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Diuretic use and bone mineral density in older USA men: the osteoporotic fractures in men (MrOS) study

SIR—It is estimated that 25–40% of adults aged 65 years and over use diuretics [1]. The three major classes of diuretics have different effects on renal calcium balance. Loop diuretics increase renal calcium excretion [2], while thiazide and potassium-sparing diuretics exert a hypocalciuric effect. Thiazides facilitate the reabsorption of calcium in the early segment of the convoluted distal tubule, and potassium-sparing diuretics promote reabsorption of calcium in the late segment of the distal tubule [3–5].

Epidemiological data [6–14] and results from randomised controlled trials [15–17] suggest that thiazide diuretic use is associated with a small increase in bone mineral density (BMD) or a decreased rate of bone loss. However, these associations were observed primarily among women.

There are few data regarding the effects of loop diuretics on BMD and findings are not consistent across studies [18, 19]. Although some studies have shown that loop diuretic use may be associated with an increased risk of hip and osteoporotic fractures [20–22], it is uncertain whether this possibly elevated fracture risk was mediated by the effect of loop diuretics on bone or rather on fall-related mechanisms, such as dizziness and orthostasis. To our knowledge, no studies have specifically examined whether potassium-sparing diuretics have an independent effect on BMD.

Therefore, we conducted a cross-sectional study among participants in the Osteoporotic Fractures in Men (MrOS) study, an ongoing prospective study of community-dwelling men, to investigate the association between current diuretic use and BMD at multiple skeletal sites. We hypothesised that compared with diuretic non-users, loop diuretic users would have a lower mean BMD, while thiazide and potassium-sparing diuretic users would have a higher mean BMD.

Methods

The MrOS cohort is comprised of 5,995 men aged 65 years and older, who were recruited between March 2000 and April 2002 from six regional areas in the USA: Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Pittsburgh, PA; Portland, OR; and San Diego, CA. Written informed consent was obtained from the participants and the Institutional Review Board at each site approved the study protocol.

During the baseline examination trained interviewers confirmed participants' use of diuretics by visual examination of all current prescription containers. Diuretics were classified as loop, thiazide, potassium-sparing and thiazide/potassium-sparing combinations (e.g. Dyazide®, Maxzide® and Moduretic®). We excluded 40 participants who were using loop and thiazide diuretics ($n=23$), loop and potassium-sparing diuretics ($n=14$) and all three diuretic combinations ($n=3$). Baseline BMD measurements were obtained at the total hip and its subregions, femoral neck and trochanter; lumbar spine, and total body using dual X-ray absorptiometry (QDR 4500 W, Hologic, Inc., Waltham, MA).

A baseline questionnaire was used to obtain information on demographic characteristics (age and race), lifestyle factors (physical activity, tobacco use and diet) and medical history. Physical activity was measured by computing the Physical Activity Scale for the Elderly score based on the activity level documented by the participant [23]. With respect to tobacco use, participants were categorised into past, current and never smokers. Dietary information was acquired using a modified version of the Block Food Frequency Questionnaire [24]. Calcium intake was estimated by summing the average daily consumption of calcium from diet and supplementation. Potassium intake was the estimated daily consumption of dietary potassium only. Participants were questioned regarding whether they had diabetes mellitus, hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), stroke, angina or myocardial infarction. Cardiovascular disease was defined as the presence of any of the latter three conditions. Participants had their body mass index (BMI) calculated from their measured weight, in kilograms, divided by the square of their height in metres (kg/m^2).

Analysis

Differences in baseline characteristics were assessed using ANOVA for continuous variables and chi-squared analyses for categorical variables. From among baseline variables with differences ($P<0.10$) between diuretic groups, we selected a final set of variables to include in the multivariate models. We used ANCOVA to assess the age- and multivariate-adjusted associations between each diuretic user group and BMD. Any overall difference in BMD between categories of diuretic users was tested using the omnibus F-test with statistical significance established at $P<0.05$. Differences between pairs of diuretic categories were then tested using the two-tailed tests of the least squares means. Pairwise comparisons were adjusted using the Bonferroni method [25]. Statistical analyses were performed using PC SAS version 8.2 (SAS Institute, Cary, NC).

Results

Our analyses involved 5,955 men (90% white) with a mean age of 73 (±5.9) years. There were significant differences among the different diuretic groups for all selected characteristics with the exception of dietary calcium and potassium intake (Table 1).

Table 1. Baseline characteristics among USA male diuretic users and non-users aged 65 years and older: the MrOS Study, 2000–2002

	Diuretic group					
	Loop	Potassium-sparing	Thiazide	Thiazide/potassium-sparing	None	*P*-value
Number (%)	250 (4.3)	100 (1.7)	546 (9.4)	120 (2.0)	4939 (84.6)	
Mean age (years)	77	75	74	76	73	<0.001
Mean BMI (kg/m^2)	29.2	27.9	28.3	28.2	27.2	<0.001
Diabetes mellitus (%)	27.6	11.0	15.4	5.0	9.4	<0.001
Hypertension (%)	67.6	87.0	93.4	91.7	33.9	<0.001
COPD (%)	20.0	8.0	9.7	10.8	10.3	<0.001
Cardiovascular disease (%)[a]	58.0	29.0	25.3	30.0	23.1	<0.001
CHF (%)	40.8	6.0	5.9	4.2	3.1	<0.001
Smokers: past (%)	65.6	64.0	59.3	65.0	58.4	0.17
Smokers: current (%)	2.8	0	4.0	1.7	3.5	<0.05
PASE[b] Score	124	128	139	130	150	<0.001
Mean daily calcium intake (mg)[c]	1075	1188	1139	1151	1141	0.46
Mean daily potassium intake (mg)[d]	2887	3055	2919	2942	2892	0.65

[a]History of myocardial infarction, angina, or stroke.
[b]Physical Activity Scale for the Elderly [23].
[c]Calcium from diet and supplements.
[d]Potassium intake from dietary sources only.

Compared with diuretic non-users, loop diuretic users had a 2.9–4.6% higher age-adjusted mean BMD at the total hip, femoral neck and total body ($P < 0.05$ for all comparisons) (Table 2). Thiazide users had a 2–3.6% greater age-adjusted mean BMD compared with diuretic non-users at all measured skeletal sites ($P < 0.05$ for all comparisons). However, multivariate adjustment diminished the average differences in BMD observed between specific classes of diuretic users and non-users. There were no statistically significant differences in mean BMD between potassium-sparing or thiazide/potassium-sparing diuretic users and diuretic non-users in both age- and multivariate-adjusted models after Bonferroni correction (Table 2). No significant differences in BMD were observed between categories of diuretic users.

Discussion

Results of this cross-sectional study suggest that recent diuretic use is not associated with BMD in older men. We observed that the higher age-adjusted mean BMD among diuretic users was largely accounted for by differences between participants in prevalent medical conditions and other factors.

Despite the previously hypothesised hypocalciuric effect of loop diuretics, we found no evidence of reduced BMD among users of loop diuretics. A previous cross-sectional study of older adults has reported no association between loop diuretics and ultrasound measurements of the calcaneus [18]. Another cross-sectional study in postmenopausal women showed that compared with loop diuretic non-users, users of loop diuretics had a 5% lower BMD at the femoral neck and trochanter [19]. However, these results have not been replicated and, to our knowledge, other studies exploring a relationship between loop diuretic use and BMD in men have not been reported in the medical literature.

We found that thiazide diuretic users had a significantly higher age-adjusted mean BMD at all five measured skeletal sites that diminished with multivariate adjustment. Previously published data in both men and women have generally shown significant age-adjusted differences that were attenuated with increased accounting for possible confounders [6, 8–11].

Table 2. Percentage difference in BMD (95% CI) between participants using specific classes of diuretics and non-users of diuretics: the MrOS Study, 2000–2002[a]

Diuretic group (*n*)		Total hip	Femoral neck	Trochanter	Lumbar spine	Total body
Loop (250)	Age-adjusted % (95% CI)	3.1 (1.3, 5.0)[b]	4.6 (2.6, 6.7)[b]	1.1 (−1.0, 3.2)	3.0 (0.8, 5.3)	2.9 (1.5, 4.3)[b]
	MV-adjusted[c] % (95% CI)	−0.3 (−2.1, 1.6)	0.9 (−1.2, 3.0)	−1.3 (−3.5, 0.9)	0.4 (−1.9, 2.8)	1.6 (0.2, 3.1)
Thiazide (546)	Age-adjusted % (95% CI)	2.8 (1.5, 4.1)[b]	2.9 (1.5, 4.3)[b]	2.3 (0.9, 3.8)[b]	3.6 (2.0, 5.1)[b]	2.0 (1.1, 3.0)[b]
	MV-adjusted[c] % (95% CI)	1.0 (−0.3, 2.3)	0.8 (−0.6, 2.3)	0.8 (−0.7, 2.4)	1.3 (−0.3, 2.9)	1.3 (0.3, 2.4)
Potassium-sparing (100)	Age-adjusted % (95% CI)	3.1 (0.2, 6.0)	3.8 (0.6, 7.0)	2.3 (−1.0, 5.6)	3.3 (−0.1, 6.8)	2.3 (0.2, 4.5)
	MV-adjusted[c] % (95% CI)	1.9 (−0.8, 4.7)	2.5 (−0.6, 5.5)	1.3 (−1.9, 4.5)	1.5 (−1.9, 4.9)	1.9 (−0.2, 4.0)
Thiazide/potassium-sparing(120)	Age-adjusted % (95% CI)	1.6 (−1.0, 4.3)	2.0 (−1.0, 4.9)	1.0 (−2.0, 4.1)	0.3 (−2.9, 3.5)	0.7 (−1.3, 2.7)
	MV-adjusted[c] % (95% CI)	0.1 (−2.4, 2.6)	0.2 (−2.6, 3.1)	−0.3 (−3.2, 2.7)	−1.6 (−4.8, 1.5)	0.2 (−1.8, 2.2)

[a]Positive values indicate that BMD for the specific diuretic group is greater than that for the comparison group (diuretic non-users, $n = 4{,}939$).
[b]$P < 0.05$, Bonferroni adjusted.
[c]MV = multivariate adjusted for age, body mass index, physical activity, diabetes mellitus, cigarette smoking, congestive heart failure, hypertension, chronic obstructive pulmonary disease, and cardiovascular disease (myocardial infarction, angina, or stroke).

A previous cross-sectional study involving 681 older men showed that thiazides had no effect on BMD [6]. Although randomised controlled studies have demonstrated a positive relationship between thiazide use and BMD [15–17], most have been performed in women. In one randomised controlled study, men who received hydrochlorothiazide did not have significant increases in BMD and no dose–response relationship was observed [16].

To our knowledge, there have been no prior studies that specifically evaluated the use of potassium-sparing diuretics on BMD. In both age- and multivariate-adjusted models, we observed that neither potassium-sparing nor combination thiazide/potassium-sparing diuretics had any significant influence on bone density in our cohort of older men.

Strengths of this study include its comprehensive evaluation of diuretic use and BMD in a large cohort of older men, and its examination of the associations of loop, thiazide, potassium-sparing and combination diuretics with BMD at multiple skeletal sites. We also made adjustments for the presence of multiple potentially confounding factors.

The present study also has several limitations. Firstly, because analyses were cross-sectional and no data are available on duration of diuretic usage, the temporality between diuretic use and BMD changes cannot be determined and causality cannot be inferred. Secondly, the lack of information on diuretic dose precluded an examination of dose–response relationships between the various diuretics and BMD. Thirdly, multivariate analyses did not account for potentially important interactions between individual covariates and BMD. For example, congestive heart failure may impact body mass index due to fluid retention and sarcopenia; and cardiovascular disease may impact exercise levels due to physical impairment or exercise intolerance. We lacked the data to match subjects for heart disease severity to run a stratified analysis. Finally, these results may not be generaliseable to a non-white or younger population of men.

In this cross-sectional study among community-dwelling men aged 65 years and older, current users of loop, thiazide, potassium-sparing and thiazide/potassium-sparing diuretics had a higher age-adjusted mean BMD compared with non-users. However, after multivariate adjustment, the magnitude of this difference was diminished and no longer significant. There were no significant differences in BMD between the four diuretic groups. Overall, the results suggest that current diuretic use is not associated with BMD in older, community-dwelling men.

Key points

- Diuretics have varying effects on renal calcium balance which could influence BMD.
- Although thiazide diuretics have been associated with modest increases in BMD, not much is known about the effects of loop, potassium-sparing and thiazide/potassium-sparing combination diuretics on BMD, particularly in older men.
- This cross-sectional study demonstrated that, after adjusting for confounding factors, no significant differences were found in BMD among men who used or did not use various diuretics.

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Second hip fracture in elderly hip fracture patients: cost and effectiveness of fracture prevention treatment

SIR—Hip fractures account for about 10% of all fractures [1], increasing by 1–3% annually [2]. About 8% of these patients sustain repeat hip fracture within the first year [3]. The probability of sustaining two hip fractures in the course of an individual's life could reach 20% [4]. Treatment with vitamin D and calcium supplements and improvement of vitamin D status play an important role in the osteoporosis therapeutic strategy and in the prevention of hip fractures in the elderly, decreasing the hip fracture rate by 30% in treated versus untreated patients [5]. Efficient fracture prevention treatment with alendronate has been reimbursed in Israel since January 2000.

We assessed standards of care, following an index hip fracture, and the rate of second hip fractures in elderly patients treated in the community clinics (community-treated patients: CTP) and compared it with the rate in the participants of a post-surgical osteoporosis treatment programme (PSOTP).

Participation in the PSOTP was offered to all elderly hip fracture patients who underwent surgical correction of hip fracture in the Department of Orthopaedic Surgery during 2001–2002. Frequent fallers, patients having major psychiatric problems, malnutrition or active malignant disease in the last 5 years and patients receiving bisphosphonates for established osteoporosis were excluded.

Methods

CTP group

Information about the first hip fracture, laboratory evaluation, concomitant diseases and medications was retrieved from the patients' discharge charts. Two years after the index fracture, the CTP were contacted by a physician from the Metabolic Bone Diseases Unit. The patients were requested to bring to the phone all their current medications and to read their names to the interviewer. Questions about calcium and vitamin D doses were specifically stressed. The patients were asked about new fractures and about past and current use of antiresorbing drugs. All reported second hip fractures were validated by data retrieval from patients' hospital charts.

PSOTP group

The PSOTP patients underwent quarterly clinical and laboratory evaluation. For details please see Appendix 1 in the supplementary data on the journal website (www.ageing.oxfordjournals.org). All the PSOTP patients were treated with 600 mg of elemental calcium and 800 IU of vitamin D_3. Treatment with alendronate was started after therapeutic correction of vitamin deficiency (serum $25(OH)D_3 \geq 18$ ng/ml).

Descriptive statistics were used to characterise the patients' groups. Comparison in fracture rates was performed using Fisher's exact test and the calculation of relative risk (RR) with 95% confidence interval (CI). To compare two groups, *t*-test or Mann–Whitney test (as appropriate) was used for continuous variables, and chi-squared test for categorical variables.

Results

Of 512 elderly hip fracture patients who met inclusion criteria, 97 (19%) consented to participate in the PSOTP and 415 (81%) were treated in their community medical care facilities. Two years after the index fracture, 29 (5.6%) were