

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 injurie 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 urolithiasis^{6,7}. 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 formers^{8–10}. 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-

tients with IH have sometimes been categorized by the presumed site of the primary abnormality. The major subtypes have included 1) 'absorptive' hypercalciuria in which a primary increase in intestinal calcium absorption 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 absorption from gut or mobilization from bone¹³. Nearly 90% of patients with idiopathic hypercalciuria have metabolic alterations that could lead to bone mass reduction and osteoporosis^{8,10,14–16}. 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 patients with absorptive hypercalciuria. In fact, several authors have shown that fasting hypercalciuria and not absorptive hypercalciuria is linked with reduced bone mineral density^{18,19}. From the aspect of bone formation process, 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 correlated with fasting calciuria, suggesting that hypercalciuria in these patients is linked to bone resorption¹⁸. Histomorphometric studies on hypercalciuric stone formers showed reduced osteoblastic bone formation with or without increased osteoclastic bone resorption, severe mineralization defect consistent with normal or low bone turnover osteoporosis⁹. Malluche et al. observed reduced osteoblastic 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 demineralization in these patients.

Increased levels of serum calcitriol observed in IH patients^{22,23} are not responsible for bone loss in IH patients since there is a positive correlation between plasma 1.25(OH)₂ vitamin D₃ levels and BMD²³.

Many genetic studies investigated an association between vitamin D receptor (VDR) polymorphisms and calcium kidney stone disease. Rendina et al.²⁴ demonstrated a genetic association between 3' VDR alleles, fasting idiopathic calciuria, and reduced bone mass density in patients with recurrent stone formation, whereas other authors 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 formation of stones^{25,26}. In those studies stone forming patients were not randomised for fasting and absorptive idiopathic 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 buffer^{7,27}

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 stimulate osteoclastic activity in vitro²⁹.

Low calcium diet which is oftenly used to treat renal calculi could cause low BMD in urolithiasis patients. Calcium intestinal absorption declines with age while requirements rises which in the combination with low calcium intake induces bone loss through PTH stimulated increase in bone remodeling. Furthermore, reduction of the calcium supply increases the oxalate absorption, enhances 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 activator for nuclear factor kappaB (RANK) ligand) signaling system as the dominant, final mediator of osteoclastogenesis represents a major advance in bone biology. RANKL, expressed on the surface of preosteoblastic/stromal 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 decoy receptor, binding RANKL and consequently blocking RANK-RANKL interaction and therefore inhibits osteoclastogenesis³². Influence of RANKL/OPG system on bone 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 osteoprotegerin bone expression was probably secondarily increased to counteract the actions of RANKL³³.

Pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) suppress OPG expression while simultaneously enhancing that of RANKL resulting in increased osteoclast formation and function. Pacifici et al.¹⁹ demonstrated that increased production of interleukin-1 (IL-1) by cultured peripheral blood monocyte is associated with decreased vertebral BMD in patients with fasting hypercalciuria. IL-1 can provoke bone resorption through osteoblasts, which are induced to transmit a signal that stimulates osteoclasts³⁴ and through a prostaglandine dependent mechanism³⁵. In addition, prostaglandine stimulate calcitriol synthesis³⁶. Thus, in idiopathic hypercalciuria the increased bone resorption and/or decreased bone formation leading to reduction of bone mass and the high plasma calcitriol level could result from activation of monocytes and the synthesis of IL-1. Considering that other cytokines like TNF- α ^{37,39} and IL-6⁴⁰ have bone catabolic effect, that granulocyte macrophage stimulating factor (GM-CSF) synthesis is induced by IL-1 and TNF- α ⁴¹, and that this factor contributes to proliferation, survival and differentiation of osteoclasts^{42,43} 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 cells⁴⁶. 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 crystals⁴⁷. 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 and elevated markers of bone resorption are all reversible with a high calcium intake⁴⁸, 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 excess⁵². It has also been shown that potassium alkali avert recurrent stone formation in a mixed group of patients with idiopathic calcium oxalate nephrolithiasis⁵³. 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 excretion⁵¹.

Thiazide diuretics, widely used in hypercalciuric patients, lower urine calcium resulting in a fall in calcium oxalate and calcium phosphate supersaturation. Reduction of calciuria is attributed to enhanced reabsorption of calcium on the renal distal convolute tubule⁵⁴. Also, latest studies showed that thiazides directly induce the produc-

tion 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 osteoporosis⁵⁵.

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 nephrolithiasis⁵⁶. 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 properties⁵⁹. Furthermore, increased osteoclastic activity and decreased osteoblastic activity are associated with an imbalance between oxidant and antioxidant status in postmenopausal osteoporosis⁶⁰ 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 fractures in postmenopausal women and in women and men with glucocorticoid induced osteoporosis⁶³. 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 rest⁶⁴. 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 urolithiasis⁶⁵.

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 beneficial 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.

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UROLITIJAZA I OSTEOPOROZA: KLINIČKA VAŽNOST I TERAPIJSKE SMJERNICE

SAŽETAK

Nekoliko kliničkih i epidemioloških studija pokazale su povećanu koštanu pregradnju i manju koštanu masu u pacijenata s urolitijazom. Gubitak koštane mase posebno je vidljiv kod idiopatske kalcijске urolitijaze. Ipak, patogeneza i čimbenici uključeni u proces gubitka koštane mase još nisu poznati. Mogući rizični čimbenici su ograničen unos kalcija, povećan unos soli i bjelančevina životinjskog podrijetla te polimorfizmi za receptor vitamina D, dok se uloga upalnih citokina, osteopontina i prostaglandina u razgradnji kosti tek treba utvrditi. Dokazano je da preparati kalcija te dijeta s visokim unosom kalcija s dodatkom kalijevih soli imaju važnu ulogu u prevenciji i liječenju i urolitijaze i osteoporoze. Tiazidski diuretici smanjuju hiperkalcemiju u bubrenim tubulima i potiču diferencijaciju osteoblasta. Konačno, postoji mogućnost da bifosfonati, koji se često primjenjuju u liječenju osteoporoze inhibiraju stvarnje kalcijских kamenaca, dok je moguć zaštitni učinak antioksidansa na gubitak koštane mase i oštećenje bubrežnog epitela potrebno dodatno istražiti.