Urolithiasis and Osteoporosis: Clinical Relevance and Therapeutic Implications

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ABSTRACT

Several clinical and epidemiological studies revealed increased bone turnover and lower bone mass in patients with urolithiasis. Bone mass loss is particularly evident in idiopathic calcium stone formers. However, pathogenetic mechanisms and factors implicated in bone loss in these patients are still unknown. Dietary calcium restriction, increased intake of salt and animal proteins, vitamin D receptor polymorphisms are likely risk factors, while role of inflammatory cytokines, osteopontin and prostaglandin mediated bone resorption is yet to be determined. Regarding treatment and prevention, it has been proven that calcium supplements and high calcium diet with the addition of potassium alkali have an important role in prevention and treatment of both, urolithiasis and osteoporosis. Thiazide diuretics reduce hypercalciuria in renal tubules, and in addition promote osteoblast differentiation. Finally, bisphosphonates, a commonly used drugs in treatment of osteoporosis, show the potential to inhibit calcium stone formation, whereas a possible protective effect of antioxidants in bone loss and renal injury needs to be investigated further.

Key words: osteoporosis, urolithiasis, bone loss, prevention, treatment

Introduction

Urolithiasis is one of the leading social and economical problems of modern society. It is estimated that in developed countries, 10% of males and 4% of females between 30 and 50 years of age have urinary tract stone disease. The major problem presents recurrence rate of urolithiasis which is 75% at 15 years with no treatment1. Clinical manifestations are characterized by lumbar pain of sudden onset that may be accompanied by nausea and vomiting, gross or microscopic hematuria2. Diagnosis of renal stone is performed by urinalysis and imaging. Urinalysis often reveals hematuria, while crystalluria is occasional and the presence of leucocyturia may suggest associated urinary tract infection. Since renal ultrasound (US) provides information about obstruction but may miss ureteral stones, the association of US with conventional abdominal X-ray may help3. Stone formation is usually a result of urinary supersaturation and lack of inhibitors of crystallization in urine4. Calcium is the major calculus component since 75–80% of renal stones is composed of calcium oxalate5, while idiopathic metabolic hypercalciuria is one of the most frequent causes of recurrent calcium urolithiasis6,7. Numerous studies showed that urolithiasis patients have higher rate of bone resorption and lower bone mineral content as well as bone mineral density, which is more evident in idiopathic calcium stone formers8–10. Exact pathogenetic mechanisms of low bone mineral density in calcium stone formers are still not defined. Since osteoporosis, as well as urolithiasis, has a huge effect on public health because of the impact of osteoporotic fractures on the health service and economy with prevalence between 10 and 15 percent11 it is very important to define common prevention and treatment guidelines.

Possible Pathogenetic Mechanisms of Bone Loss in Urolithiasis Patients

Hypercalciuria could be defined as any level of urine calcium that exceeds net intestinal absorption, leading to net loss of calcium. In practice, this is usually defined as a daily calcium excretion over 250 mg/day in women or 300 mg/day in men6. Idiopathic hypercalciuria (IH) is defined as excess calcium excretion in spite of normal or restricted calcium intake with no identifiable metabolic cause, while dietary calcium-dependent hypercalciuria (DH) is caused by an excessive intake of calcium12. Pa-
patients with IH have sometimes been categorized by the
 presumes site of the primary abnormality. The major
 subtypes have included 1) 'absorptive' hypercalciuria in
 which a primary increase in intestinal calcium absorp-
 tion may result in increased urine calcium; 2) fasting
 resorptive hypercalciuria, caused by an increase in bone
 turnover, leading to loss of bone calcium in the urine; and
 3) 'renal leak' hypercalciuria, in which a primary defect
 in renal tubule calcium transport allows loss of calcium
 in the urine, with compensatory increase in calcium abso-
 rption from gut or mobilization from bone13. Nearly
 90% of patients with idiopathic hypercalciuria have met-
 abolic alterations that could lead to bone mass reduction
 and osteoporosis8,10,14–16. However, some studies did not
 find any influence of this metabolic alteration on bone
 mass17 which could be explained by lack of significant
differences in BMD between control subjects and pa-
 tients with absorptive hypercalciuria. In fact, several au-
 thors have shown that fasting hypercalciuria and not ab-
sorptive hypercalciuria is linked with reduced bone min-
eral density18,19. From the aspect of bone formation pro-
cess, lower bone mass in urolithiasis patients may be
 caused by increased bone resorption and/or decreased
 bone formation. Hydroxyprolinuria, a known marker of
 bone resorption, is higher in IH than in DH and is corre-
lated with fasting calciuria, suggesting that hypercalciu-
 ria in these patients is linked to bone resorption19. Histo-
morphometric studies on hypercalciuric stone formers
 showed reduced osteoblastic bone formation with or with-
 out increased osteoclastic bone resorption, severe miner-
alization defect consistent with normal or low bone turn-
 over osteoporosis9. Malluche et al. observed reduced osteo-
 blastic formation of bone matrix and delayed or absent
 secondary mineralization20.

Secondary hyperparathyroidism is extremely rare in
 IH patients who have mainly normal or low values of
 plasma parathormone (PTH)21, indicating that a PTH-
 independent mechanism is responsible for bone demin-
eralization in these patients.

Increased levels of serum calcitriol observed in IH
 patients22,23 are not responsible for bone loss in IH pa-
tients since there is a positive correlation between plas-
 ma 1.25(OH)2 vitamin D3 levels and BMD23.

Many genetic studies investigated an association be-
tween vitamin D receptor (VDR) polymorphisms and cal-
cium kidney stone disease. Rendina et al.24 demonstrated
 a genetic association between 3' VDR alleles, fasting idio-
pathic calciuria, and reduced bone mass density in pa-
tients with recurrent stone formation, whereas other au-
thors showed that patients with VDR polymorphism had
 a significantly higher risk of having more stone episodes at
 younger age although it was not associated with the forma-
tion of stones25,26. In those studies stone forming patients
 were not randomised for fasting and absorptive idio-
pathic calciuria which could explain given discrepancies.

A diet rich in animal proteins has been implicated in
 producing bone loss through a variety of mechanisms.
 Metabolic acidosis caused by protein rich diet induces
 bone dissolution releasing calcium to act as a buffer7,27
 and increase in renal mass and calcitriol levels28, which
 then consequently lead to hypercalciuria and bone loss.
 Also, acidosis is proven to inhibit osteoblastic and stimu-
late osteoclastic activity in vitro29.

Low calcium diet which is often used to treat renal
 calculi could cause low BMD in urolithiasis patients. Cal-
cium intestinal absorption declines with age while re-
quirements rises which in the combination with low cal-
cium intake induces bone loss through PTH stimulated
 increase in bone remodeling. Furthermore, reduction of
 the calcium supply increases the oxalate absorption, en-
hances urinary saturation for oxalate salts which explains
 why low-calcium diet increases the risk of calcium
 oxalate stone formation30.

The identification of the RANKL/RANK (receptor ac-
 tivator for nuclear factor kappaB (RANK) ligand) signal-
ing system as the dominant, final mediator of osteo-
 clastogenesis represents a major advance in bone biology.
 RANKL, expressed on the surface of preosteoblastic/stro-
mal cells, binds to RANK on the osteoclastic precursor
 cells, therefore initiating process of differentiation and
 fusion of osteoclast precursors and stimulate activity of
 mature osteoclasts31. Osteoprotegerin (OPG), member of
 TNF (tumor necrosis factor receptor) family, acts as a de-
cyte receptor, binding RANKL and consequently blocking
 RANK-RANKL interaction and therefore inhibits osteo-
 clastogenesis32. Influence of RANKL/OPG system on bo-
 ne turnover in patients with urolithiasis remains yet to
 be investigated, although latest research demonstrated
 higher expression of RANKL in bone tissue in patients
 with idiopathic hypercalciuria suggesting that increased
 bone resorption is mediated by RANKL, while osteopro-
tegerin bone expression was probably secondarily in-
 creased to counteract the actions of RANKL33.

Pro-inflammatory cytokines such as interleukin-1
 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-al-
 pha (TNF-α) supress OPG expression while simulta-
 neously enhancing that of RANKL resulting in increased
 osteoclast formation and function. Pacifi et al.24 dem-
 onstrated that increased production of interleukin-1 (IL-1) by
 cultured peripheral blood monocyte is associated with
decreased vertebral BMD in patients with fasting hyper-
caliuria. IL-1 can provoke bone resorption through os-
teoblasts, which are induced to transmit a signal that
 stimulates osteoclasts34 and through a prostaglandine
 dependent mechanism35. In addition, prostaglandine sti-
mulate calcitriol synthesis36. Thus, in idiopathic hyper-
calciuria the increased bone resorption and/or decreased
 bone formation leading to reduction of bone mass and
 the high plasma calcitriol level could result from activa-
tion of monocytes and the synthesis of IL-1. Considering
 that other cytokines like TNF-α37,38 and IL-640 have bone
 catabolic effect, that granulocyte macrophase stimulating
 factor (GM-CSF) synthesis is induced by IL-1 and
 TNF-α41, and that this factor contributes to prolifera-
tion, survival and differentiation of osteoclasts42,43 and
 osteoblasts44, it can be concluded that cytokine activation
 may be involved in the bone loss of calcium stone formers
 with IH45.
It is well known that in urinary stone formation process pre-urine CaOx supersaturation triggers inflammation in the long Henle’s loop cells. This in turn induces differentiation of these cells toward the osteogenic lineage, determining the synthesis of typical bone osteoid proteins (osteopontin, osteocalcin, BMP-2, etc)\(^46\). In the normal rat kidney, osteopontin has been shown to be localized precisely in the Golgi apparatus of the thin loop of Henle’s loop cells. It is a strong inhibitor of crystal formation and growth in vitro, but there is still debate regarding its effects upon crystal adhesion to tubular epithelial cells\(^46\). OPN influences bone turnover, both by promoting differentiation of osteoclasts and by enhancing osteoclasts activity. Moreover, osteopontin is a potent inhibitor of the mineralization process, since binding of OPN to hydroxyapatite (HA) inhibits growth of HA crystals\(^47\). As OPN promotes calcium stone formation and bone catabolism, it could play an important role in bone mass decrease in urolithiasis patients.

**Prevention and Treatment – Common Guidelines in Urolithiasis and Osteoporosis Patients**

Calcium supplements and high calcium intake are widely used for the prevention of bone loss in postmenopausal women, but they potentially enhance the risk of calcium oxalate stone formation by increasing urinary calcium. The abnormal parathyroid secretory physiology, high circulating PTH levels an elevated markers of bone resorption are all reversible with a high calcium intake\(^48\), whereas calcium supplementation reduces both bone loss and fracture rate in the elderly\(^49,50\). Sakhaee et al.\(^51\) demonstrated that calcium citrate supplementation may be provided to stone-free postmenopausal women without fear of increased risk of stone formation.

As pointed earlier, protein rich diet induces bone loss as well as hypercalciuria due to metabolic acidosis. Administration of potassium citrate by providing an alkali load may avert the bone resorbing effect of acid excess\(^52\). It has also been shown that potassium alkali avert recurrent stone formation in a mixed group of patients with idiopathic calcium oxalate nephrolithiasis\(^53\). Therefore, the addition of potassium citrate among postmenopausal women with urolithiasis, would be reasonable since it reduces urinary saturation of calcium oxalate and provides greater inhibitor activity against stone formation from further enhancement of citrate excretion\(^54\).

Thiazide diuretics, widely used in hypercalciuric patients, lower urine calcium resulting in a fall in calcium oxalate and calcium phosphate supersaturation. Reduction of calcium is attributed to enhanced reabsorption of calcium on the renal distal convolute tubule\(^54\). Also, latest studies showed that thiazides directly induce the production of the osteoblast differentiation markers runt-related transcription factor 2 (runx2) and osteopontin, therefore stimulating osteoblast differentiation and bone mineral formation independent of their effects in the kidney. These results suggest that thiazides may find a role in the prevention and treatment of osteoporosis\(^55\).

It is well known that hyperoxaluria induces free radical generation which results in peroxidative injury in renal tubular cells. This can lead to calcium deposition and nephrolithiasis\(^56\). Many studies have shown that various antioxidants, such as vitamin E and green tea, could have protective effect on renal epithelium and prevent crystal deposition\(^57,58\). Also, nitrosative stress is considered to be an important risk factor in urolithiasis, which would mean that L-arginin, a precursor of nitric oxide (NO) should have antilithic and antioxidative properties\(^59\). Furthermore, increased osteoclastic activity and decreased osteoblastic activity are associated with an imbalance between oxidant and antioxidant status in postmenopausal osteoporosis\(^60\) suggesting that antioxidant reach diet, as well as other antioxidants (NO, carotenoids) could be used in bone loss prevention and treatment of osteoporosis\(^61,62\).

Bisphosphonates are one of the most common used drugs in treatment of osteoporosis. They reduce osteoclast-mediated bone resorption by enhancing programmed cell death and inhibiting enzymes in the cholesterol biosynthetic pathway causing slower bone turnover. They have proven efficacy for prevention of bone loss caused by aging, estrogen deficiency, and glucocorticoid use and for prevention of fracuters in postmenopausal women and in women and men with glucocorticoid induced osteoporosis\(^63\). Recent study performed on healthy males during 90-day bed rest which has potential risks of bone loss and renal stone formation, showed that intravenous pamidronate could preserve bone mineral density and reduce the risk of renal stone formation during prolonged bed rest\(^64\). Also, in vitro studies performed on Madin-Darby canine kidney (MDCK) cells investigated the inhibitory effects of alendronate on calcium phosphate microlith formation. The results demonstrated that alendronate inhibited calcium stone formation, suggesting that it could be effective in the prevention of urolithiasis\(^65\).

In conclusion, it has been clearly demonstrated that disorders of mineral metabolism responsible for lower bone mineral density are present in patients with idiopathic hypercalciuria ultimately leading to osteopenia/osteoporosis. Furthermore, high calcium intake and alkali load have beneficiary effect in prevention and treatment of renal stone disease and osteoporosis, while the effect of bisphosphonates on calcium stone formation and protective role of antioxidants and thiazides in osteoporosis remains to be determined.

**REFERENCES**

Nekoliko kliničkih i epidemioloških studija pokazale su povećanu koštanu pregradnju i manju koštanu masu u pacijentima s urolitijazom. Gubitak koštanog materijala posebno je vidljiv kod idiopatske kalcijske urolitijaze. Ipak, patogeneza i terapija ove bolesti potiču na potrebu za novim istraživanjima.