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Urinary calcium is a determinant of bone mineral density in elderly men participating in the InCHIANTI study

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Background. It is generally acknowledged that calcium excretion is a determinant of bone mineral density. Since data confirming this hypothesis are not conclusive, the present study evaluates the relationship between calcium excretion and volumetric bone mineral density (vBMD) in a sample of general population mostly composed of elderly subjects.

Methods. This relationship was studied in 595 subjects in good health (M/F 302/293), selected from the InCHIANTI population, an epidemiologic survey on aging in Tuscany (Italy). Of these subjects, 432 (72.6%) were 65 years old or older. Trabecular and cortical apparent vBMDs were measured by peripheral quantitative computed tomography at right tibia and standardized to age and body mass index (BMI) in each gender (z-score).

Results. Men in the highest tertile of calcium excretion had significantly lower trabecular vBMD, and were more likely to have a trabecular z-score of −1 or less. These results were confirmed in men older than 64 years, but not in women and younger men. Sodium excretion and 25-hydroxycolecalciferol (25(OH)D) were greater in men and women in the highest tertile. No differences among tertiles were observed for cortical vBMD, circulating levels of interleukin-1β and interleukin-6, and intake of principal nutrients and calcium. The lower levels of vBMD z-score were confirmed in men in the highest tertile of calcium excretion, standardized to creatinine clearance, sodium excretion, plasma calcium, and logarithm of circulating 25(OH)D, and resulted to be associated with calcium excretion at multiple regression analysis in men.

Conclusion. High calcium excretion is associated with a decreased trabecular BMD in elderly men and may predispose men to trabecular bone loss.

Key words: bone mineral density, urinary calcium excretion, cytokines, hypercalciuria, calcium intake.

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Osteoporosis is a chronic and potentially invalidating disorder that negatively influences bone strength, determining a high risk of bone fractures. Osteoporosis typically affects postmenopausal or elderly women, but may also occur in premenopausal women and men at different ages [1–3]. Bone mass decline in women is accelerated by the privation of the protective activity provided by estrogens [4], but also other factors, like vitamin D deficiency with secondary hyperparathyroidism, inadequate dietary calcium intake, or polymorphisms of specific genes [5, 6], may influence bone mass preservation, predisposing to osteoporosis. These defects may also contribute to bone mass loss in men, but the specific causes for male osteoporosis remain still unclear [2, 3, 7]. In keeping with these findings, osteoporosis is considered as a complex disease with a multifactorial pathogenesis [2, 6].

Elevated calcium excretion is generally included among the factors predisposing to osteoporosis [2, 7, 8], but scarce information is available about the relationship between urinary calcium excretion and bone mineral density (BMD) in general healthy population. This point has been mainly explored in osteoporotic or stone-forming patients with primary hypercalciuria, a defect characterized by high calcium excretion without any apparent alterations justifying its presence. Primary hypercalciuria can be detected in 19% of osteoporotic postmenopausal women [9] or men [7, 8], while it is observed in 5% to 10% of the general population. Among calcium stone-forming patients primary hypercalciuria is present in 40% to 50% of cases. Low values of BMD and increased risk of bone fractures have been observed in hypercalciuric stone formers [10–17]. A progressive bone loss in stone formers could result from a urinary calcium excretion exceeding the amount of calcium absorbed in intestine [11, 18], but could also result from a great ingestion of protein that increases dietary acid load, thus stimulating calcium

release from bones and reducing tubular calcium reabsorption [11, 17, 18]. Furthermore, an increased production of cytokines could enhance calcium excretion and bone loss stimulating osteoclast activity and bone resorption [13–15].

The present work was aimed to explore the relationship between calcium excretion and bone density in an elderly general population. To address this issue, we used data from InCHIANTI, a population-based epidemiologic study on life quality decline in older people, performed in Tuscany, Italy [19]. InCHIANTI is particularly suited for this purpose because participants were 65 years old or older, with the exception of a smaller sample of subjects younger than 65 years. Volumetric BMD (vBMD), estimated by peripheral quantitative computed tomography (pQCT) and 24-hour calcium excretion, were measured in all participants. In addition, nutrient intake and cytokine serum concentrations were estimated [20].

METHODS

Study population

InCHIANTI is an epidemiologic survey performed in 2 Italian towns located in the Chianti countryside [19]: *Greve in Chianti* (11,709 inhabitants; rural area) and *Bagno a Ripoli* (4704 inhabitants; suburban area of Florence). The InCHIANTI population consisted of a random sample of the population aged 65 years or older, living in the 2 catchment areas and selected from the population registries. In addition, 30 men and 30 women were randomly selected in each decade between 20 and 65 years and enrolled in the study population. The participation rate was 69.4% in individuals with age younger than 65 years, and 91.6% in older subjects. The original sample was composed of 1530 subjects, but only 1012 underwent a complete interview, medical examination, and pQCT assessment, and were resulted to have correctly collected 24-hour urine. From this sample, we excluded participants who were or had been under treatment with postmenopausal hormonal replacement therapy ($N = 48$), diuretics ($N = 113$), bisphosphonates ($N = 27$), steroids ($N = 78$), vitamin D metabolites ($N = 19$), chemotherapies ($N = 1$), or other drugs affecting calcium metabolism ($N = 3$). We also excluded participants with cancer ($N = 47$), diabetes ($N = 96$) or other endocrine disorders ($N = 55$), renal failure (plasma creatinine >1.3 mg/dL, $N = 28$), hypercalcemia (plasma calcium >2.60 mmol/L, $N = 9$), chronic hepatitis ($N = 6$), those who had undergone colon or stomach resection ($N = 11$), those in bad general condition due to neurologic disorders or other causes ($N = 29$), and the women with early menopause due to surgical ovarian excision ($N = 29$). After exclusion of these subjects, 595 (M/F 302/293) were admitted to our study: 432 older than 64 years (M/F 219/213), and 163 younger than 65 years (M/F 83/80).

Participants were divided in 3 percentile groups (tertiles) according to urinary calcium excretion in each gender. Individuals below the 33.3rd percentiles were assigned to the lowest tertile of calcium excretion (tertile 1; M/F 100/98), those between the 33.3rd and 66.6th percentile to the middle tertile of calcium excretion (tertile 2; M/F 101/98), and those above the 66.6th percentile to the highest tertile of calcium excretion (tertile 3; M/F 101/97).

Participants were considered hypercalciuric when their 24-hour calcium excretion was greater than 7.5 mmol in men or 6.25 mmol in women, or greater than 100 μmol/kg of body weight independent of gender [21].

The InCHIANTI study protocol was approved by the ethical committee of National Institute of Research and Care on Aging in Florence. All subjects received an extensive description of the purposes and known risks of the study procedures; all gave their informed consent.

Methods

Participants received a prestructured interview, a medical and functional examination, and extensive testing. At the end of the interview, the interviewers explained to the participants and their relatives the correct method for the 24-hour urine collection, and provided a large plastic bottle containing 1 g of boric acid as preservative. The participants were instructed to collect in a bottle all the urine produced in the following 24 hours, and to make the maximum effort to avoid dispersing urine during the collection period. Time of start and end of urine collection and episodes of urine dispersion had to be annotated in a diary. Participants carried the entire container to the study clinic and were immediately questioned about possible problems encountered during the collection, and any comment was reported in the database. The urine volume was measured, and 7 aliquots of 10 mL were stored at −80°C. Only samples from subjects who reported no episodes of dispersion were taken into account for this analysis. Height and weight were measured in each participant, and body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m).

Creatinine, calcium, and sodium excretions were measured in 24-hour urine. Calcium, parathyroid hormone (PTH), 25-hydroxycolecalciferol (25(OH)D), and creatinine concentrations were measured in plasma. N-Telopeptide cross-links of the type I collagen (NTx) were measured in 24-hour urine only in participants from Greve in Chianti (146 men and 148 women).

Serum levels of 25(OH)D were measured by radioimmunoassay (DiaSorin, Inc., Stillwater, MN, USA) after extraction of samples with acetonitrile. Intra- and interassay coefficient of variations (CVs) were 8.1% and 10.2%. Serum intact parathyroid hormone levels (PTH) were measured using a 2-site immunoradiometric assay (N-tact