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ORIGINALS

Relationship between renal function and bone mineral density in postmenopausal women that undergo bone mass evaluation

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SUMMARY

As osteoporosis and renal insufficiency are two prevalent pathologies in the aging population we decided to evaluate retrospectively the renal function (estimated by formula) in postmenopausal women who came to our Institute for bone mass determination to establish the relationship between them. Thus, we studied 300 postmenopausal women with a mean age of 66.9 ± 6.8 years who had a bone densitometry performed; we chose total femur bone mineral density (TFBMD) for defining osteopenia and osteoporosis as this measurement included substantial amounts of both trabecular and cortical bone; osteopenia/osteoporosis was diagnosed using T score criteria recommended by the WHO. We also measured BMD at the femoral neck. Renal function was estimated by the Cockcroft-Gault formula using serum creatinine determination. We found osteoporosis in 61 patients (20.3%). Of them, el 81.9% have renal insufficiency (estimated creatinine clearance-ECrC ≤ 60 ml/min), compared to 54% of 239 women who had normal BMD/osteopenia (p < 0.001). Six of 61 (9.8%) women with osteoporosis had severe renal insufficiency (ECrC ≤ 36 ml/min) versus *4/239 (1.6%) women with normal BMD/osteopenia (p = 0.001). Women with osteoporosis were older, and had a significantly lower weight and ECrC compared to patients without osteoporosis (ECrC 52 ± 11 ml/min* vs *59 ± 12 ml/min; p < 0.0001). We found a significant positive correlation between TFBMD and ECrC (r = 0.389) as well as with weight (r = 0.422) and a negative correlation between age and ECrCE (r = -0.51) and with TFBMD (r = -0.22). In the multiple regression analysis only weight continued to correlate significantly with TFBMD (Beta = 0.344). When FNBMD was considered as the dependent variable, we found a significantly negative correlation with age (r = -0.30) and significantly positive correlations with height (r = 0.16), weight (r = 0.33) and ECcr (r = 0.39). In the multiple regression analysis only age (Beta = -0.20) and weight (Beta = 0.20) continued having an independent correlation FNBMD. We conclude that our data confirm that there exists a substantial prevalence of renal insufficiency, even severe, among patients with densitometric osteoporosis that should be kept in mind when one is considering the prescription of medications as bisphosphonates that have renal clearance, so as not to jeopardize the efficacy and the security of these drugs.*

Key words: ***Postmenopausal osteoporosis. Renal insufficiency. Prevalence. Bisphosphonates.***

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RELACIÓN ENTRE FUNCIÓN RENAL Y DENSIDAD MINERAL ÓSEA EN MUJERES POSMENOPÁUSICAS QUE REALIZAN EVALUACIÓN DE MASA ÓSEA

RESUMEN

Ya que la osteoporosis y la insuficiencia renal son dos patologías prevalentes en la población que envejece quisimos evaluar en forma retrospectiva la función renal (estimada por fórmula) en mujeres postmenopáusicas que concurrían a nuestro Instituto para evaluación de su masa ósea y establecer que tipo de relación existía entre las mismas. Así estudiamos 300 mujeres postmenopáusicas con una edad promedio de 66,9 ± 6,8 años a las que se les efectuó una densitometría ósea de cadera total (DMOCT) y cuello femoral (DMOCF); se diagnosticó osteoporosis sobre la base de los criterios de T score de la OMS. La función renal se estimó por fórmula de Cockcroft-Gault sobre la base de la medición de la creatinina sérica. Encontramos osteoporosis en cadera total en 61 pacientes (20,3%). De ellas, el 81,9% presentó insuficiencia renal (clearance de creatinina estimado —CcrE ≤ 60 mil/min), contra el 54% de 239 mujeres que presentaron DMO normal u osteopenia (p < 0,001). Seis de 61 (9,8%) mujeres con osteoporosis presentaron insuficiencia renal severa (CcrE ≤ 36 ml/min) contra 4/239 (1,6%) mujeres con DMOCT normal u osteopenia (p = 0,001). Las mujeres con osteoporosis fueron más añosas, y tuvieron un peso y un CcrE significativamente menor que el de las pacientes sin osteoporosis (CcrE 52 ± 11 ml/min vs *59 ± 12 ml/min; p < 0,0001). Encontramos una correlación positiva significativa entre DMOCT y CcrE (r = 0,389) así como con el peso (r = 0,422) y una correlación negativa entre la edad y CcrE (r = -0,51) y con la DMOCT (r = -0,22). En la correlación múltiple solo el peso continuó correlacionando en forma significativa con la DMOCT (Beta = 0,344). Cuando se consideró la DMOCF como la variable dependiente, encontramos una correlación negativa significativa con la edad (r = -0,30) y correlaciones significativas positivas con la talla (r = 0,16), con el peso (r = 0,33) y con el CcrE (r = 0,39). En el análisis de correlación múltiple solo la edad (Beta = -0,20) y el peso (Beta = 0,20) continuaron presentando una correlación significativa independiente con la DMOCF. En conclusión, nuestros datos confirman que existe una sustancial prevalencia de insuficienica renal, incluso severa, entre las pacientes que presentan osteoporosis densitométrica que debería ser tenida en consideración al decidir la prescripción de medicaciones que como los bisfosfonatos se eliminan por vía real, para no comprender la eficacia o la seguridad de estas drogas.*

Palabras clave: ***Osteoporosis postmenopáusica. Insuficiencia renal. Prevalencia. Bisfosfonatos.***

INTRODUCTION

A recent study on data from the U.S. NHANES III (Third National Health and Nutrition Examination Survey 1988-1994) found a high prevalence of renal function impairment in patients with osteoporosis[1], and age-specific prevalence abruptly increased from 59 years old. In that study, the prevalence of severe renal impairment was greater for women than for men (24% vs. 11%). Yendt et al. had previously identified creatinine clearance (CrCl) as a factor positively correlating with lumbar and radial bone mass in normal aging women[2]. This relationship was age-independent and stronger than the height-bone mass correlation. Later on, they found that CrCl was significantly lower in osteoporotic women with vertebral fractures/crushing than in aged-paired normal women[3].

In this retrospective study we wanted to assess renal function (estimated by formulas) in postmenopausal women that attended our Institute for determining their bone mass and we then tired to establish the relationship existing between both.

MATERIAL AND METHODS

We studied postmenopausal women aged 50 to 80 years that attended our Institute for assessing their bone mass. Patients that could suffer from secondary

causes for their osteoporosis (hyperthyroidism, chronic use of steroids, hyperparathyroidism, etc.) were ruled out. Three hundred women were finally included, with a mean age of 66.8 ± 6.8 years.

Renal function estimate

Renal function was estimated by the Cockcroft-Gault formula based on determination of serum creatinine: CrCl = [(140 – age) (weight in kg)] / [72 × sCr (mg/100 mL], minus 15% for women. Serum creatinine was determined by the Jaffé's kinetic method using a Synchron CX3 autoanalyzer (Beckman Instruments Inc., USA).

Renal failure was defined as an estimated creatinine clearance (ECrCl) < 60 mL/min. The inverse of serum creatinine was used as another weight- and age-independent renal function estimate.

Bone mass determination

Total hip bone mineral density (THBMD) was used as the main parameter to determine bone mass since this parameter includes a substantial amount of both trabecular and cortical bone. THBMD was measured by using dual X-Ray absorptiometry (DEXA) using a DPX-L densitometer (Lunar, Madison, WI). BMD was also determined from the femoral neck (FNBMD). Results are expressed as absolute values and as T scores, which compare BMD of patients and normal young adult females and which are used in the definition of osteopenia and osteoporosis proposed by the World Health Organization expert committee. The reference population from which T scores are derived is that included in the densitometer software. BMD T scores > -1 are considered normal; those between –1 and –2.5 are considered within the osteopenia range, and those < -2.5 are considered within the osteoporosis range.

Since osteoporosis screening did not include a mid and low spine radiograph, densitometry of lumbar spine was not performed due to the impossibility of ruling out osteoarthritis that could overestimate mineral density in an aged population.

STATISTICS

Data were analyzed by CSS software: Statistica (StatSoft Inc., Tulsa, OK, USA). Results are expressed as mean ± SD. Continuous variables were compared using the Student's t test for independent samples. Dichotomous variables were analyzed by the Chi-squared. Simple correlation were done using BMD and total hip T score and femoral neck T score as dependent variables, and height, weight, serum creatinine, inverse of serum creatinine, and estimated CrCl as independent variables. We then perform a multiple regression analysis using those variables that were significant with a p value £ 0.05 in the univariate analysis.

RESULTS

Sixty-one patients (20.3%) had osteoporosis at the FN level. Of them, 81.9% had renal failure versus 54% in 239 women that had normal BMD or osteopenia ($p < 0.001$). Six of 61 (9.8%) women with osteoporosis had severe renal failure (ECrCl £ 36 mL/min) versus 4/239 (1.6%) women with normal FNBMD or osteopenia ($p = 0.001$).

Women with osteoporosis were on average three years older and had significantly less weight that those with normal or osteopenic bone mineral density (table I). ECrCl in osteoporotic women was significantly lower than that of women without osteoporosis (52 ± 11 mL/min vs. 59 ± 12 mL/min; $p < 0.001$).

We found a significant positive correlation between THBMD and ECrCl ($r = 0.389$) (fig. 1) and age ($r = 0.422$) (fig. 2), and a negative correlation between age and ECrCl ($r = 0.51$) (fig. 3) and with THBMD ($r = 0.22$) (fig. 4). There was no correlation between THBMD and creatinine, the inverse of creatinine, or height. In multiple correlation analysis, only weight still presented a significant independent correlation (Beta = 0.344) with THBMD. When FNBMD was considered as the dependent variable, we found a significant negative correlation with age ($r = -0.30$) and significant positive correlations with height ($r = 0.16$), weight ($r = 0.33$), and ECrCl ($r = 0.39$). In

Table I. Clinical and densitometry variables of patients with osteoporosis and with normal or osteopenic bone mineral density

Variable	Osteoporosis n: 61	Normal/Osteopenia n: 239
Age (years)	69.1 ± 7.3	66.3 ± 6.6*
Height (cm)	156.0 ± 5.8	156.1 ± 5.8
Weight (kg)	52.0 ± 7.7	61.6 ± 8.98*
ECrCl (ml/min)	52.0 ± 11.3	59.1 ± 12.7*
THBMD mg/cm^2	0.637 ± 0.046	0.799 ± 0.072
TH T score	-3.02 ± 0.38	-1.66 ± 0.61

ECrCl: estimated creatinine clearance; THBMD: total hip bone mineral density; TH: total hip; *$p < 0.01$.

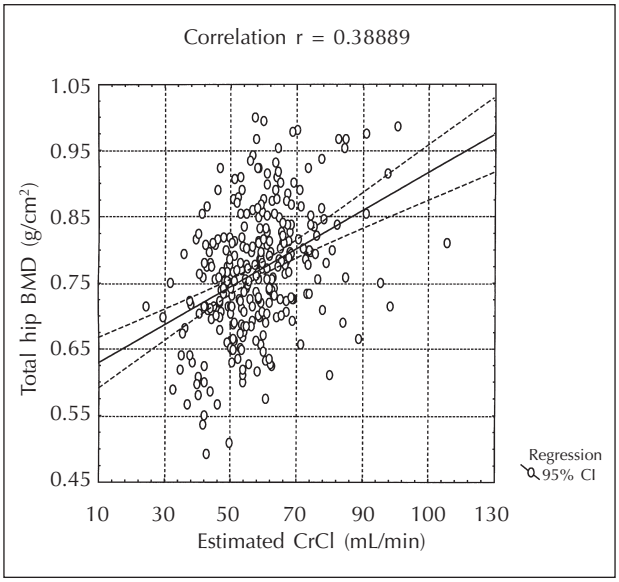

Fig. 1.—Correlation between estimated CrCl and total hip BMD.

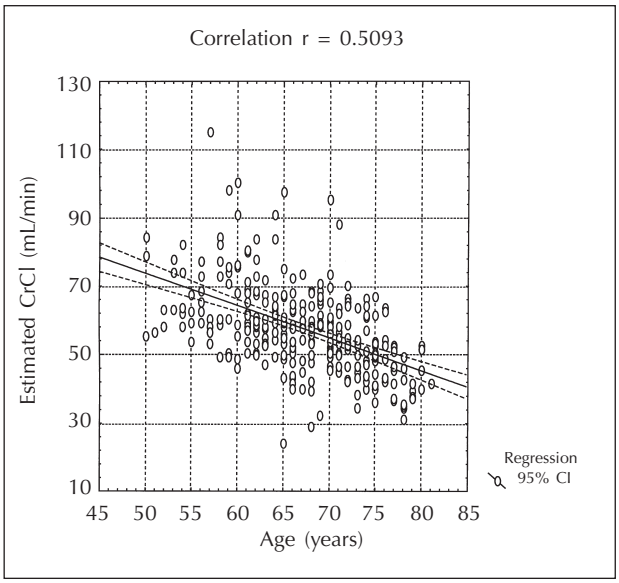

Fig. 3.—Correlation between age and estimated CrCl.

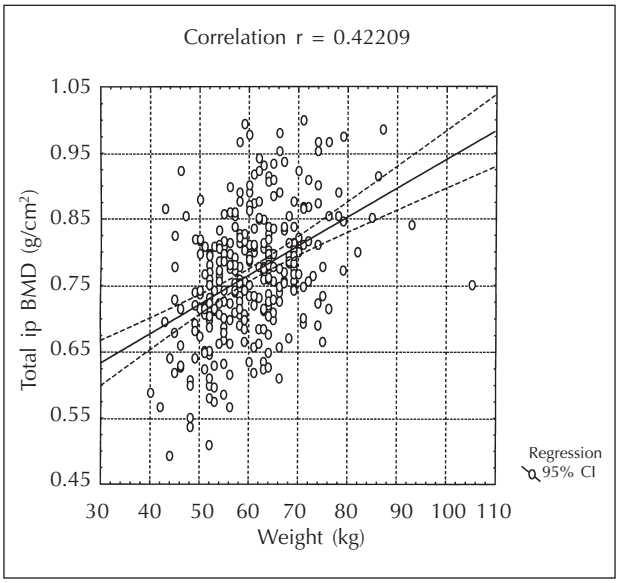

Fig. 2.—Correlation between weight and total hip BMD.

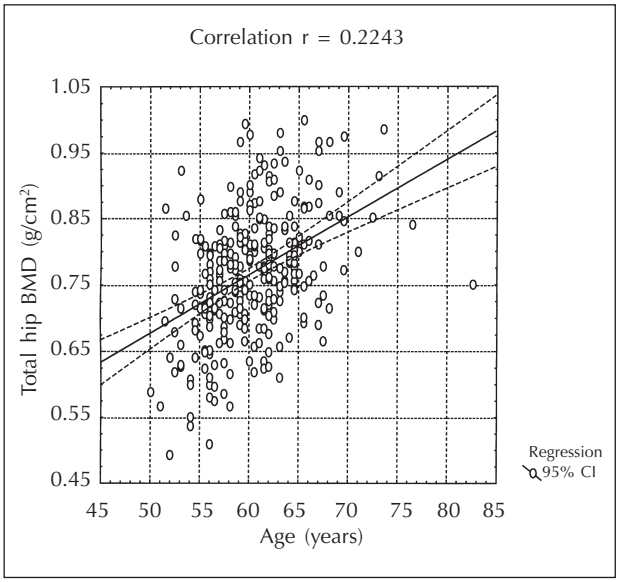

Fig. 4.—Correlation between age and total hip BMD.

multiple correlation analysis, only age (Beta = -0.20) and weight (0.20) still presented a significant independent correlation with FNBMD.

DISCUSSION

It has been estimated that bone mass measured by densitometry accounts for a big part of the variance of bone tissue resistance[4]. On the other hand, prospective studies have shown that bone mass determination may predict fractures[5,6], so that identifying factors that have a significant relationship with bone mass may be important. Osteoporosis risk factors established so far include age, early (before age 40) or surgical (before age 45) menopause, low weight (weight < 57 kg or BMI < 20), white origin, family or personal history of bone fractures, cigarette smo-

king, and chronic use of steroids. More than a decade ago, Yendt et al. identified another factor, creatinine clearance calculated from blood and serum creatinine. This factor positively correlated with lumbar and radial bone mass in normal aged women and was age-independent[2]. In a further study, they examined the relationship between bone mass and calculated CrCl and other variables in an older group that included the 77 previously studied women and 37 other with primary osteoporosis. In that study, they confirmed that there was an age-independent positive correlation between calculated CrCl and radial and lumbar bone mass. They also found that calculated CrCl was lower in osteoporotic women with vertebral fractures than in normal women aged-paired, and that calculated CrCl had a significant predictive value for bone mass in individual subjects[3]. In our study, we found that there is a substantial prevalence of renal failure, even severe renal failure, among patients that present osteoporosis by densitometry, and we observed a simple and significant correlation between estimated CrCl and THBMD. For CrCl determination, we used the Cockcroft and Gault formula, but not CrCl calculated from 24-h urine creatinine, as Yendt et al. did in their study. In multiple correlation that included all variables showing a simple correlation with THBMD (weight, age, and CrCl calculated by Cockcroft and Gault formula) only weight still independently correlated with THBMD. When femoral neck BMD was used as the dependent variable, it independently correlated with age and weight. This is in agreement to what Hsu et al. found[7]. These authors analyzed data from 13,848 adults older than 20 years from the NHANES III 1988-1994, and they used regression models to determine the relationship between femoral neck BMD and serum creatinine, BUN, and creatinine clearance by the Cockcroft and Gault formula. They found that, although the analysis was not adjusted, there was an association between renal failure and low mineral density; this association was lost when controlling for gender, age, and weight in the multivariate analysis.

Patients candidate to osteoporosis therapy receive medications such as biphosphonates, which excreted through the kidney. Therefore, an important reduction in renal function may decrease their excretion and influence on efficacy and safety of these drugs because of the possibility of inducing excessive reduction of bone remodeling.

Recently, Odvina et al.[8] reported on 9 patients that had no-spinal spontaneous bone fractures, 6 of them having delayed or absent fracture healing for months during alendronate therapy, the most frequently used biphosphonate in osteoporosis therapy. The histomorphometric analysis of bone biopsies from these patients showed a marked suppression of bone remodeling.

The prevalence of renal impairment increases with age, as shown by Jones et al. using data from NHANES III and analyzing serum creatinine as a renal function estimate[9]. More recently, Klawansky et al.[1], also based on NHANES III data, but estimating creatinine clearance by the Cockcroft and Gault formula, found that renal failure prevalence, even when severe, was higher in the population of osteoporosis patients than in those with osteopenia or normal bone mass.

Curiously enough, many of the large clinical studies on efficacy and safety of biphosphonates have excluded patients with a high level of renal failure. One of the first phase III studies with alendronate on 994 women with postmenopausal osteoporosis excluded individuals with serum creatinine > 1.5 mg/dL or 130 mmol/L[10]. The FIT (Fracture Intervention Trial) study, with 6469 participants, specifically excluded patients with impaired renal function (> 144 mmol/L)[11,12]. The study with once weekly alendronate that included 1258 postmenopausal osteoporotic women also excluded those with renal dysfunction[13]. Finally, the international FOSIT study, which comprised 1908 postmenopausal women with low bone mass, excluded patients with renal dysfunction defined as serum creatinine > 150 mmol/L[14]. The VERT study on efficacy of risedronate therapy on vertebral and non-vertebral fractures in postmenopausal women with osteoporosis did not excluded patients with renal failure[15,] , whereas the study assessing the effect of risedronate on hip risk in 5445 women aged 70-79 years excluded those with significant impairments in laboratory values[16].

In conclusion, our data confirm that there is a substantial prevalence of renal failure, even severe failure, among patients that present with osteoporosis on densitometry. That is the reason why doctors treating aged patients with osteoporosis should take into account the possibility of decreased renal function in that population when deciding the prescription medications that, such as biphosphonates, are excreted through the kidney, in order to avoid compromising efficacy and safety of these drugs.

It would be convenient to base decisions on creatinine clearance estimated from the isolated serum creatinine value.

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