CLINICAL STUDY

Kidney function and age related mineral imbalance in postmenopausal women with osteopenia/osteoporosis

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Abstract

Background: **Negative mineral balance in postmenopausal women appears to be an important risk factor for osteoporosis and subsequent bone fractures. Its pathogenesis has not been elucidated.**
Objectives: **To elucidate the participation of the kidney and ageing on mineral balance in postmenopausal women.**
Methods: **36 postmenopausal women with osteopenia or osteoporosis, aged 46–75 years were evaluated by determination of mineral balance, kidney functions, 25(OH)-cholecalciferol [25(OH)D], 1,25$(OH)_2$-cholecalciferol [1,25$(OH)_2$D] and intact parathormone plasma levels.**
Results: **Plasma calcium (Ca) concentrations were low and they did not decrease further with ageing. Urinary Ca excretion decreased ($r=-0.425$, $p<0.01$) with age without changes in the fractional excretion of Ca. A similar decrease of urinary excretion was found in the urinary excretion of phosphorus (Pi) ($r=-0.335$; $p<0.03$) and magnesium (Mg) ($r=-0.355$; $p<0.03$). All patients' kidney functions were in the age-related reference range. Plasma 25(OH)D concentrations were in the range of moderate to severe deficiency, related inversely to age ($r=-0.357$; $p<0.03$) and Ca urinary excretion ($r=0.343$; $p<0.04$) and to plasma creatinine concentration ($r=0.381$; $p<0.02$). Plasma 1,25$(OH)_2$D concentrations were also low, they did not change with age and were highly correlated with Ca urinary excretion ($r=0.458$; $p<0.005$). The intact parathormone (iPTH) plasma concentrations were in the reference range, without any changes during aging.**
Conclusions: **Pi, Mg and dominantly Ca imbalance in postmenopausal women with osteopenia or osteoporosis accentuates with age and besides their insufficient intake the vitamin D deficiency takes part. These data support the need for increased supplementation of Ca and vitamin D with increasing age.** ***(Tab. 3, Fig. 4, Ref. 18.)***
Key words: Osteopenia/osteoporosis, mineral balance, 25(OH)-cholecalciferol, 1,25$(OH)_2$-cholecalciferol, intact parathormone, kidney.

Mineral imbalance participates in the development of osteoporosis in postmenopusal women. This could be prevented by calcium (Ca) (Kocián, 1968; Poršová-Dutoit et al, 1992), magnesium (Mg) (Steidl et al, 1990) and vitamin D. Mineral imbalance could develop even as a consequence of effective treatment by antiosteoporotic drugs (Blahoš, 1995; Spustová et al, 1998). In addition to the deficient intake by food, altered mineral absorption in intestine could participate. Ca, vitamin D and potentially Mg supplementation are therefore the preconditions of any effective prevention and treatment of osteoporosis.

Age and kidney participate also in mineral imbalance. Unfortunately, pertinent data about their significance and participation are not at the disposal yet. Their significance was evaluated in the presented study.

Patients and methods

Patients

Thirty-six postmenopausal women with densitometrically proven osteopenia (17 patients) or osteoporosis (19 patients) were included into the study. Women with secondary osteopenia/osteoporosis were excluded. Pertinent data are presented in Table 1. All patients were supplemented only with 0.5 g Ca/d in the form

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Tab. 1. Clinical characteristics of the study population.

Diagnosis osteopenia/osteporosis	17/19
Number	36
Age (year)	63.0±1.2
Menopause duration (year)	14.8±1.1
BMD femoral neck (g/cm^2)	0.846±0.02
T-score femoral neck (SD)	-1.13±0.13
BMD L_1-L_4 (g/cm^2)	0.948±0.02
T-score L_1-L_4 (SD)	-1.84±0.19

Tab. 2. Basal laboratory values.

	x±SEM	Reference range
Plasma calcium (mmol/l)	2.26±0.02	2.25-2.65
Urinary calcium (mmol/d)	3.99±0.30	2.5-7.0
Calcium fractional excretion	0.017±0.001	0.01-0.04
Plasma magnesium (mmol/l)	0.823±0.01	0.75-0.95
Urinary magnesium (mmol/d)	3.13±0.21	1.4-6.8
Magnesium fractional excretion	0.037±0.002	0.02-0.07
Plasma phosphate (mmol/l)	1.06±0.03	0.75-1.45
Urinary phosphate (mmol/d)	14.44±1.16	
Phosphate fractional excretion	0.125±0.008	0.07-0.25
Plasma creatinine (µmol/l)	71.5±1.5	62-110
Clearance creatinine (ml/s)	1.34±0.05	
25(OH)-cholecalciferol (ng/ml)	29.7±5.7	16-74
1,25$(OH)_2$-cholecalciferol (pg/ml)	21.6±1.91	20-67
Intact parathormone (pg/ml)	56.3±3.4	12-72

of calcium carbonate before the study. The study was performed between December and April, i.e. at the lowest reserves of vitamin D and Ca.

Methods

Analyses: Blood samples were collected in the fasting state (i.e. morning hours) into heparinized tubes and centrifuged at 4 °C. Urine was collected for 24 hours and the collection finished just before venipuncture. Urine was acidified to dissolve mineral compounds. Biochemical analyses were performed in Vitros 250 (Johnson&Johnson, Rochester, NY, USA). Intact parathormone (iPTH) concentration was determined by IRMA method (immunoradiometric analysis) (Diagnostic Products Corporation, Los Angeles, CA, USA), 25(OH)-cholecalciferol (25(OH)D) by RIA method (Nicols Institute Diagnostics, SanJuan Capistrano, CA, USA) and 1,25$(OH)_2$-cholecalciferol (1,25$(OH)_2$D) by RIA (Nicols Institute Diagnostics, Nijmegen, The Netherlands).

Densitometry: Bone mineral density (BMD) was determined by dual photone x-ray absorptiometry (DPXA) on Lunar-DPXL (Lunar Corporation, Madison, WI, USA). BMD was determined in the femoral neck and lumbal column. The results were evaluated according to the WHO expert criteria. Osteopenia was defined by BMD -1 SD -2.5 SD mean values of young healthy probands (T-score). Osteoporosis was defined by BMD <2.5 SD (Kanis et al, 1994).

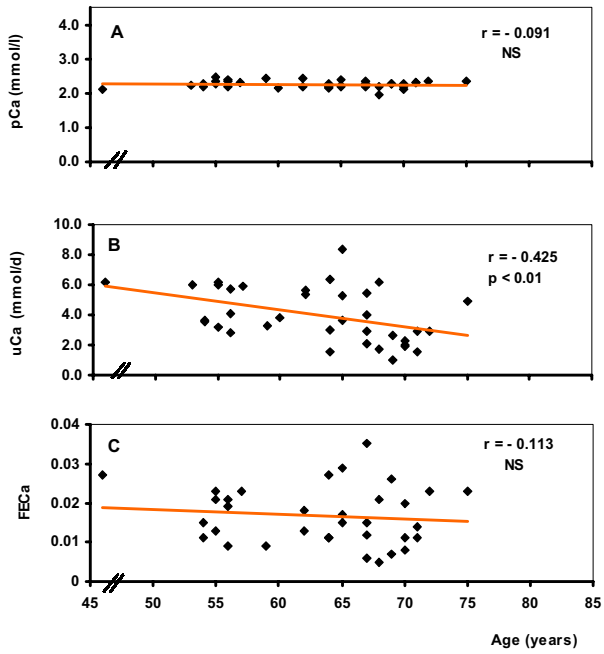

Fig. 1. Correlation of calcium parameters with age.

Results

Mineral balance

Balance of Ca metabolism was our primary interest, but the balance of additional minerals was also determined.

Ca balance: Plasma Ca concentrations were at the lower reference range. Both urinary Ca excretion and fractional Ca excretion (FE_{Ca}) were within the reference range (Tab. 2). While no relationship was found between plasma Ca concentrations and age (Fig. 1A), the urinary Ca excretion decreased significantly (Fig. 1B). This decrease was not caused by changes in tubular reabsorption, because FE_{Ca} did not change with age (Fig. 1C). The urinary Ca excretion did not correlate with the plasma Ca concentration (r=-0.035, NS).

Mg balance: Plasma Mg concentration was within the reference range (Tab. 2) and did not depend on age (Fig. 2A). Urinary Mg excretion, like the excretion of Ca, decreased with increasing age (Fig. 2B), without any significant change of FE_{Mg} (Fig. 2C).

Plasma Ca and Mg did not correlate (r=-0.074; NS), but their urinary excretions did correlate (Fig. 3).

Phosphate balance: Pi plasma concentration was within the reference range (Tab. 2) and did not correlate with age (Fig. 4A). Urinary Pi excretion decreased with the increasing age (Fig. 4B), but also without changes in FE_{Pi} (Fig. 4C). Plasma Pi concentration did not correlate even with Ca plasma concentration (r=0.12; NS).

Regulations

25(OH)D: The plasma concentrations of 25(OH)D were, with some exceptions, in the range of marked deficiency (Tab. 2) and

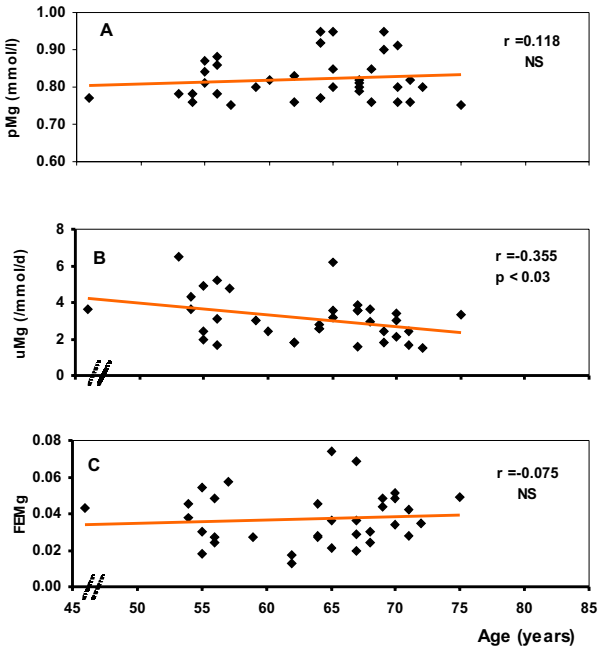

Fig. 2. Correlation of magnesium parameters with age.

they decreased even more with increasing age (Tab. 3). They correlated with urinary calcium excretion, but did not correlate with plasma Ca concentrations (Tab. 3).

1,25(OH)$_2$D: Plasma concentrations of 1,25(OH)$_2$D were also low (Tab. 2), however they did not change with increasing age (Tab. 3). On the other hand they correlated with Ca excretion, but they did not correlate with plasma Ca concentration (Tab. 3).

Intact parathormone: Plasma concentrations of iPTH were within the reference range (Tab. 2) and did not correlate with age, plasma concentration or urinary excretion of Ca and no relationship was found even between iPTH and 25(OH)D or 1,25(OH)$_2$D (Tab. 3).

Discussion

Ca excretion in urine decreased with increasing age without changes in plasma calcium concentrations, which is in accordance with others (Kotowicz et al, 1990; Morris et al, 1991; Tsuboi et al, 2000). This decrease could have been caused by the decreased Ca intake in food or by its decreased absorption in the gut. The calcium intake of the investigated women in food was 700–800 mg Ca/d and they were supplemented by 500 mg Ca/d in the form of calcium carbonate. Thus, it was more probable that the decreased intestinal absorption caused hypocalcemia and age related decrease of urinary excretion of calcium. Low 1,25(OH)$_2$D and low and falling plasma 25(OH)D concentrations with increasing age participated in the low absorption of Ca. Moreover, the decreased synthesis of 1,25(OH)$_2$D in the kidney (Orwoll and Meier, 1986) and its decreased effectiveness at the postreceptor level (Chen et al, 2000) even in the case of an increased number of vitamin D receptors (Martinez et al, 1993)

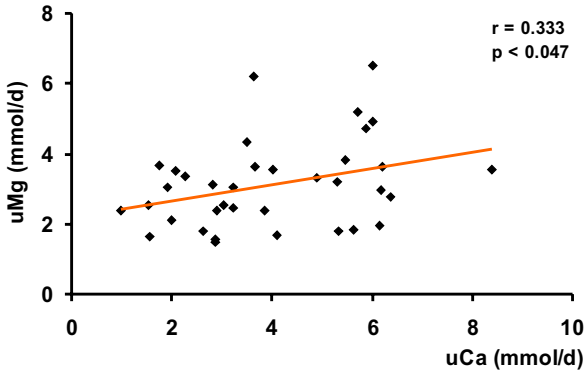

Fig. 3. Correlation of calcium excretion with magnesium excretion.

surely participated. In any case both mineral and vitamin D balance were unfavourable and required more intensive Ca and vitamin D supplementation. In agreement with this view are the results of our recent paper in postmenopausal women supplemented by 0.5 g/d Ca and 800 IU/d vitamin D (nutritional dosage): in spite of supplementation, plasma Ca did not change and 25(OH)D concentration remained in the range of deficiency (Štefíková et al, 1999). 25(OH)D plasma concentration increased over the deficiency range only after supplementation with vitamin D in doses >2000 IU/d (Štefíková et al, 2003). Moreover, even the dose 4000 IU/d vitamin D for 5 months did not increase 25(OH)D concentration >160 nmol/l (Vieth et al, 2001), which is the upper safety limit.

Plasma Mg concentrations were in a reference range and did not depend on age. Mg urinary excretion correlated with the Ca excretion. However, even plasma Mg concentrations within reference range did not exclude its masked deficiency (Tsuboi et al, 2000), which could be a consequence of the decreased Mg intake or its decreased absorption in the gut because of 25(OH)D deficiency; it was repeatedly shown, that 25(OH)D decreased not only Ca but even Mg absorption in the gut (Holick, 1998; Angelo et al, 2002).

Tab. 3. Correlation of some mineral metabolism parameters with age, vitamin D and intact parathormone.

y	x	r	p
Ccr	age	-0.267	NS
25(OH)D	age	-0.373	<0.02
1,25(OH)2D	age	-0.104	NS
iPTH	age	0.211	NS
uCa	25(OH)D	0.343	<0.04
pCa	25(OH)D	0.302	NS
iPTH	25(OH)D	-0.249	NS
uCa	1,25(OH)2D	0.458	<0.005
pCa	1,25(OH)2D	-0.09	NS
iPTH	1,25(OH)2D	0.006	NS
pCa	iPTH	0.261	NS
uCa	iPTH	-0.333	NS

Notes: Ccr = clearance creatinine, 25(OH)D = 25(OH)-cholecalciferol, 1,25(OH)$_2$D = 1,25(OH)$_2$-cholecalciferol, iPTH = intact parathormone, uCa = urinary calcium, pCa = plasma calcium, r = coefficient of correlation, p = statistical significance

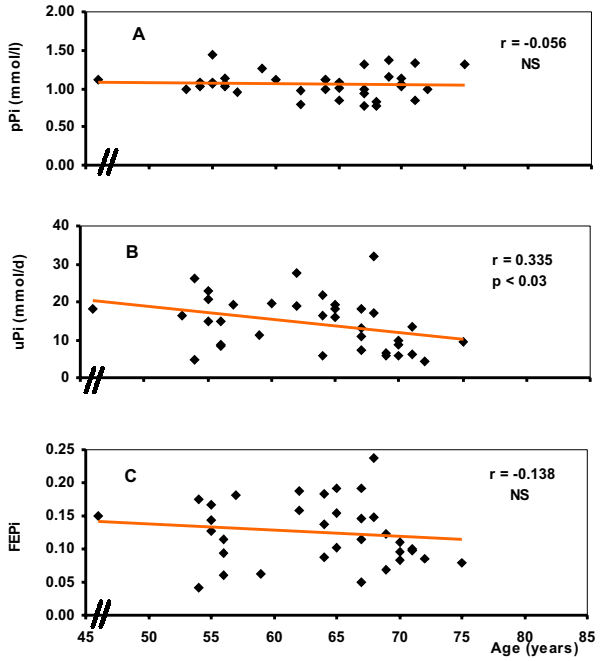

Fig. 4. Correlation of phosphate parameters with age.

Similarly, also Pi plasma concentrations and FEPi did not depend on age, but Pi urinary excretion decreased in an age-dependent fashion.

Ca, Mg and Pi excretions decreased with increasing age of osteoporotic women. Because no changes were found in FE of minerals and glomerular filtration rate decreased just slightly and insignificantly, additional factors participated. The simultaneous decrease of plasma 25(OH)D concentration probably decisively influenced mineral balance with the decreased excretion of minerals. However, the participation of additional factors could not be excluded.

Vitamin D deficiency and the decreased plasma 25(OH)D and $1,25(OH)_2D$ were the principal causes of the decreased Ca resorption in the gut. This has been shown in the preceding studies with the nutritional dosage vitamin D (Štefíková et al, 1999) and the need of increased vitamin D dosage (Štefíková et al, 2003). Besides a deficiency a decreased vitamin D metabolism participated (Tsuboi et al, 2000; Vieth et al, 2001) and in the case of heavy deficiency of 25(OH)D the synthesis of $1,25(OH)_2D$ was also inhibited (Schoming and Ritz, 2000).

Plasma concentrations of $1,25(OH)_2D$ were evidently low. The most surprising finding was the high correlation between $1,25(OH)_2D$ plasma concentration and urinary excretion of Ca. This finding pointed out a sensitive reaction of the kidney on $1,25(OH)_2D$ plasma concentration. Besides the decreased synthesis of $1,25(OH)_2D$ additional mechanisms such as the stimulation of 24-hydroxylase in the kidney and a postreceptor defect of vitamin D receptor caused by vitamin D response element binding protein discovered just recently (Martinez et al, 1993; Angelo et al, 2002) probably participated.

Menopause in concert with additional factors leads to negative Ca balance causing bone pathology. A simple preventive measure appears to be supplementation of Ca and vitamin D which influences also Mg balance. However, higher doses of vitamin D than used now are to be recommended (Holick, 1998; Utiger, 1998). Moreover, besides a simple deficiency vitamin D resistance participates; unfortunately its evaluation is still unknown.

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