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LETTER TO EDITOR

Kidney stones and metabolic bone diseases not linked to parathyroid disfunction: A proposal for an integrated management

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Summary *Nephrolithiasis (KS) and metabolic bone diseases (MBDs) not linked to parathormone (osteoporosis, Paget's disease of bone and renal phosphate leak) are related as demonstrated by epidemiological and experimental data. Moreover, patients affected by monogenic kidney stone disorders (idiopathic hypercalciuria, primary hyperoxaluria, hypocitraturia, cystinuria and defects in purine metabolism) showed a bone phenotype.*
A significant economic and social burden is associated with KS and MBDs, due to high mortality and morbidity rate. Concerning this point of view, an integrated screening could be a cost-saving strategy.
We suggest a new clinical management for patients affected by KS and MBDs. The assessment of bone mineral density by Dual X-ray absorptiometry and bone turnover markers should be proposed in KS patients. On the contrary, the evaluation of KS-related metabolic risk factor and an abdomen ultrasound exam should be offered to MBD patients. Moreover, in patients with early and/or recurrent KS, an extended gene-panel should be suggested.

KEY WORDS: *Nephrolithiasis; Osteoporosis; Paget disease of bone; Osteomalacia; Phosphate leak.*

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To the Editor,

Given the strong association between metabolic bone diseases and kidney stones, we propose a new public health strategy aimed at improving the management of patients affected by these conditions. This novel diagnostic protocol is designed to ensure the most effective treatment possible.

BONE TISSUE STRUCTURE AND FUNCTIONS

Bone is a complex multifunctional tissue that, for many years, was considered merely a mechanical support structure with limited biological significance. However, over the last few decades, numerous experimental and clinical studies have highlighted the complexity and heterogeneity of bone's biological functions (1).
Bone is the only physiologically mineralized connective tissue in the human body. It is composed of approximately 60% inorganic components – mainly hydroxyapatite – 10% water, and 30% organic components, primarily collagen proteins (2). A healthy bone turnover, characterized by continuous and finely regulated bone formation and resorption, preserves the mechanical properties of bone. The main actors involved in this dynamic process are osteoblasts and osteoclasts, which operate within the *bone multicellular units* (BMU) (3).
Osteoblasts are mononuclear cells derived from mesenchymal stem cells and play the key role in bone formation. Conversely, osteoclasts are multinucleated cells originating from hematopoietic stem cells and are essential for bone resorption (4). Throughout life, the balance between osteoblast and osteoclast activity ensures the maintenance and regeneration of bone mass (5).
Bone tissue is an endocrine organ and produces molecules with endocrine and paracrine functions, such as *Fibroblast Growth Factor 23* (FGF 23), *osteopontin* (OPN), *sclerostin* (SOST), and osteocalcin (6). Through these bone-derived hormones, bone communicates with extra-skeletal organs and systems (7, 8).
The skeletal and immune systems are intricately connected, a relationship studied under the fields of osteoimmunology (9). This interplay is achieved through several molecular mechanisms, cytokines and signaling transducers. Immune and bone cells not only share a common origin and microenvironment – such as the bone marrow – but also influence each other's activation, proliferation and senescence (9). Recent evidence supports a mutual regulation between immune and bone cells. For instance, the immune system supports bone development: macrophages promote osteoblastogenesis via *interleukin 18*

(IL18) (10), and T cells regulate osteoclastogenesis through IL1, IL6, IL4 and interferon-γ (11, 12). In turn, osteoclasts can activate T-cell through *Receptor Activator of Nuclear Factor Kappa B* (RANK) - *RANK ligand* (RANKL) - *osteoprotegerin* (OPG) signalling axis (13). Moreover, studies suggest that osteoblasts and osteoclasts contribute to hematopoietic niche formation and mobilization respectively, although the precise mechanisms remain incompletely understood (14).
Bone also plays a critical role in mineral metabolism regulation. FGF23, secreted by osteoblasts and osteocytes, reduces phosphate reabsorption by inhibiting the expression of the type IIa sodium-phosphate co-transporter (NaPi-2a) in renal proximal tubules. FGF23 also regulates calcium and sodium reabsorption, through the *transient receptor potential vanilloid-5* (TRPV5) channel and sodium-chloride co-transporter (NCC), respectively (15). Additionally, FGF23 suppresses *parathyroid* (PTH) hormone, which normally increases calcium release from bone and absorption from the gut and kidney, as well as the synthesis of 1,25-dihydroxy-vitamin D (15).
Bone health can be assessed using *Dual-Energy X-ray Absorptiometry* (DXA), the gold standard for evaluating *bone mineral density* (BMD). DXA employs low-dose X-rays to measure the BMD in lumbar spine and total hip (16). Results are reported as *standard deviation* (SD) from the mean BMD of healthy 30-year-old subjects of the same sex and ethnicity (T-score), or the same sex, age and ethnicity (Z-score) (17). In addition to DXA, the *trabecular bone score* (TBS) is an indirect marker of bone microarchitecture, assessing variations in pixel gray levels in DXA image. TBS may be an independent predictor of frailty fracture (18). Other diagnostic technics are represented by *Quantitative ultrasound* (QUS) and *quantitative computed tomography* (QTC). QUS uses ultrasound waves that interact with the bone surface. The physical and mechanical bone features modify the return waves, allowing the evaluation of elasticity and strength, two bone quality parameters (19). QTC employs standard X-ray computed tomography and converts attenuation values into BMD values. It is particularly useful in patients in whom DXA in unsuitable (e.g., scoliosis) or where DXA may overestimate BMD (e.g., osteophytes, aortic calcification, arthritis) (20). A recent innovative is *Radiofrequency Echographic Multi Spectrometry* (REMS), a non-ionizing technique that analyses raw, unfiltered ultrasound signals acquired during scans of the lumbar spine and/or femoral neck to provide DXA-equivalent BMD values (21). REMS has been clinically validated through a multicentre observational trial involving 7 Italian centres (22), and the *European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases* (ESCEO) has recognized REMS as the first clinically available, non-ionized method for assessing lumbar and femoral BMD and predicting fracture risk (21).
In addition to instrumental technics, bone turnover markers (BTMs) can be evaluated. BTMs are peptides produced during bone formation or reabsorption. N-terminal (P1NP) and C-terminal (P1CP) propeptides are products of osteoblast-derived procollagen synthesis, and their blood concentration reflect bone formation rates (23, 24). OC and *bone-specific alkaline phosphatase* (bALP) are also produced by osteoblasts. OC is specific to bone, but it is hard to analyse, due to molecular instability and the impact of renal failure on its blood concentration (25). In contrast, bALP remains a reliable marker even in chronic kidney disease and is a specific marker of bone formation (26). For bone resorption, C-terminal (CTX) and N-terminal (NTX) telopeptides, both products of collagen degradation, are the most widely used markers (27). CTX measurement is influenced by circadian rhythm and food intake, while NTX is affected by liver and renal function (28). Another BTM is OPG, which reflects the bone microenvironment and osteocyte activity (28).

Kidney stones and metabolic bone disease

Kidney stones (KS), also known as nephrolithiasis or urolithiasis, are crystal concretions typically formed in the kidney and/or the urinary tract, including the renal pelvis, ureters, bladder, and urethra (29). KS affect approximately 13% of the population in North America, 9% in Europa, and 5% in Asia (30). The regional differences in prevalence and incidence worldwide are influenced by geographical, climatic, ethnic, dietary and genetic factors (31). KS have a significant economic impact, including direct treatment costs and loss of productivity. In 2021, the annual cost of treating KS in the United States was estimated at $9 billion. The global market for KS management is projected to reach $4.02 billion by 2034 (32, 33). About 85% of KS are composed of calcium oxalate and calcium phosphate salts, 10% of struvite (magnesium ammonium phosphate produced during infections by urease-producing bacteria), 9% of uric acid (UA), and the remaining 1% of cystine, ammonium acid urate, or drug-related stones (34).
Metabolic bone disease (MBDs) are disorders affecting bone remodelling. The more common MBDs include primary and secondary *osteoporosis* (Op), *Paget's disease of bone* (PDB), rickets, and osteomalacia (35). The conditions carry a growing social and economic burden, especially with the aging global population (36). In Italy alone, the economic burden of Op is estimated at €2.2 billion, with about 80% of costs related to hospitalisations, 16% to pharmacological treatment, and about 3% to outpatient visits. These data show that Op is one of the main health problems (37).
Since both MBDs and KS are linked to the precipitation and crystallization of salts, an association between them has been hypothesized (38).

Osteoporosis and kidney stones

Op is the most prevalent MBD worldwide, affecting a large proportion of individuals over 60 years of age (39). Op is characterised by a reduction in bone mass and deterioration of bone microarchitecture due to an imbalance between bone resorption and formation. This results in decreased bone strength and increased fracture risk (40). Fracture prevalence in KS patients is estimated between 19-24% (41). Both Op and KS are multifactorial disorders with modifiable and non-modifiable risk factors (42). Modifiable risk factors include high salt, protein, and sugar consumption, inadequate

calcium and vitamin D intakes, smoking, and physical inactivity (43-46). Non-modifiable risk factors are mainly genetic and epigenetic, although not fully understood (47).
Hypercalciuria (HCa), defined as daily urinary calcium excretion higher than 300 mg/day in men and higher than 250 mg/day in women (48), is found in 20-30% of individuals with primary Op (49, 50). HCa is associated with persistent overproduction of cytokines predisposing bone loss (51), PTH/calcitriol pathways (52), and disruptions in calcium-phosphate homeostasis (53). Genetic variants of *Claudin 14* (CLDN14) gene, involved inWnt signalling and osteoblast function, have been linked to both Op and Ks (53).
Unhealthy dietary habits represent a common risk factor. High salt consumption increases urinary calcium excretion (54), while low calcium and potassium intake and low physical activity contribute to the development of both conditions. The role of calcium intake and supplementation remains debated. *Jackson and coll.* report a higher incidence of KS after calcium supplementation (55), while in his meta-analysis, Heaney RP did not find differences between women with and without calcium supplementation (56). Other authors showed a lower risk of KS in subjects with calcium intake > 1 g/day, due to the reduced intestinal absorption of oxalate and production of calcium-oxalate stones (57). In addition, in subjects with KS and low BMD, calcium intake through water and fibre seems to prevent KS (57). Another important point is the salt dietary consumption. *Kleeman and coll.* demonstrated that increasing salt intake, the 24h urinary calcium excretion increased (54). Indeed, an increase of 6 g/day in salt consumption results in a 40 mg/day increase in 24h urinary calcium excretion (58). Furthermore, *Nouvenne and coll.* showed that high sodium intake raised KS and Op risk, due to both higher calcium and lower citrate excretion (59). Sugars are also involved in the pathogenesis of these conditions, causing a higher urinary calcium excretion (60, 61). Overall, these data are emphasized in metabolic syndrome, a recognized risk factor for both Op and KS (62). On the contrary, a diet rich in fruit and vegetables, with a low consumption of salt and animal protein and a calcium intake > 1 g/day is able to avoid KS and Op (63).
KS is characterized by higher levels of inflammatory markers (64), with potential role in bone resorption. In particular, elevated serum levels of IL1, IL-6, and tumor necrosis factor-α (TNF- α) influence the osteoclasts activation and stimulate the synthesis of other bone remodelling mediators, such as prostaglandin E (65).
In their meta-analysis, *Lucato and colleagues* examined 24 case-control studies involving 1595 subjects with nephrolithiasis and 3402 healthy controls. KS formers showed lower *bone mineral density* (BMD), an increased risk of Op, and a significantly higher risk of bone fractures compared to healthy controls (66). In a multicenter prospective study involving 107,001 women followed for 32 years and 50,982 men followed for 26 years, KS was associated with a higher risk of wrist fracture in both women and men, also correcting for race, *body mass index* (BMI), diet and other confounding factors (67). Another study, based on Veterans Health Administration data, found that 1 in 4 male KS formers had a history of Op or frailty fractures, suggesting that the risk of Op in KS is high also in men and supporting the BMD screening in all KS formers (68). Furthermore, *Dhayat and colleagues* identified KS constituents as predictors of low BMD. In particular, calcium-oxalate stones are negatively associated with BMD at the femoral neck (69).
In contrast, *Sakhaee and colleagues* (70) did not find a significant association between urinary calcium excretion and BMD in KS, in agreement with *Fink and coll.* (71), that in a cohort of men with Op and KS, did not find any relationship between Op and 24h urinary calcium excretion. These results suggest that 24h urinary calcium may be a marker, but not a cause of bone loss. Also, in a large cohort of multiethnic post-menopausal KS women, no significant association between KS and changes in BMD was found at multiple skeletal sites, after adjustment for confounders associated with Op and/or KS (72).
Overall considered, data demonstrate that Op is a risk factor for occurrence of KS and that KS is a risk factor for Op (73). Thus, we can look at Op and KS as the two sides of the same coin (74).

Paget's disease of bone and kidney stones

Paget's disease of bone (PDB, OMIM 602080) is the second most common metabolic disease characterized by increased and disorganized bone turnover, involving one or more regions of the skeleton. PDB affects a significant percentage of peoples over 40 years old, with a prevalence between 1 and almost 8%. (75). The increased osteoclastic bone resorption, followed by marrow fibrosis, increased and disorganized vascularity and bone formation, represents the main pathophysiologic mechanism (75). The PDB osteoclasts show peculiar morphological and functional properties, such as hyper-responsivity to calcitriol, enhanced sensitivity to RANK ligand, increased expression of IL 6, IL 6 receptor, and paramyxovirus transcript. PDB can evolve into malignant or non-malignant complications. In particular, KS is a non-malignant metabolic complication of PDB patients.
PDB patients are at increased risk of KS independently of PDB activity or hyperparathyroidism. The involvement of multiple skeletal sites can influence the recurrence of KS. Polyostotic patients have often KS and KS recurrences. In a recent study, it was demonstrated that the prevalence of KS in PDB patients without primary hyperparathyroidism is significantly higher compared with healthy control, also adjusted for age, gender, BMI, and *estimated glomerular filtration rate* (eGFR). Furthermore, PDB patients with KS showed a higher prevalence of HCa, hypocitraturia, hyperoxaluria, and hyperuricuria compared with PDB patients without nephrolithiasis (76).

Renal phosphate leak and kidney stones

The renal phosphate leaks are disorders of phosphate homeostasis with a reduced tubular reabsorption of phosphate not PTH-related. It is characterized by low serum levels of phosphate (< 0.8 mmol/l or < 2.5 mg/dl), low threshold of tubu-

lar phosphate reabsorption, and calcium, PTH, 25-hydroxy vitamin D serum levels within the normal range (77).
The maintenance of phosphate balance is crucial for bone health. Indeed, different organs contribute to phosphate homeostasis: gut, kidney, and bone (78, 79). Moreover, three main regulators of phosphate homeostasis had been identified: i) calcitriol increases phosphate absorption from the gut and bone; ii) PTH increases phosphate resorption from bone and decreases its reabsorption in the proximal tubule; iii) *fibroblast growth factor-23* (FGF-23) increases renal phosphate excretion (78, 80-82). Notably, FGF23 controls cellular expression of type 2 sodium-phosphate cotransporter (NTP2a) in proximal renal tubule, independently from PTH (83).
Hypophosphatemia causes osteomalacia, a clinical disorder characterised by under-mineralized soft bone. Osteomalacia usually manifests with reduced bone mineral density, bone pain, frailty fractures, and muscle weakness, i.e. the osteomalacic syndrome (84).
Epidemiological studies indicate that 20% of patients with KS and normal level of PTH show hypophosphatemia caused by renal phosphate leak, without complete phenotypic expressions of osteomalacia (85). The renal phosphate leak affects calcium salt urinary saturation and contributes to the pathogenesis of KS (86).
Some patients affected by KS and renal phosphate leak show genetic mutations in Solute Carrier Family 34 member 1 (SLC34A1, OMIM 182309), Solute Carrier Family 34 member 3 (SLC34A3, OMIM 609826), and Sodium-hydrogen antiporter 3 regulator 1 (NHERF1, OMIM 604990) genes (87). The identification of these gene mutations in patients with both hypophosphatemia, skeletal alterations and KS contribute to the common pathogenesis of these disorders.
KS patients with renal phosphate leak show higher serum levels of FGF23 compared with KS patients without renal phosphate leak and healthy controls (88). In addition, in FGF23-dependent forms of renal phosphate leak, calcitriol can worsen KS, due to increased renal excretion of calcium (88).
An isoform of FGF23, FGF23239M, occurring in 10% of Caucasian population, is associated with recurrent KS in patients with phosphate renal leak. The mutant region C716T influences FGF23 biological proprieties and its interaction with FGF-receptor and Klotho (89). In addition, the same allelic variant of FGF23 is involved in bone modelling in growing young children (90).

Bone health and monogenic kidney stones

Frequently, KS represents only the first symptom of an unknown disease. Patients with early renal failure, severe and multiple KS, abnormal family history need to evaluate for genetic of KS, including idiopathic HCa, *primary hyperoxaluria* (PH), *hypocitraturia* (hCtr), cystinuria and defects in purine metabolism. Moreover, these pathological conditions are associated to bone impairment.
Idiopathic HCa (OMIM 143870-607258) is a metabolic condition affecting both children (91) and adult (92) with a diagnosis of KS. HCa is defined as urinary calcium levels ≥ 4 mg/kg body weight/day (93). We recognized three different pathway and metabolic disorders, involving intestinal calcium absorption, renal phosphate leak, and renal calcium leak, respectively: i) absorptive HCa type I; ii) absorptive HCa type III; iii) renal HCa (94). Different studies show the association between idiopathic HCa and loss in BMD. In children, an increased bone reabsorption and a decreased bone formation cause a low BMD, while in adult, the bone reabsorption is prevalent (95). *Freundlich and coll.* evaluated the BMD and BTM in 21 children with a diagnosis oh idiopathic HCa and in their mothers, founding osteopenia in 38% and 33%, respectively. Furthermore, mothers with osteopenia showed an increasing in BTM by 57% (96). Also, *García-Nieto and coll.* studied 40 girls with idiopathic HCa and their pre-menopausal mothers. They found a Z-score < - 1 at the lumbar spine in 42.5% of girls and in 47.5% of their mothers, suggesting the necessity to measure early BMD in these patients (97). The skeletal sites involved are mainly represented by trabecular bone (98), but the mechanism causing the bone loss are poorly understood.
PH are a group of autosomal recessive disorders linked to a liver overproduction of oxalate and characterized by KS (99). PH 1 (OMIM 259900; AGXT gene mutation) is the most severe form with a higher risk of end-stage renal disease, while PH2 (OMIM 260000; GRHPR gene mutation) and PH3 (OMIM 613616; HOGA1 gene mutation) are less severe (99). The PH cause osteodystrophy related to chronic kidney disease, but PH patients show bone pain, fractures, bone deformations and subperiosteal tophi, independently of kidney disease (100). the exact pathophysiology remains unknown.
hCtr is a common risk factor for KS, with an incidence that ranges from 20% to 60% in KS formers (101). The low 24h urinary citrate excretion is a marker of acid load of the body. To maintain acid-base balance, kidney retains and bone releases alkali (citrate), causing a reduction in BMD and an increasing of BTM (102). *Pak and coll.* described a significant improvement of BMD in lumbar spine in KS formers treated with a long-term potassium citrate salt (mean 44 months), suggesting that this drug, used for KS, may prevent bone loss (103).
Cystinuria (OMIM: 220100) is a rare genetic disease caused by cystine tubular transport alteration, and it is considered as the most frequent monogenic form of KS. Cystinuria is classified as: i) type A characterized by SLC3A1 gene mutation; ii) type B characterized by SLC7A9 gene mutation (104). Cystinuric patients have a higher prevalence of chronic kidney disease and failure, caused by recurrent KS. This latter is associated to low BMD. An animal study by *Peters and coll.*, the SLC3A1 gene mutation was associated to low BMD independently of renal failure, assuming a direct role of cystinuria in skeletal alteration (105). The high prevalence of low BMD in this setting was showed by *Bijelic and coll.* compared to KS formers and healthy controls (106) and it was confirmed by *D'Ambrosio and coll.* (107).
The main defect in purine metabolism is the deficiency of *hypoxanthine-guanine phosphoribosyltransferase* (HPRT), resulting in an accumulation of *uric acid* (UA) (108). UA has a double action on bone. In the normal range, it acts as an antiox-

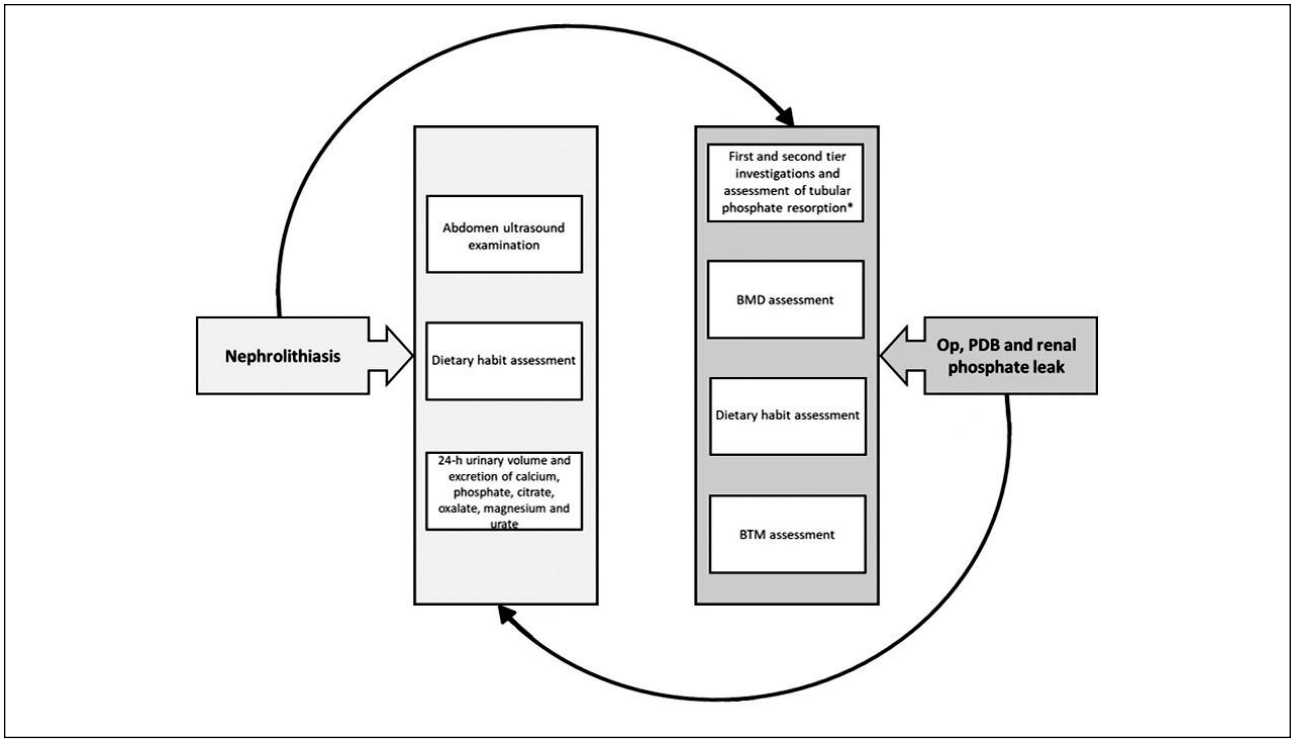
idant and reduces the incidence of Op by 23-26% (109). Meanwhile, elevated UA levels cause destructive effects on bone health through *reactive oxygen species* (ROS) and increase of inflammation (110).

An integrated approach to KS and MBDs to reduce the financial and social burden

Growing epidemiological and experimental data support a non-stochastic association between idiopathic KS and common MBDs, such as Op, PDB and renal phosphate leak not PTH related. MBDs and KS share common environmental and genetic backgrounds. Based on such evidence, a different clinical approach and management of KS and MBD patients should be evaluated. Additionally, KS and MBDs account for an increased economic burden, linked to hospitalisation and pharmacological treatment costs, and ambulatory visits (111, 112). An integrated screening protocol could be able to impact positively, reducing mortality, morbidity and overall costs.

We propose the evaluation of metabolic risk factors for nephrolithiasis (measurement of 24-h urinary excretion of calcium, phosphate, citrate, magnesium and urate), and an abdomen ultrasound exam in patients with Op, PDB and renal phosphate leak. On the contrary, the assessment of bone mineral density by DXA or REMS, BTMs and threshold of tubular phosphate resorption should be evaluated in patients with nephrolithiasis. Both in KS and MBD patients, the evaluation of daily calcium and salt intake, and the adherence to a balanced diet is recommended. Moreover, in case of KS in young patients or recurrent KS, without any metabolic causes, it could be essential to search for gene mutations related to KS. This new diagnostic protocol guarantees the best possible treatment of any type of metabolic bone disorders, and, for this reason, it is necessary to develop a specific public health strategy.

Figure 1.
Suggested flow-chart for the management of nephrolithiasis and metabolic bone disorders.



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