LIFESTYLE RISK FACTORS AND BONE MASS IN RECURRENT STONE-FORMING PATIENTS: A CROSS-SECTIONAL STUDY IN 144 SUBJECTS

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SUMMARY – Patients with urolithiasis, particularly hypercalciuria, may have reduced bone mineral density (BMD). There are numerous risk factors contributing to reduction of BMD such as advanced age, sedentary lifestyle, smoking, low calcium intake, etc. The aim of our study was to investigate the association of lifestyle risk factors and daily intake of milk and dairy products with determinants of BMD in a group of recurrent calcium stone formers (RSF) compared with healthy subjects (HS). The study was carried out at the Department of Mineral Research, Faculty of Medicine in Osijek, Croatia. The study included 144 subjects, i.e. 56 RSF and 78 HS. BMD was assessed by dual-energy x-ray absorptiometry. A standard self-reported questionnaire was used to collect data on lifestyle risk factors. Current dietary intake was assessed by personal interview that included questions about milk and dairy product intake. Low BMD was observed in 44.64% of RSF and 35.90% of HS. RSF consumed significantly less milk and dairy products than HS. Calcium restriction in dietary recommendations might be unnecessary due to the impact on bone mineral loss in RSF and dual-energy x-ray absorptiometry should be included in the routine evaluation of RSF.

Key words: urolithiasis, bone mineral density, body weight, body mass index, physical activity, smoking, calcium intake

Introduction

Urolithiasis remains a common health, social and economic problem of modern society and occurs at least once in life in 15% of Caucasian men and 6% of women1,2, with a recurrence rate of around 50% over 10 years and 75% over 15 and 20 years, respectively3,4. Recurrent urolithiasis is defined as three or more episodes of kidney stones in a 5-year period5. The prevalence of urolithiasis has increased in recent decades in both males and females6. Calcium oxalate and calcium phosphate are the most common types of kidney stones, accounting for >80% of stones7. Idiopathic hypercalciuria is the most prevalent abnormality in calcium kidney stone formers; metabolic analyses performed in these patients yielded a rate of hypercalciuria of 60%8. In practice, hypercalciuria is defined as daily calcium excretion of over 250 mg/day in women and 300 mg/day in men9.

The association between urolithiasis and bone mineral density (BMD) is already known and according to several clinical and epidemiological studies performed in recurrent calcium stone formers (RSF), patients with urolithiasis, particularly hypercalciuria, may have reduced bone density. Bone loss in these patients is caused by increased resorption and/or decreased bone formation10-11. Dietary habits and lifestyle play an important role in the formation of kidney stones, as well as in BMD.
The aim of our study was to investigate the association of age, anthropometric parameters and lifestyle factors with determinants of BMD in a group of RSF compared with healthy subjects (HS).

Material and Methods

Subjects

We investigated 56 unrelated patients with recurrent urinary stone formation who consecutively visited the Department of Urology, Osijek University Hospital Centre. The diagnosis of recurrent urolithiasis was based on the history of two or more episodes of renal colic, radiographic evidence of stones and report of stone analysis, and only patients with confirmed calcium oxalate urolithiasis were included in the study.

Control group consisted of 78 patients without a known history of renal stone disease and with ultrasound confirmation of the absence of kidney stones who were undergoing osteoporosis evaluation at the Department of Mineral Research, Faculty of Medicine in Osijek. The following subjects were excluded: subjects with gastrointestinal diseases (ulcerative colitis, malabsorption syndrome, chronic pancreatitis), renal tubular acidosis, pregnant women, subjects with primary hyperparathyroidism and other diseases affecting calcium metabolism (hyperthyroidism, acromegaly, sarcoidosis, diabetes or cancer), and those using medications such as corticosteroids, barbiturates, estrogen, calcium or vitamin D. A written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the Faculty of Medicine, Osijek, Croatia.

Anthropometric measurements

Body weight and height were measured with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m²); BMI >30 kg/m² was used as a parameter for obesity and BMI >24.9 kg/m² as excess weight.

Lifestyle risk factors

Data on lifestyle (smoking status, current physical activity, sports activity in the past) were collected by use of standard self-reported questionnaire. The questions regarding sports activity in the past included specific questions about frequency and duration of previous sports activities (in hours) on a weekly basis (performing regular exercise for more than 30 minutes two times a week). Current physical activities (walking, biking, manual work, etc.) were classified into three levels, as follows: very active (>4.5 hours per week), moderately active (1.5-4.5 hours per week), and less active (<1.5 hours per week).

Smoking habit was categorized as current, past or never used. Current dietary intake was assessed by personal interview that included questions about milk and dietary product intake. Answers were classified into three groups, as follows: never or less than once a day, once a day, and more than once a day.

Bone density measurement

Bone mineral density and bone mineral content (BMC) were assessed by dual-energy x-ray absorptiometry (Lunar Prodigy, GE Healthcare, USA). BMD and BMC measurements were performed at lumbar spine and femoral neck. Areal BMD was expressed in g/cm² and standard deviation from the young normal mean (T-score) based on the World Health Organization (WHO) criteria. A score from -1 to -2.5 SD below the norm indicates low bone mass or osteopenia, and a score of equal or more than -2.5 SD below the norm indicates osteoporosis.

Statistical analysis

Categorical data were presented as absolute and relative frequencies, and numerical data as mean with standard deviation or median with interquartile range. Differences between categories were tested with $\chi^2$-test and comparison between groups was done with the independent samples T-test or Mann-Whitney U Test. Statistical analyses were conducted using SAS software (version 8.02, SAS Institute Inc., Cary, NC, USA) with the level of statistical significance set at $p<0.05$.

Results

Clinical characteristics of RSF and HS groups are presented in Table 1.

The RSF group included 51.79% of men and 48.21% of women; there was no statistically significant difference according to age or sex between RSF and HS groups. However, RSF had higher BMI (27.56 kg/m²; interquartile range 25.27 kg/m² to 29.73 kg/m²) compared to HS (26.81 kg/m²; interquartile range 23.92
BMD was lower in RSF at all measured sites but without statistical significance (Table 2).

A significant difference was obtained for more than once daily milk consumption between RSF (14.29%) and HS (21.79%) ($\chi^2$-test, $p=0.017$). Smoking habit, current physical activity, previous sports activity and level of education did not differ significantly between the two groups (Table 3).

**Discussion**

We investigated the influence of lifestyle factors on BMD in RSF. Although kidney stones are more com-

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Table 1. Age and anthropometric parameter distribution of recurrent stone formers (RSF) and healthy subjects (HS)

| Parameter                  | RSF (n=56)     | HS (n=78)     | p     |
|----------------------------|----------------|---------------|-------|
| Age (yrs) mean±SD          | 49.16±11.59    | 52.51±7.73    | 0.116 |
| Height (cm) mean±SD        | 170.91±9.66    | 167.64±6.81   | 0.030 |
| Weight (kg) mean±SD        | 80.57±12.83    | 75.78±14.54   | 0.050 |
| BMI (kg/m²) median (25th percentile, 75th percentile) | 27.56 (25.27, 29.73) | 26.81 (23.92, 29.73) | 0.283* |

Independent samples T-test; *Mann-Whitney U test

Table 2. Distribution of T scores, bone mineral density (BMD) and bone mineral contents (BMC) for lumbar spine and femoral neck in recurrent stone formers (RSF) and healthy subjects (HS)

| Parameter                  | RSF (n=56)     | HS (n=78)     | p     |
|----------------------------|----------------|---------------|-------|
| T-score (lumbar spine) median (25th percentile, 75th percentile) | -0.25 (-1.20, 0.70) | 0.00, (-0.70; 1.00) | 0.131* |
| T-score (femoral neck) median (25th percentile, 75th percentile) | -0.50 (-1.28, 0.00) | -0.50 (-1.30, -0.08) | 0.678* |
| BMD (lumbar spine) mean±SD | 1.16±0.16      | 1.21±0.18     | 0.109 |
| BMD (femoral neck) mean±SD | 0.95±0.12      | 0.98±0.14     | 0.148 |
| BMC (lumbar spine) mean±SD | 70.61±14.50    | 71.33±16.43   | 0.792 |
| BMC (femoral neck) median (25th percentile, 75th percentile) | 4.97 (4.40, 5.83) | 5.00 (4.50, 5.54) | 0.883* |

Independent samples T-test; *Mann-Whitney U test

kg/m² to 29.73 kg/m²) (Mann-Whitney U test, $p=0.283$).

Low BMD was observed in 44.64% of RSF (osteoporosis 20%) and 35.90% of HS (osteoporosis 10.71%).

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Table 3. Demographic and lifestyle risk factors in recurrent stone formers (RSF) and healthy subjects (HS)

| Parameter                  | RSF n (%) | HS n (%) | p     |
|----------------------------|-----------|----------|-------|
| Age group (yrs):           |           |          |       |
| ≤60                        | 47 (83.93) | 67 (85.90) | 0.752 |
| >60                        | 9 (16.07)  | 11 (14.10) |       |
| Body mass index:           |           |          |       |
| ≤24.9                      | 13 (23.22) | 27 (34.62) |       |
| 25.0-29.9                  | 32 (57.14) | 34 (43.59) |       |
| ≤30.0                      | 11 (19.64) | 17 (21.79) |       |
| Smoking:                   |           |          |       |
| Current smoker             | 16 (28.57) | 28 (35.90) |       |
| Past smoker                | 13 (23.22) | 18 (23.08) |       |
| Never smoked               | 27 (48.21) | 32 (41.03) | 0.633 |
| Current physical activity: |           |          |       |
| Very active                | 3 (5.36)   | 10 (12.82) |       |
| Moderately active          | 39 (69.64) | 49 (62.82) |       |
| Less active                | 14 (25.00) | 19 (24.36) | 0.349 |
| Previous sports activity: |           |          |       |
| Yes                        | 27 (48.21) | 30 (38.46) | 0.260 |
| No                         | 29 (51.79) | 48 (61.54) |       |
| Milk consumption:          |           |          |       |
| Never/less than once a day | 31 (55.36) | 24 (30.77) |       |
| Once a day                 | 17 (30.35) | 37 (47.43) |       |
| More than once a day       | 8 (14.29)  | 17 (21.79) | 0.017 |
| Educational level:         |           |          |       |
| Elementary school          | 10 (17.86) | 14 (17.95) |       |
| High school                | 29 (51.79) | 31 (39.74) |       |
| University                 | 17 (30.35) | 33 (42.31) | 0.316 |
| Total                      | 56 (100.00)| 78 (100.00)|       |

$\chi^2$-test

BMD was lower in RSF at all measured sites but without statistical significance (Table 2).

A significant difference was obtained for more than once daily milk consumption between RSF (14.29%) and HS (21.79%) ($\chi^2$-test, $p=0.017$). Smoking habit, current physical activity, previous sports activity and level of education did not differ significantly between the two groups (Table 3).

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**Discussion**

We investigated the influence of lifestyle factors on BMD in RSF. Although kidney stones are more com-
mon in men than in women, male predominance was not confirmed in our study. However, in our study RSF had a significantly higher body weight than HS and this finding is consistent with previous studies.

Recent evidence shows that an increase in body weight and BMI is associated with the increasing risk of urolithiasis. Weight gain from early adulthood was associated with an increased risk of kidney stones in both men and women. Studies in patients with urolithiasis showed higher BMI to be significantly associated with lower urinary pH level. The reasons for progressive decline in urine pH with increasing BMI in urolithiasis patients have not been defined yet. Obesity is associated with insulin resistance and hyperinsulinemia, metabolic disorders known to have a strong influence on urine composition, thus increasing the kidney fractional excretion of calcium, uric acid and oxalate, resulting in lower urinary pH. A high animal protein diet results in subtle metabolic acidosis and potentially could lead to increased bone turnover. Metabolic acidosis caused by the high protein diet induces the release of bone calcium to buffer acid load, consequently leading to hypercalciuria and bone loss.

On the other hand, decreased bone mass in patients with urolithiasis was demonstrated in several clinical and epidemiological studies.

In our study, a significant bone loss in patients with urolithiasis was confirmed by the rate of osteoporosis of 20% and 10.71% in the RSF and HS group, respectively.

In their study performed using dual-energy x-ray absorptiometry, Trinchieri et al. found that BMD was lower in hypercalciuric patients (57%) than in normocalciuric patients (44%), while the rate of osteopenia and osteoporosis in hypercalciuric patients was 48 and 6%, respectively. In their study that included normocalciuric patients with recurrent calcium stones, Tugcu et al. found BMD to be decreased in 76.7% and 20.0% of patients and healthy subjects, respectively. In a follow-up study, Cvijetic et al. also found greater BMD reduction in stone formers as compared with controls.

Milk and dairy products are primary sources of calcium and have an impact on bone density. According to our results, HS consumed significantly more milk and dairy products than RSF. This finding is interesting and intriguing because a calcium restricted diet which is often recommended in urolithiasis patients might increase bone resorption leading to bone loss.

However, reduction of calcium supply increases oxalate absorption and enhances urinary saturation with oxalate salts, which might explain why low-calcium diet increases the risk of calcium oxalate stone formation. This point has been supported by another study where stone-formers reported reduced dietary calcium intakes when factored for body weight but urinary calcium excretion was comparable between the two groups suggesting that stone formers were in more negative calcium balance compared to non-stone-formers.

Borghi et al. found that in men with recurrent calcium oxalate stones and hypercalciuria, low animal protein and salt diet in combination with normal calcium intake had a protective effect in the prevention of stone recurrence. Similar results were obtained by other research groups. Therefore, obesity and low calcium diet in RSF might explain the high rate of decreased BMD in our study as well.

On the other hand, in our study, smoking habit, physical activity and level of education were not significantly different between RSF and HS. These data are concordant with the findings of several research groups which do not support the possible association between smoking and urinary tract stones.

However, there are research groups that might argue these findings since their data claim that cigarette smoking may induce urolithiasis by decreasing urinary flow and increasing serum cadmium in healthy subjects. Also, there are some reports suggesting that adult smokers had twice the odds of having urinary stones (OR 2.1, 95% CI 1.1-4.0) as compared with age-matched non-stone formers. In contrast, cigarette smoking is associated with low BMD and increased risk of fracture in both genders. Although the underlying mechanisms of the association between smoking and low BMD are not completely known, this could be attributed to the adverse effect of smoking on skeletal remodeling and bone cells, decreased intestinal calcium absorption due to smoking, and its impact on sex hormones. There are limited literature data on the impact of physical activity on the formation of kidney stones but the importance of physical activity in the prevention of many chronic diseases is well known.

In a study that included 84,225 postmenopausal women, Sorensen et al. found that physical activity might reduce the risk of incident kidney stones. They found that the intensity of the activity was not impor-
tant because only mild to moderate weekly activity was enough to be protective against kidney stone formation\textsuperscript{49}. These results are in contrast to a recent study that examined the association between physical activity and incidence of kidney stones. In this prospective cohort study, age-adjusted and multivariate-adjusted analyses failed to confirm significant associations between physical activity and kidney stones\textsuperscript{50}. Although physical inactivity appears to be a risk factor for kidney stones, the pathogenetic mechanisms remain elusive and need to be further investigated.

Gur et al. report on a significant correlation between educational level and BMD. In their study, the prevalence of osteoporosis showed an inverse relationship with the level of education, ranging from 18.6% for high educated to 34.4% for low educated women\textsuperscript{51}. However, the mechanisms of association between educational level and low BMD remain partly unexplained, the higher BMD values in the highest education group may be attributed to sufficient calcium intake.

Our study had several limitations. Daily fluid, salt and protein intakes as important factors for stone disease were not assessed. An additional limitation of the study may be that the questionnaire used provided limited information on the quantity of calcium intake, as well as on precise physical activities of our participants. These limitations should be taken into account interpreting the study results.

These results suggested that patients with recurrent calcium stones had greater BMD decline compared to patients without lithiasis. The most important predictors of BMD in our study were body weight and dairy intake. Therefore, BMD analyses should be included in the routine evaluation of RSF. However, calcium restriction in dietary recommendations might be unnecessary due to the impact on bone mineral loss in RSF.

Acknowledgment

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Sažetak

RIZIČNI ČIMBENICI I KOŠTANA MASA U BOLESNIKA S RECIDIVIRAJUĆOM UROLITIJAZOM: PREŠJEČNO ISTRAŽIVANJE NA 144 ISPITANIKA

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Bolesnici s urolitijazom, osobito oni s hiperkalciurijom, imaju smanjenu koštani mineralnu gustoću (bone mineral density, BMD). Rizični čimbenici gubitka koštane mase su uznapredovala dob, sjedilački način života, pušenje i smanjen unos kalija. Cilj našeg istraživanja bio je ustanoviti povezanost rizičnih čimbenika i dnevnog unosa mlijeka i mliječnih prerađevina s odrednicama BMD u bolesnika s recidivirajućom kalcijom urolitijazom te ih usporediti sa zdravim ispitanicima. Istraživanje je provedeno na Zavodu za mineralni metabolizam Medicinskog fakulteta u Osijeku. U istraživanju su sudjelovala 144 ispitanika, od čega 56 bolesnika s recidivirajućom kalcijom urolitijazom i 78 zdravih ispitanika. BMD je određen metodom dvoenergetske apsorpciometrije X zraka (DXA). Podatci o čimbenicima rizika dobiveni su anketnim upitnikom, a unos hrane je ocijenjen osobnim intervjuom koji je uključivao pitanja o unosu mlijeka i mliječnih proizvoda. Snižen BMD zabilježen je u 44,64% bolesnika s recidivirajućom urolitijazom i u 35,90% zdravih ispitanika. Bolesnici s recidivirajućom urolitijazom konzumirali su znatno manje mlijeka i mliječnih proizvoda u odnosu na zdrave ispitanike. Nepotrebna je preporuka smanjenog unosa kalija bolesnicima s recidivirajućom urolitijazom zbog utjecaja na gubitak koštane mase, a DXA treba biti dio rutinske procjene bolesnika s recidivirajućom urolitijazom.

Ključne riječi: urolitijaza; mineralna gustoća kosti; tjelesna težina; indeks tjelesne mase; tjelesna aktivnost; pušenje; unos kalija

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