REVIEW ARTICLE

Calcium renal lithiasis and bone mineral density. Importance of bone metabolism in urinary lithiasis

M.Á. Arrabal-Polo a,*, M. Sierra Girón-Prieto b, J. Orgaz-Molina c, A. Zuluaga-Gómez a, S. Arias-Santiago c, M. Arrabal-Martín a

a Servicio de Urología, Hospital Universitario San Cecilio, Granada, Spain
b Medicina General, Distrito Metropolitano de Granada, Granada, Spain
c Departamento de Medicina, Facultad de Medicina, Universidad de Granada, Granada, Spain

Received 5 September 2012; accepted 25 October 2012
Available online 5 October 2013

KEYWORDS
Calcium nephrolithiasis; Bone mineral density; Bone resorption; Bone formation; Urinary and bone markers

Abstract
Context: Calcium nephrolithiasis is a multifactorial disease; in its pathophysiology is involved various minerals and metabolic factors that may be altered, including bone and phosphorus-calcium metabolism.
Objective: To establish the scientific evidence and demonstrate the relationship between calcium nephrolithiasis and bone mineral density loss, through the use of bone turnover markers, serum and urinary metabolites.
Evidence acquisition: We performed a PubMed literature review using different MeSH Terms like “Nephrolithiasis”, “Bone mineral density”, “Urinary stones”, “Calcium”, “Bone resorption” and “Bone formation”, with different combinations. We only selected articles with abstracts in English or Spanish and discarded clinical cases and articles with inappropriate statistical study. A total of 40 articles were selected.
Evidence synthesis: In different studies reviewed, it has been observed that patients with hypercalcemia have a higher bone mineral density loss with respect to normocalcemic. Among patients with calcium stones (normocalcemic or hypercalcemic), there is loss of bone mineral density, being more evident in patients with stones and hypercalcemia. This mineral density loss is marked and important in patients with recurrent calcium stones. Increased markers like fasting calcium/creatinine and β-CrossLaps are determinant of nephrolithiasis and mineral density loss in these patients.
Conclusion: We recommend performing markers of bone turnover and fasting calcium/creatinine in patients with recurrent calcium stones by the significant presence of bone mineral density loss, with a level of evidence III.
© 2012 AEU. Published by Elsevier España, S.L. All rights reserved.

* Corresponding author.
E-mail address: arrabalp@ono.com (M.Á. Arrabal-Polo).

2173-5786/$ - see front matter © 2012 AEU. Published by Elsevier España, S.L. All rights reserved.
PALABRAS CLAVE
Litiásis renal cálcica; Densidad mineral ósea; Resorción ósea; Formación ósea; Marcadores óseos y urinarios

Litiásis renal cálcica y densidad mineral ósea. Importancia del metabolismo óseo en la litiásis urinaria

Resumen
Contexto: La litiásis renal cálcica es una enfermedad multifactorial, en la que intervienen en su fisiopatología diferentes factores minerales y metabólicos que pueden encontrarse alterados, entre ellos el metabolismo óseo y fosfolítica.

Objetivo: Establecer la evidencia científica y demostrar la relación existente entre litiásis renal cálcica y pérdida de densidad mineral ósea, mediante el uso de marcadores de remodelado óseo y metabolitos urinarios y séricos.

Adquisición de la evidencia: Se realiza una revisión bibliográfica en PubMed utilizando diferentes MeSH Terms como Nephrolithiasis, Bone mineral density, Urinary stones, Calcium, Bone resorption y Bone formation, usando diferentes combinaciones. Se seleccionan únicamente los trabajos con resúmenes en inglés o español y se descartan casos clínicos y trabajos con estudio estadístico inapropiado. Se seleccionan un total de 40 publicaciones.

Síntesis de la evidencia: En los diferentes estudios analizados se observa que los pacientes con hipercaleíria presentan una mayor pérdida de mineral óseo a la con respecto a los normocalciúricos. Entre los pacientes con litiásis cálcica, tanto los que tienen hipercaleíria como los que tienen normocalciúria presentan pérdida de densidad mineral ósea, siendo más evidente en estos últimos. Esta pérdida de densidad mineral está acentuada y es importante en los pacientes con litiásis recidivante. El aumento de los marcadores calcio/creatinina en ayunas y β-crosslaps son los más determinantes de litiásis y pérdida de densidad mineral en estos pacientes.

Conclusión: Se recomienda solicitar marcadores de remodelado óseo y calcio/creatinina en ayunas en pacientes con litiásis cálcica recidivante por la importante presencia de pérdida de densidad mineral ósea, con un nivel de evidencia III.

© 2012 AEU. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Context
Calcium renal lithiasis is a high-prevalence condition, which is regarded as a major socio-economic problem for human beings due to renal colic pain, the frequency of recurrence and pharmaceutical expenditure. Its physiopathology is determined by different factors, the most important being metabolic factors, with almost 50% of patients presenting hypercalciuria, which is considered the most frequent metabolic risk factor in this type of lithiasis, after genetic studies were conducted to try to determine if gene modifications enhance the presence of this factor with controversial success.1 For years, hypercalciuria has been the subject of study, which tried to relate it not only to renal lithiasis but also to other pathologies such as bone mineral density loss, which results in osteopenia or osteoporosis. Different types of cytokines may be involved in bone mineral loss in patients with hypercalciuria,1,2 and the presence of high levels of iPTH may determine an increase in bone resorption in those patients, although other factors such as calcemia, tubular phosphate reabsorption, alkaline phosphatase, osteocalcin, and fasting calcemia might be altered,3 as we shall see later. In densitometric terms, it has been observed that bone mineral density is lower in patients with absorptive and fasting hypercalciuria,4 which already determined that bone metabolism alterations may occur in patients with calcium renal lithiasis. A decrease in bone matrix formation and bone histomorphometric changes5-10 which are confirmed by bone densitometry11 and which, for some authors, may be related with increased levels of 1.25 vitamin D3,12 have been demonstrated in patients with calcium lithiasis and hypercalciuria. As we can see, since 1976 with the study carried out by Alhava et al.,1 research has been conducted on the binomial calcium lithiasis-loss of bone mineral density. This association is vitally important, as reflected in the fact that studies have shown an increased rate of bone fractures in these patients,12 who therefore require strict and exhaustive follow-up to avoid them, and which determine that recurrent calcium nephrolithiasis is a risk factor for fracture. Recently, a genetic study carried out in Iceland and the Netherlands has even shown that sequence variants in the CLDN14 gene demonstrate the association between renal lithiasis and bone mineral density, since this gene is expressed in the kidney and regulates epithelial permeability, it is altered in patients with renal lithiasis, and, furthermore, it has been associated with a loss of bone mineral density both at the hip and the lumbar spine.13

As we can see, there is enough data that leads us to believe that there may be a link between renal lithiasis and osteopenia-osteoporosis; hence, this review aims to analyze the most important and determining studies on this relationship to establish a level of evidence. To that end, an exhaustive bibliographic research was made, which is detailed below.

Objective
To conduct a bibliographic review of PubMed with certain MeSH Terms, in order to establish the level of evidence and the relationship between calcium renal lithiasis and bone mineral density loss and the significance of bone and mineral markers in these patients.
Evidence acquisition

A systematic search was conducted in the PubMed database using MeSHTerms, and obtaining a different number of publications, as follows: Bone mineral density AND Nephrolithiasis, 176 publications; Bone mineral density AND Urinary stone, 159 publications; Bone resorption AND Nephrolithiasis, 98 publications; Bone resorption AND urinary stone, 125 publications; Bone formation AND urinary stone, 178 publications; Bone formation AND nephrolithiasis, 133 publications; Bone mineral density AND calcium AND nephrolithiasis, 140 publications; and Nephrolithiasis OR Urinary stone AND bone mineral density AND calcium, 171 publications.

Clinical cases and non-comparative studies and without an appropriate statistical analysis were excluded from the search, selecting only those papers with a structured abstract in English. Many of the studies previously analyzed in order to include them in this review were repeated in the different searches detailed above using MeSHTerms. Eventually, a total of 40 studies were selected to conduct this review.

Evidence synthesis

In order to achieve a better understanding of the reviewed subject, the analyzed studies were divided into 3 parts, which we entitled: ‘‘Relationship bone-hypercalciuria’’, ‘‘Relationship renal lithiasis-bone’’ and ‘‘Bone and mineral markers in patients with lithiasis and bone mineral density loss’’.

Relationship bone-hypercalciuria

Generally, hypercalciuria is defined as a 24-h urine excretion greater than 260 mg, and it can be divided, according to the traditional classification, into absorptive, resorptive, or renal hypercalciuria; however, in recent years, the trend has been towards simplifying this classification and readjusting it, thus establishing 2 types of hypercalciuria: absorptive hypercalciuria and fasting hypercalciuria.11 That seems to be a more accurate classification, as described below. Absorptive hypercalciuria is associated with increased calcium excretion mainly due to diet and gastrointestinal tract disorders; nevertheless, fasting hypercalciuria is more prevalently associated with bone mineral density loss, regardless of age, and it is more significant in patients with long-term lithiasis.12 In patients with fasting hypercalciuria, a significant decrease in bone mineral density was observed, both at the lumbar spine13 and the hip,14 when compared with noncalciuric individuals, and, on many occasions, this decrease in bone mineralization is independent of PTH levels, and it may relate to kidney disorders which induce disorders of phosphorus and calcium metabolism.14,15 Disorders of bone metabolism are not only present in patients with fasting hypercalciuria as we have seen, but they have also been observed in patients with absorptive hypercalciuria, fundamentally type I, where not only an increase in intestinal absorption of calcium may contribute to this increase in urinary excretion, but an increase in bone resorption may also be present.16 Therefore, it was observed that not only fasting hypercalciuria determines the existence of osteopenia-osteoporosis, but absorptive hypercalciuria may also have a bone component which determines an increase in the renal excretion of this ion. This relationship has not only been shown in adults, but in children with hypercalciuria, with respect to children without hypercalciuria, it has been observed that loss of bone mineral density occurs in up to 35% of them, and thorough analysis is recommended in this type of patients in order to avoid osteoporosis and bone fractures.17,18

The analyzed studies present in the literature are mostly cross-sectional and case–control studies, which show the relationship between hypercalciuria and bone mineral density loss with level of evidence III.

Relationship renal lithiasis-bone

Low bone mineral density in patients with calcium lithiasis is present in a high percentage of patients, particularly in those patients who also have fasting hypercalciuria.19 An increase of certain cytokines such as IL-1 beta, TNF-alpha and GM-CSF may induce an increase in the negative balance of calcium in bones and contribute to the appearance of these disorders in patients with lithiasis.20,21 In general, patients with recurrent calcium lithiasis tend to take a smaller amount of calcium in their diet, with the false hope of reducing lithiasis episodes; this leads to a non-significant decrease of calcemia, but it is important enough to cause an increase in bone resorption and in the negative balance of calcium in bones, a phenomenon observed in patients with recurrent lithiasis with or without hypercalciuria.22–24 Nevertheless, mineral density loss is more evident among those patients with calcium lithiasis and hypercalciuria,25,26 since this dietary factor involving lower calcium intake may come together with an increase in bone resorption (IPTH independent) and an alteration in tubular reabsorption of calcium, although this fact is less common. It is important to differentiate between patients with calcium lithiasis who have experienced a single episode, or who experience sporadic episodes, and patients with established lithiasis, with annual recurrent episodes or multiple episodes within a 2–3 year period. In patients with recurrent lithiasis, a progressive loss of bone mineral density is observed, which is objec-
tivable both in terms of bone mineral density g/cm2 and in bone mineral content and bone area.27 Decreased bone mineral density and increased resorptive activity occur mainly in those patients with lithiasis and severe lithogenic activity, with a pathophysiological circle of hypercalciuria, an increased negative balance of calcium in bones and formation of renal lithiasis. This circle and this relationship observed in this type of patients with significant lithogenic activity are not detected in patients with calcium lithiasis and a single episode or mild lithogenic activity, who only experience a slight increase in calciuria, without altered bone mineral metabolism.28 Undoubtedly, the presence of certain risk factors, as in the case of post-menopausal women, increases the incidence of bone mineral density loss in patients with lithiasis induced by well-known hormonal disorders.29 As a consequence of this pairing of recurrent calcium renal lithiasis and osteopenia-osteoporosis, an increase in the prevalence of fractures caused by this is observed30.
hence, early diagnosis of bone mineral density loss is essential in patients with calcium lithiasis in order to start primary prevention of fractures and secondary prevention of new lithogenic episodes.

Most of the analyzed studies present in the literature are cross-sectional and case–control studies, due to the difficulty and the high cost of cohort studies in this type of patients, so there is a relationship between recurrent calcium renal lithiasis and bone mineral density loss with level of evidence III.

**Bone and mineral markers in patients with lithiasis and bone mineral density loss**

Studying bone mineral metabolism basically comprises the measurement of serum calcium and phosphorus levels, along with the determination of plasma levels of vitamin D and iPTH. Polymorphic alterations in genes encoding the production of vitamin D may be present in patients with lithiasis and alterations in bone mineral metabolism, but they are not frequent and they are not often associated with increases and decreases in calcium. Although the meaning of iPTH in patients with lithiasis and bone mineral density loss is evident in primary hyperparathyroidism, aside from this disease, it does not seem to play a major role in the development of decreased bone mineral density in this type of patients, as proved in recent studies. Thus, it does not appear decisive that serum values of these hormones play a key role in most patients with calcium lithiasis, with the exception of specific cases and pathologies.

Urinary biochemical markers analyzed in the metabolic study of patients with renal lithiasis are extensive; however, only a few have proved useful in patients with calcium lithiasis and bone mineral density loss. Hypercalciuria in these patients is the most important and common metabolic factor, since it is elevated in a high percentage of patients. More specifically, fasting calciuria, measured using the fasting calcium/creatinine ratio, has proven itself to be one of the most reliable urinary markers in patients with lithiasis and bone mineral density loss, and it is gradually becoming a biochemical determinant independently associated with this type of patients. They have a high fasting calcium and creatinine ratio far above the established reference value of 0.11, thus indicating that the presence of calcium in urine under fasting conditions almost certainly derives from the negative balance of calcium in bones. In addition to this ratio, other studies have shown an elevation in the calcium/citrate ratio above 0.25 in patients with lithiasis and bone mineral density loss, which is also considered a decisive indicator in these individuals, as well as hypocitraturia, which can lead to elevated bone resorptive activity as a result of persistent metabolic acidemia. Therefore, the major mineral factors in urine that appear related and elevated in patients with lithiasis and bone mineral density loss are the following: hypercalciuria, hypocitraturia, calcium/citrate, and fasting calcium/creatinine. The fasting calcium/creatinine ratio is precisely the connection point between bone mineral density and bone remodelling markers. This fasting calcium/creatinine is positively and significantly correlated with certain bone resorption markers, such as β-crosslaps, and it may be considered as a resorption marker in patients with calcium lithiasis.

The major bone remodelling markers studied in patients with calcium lithiasis are alkaline phosphatase and osteocalcin as bone formation markers, and hydroxyproline and β-crosslaps as bone resorption markers, although others have also been assessed. Plasma levels of these substances have not only been measured in human beings, but they have also been experimentally studied, and variations and modifications have been observed in some of them. In plasma from patients with lithiasis, an increase in the bone isoenzyme of alkaline phosphatase and osteocalcin was observed when compared to patients without lithiasis. Although the highest increase in these patients corresponds to bone resorptive activity, which is expressed in elevated serum β-crosslaps levels, far above reference values, and an increase in the β-crosslaps/osteocalcin ratio, which reliably indicates that there is increased bone resorption compared with bone formation, there is bone mineral density loss. For this reason, these bone remodelling markers might be considered in patients with severe lithogenic activity as determinants of lithiasis and bone mineral density loss.

Hypercalciuria and hypocitraturia, along with high fasting calcium/creatinine and calcium/citrate ratios, are present in patients with calcium lithiasis and bone mineral density loss, with evidence level III. There is an increase in bone remodelling markers, especially β-crosslaps (bone resorption marker) in patients with calcium lithiasis and bone mineral density loss, with evidence level III.

**Conclusions**

The relationship between calcium lithiasis and bone mineral density loss is present in those patients with recurrent disease. In addition to metabolic studies in these patients, which include 24-h serum and urinary determinations of different electrolytes and minerals, we recommend the inclusion of bone remodelling markers such as alkaline phosphatase, osteocalcin and β-crosslaps, since they may be higher in these patients and may contribute to an effective early diagnosis of osteopenia-osteoporosis measured by bone densitometry systems. Although the evidence level is III due to the difficulty of conducting cohort studies that offer greater scientific evidence, we believe that at least an in-depth analysis of bone activity and metabolism would be appropriate in patients with calcium lithiasis and severe lithogenic activity.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**References**

2. Weisinger JR, Alonzo E, Bellorin-Font E, Blasini AM, Rodriguez MA, Paz-Martinez V, et al. Possible role of cytokines on the
Calcium renal lithiasis and bone mineral density. Importance of bone metabolism in urinary lithiasis