood calcium, mg/dl	9.6 ± 0.7	9.8 ± 0.3	9.4 ± 0.4	9.4 ± 0.5	9.5 ± 0.5	9.7 ± 0.3	9.4 ± 0.4	–
GFR, ml/min	112 ± 31	111 ± 29	114 ± 31	113 ± 32	111 ± 32	120 ± 38	113 ± 33	–
Hypercalciuria, n (%)	914 (30.4)	352 (35.4)	49 (43.7)	95 (17.0)	239 (42.1)	1 (14.2)	178 (23.2)	–
Hyperoxaluria, n (%)	382 (12.7)	128 (12.9)	12 (10.7)	73 (13.1)	71 (12.5)	1 (14.0)	97 (12.6)	–
Calciuria, mg/24 h	211 [143–296]	220 [151–307]	222 [149–314]	214 [142–294]	215 [143–307]	232 [165–304]	216 [141–305]	(1) vs. (5)
Oxaluria, mg/24 h	28 [22–34]	28.7 ± 10.0	28.9 ± 8.8	29.3 ± 9.9	29.6 ± 9.7	35.5 ± 17.7	29.4 ± 9.4	–
Phosphaturia, mg/24 h	789 ± 279	757 ± 274	818 ± 287	776 ± 281	817 ± 274	706 ± 173	816 ± 284	(1) vs. (4) vs. (6)
Sodiuria, mEq/24 h	163 [123–205]	165 [125–209]	161 [127–207]	161 [123–206]	171 [129–214]	165 [126–213]	165 [126–212]	(1) vs. (4)
Potassiuria, mEq/24 h	54.3 ± 19.3	52.2 ± 18.0	55.4 ± 19.5	53.8 ± 21.0	55.8 ± 18.4	50.2 ± 14.5	56.1 ± 19.7	(1) vs. (4) vs. (6)
Magnesiuria, mg/24 h	88 ± 35	85 ± 31	90 ± 37	87 ± 32	91 ± 33	87 ± 42	89 ± 44	–
Sulfaturia, mmol/24 h	21 ± 7	20 ± 7	22 ± 9	20 ± 7	22 ± 7	22 ± 14	22 ± 7	(1) vs. (2) vs. (4); (1) vs. (6)
Ammoniuria, mmol/24 h	36 ± 13	35 ± 12	35 ± 12	36 ± 13	36 ± 13	47 ± 21	36 ± 13	–
Citraturia, mg/24 h	562 [393–752]	566 [395–754]	584 [411–767]	561 [398–734]	567 [391–762]	575 [410–763]	568 [410–750]	–
Uricuria, mg/24 h	566 ± 196	546 ± 80	588 ± 216	564 ± 205	581 ± 191	637 ± 217	578 ± 206	(1) vs. (4) vs. (6)
Urinary volume, ml/24 h	1772 ± 751	1765 ± 764	1738 ± 764	1805 ± 804	1812 ± 755	1400 ± 512	1736 ± 605	–
Urine pH	5.95 ± 0.54	6.01 ± 0.52	6.03 ± 0.63	6.03 ± 0.52	5.85 ± 0.52	5.86 ± 0.56	5.87 ± 0.55	(1) vs. (4) vs. (6)

Data are presented as number (percentage), mean ± standard deviation or median [interquartile range] according to the distribution of values. In multiple comparisons, the group (1) of stone formers without metabolic syndrome traits was considered as reference

BMI body mass index, *GFR* glomerular filtration rate

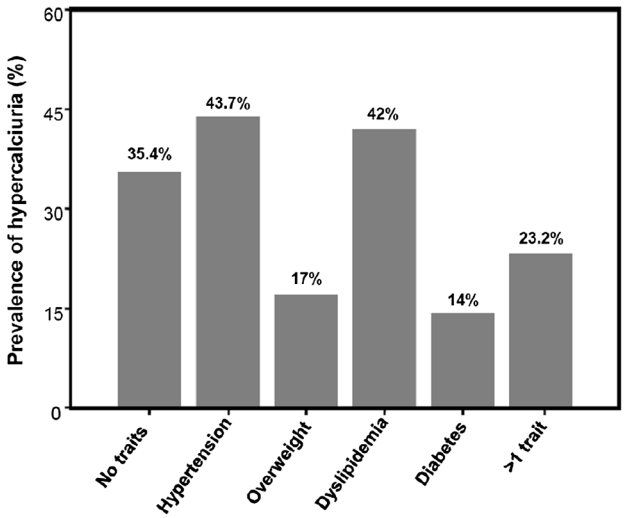

Fig. 1 Prevalence of hypercalciuria (≥4 mg/kg/24 h) according to number and type of metabolic syndrome traits in a group of 3003 Italian calcium stone formers (SFs). SFs are classified as: no metabolic syndrome traits, hypertension alone, overweight alone, dyslipidemia alone, diabetes alone, more than one trait

MetS traits and UOE

The median value of UOE in 3003 SFs was 28 mg/24 h (IQR 22–34). Hyperoxaluria (UOE > 40 mg/day) was present in 382 SFs (12.7%). The prevalence of hyperoxaluria was 12.9% in those without MetS traits, 10.7% in those with hypertension alone, 13.1% in those with an overweight condition alone, 12.5% in those with dyslipidemia alone, 14.2% in those with diabetes alone, and 12.6% in those with more than one MetS trait (Table 1; Fig. 2). Unadjusted Pearson correlation analysis showed that no MetS trait was correlated with hyperoxaluria (Table 2).

At multivariate linear regression analysis, accounting for multiple potential confounding factors, none of the MetS traits resulted significantly associated with UOE (Table 4). Instead, we found a positive correlation for age, date of examination, family history of stones, GFR, urinary pH and excretion of sodium, sulfate, citrate and ammonium.

Discussion

Our retrospective analysis has shown that, in a large group of Italian calcium SFs, hypertension was the only MetS trait significantly and independently associated with calcium excretion. The association of other traits, i.e. dyslipidemia, overweight and diabetes, was instead not independent of covariates. Moreover, no MetS trait was significantly associated with the urinary excretion of oxalate.

To our knowledge, this is the first study comprehensively investigating the association between different MetS traits and the major metabolic determinants of calcium urolithiasis, i.e. urinary calcium and oxalate excretion, in a large Caucasian population of calcium SFs. Our results show that the presence of MetS traits may have little influence on urinary metabolic abnormalities, with the only exception of hypertension which emerged as a significant determinant of calcium excretion.

The association between hypertension and urolithiasis has already been studied at both epidemiologic and pathophysiologic level. Previous studies have demonstrated that calciuria is generally higher if hypertension is present, both in subjects without nephrolithiasis [15] and in SFs [16]. Anti-hypertensive medications, namely thiazide diuretics, can decrease UCE, so that the association between hypertension and hypercalciuria detected in our population of SFs might have been even underestimated, even if thiazide diuretics were withdrawn 1 week before urine collection and their chronic use was considered as a potential confounder in the multivariate analysis. As such, it can be hypothesized that, in hypertensive SFs, hypercalciuria, when present, is poorly influenced by covariates, such as dietary protein and salt intake, representing a marker of salt resistance [17].

Table 2 Unadjusted Pearson correlation matrix between metabolic syndrome traits and 24-h urinary calcium and oxalate excretion in 3003 Caucasian calcium stone formers

	Calcium excretion	Oxalate excretion	Hypertension	Diabetes	Dyslipidemia	Overweight
Calcium excretion	–	r = 0.25 (p < 0.001)	r = 0.03 (p = 0.04)	r = 0.01 (p = 0.48)	r = 0.04 (p = 0.02)	r = −0.02 (p = 0.34)
Oxalate excretion	–	–	r = −0.01 (p = 0.42)	r = 0.03 (p = 0.09)	r = 0.03 (p = 0.07)	r = 0.01 (p = 0.33)
Hypertension	–	–	–	r = 0.15 (p < 0.001)	r = 0.04 (p = 0.02)	r = 0.19 (p < 0.001)
Diabetes	–	–	–	–	r = 0.03 (p = 0.09)	r = 0.11 (p < 0.001)
Dyslipidemia	–	–	–	–	–	r = 0.03 (p = 0.07)
Overweight	–	–	–	–	–	–

Table 3 Multivariate linear regression analysis testing the relationship between metabolic syndrome traits and log-transformed values of urinary calcium excretion in a group of 3003 calcium stone formers

Parameters	β	SE	p (fully-adjusted)
Arterial hypertension	0.23	0.07	**0.002**
Dyslipidemia	0.01	0.02	0.54
Overweight	−0.01	0.02	0.45
Diabetes mellitus	−0.04	0.07	0.54
Age	−0.002	0.0007	**0.001**
Date of examination	−0.00001	0.000005	**0.023**
Sex (M vs. F)	−0.01	0.02	0.30
Family history of stones	0.08	0.02	< **0.001**
Anti-hypertensive treatment	−0.17	0.08	**0.027**
GFR	0.0008	0.0003	**0.015**
Diet (free vs. restricted)	−0.01	0.006	0.11
Total blood calcium	0.003	0.002	0.16
Urinary volume	−0.000001	0.00001	0.99
Urinary sodium excretion	0.001	0.0001	< **0.001**
Urinary citrate excretion	0.0003	0.00004	< **0.001**
Urinary sulfate excretion	0.01	0.002	< **0.001**
Urinary ammonium excretion	0.007	0.0009	< **0.001**
Urinary pH	0.09	0.01	< **0.001**

Significant p values ($p \leq 0.05$) are indicated in bold

SE standard error, *GFR* glomerular filtration rate

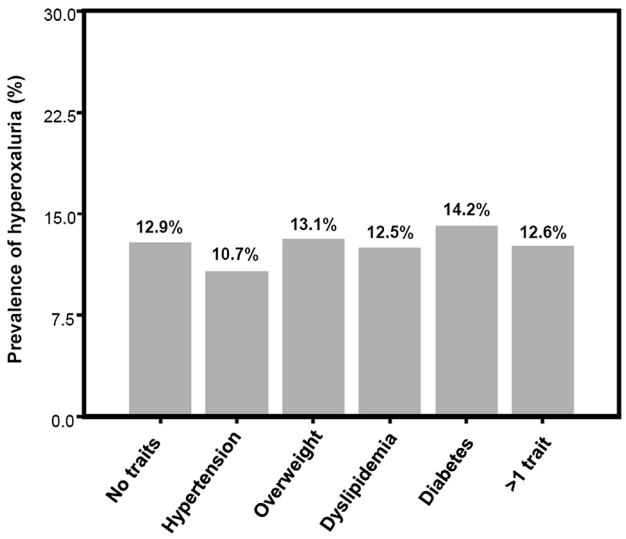

Fig. 2 Prevalence of hyperoxaluria (≥ 40 mg/kg/24 h) according to number and type of metabolic syndrome traits in a group of 3003 Italian calcium stone formers (SFs)

Table 4 Multivariate linear regression analysis testing the relationship between metabolic syndrome traits and log-transformed values of urinary oxalate excretion in a group of 3003 calcium stone formers

Parameter	β	SE	p (fully-adjusted)
Arterial hypertension	0.05	1.45	0.97
Dyslipidemia	−0.04	0.36	0.89
Overweight	0.32	0.36	0.36
Diabetes mellitus	1.90	1.40	0.17
Age	0.03	0.01	**0.016**
Date of examination	0.0002	0.00006	**0.001**
Sex (M vs. F)	−0.28	0.35	0.42
Family history of stones	0.76	0.35	0.03
Anti-hypertensive treatment	−0.74	1.52	0.62
GFR	0.04	0.006	< **0.001**
Diet (free vs. restricted)	0.04	0.12	0.70
Total blood calcium	0.05	0.04	0.22
Urinary volume	−0.00009	0.0002	0.71
Urinary sodium excretion	0.023	0.003	< **0.001**
Urinary citrate excretion	0.001	0.0006	**0.004**
Urinary sulfate excretion	0.19	0.03	< **0.001**
Urinary ammonium excretion	0.09	0.017	< **0.001**
Urinary pH	0.65	0.37	0.07

Significant p values ($p \leq 0.05$) are indicated in bold

SE standard error, *GFR* glomerular filtration rate

It is also noteworthy that, even if hypercalciuria is the most important metabolic risk factor for calcium urolithiasis, its prevalence in our population was lower than that reported in American SFs [18]. In fact, approximately 70% of calcium SFs who participated in our study had a normal calcium excretion, but this is in line with our previous observations in Italian SFs [19]. Different genetic background, lifestyle and dietary habits could explain this discrepancy. The importance of environmental factors is indirectly supported by our finding that there was a slight, but significant, "secular trend" towards the increase of calcium and oxalate excretion across the long time-span of SF enrolment.

The epidemiologic link between nephrolithiasis and hypertension is bidirectional, since stones are a known risk factor for incident hypertension [20, 21] and, conversely, hypertension can lead to a higher incidence of kidney stone disease [15]. Hypercalciuria could thus represent the pathophysiological substrate of this epidemiologic connection. However, Taylor and colleagues failed to demonstrate an association between urinary calcium excretion and prevalent hypertension in a large population-based prospective study performed in the United States [22], but their study was not exclusively focused on SFs. Consistently with our findings, Kim et al. found that hypertension was the only MetS trait associated with nephrolithiasis in a Korean population, but did not report data on urinary lithogenic factors [23]. In a

large group of SFs with different stone composition, Kohjimoto et al. instead showed a positive association between hypertension and hypercalciuria, but also demonstrated a similar association for dyslipidemia [3]. Interestingly, in their study dyslipidemia was also significantly associated with an increased oxalate excretion [3].These findings are apparently in contrast with our results which did not find dyslipidemia to be associated with UCE or UOE. Even if dyslipidemia has been proposed as an important risk factor for urolithiasis, its effects on urinary lithogenic risk factors are not well studied. Miranda Torricelli et al. [24] showed that urinary calcium excretion is higher in Caucasian SFs with hypercholesterolemia, but not in SFs with hypertriglyceridemia. This relationship is perhaps influenced by dietary habits and not independent of covariates. Genetic or racial factors could also contribute to explain the difference of our findings with those of Kohjimoto et al [3].

The relationship between BMI and urinary calcium excretion, despite the fact that it has been much more investigated, is in the same way controversial. Even if some researchers have demonstrated a positive independent association between BMI and UCE in American SFs [25], a recent European larger study showed that this association was not independent of covariates in the overweight range [26]. Moreover, in healthy females, a higher abdominal adiposity ratio was not associated with a higher UCE [27]. Overweight is instead a risk factor for uric acid nephrolithiasis, mainly due to the low urinary pH [26]. Interestingly, in large population-based American studies, Taylor & Curhan identified an increasing trend in UOE with increasing BMI and weight, independent of a long list of covariates [9]. These data were not confirmed by our findings, but the prevalence of obesity and overweight in our population was lower. Different lifestyle and dietary habits could also account for this difference, considering also the high complexity of oxalate handling in human metabolism [9].

Finally, our finding that the presence of type 2 diabetes was not associated with hypercalciuria is not surprising in the light of the existing literature. In fact, the epidemiological association between diabetes and nephrolithiasis is mainly explained by low urine pH, which is a result of reduced ammonium buffer excretion [28]. This urinary microenvironment promotes uric acid, and not calcium, stone formation [28]. In fact, even if hyperinsulinemia is pathophysiologically able to promote urinary calcium excretion, this mechanism has little clinical relevance [29]. Diabetes might instead promote oxalate excretion, and has been recognized as a major determinant of oxaluria [9]. According to the literature, the main urinary metabolic differences between diabetic and non-diabetic SFs are only higher uric acid excretion, lower urinary pH [30] and, possibly, lower ammonium excretion. However, a low ammoniuria may be typical of diabetic uric acid SFs, and not of all diabetic SFs, and may be observed only under controlled dietary regimens, as recently suggested by studies carried out in animal models [31]. This circumstance may help to explain why ammonium excretion was actually higher in the diabetic SFs with respect to non-diabetic SFs who participated in our study.

Some limitations should be considered when interpreting our results. First, the retrospective design with a long period of enrolment does not allow to exclude bias in data acquisition, especially considering the significant progress made in the management of all MetS traits throughout the years, even if the methodology of clinical and laboratory assessment of urolithiasis has remained consistent. Some data included in the consensus definitions of MetS only in recent years, such as abdominal circumference, could not be extrapolated from clinical records, and were substituted by proxies. Second, the considered population represent the case-mix and experience of a single Italian center, and may have a limited generalizability to other contexts, due to the strong influence of environmental factors on the development of urolithiasis. Third, the low number of SFs with diabetes did not allow to fully understand the influence of this disease on urinary metabolic risk factors. Finally, a comprehensive analysis of dietary and lifestyle habits was not made, and correction for some potential confounders, such as total calorie, calcium and fructose intake, or use of sweetened soft drinks, was not possible.

Conclusions

In a large group of Caucasian calcium SFs, the only MetS trait independently associated with calcium excretion was hypertension. Dyslipidemia, overweight and type 2 diabetes were instead not independently associated with calciuria. None of the MetS traits showed an association with oxalate excretion. These findings reinforce the need for a urinary metabolic evaluation in patients where calcium nephrolithiasis and hypertension coexist. Further prospective population-based studies are needed to clarify the association between MetS and nephrolithiasis, considering also genetic predisposition and ethnic differences.

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Compliance with ethical standards

Conflict of interest All the authors have read and understood the Journal of Nephrology's policy on disclosing conflict of interest. All the authors have no conflict of interest to declare, with the exception of Tiziana Meschi, who received an unconditioned grant for research in the field of nephrolithiasis by Acqua&Terme Fiuggi S.p.A. (Fiuggi, Frosinone, Italy).

Ethical approval The study protocol was approved by the local Ethics Committee (ID 16280). All investigations were carried out in conformity with the Declaration of Helsinki principles.

Informed consent Written informed consent was obtained from participants, according to current legislation for retrospective studies.

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