ORIGINAL ARTICLE

Calcium and phosphorus metabolism and lithogenic factors in patients with osteoporotic fracture

M.Á. Ochoa-Hortal Rull a, M.C. Cano-García b, M. Arrabal Martín c, R. Cano Gea a, R. Reyes García d, M.A. Arrabal-Polo b,*

a Servicio de Cirugía, Ortopedia y Traumatología, Hospital Rafael Méndez, Lorca, Spain
b UGC Urología Intercentros, Hospital La Inmaculada, Huércal Overa, Spain
c UGC Urología Intercentros, Hospital San Cecilio, Granada, Spain
d Servicio de Endocrinología y Nutrición Clínica, Hospital Rafael Méndez, Lorca, Spain

Received 25 October 2014; accepted 12 December 2014
Available online 1 May 2015

KEYWORDS
Osteoporosis;
Osteoporotic fracture;
Lithogenic factors;
Fasting hypercalciuria

Abstract

Objectives: To demonstrate the presence of mineral metabolism disorders and lithogenic factors in the urine of patients with osteoporotic fracture without previously known stones.

Material and methods: 67 patients with osteoporotic fractures surgically treated in trauma service are included. The area of the fracture site, fracture mechanism and the presence of osteoporosis were the factors taken into account to diagnose osteoporotic fracture. Mineral metabolism, calcitria, oxaluria, uricosuria and citraturia in 24-h urine were analyzed. The presence of abnormal calcium and phosphorus metabolism was proved comparing hypercalciuria patients with normocalciuria ones.

Results: 12 men and 55 women with mean age 68.8 ± 14.5 years old were included. Mean body mass index (BMI) was 27.4 ± 4.1 kg/m². 42% of patients showed hypercalciuria, 34% hyperoxaluria, 34% hypocitraturia and 7% hyperuricosuria. Statistically significant differences were observed only in fasting calcium/creatinine ratio (0.17 versus 0.08; p < 0.0001) when comparing patients with hypercalciuria with those with normocalciuria.

Conclusions: Patients with osteoporotic fractures show different lithogenic factors in urine, mainly hypercalciuria, always in fasting conditions.

© 2014 AEU. Published by Elsevier España, S.L.U. All rights reserved.

* Corresponding author.
E-mail address: arrabalp@ono.com (M.A. Arrabal-Polo).
PALABRAS CLAVE
Osteoporosis; Fractura osteoporótica; Factores litogénicos; Hipercalciuria de ayunas

Metabolismo fosfocálcico y factores litogénicos en pacientes con fractura osteoporótica

Resumen
Objetivos: Demostrar la presencia de alteraciones del metabolismo del fósforo y calcio y la presencia de factores litogénicos en orina de pacientes con fractura osteoporótica sin litiasis previamente conocida.

Material y métodos: Se incluyen 67 pacientes con fractura osteoporótica tratados quirúrgicamente en un servicio de traumatología. Se incluyen pacientes con fractura osteoporótica demostrada por la zona de la fractura, mecanismo de fractura y presencia de osteoporosis en la densitometría ósea. Se analiza el metabolismo fosfocálcico, el estudio de calcioria, la oxaluria, la citraturia y la uricosuria de 24h. Se compara entre los pacientes con hipercalciuria versus normocalciuria y la presencia de alteraciones del metabolismo fosfocálcico.

Resultados: Doce hombres y 55 mujeres incluidos con edad media de 68,8 ± 14,5 años. El IMC medio fue de 27,4 ± 4,1 kg/m². Presentan hipercalciuria el 42% de los pacientes, hiperoxaluria el 34% de los pacientes, hipocitraturia el 34% de los pacientes e hiperuricosuria el 7% de los pacientes. Al comparar los pacientes con hipercalciuria versus normocalciuria únicamente hay diferencias estadísticamente significativas en el calcio/creatinina en ayunas (0,17 versus 0,08; p < 0,0001).

Conclusión: Los pacientes con fractura osteoporótica presentan diversos factores litogénicos en la orina, fundamentalmente hipercalciuria, siendo siempre de ayunas.
© 2014 AEU. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The relationship between osteoporosis and urolithiasis is being widely studied in recent years, and there are several articles that corroborate that the presence of recurrent calcium renal lithiasis, along with fasting hypercalciuria (calcium ratio/fasting creatinine >0.11), is associated with loss of bone mineral density in varying degrees. The role of calciuria has been discussed for years and it had not been taken into account in routine evaluation of patients with osteopenia/osteoporosis; however, recent studies advise its determination both in men and women with bone mineral density loss,2 since when it is usually high, it is a good determinant of osteopenia, and it increases the risk of loss of bone mineral density in patients with calcic renal lithiasis.3,4 Calcioria in patients with osteoporosis can be affected by the increase of acid removal, a linear correlation being observed between acid excretion and calcium excretion in urine, although hypercalciuria cannot be considered itself a risk factor that contributes to the presence of bone mineral density loss, but it is an important lithogenic factor.5,6 Another factor that may be present in the loss of bone mineral density is the alterations in the phosphocalcic metabolism and participation of the 2 main hormones that regulate it, iPTH and vitamin D.

In patients with calcium lithiasis with hypercalciuria, we have observed elevated levels of 1,25-OH vitamin D in up to 40–60% of them, although it is true that 1,25-OH vitamin D is a less stable form and that more variations are produced in this than in 25-OH vitamin D.7 Currently, even though it has not been possible to establish the cause-effect relationship between calcic renal lithiasis and osteoporosis, we know that there is a relationship between both pathological phenomena (litiasis–osteoporosis), but we do not know if the relationship is bidirectional or unidirectional and what happens first. In routine evaluation of a patient with osteoporosis, and in the presence of osteoporotic fracture, we should consider various risk factors that influence the loss of bone mineral density, such as age, sex, race, alcohol intake, smoking, treatment with glucocorticoids, and other concomitant diseases, in this case the lithiasis, which has proved to increase the risk of osteoporotic fracture.7,8 The aim of this study is to analyze in a sample of patients with osteoporotic fracture with no history of calcium renal lithiasis the presence of alterations in the phosphocalcic metabolism and the presence of lithogenic factors in urine.

Material and methods

From January 2013 to June 2014, a total of 67 patients diagnosed with osteoporotic fracture were included in this study, verifying the presence of osteoporosis by dual densitometry-Rx absorptiometry. The patients studied are from the trauma unit where patients undergo surgery after suffering an osteoporotic fracture, the locations being as follows: 58% hip, 35% wrist, 2% spine, and 5% other locations. Inclusion criteria were male and female patients with osteoporotic fracture after being checked by the location of the fracture, fracture mechanism, and presence of osteoporosis in bone densitometry without lithiasis (the patient’s history was reviewed and abdominal X-ray was performed in all patients along with urinary sediment), whereas exclusion criteria were patients with known history of renal lithiasis, known history of bone disease, under treatment with vitamin D, calcium, antiresorptive drugs, corticosteroids, thiazides, indapamide, potassium citrate, and other lithogenic drugs or which induce loss of bone
mineral density. The variables analyzed were: age, sex, body mass index (BMI) (kg/m²), serum creatinine (mg/dl), serum calcium (mg/dl), serum phosphorus (mg/dl), serum alkaline phosphatase (U/l), intact parathyroid hormone (iPTH) (pg/ml), 25-OH vitamin D (U/l), serum pH, urine pH, calcium 24h, citraturia 24h, oxaluria 24h, uricosuria 24h, and calcium/fasting urine creatinine. Statistical analysis of the results was performed using Student’s t-test for analysis of qualitative-quantitative variables and Chi-square test for analysis of qualitative variables. Normality of the variables is checked using the Kolmogorov–Smirnov test and analysis of variance with Levene test. We consider statistical significance if \( p \leq 0.05 \). Analysis was conducted with SPSS 17.0 for Windows. All patients read and signed the informed consent to participate in the study and this study was approved by the ethics committee of the Hospital Rafael Méndez de Lorca (Spain).

**Results**

Patients included in the study were divided by sex as 12 men and 55 women, with a mean age of 68.8 ± 14.5 years. The mean BMI was 27.4 ± 4.1 kg/m². The mean values of serum and urinary variables studied are reflected in Table 1. After analyzing the mean values obtained in the studied variables, we divided patients according to whether or not they present hypercalciuria (>260 mg/24h), hyperoxaluria (>40 mg/24h), hypocitraturia (<320 mg/24h), and hyperuricosuria (>750 mg/24h). 42% of the patients have hypercalciuria, 34% of patients have hypocitraturia, 34% of patients have hyperoxaluria, and 7% of patients have hyperuricosuria. We divided patients according to whether they have hypercalciuria or normocalciuria (28 versus 39) and studied whether there are significant differences in the phosphocalci metabolism and fasting calcium/creatinine ratio. Only statistically significant differences were observed between patients with osteoporotic fracture with hypercalciuria versus those with normocalciuria in the calcium/creatinine ratio in fasting urine (0.17 ± 0.04 versus 0.08 ± 0.02; \( p < 0.0001 \)).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Means of serum and urinary variables in osteoporotic fracture patients with no prior history of stones and with abdominal radiography and normal urinary sediment.</th>
<th>Mean values (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum creatinine (mg/dl)</td>
<td>1.1 (0.6)</td>
</tr>
<tr>
<td></td>
<td>Serum calcium (mg/dl)</td>
<td>9.1 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Serum phosphorus (mg/dl)</td>
<td>3.4 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Serum alkaline phosphatase (U/l)</td>
<td>79.9 (30.1)</td>
</tr>
<tr>
<td></td>
<td>iPTH (pg/ml)</td>
<td>55.8 (36.7)</td>
</tr>
<tr>
<td></td>
<td>25-OH vitamin D (U/l)</td>
<td>22.2 (13.3)</td>
</tr>
<tr>
<td></td>
<td>Serum pH</td>
<td>7.4 (0.1)</td>
</tr>
<tr>
<td></td>
<td>Calcium (mg/24h)</td>
<td>151.7 (207.1)</td>
</tr>
<tr>
<td></td>
<td>Uricosuria (mg/24h)</td>
<td>325.3 (226.7)</td>
</tr>
<tr>
<td></td>
<td>Oxaluria (mg/24h)</td>
<td>22.3 (11.6)</td>
</tr>
<tr>
<td></td>
<td>Citraturia (mg/24h)</td>
<td>329.1 (284.4)</td>
</tr>
<tr>
<td></td>
<td>Urine pH</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Fasting urine calcium/creatinine</td>
<td>0.12 (0.05)</td>
</tr>
</tbody>
</table>

**Discussion**

**Osteoporosis and renal lithiasis**

Osteoporosis is a very common disease that is influenced by different factors, including smoking, sex hormones, alcohol intake, intake of drugs, and others, producing a series of changes and alterations in the metabolism of phosphorus and calcium mediated mainly by vitamin D and iPTH.9 Among many other diseases that osteoporosis may be associated to, it has proved to be an independent factor to produce symptomatic nephrolithiasis, being up to 1.38 times more frequent in patients with osteoporosis than the control group,10 and these patients with osteoporosis-calcium lithiasis presenting major alterations in fasting calcium and markers for bone remodelling.11 Calcium is an essential element in bone health and its mineralization is intensely regulated by iPTH and vitamin D, so, small variations in serum calcium concentration will produce increased or decreased iPTH fundamentally.

**Loss of bone mineral density and hypercalciuria**

In many patients with loss of bone mineral density, we observed the presence of hypercalciuria without a clearly justifiable cause, possibly related to an intrinsic distortion of the bone metabolism.12 One of the most commonly used markers in lithiasic patients with hypercalciuria is the fasting calcium/creatinine ratio, which allows us to differentiate hypercalciuria in absorptive hypercalciuria (calcium/creatinine <0.11) and fasting hypercalciuria (calcium/creatinine >0.11).13,14 It is precisely fasting hypercalciuria which relates more directly to the loss of bone mineral density, the fasting calcium/creatinine ratio being considered a reliable marker of increased bone resorption.14 In our present study, we observed that up to 42% of patients have hypercalciuria, and if we compare patients with hypercalciuria to those who are normocalciuric, the only difference between them is the calcium/creatinine ratio, which is higher in the first group of patients with osteoporotic fracture and hypercalciuria, which corroborates findings of previous studies that found that fasting hypercalciuria is associated with loss of bone mineral density, being the most common idiopathic cause. In fact, in our study, 100% of patients with osteoporotic fracture and hypercalciuria have a calcium/creatinine ratio in fasting urine greater than 0.11. We observed no differences in hormones regulating the phosphocalci metabolism in patients with hypercalciuria versus normocalciuria. These results confirm that the role of vitamin D and iPTH is not very decisive in this type of cases of hypercalciuria.15 We observed no significant differences regarding blood pH, although increased acid excretion would contribute to an increase in calcium excretion in urine, as it has been seen in other studies.2,6 What does seem clear is that along with the presence of hypercalciuria, other changes can be seen in urine that are important lithogenic factors, such as hypocitraturia and hyperoxaluria, both present in 34% of patients. Another fact to note is that although the patients in our study were not lithiasic, the lithiasis itself in the presence of osteoporosis is considered a risk factor for osteoporotic...
fracture,\textsuperscript{7,16} and therefore must be considered in the diagnosis and follow-up of these patients.

Although the presence of lithogenic factors does not determine the presence of lithiasis, since this is multifactorial, it does represent another warning sign of a possible occurrence of a future lithiasic event if other physical, anatomical, or dietary conditions are given. The importance of this study lies in the fact that the presence of hypercalciuria in a patient with osteoporotic fracture without lithiasis can help us make decisions in the prescription of medical treatment for osteoporosis. Usually in the daily treatment of a patient with osteoporosis an antiresorptive drug plus calcium and vitamin D\textsuperscript{12} supplements is recommended, since in cases where there is hypercalciuria, treatment with a thiazide can replace the calcium and vitamin D supplement without increasing the lithogenic risk and reducing the risk of fracture.\textsuperscript{18} Although there are no studies that recommend follow-up of osteoporotic patients with hypercalciuria due to the risk of developing lithiasis, it is another factor to be assessed in the clinic.

In conclusion to this study, patients with osteoporotic fractures may present alterations in calcium metabolism which are mainly manifested in the appearance of hypercalciuria, this being in all cases of fasting. Furthermore, in a third of them, hyperoxaluria and hypocitraturia are observed.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

This study is part of the doctoral thesis of Miguel Ángel Ochoa-Hortal Rull.

References