Idiopathic Osteoporosis

Subjects: Others

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Osteoporosis is defined as a decrease in bone density that results in micro-architecture deterioration, predisposing the affected patients to fractures. Operationally, osteoporosis has been defined on the basis of a bone mineral density assessment using dual energy X-ray absorptiometry.

Keywords: osteoporosis risk factors ; vitamin d ; metabolic bone disease

1. Introduction

Osteoporosis is recognized as the most common form of metabolic bone disease, with an estimated 200 million people affected worldwide; in particular, approximately 30% of postmenopausal women have osteoporosis in industrialized countries, including Europe and United States [1]. Great attention has been recently paid to pediatric osteoporosis and much has changed in the field of pediatric bone health since the first positions of the International Society for Clinical Densitometry were published in 2003 [2]. Some scientific societies have included bone health screening in their clinical guidelines for chronic childhood diseases [3]. Osteoporosis in childhood and adolescence is a condition characterized by a low bone mineral density or bone mineral content (z-score ≤ −2.0, adjusted for race, age and gender) and the presence of a clinically significant history of skeletal fractures [4]. In the absence of a history of fractures, unlike the T-score in adults, the z-score < −2 cannot be used for diagnosis of osteoporosis and thus the preferred term is reduced bone density according to chronological age [5]. Primary osteoporosis in children is a rare condition, recognizing a genetic background. More commonly, secondary osteoporosis (or, more frequently, reduced mineral density) can result from chronic diseases affecting mineral metabolism and/or from significant nutritional perturbations [6].

2. Pathogenesis

2.1. Modifiable Risk Factors

Diet. Among the modifiable risk factors, unhealthy eating habits involving high salt, high protein, high sugar and inadequate calcium intakes play a central role in the pathogenesis of osteoporosis [7][8]. Excessive salt intake has been focused on in the last few years as one of the main elements that influence health status [9]; in particular, high salt intake is linked to hypertension and its cardiovascular complications [10]. There is strong evidence of excessive salt intake starting in childhood and adolescence [11]. This is worth special attention, because the effect of the high salt intake will add a high amount of exposure time. Accordingly, many organizations have issued strong recommendations to reduce salt intake [12][13][14][15]. Bone is a target organ of a high dietary sodium intake [16][17]. Several experimental studies indicate that high salt intake increases urinary calcium excretion, a well-recognized risk factor for osteoporosis [18][19].

Moreover, a high dietary intake of simple sugars is another factor able to increase the risk of reduced bone mineral density and osteoporosis [20]. This increased risk has been attributed to the elevated urinary excretion of calcium and magnesium which occurs after the ingestion of common nutritive sugars such as glucose and sucrose [21], to the $1,25OH_2D_3$ -dependent inhibition of intestinal and renal calcium transport, which occurs after a high dietary intake of fructose in experimental models [22], and to the impairment of bone formation caused by the reduced osteoblast proliferation, the increased osteoclast activation, and the increased lactic acid production which has observed in experimental models after high glucose dietary intake and has be linked to impairment of bone strength observed in type 1 and 2 diabetes [20][22][23][24]. In this regard, it should be noted that the regular consumption of soft drinks, a notoriously high source of added sugar, is strongly associated with an increased risk of developing fractures in children and adolescents [25][26][27][28].

Low physical activity. An additional lifestyle risk factor for the occurrence of osteoporosis may be identified in physical inactivity, which was reported to be a risk factor for both disorders, at least in post-menopausal women [29][30].

Smoking. Cigarette smoking is also a significant risk factor for osteoporosis [31][32]. Cigarette smoking predisposes patients to osteoporosis by different pathophysiologic mechanisms. In effect, cigarette smoking influences the metabolism of calciotropic, cortical and sexual hormones [33][34]. In addition, it directly induces alteration in the RANK—Receptor Activator of NF-kB Ligand (RANKL)—osteoprotegerin (OPG) system in collagen metabolism and in bone angiogenesis. Nicotine also has an inhibitory effect on osteogenesis [33][34].

An adequate vitamin D status is fundamental for bone health [35][36][37]. The pivotal role of the vitamin D system in regulating calcium-phosphate homeostasis has been demonstrated [35][36] associated also with a higher prevalence of vitamin D deficiency (i.e., serum 25-hydroxyvitamin D levels < 50 nmol/L or 20 ng/mL) worldwide and at all ages [38][39][40][41].

2.2. Non-Modifiable Risk Factors

Osteoporosis seem to be a genetically heterogeneous disease, related to multiple genetic factors [35][36], identified on family-based or case–control studies.

All humans carry many risk alleles for all common diseases, and each affected individual likely carries a higher burden and unique portfolio of risk variants. While the description of a polygenic model at the population level is very simply defined, it generates considerable genetic heterogeneity between individuals, which, in turn, is consistent with the characteristics of common complex diseases, such as heterogeneity in clinical presentation and variation in response to treatments. Understanding the consequences of polygenicity for individuals also links to an understanding of epistasis, the interacting effects of risk loci [42].

Calcium-sensing receptor (CASR). The calcium-sensing receptor is a plasma membrane G protein-coupled receptor that is expressed in the parathyroid hormone-producing chief cells of the parathyroid gland and in the cells lining the kidney tubule. In the parathyroid gland, the CASR senses small changes in circulating calcium concentration and couples this piece of information to intracellular signaling pathways that modify PTH secretion. In the kidney, the CaSR is expressed in all tubular segments and regulates tubular cell function in response to the increase in calcium concentrations in the interstitium or tubular lumen. In the proximal tubule, the CaSR inhibits PTH-induced phosphate excretion. In addition, CaSR inhibits calcium reabsorption in the medullary thick ascending limb and water reabsorption in the collecting duct. These CaSR-mediated effects ensue to dilute the tubular calcium load in a larger fluid volume and decrease the risk of salt precipitation, crystal aggregation and growth, leading, in the end, to stone formation and a reduced bone mineral density [37][43][44][45]. Natural polymorphic variants of CASR are associated to an increased risk of osteoporosis, directly influencing calcium tubular handling [37][43][44].

Vitamin D receptor (VDR). The vitamin D receptor is an intracellular hormone receptor that specifically binds $1,25(OH)_2D_3$ and mediates its biological effects. VDR contains a zinc-finger DNA-binding and transcriptional activation domain and a ligand-binding domain [46]. Natural polymorphic variants of VDR are associated to an increased risk of osteoporosis, by directly affecting calcium and citrate tubular metabolism [47][48][49][50][51][52]. In addition, a natural polymorphic variant of VDR, which lacks only the first three amino acids, was shown to interact more efficiently with its transcription factor and to possess elevated transcriptional activity. This defect resulted in an increase in 1,25-dihydroxyvitamin D3 levels, hypocalcemia with secondary hyperparathyroidism and hypophosphatemia, leading to rickets. In addition, these patients also showed increased serum alkaline phosphatase levels, generalized aminoaciduria, total alopecia [53].

Alkaline phosphatase (ALPL). Alkaline phosphatase are membrane-bound glycoproteins that hydrolyze various monophosphate esters at a high pH optimum. The enzyme acts physiologically as a lipid-anchored phosphoethanolamine and pyridoxal-5-prime-phosphate [54]. Allelic variants of the *ALPL* gene have been linked to an increased risk of osteoporosis [55][56]. In addition, twenty-three allelic variants have been isolated in children affected by hypophosphatasia and kidney stones. Every mutation disrupts the spatial relationship between two essential components of the ALP active pocket in the calcium binding domain [57].

Osteopontin (SPP1). Osteopontin is a multifunctional glycosylated phosphoprotein and is a member of the small integrin-binding ligand, N-linked glycoprotein (SIBLING) family. An analysis of gene expression using microarray technology has shown that the *SPP1* gene was markedly upregulated in rats during the development of calcium stone formation [58]. SPP1 seems to be involved in the early and in the late stages of the stone-forming process. In fact, that SPP1 plays a role in stimulating the deposition and adhesion of crystals to cells, due to increased adhesion tendency. Furthermore, many studies suggested that SPP1 is also an inhibitor of abnormal calcification and has a vital inhibitory role during crystallization, crystal retention, crystal congregation, and stone formation in vitro or in vivo [59][60]. Experimental studies also demonstrate that SPP1 plays a role in anchoring the osteoclasts on the bone mineral matrix, stimulated by calcitriol.

In this condition, SPP1 accumulates along the bone surface and binds osteoclasts that allow local bone resorption [61]. Some polymorphic variants of *SPP1* gene are associated to an increased risk of osteoporosis, directly influencing calcium tubular handling [62][63].

Claudin-14 (CLDN14). Claudin-14 is an integral membrane protein and a component of tight junction strands, which regulates paracellular permeability at epithelial tight junctions, and its expression is regulated by extracellular calcium changes [64]. It has been reported to be associated with levels of urinary calcium and serum parathyroid hormone and may therefore regulate bone development through its regulatory effect on calcium metabolism. Transgenic overexpression of claudin-14 in mouse kidneys generated renal defects characterized by an uncontrolled loss of calcium and magnesium [64]. Some polymorphic variants of *CLDN14* gene are also associated to reduced bone mineral density in the hip and spine as well as to nephrolithiasis [65][66][67].

Fibroblast growth factor 23 (FGF23). Fibroblast growth factor 23 is a phosphaturic hormone whose physiological actions on renal tubule tissue are mediated by FGF receptors (FGFR) and klotho, which functions as a co-receptor, increasing the binding affinity of FGF23 for FGFRs. In the renal tubule, FGF23 regulates vitamin D metabolism and tubular phosphate reabsorption by modulating the metabolic activity of 1α 25OH Vitamin D Hydroxylase (Cyp27b1) and decreasing the tubular expression of type IIa sodium–phosphate cotransporter independently from PTH [68][69]. An excess of FGF23 serum levels is implicated in the pathogenesis of renal phosphate leak, a clinical disorder characterized by PTH- and vitamin D independent hypophosphatemia and reduced renal phosphate reabsorption [70][71]. This disorder predisposes patients to both osteoporosis and nephrolithiasis [70][71][72]. A functional allelic variant of the *FGF23* gene (*T239M, rs7955866*) has been described in stone-forming patients with renal phosphate leak. In vitro studies showed that the *T239M* change increases FGF23 secretion and that the *FGF23(239M)* variant induces a higher activation of the FGF receptor/ERK pathway compared to *FGF23(239T)* [73].

Type 2a sodium–phosphate cotransporter (*SLC34A1*). The type 2a sodium–phosphate cotransporter (NPT2a) is expressed in the apical membrane of renal proximal tubular cells and is a key-regulator of phosphate homeostasis, modulating urinary phosphate excretion [74]. In effect, phosphate filtered by the glomerulus is subsequently reabsorbed in the proximal tubule, in which the rate-limiting step is the uptake of phosphate through NPT2a [69][74]. Priè et al. identified two mutations in *SLC34A1* gene in two patients with a renal phosphate leak causing osteoporosis and nephrolithiasis [72].

Vitamin D 24-hydroxylase (CYP24A1). CYP24A1 is a mitochondrial enzyme responsible for inactivating vitamin D metabolites through the C-24 oxidation pathway. The 1,25-(OH)2D3 induces the 24-hydroxylase, whereas hypocalcemia, through increased parathyroid hormone, suppresses this enzyme. The mutant CYP24A1 enzymes revealed complete or near-complete loss of function, characterized by a weak binding of 1,25-dihydroxyvitamin D3 to 24-hydroxylase, leading, in the end, to hypercalcemia, nephrolithiasis and pseudovitamin D-deficient rickets [75][76]. A mutation of the *CYP24A1* gene has been reported in a 22-year-old male patient with recurrent nephrolithiasis, nephrocalcinosis, hypercalcemia, low parathyroid hormone levels, hypercalciuria and low bone mass [73].

References

1. International Osteoporosis Foundation Facts and Statistics. Available online: https://www.iofbonehealth.org/facts-statistics (accessed on 2 May 2020).
2. Ward, L.M.; Weber, D.R.; Munns, C.F.; Högler, W.; Zemel, B.S. A Contemporary View of the Definition and Diagnosis of Osteoporosis in Children and Adolescents. J. Clin. Endocrinol. Metab. 2020, 105, dgz294.
3. Centres de Référence des Maladies Rares du Calcium et du Phosphate Protocole National de Diagnostic et de Soins (PNDS) Fragilités Osseuses Secondaires de L'enfant. Available online: https://www.has-sante.fr/upload/docs/application/pdf/2019-10/pnds_fragilites_osseuses-27-09-2019.pdf (accessed on 31 July 2020).
4. Bianchi, M.L.; Baim, S.; Bishop, N.J.; Gordon, C.M.; Hans, D.B.; Langman, C.B.; Leonard, M.B.; Kalkwarf, H.J. Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents. Pediatr. Nephrol. 2010, 25, 37–47.
5. Crabtree, N.J.; Arabi, A.; Bachrach, L.K.; Fewtrell, M.; El-Hajj Fuleihan, G.; Kecskemethy, H.H.; Jaworski, M.; Gordon, C.M. Dual-energy X-ray absorptiometry interpretation and reporting in children and adolescents: The revised 2013 ISCD Pediatric Official Positions. J. Clin. Densitom. 2014, 17, 225–242.
6. Laine, C.M.; Laine, T. Diagnosis of osteoporosis in children and adolescents. Eur. Endocrinol. 2013, 9, 141–144.
7. Gambaro, G.; Croppi, E.; Coe, F.; Lingeman, J.; Moe, O.; Worcester, E.; Buchholz, N.; Bushinsky, D.; Curhan, G.C.; Ferraro, P.M.; et al. Metabolic diagnosis and medical prevention of calcium nephrolithiasis and its systemic manifestations: A consensus statement. J. Nephrol. 2016, 29, 715–734.

8. Muñoz-Garach, A.; García-Fontana, B.; Muñoz-Torres, M. Nutrients and dietary patterns related to osteoporosis. Nutrients 2020, 12, 1986.
9. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019, 393, 1958–1972.
10. Strazzullo, P.; D'Elia, L.; Kandala, N.B.; Cappuccio, F.P. Salt intake, stroke, and cardiovascular disease: Meta-analysis of prospective studies. BMJ 2009, 339, b4567.
11. Campanozzi, A.; Avallone, S.; Barbato, A.; Iacone, R.; Russo, O.; De Filippo, G.; D'Angelo, G.; Pensabene, L.; Malamisura, B.; Cecere, G.; et al. High sodium and low potassium intake among Italian children: Relationship with age, body mass and blood pressure. PLoS ONE 2015, 10, e0121183.
12. World Health Organization. Available online: https://www.who.int/news-room/fact-sheets/detail/salt-reduction (accessed on 2 May 2020).
13. Centers for Disease Control and Prevention. Available online: https://www.cdc.gov/salt/reduce_sodium_tips.htm (accessed on 2 May 2020).
14. World Action on Salt and Health. Available online: http://www.worldactiononsalt.com/ (accessed on 2 May 2020).
15. Società Italiana Nutrizione Umana. Available online: https://sinu.it/meno-sale-piu-salute/ (accessed on 2 May 2020).
16. Cappuccio, F.P.; Kalaitzidis, R.; Duneclift, S.; Eastwood, J.B. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. J. Nephrol. 2000, 13, 169–177.
17. Van der Wijst, J.; Tutakhel, O.A.Z.; Bos, C.; Danser, A.H.J.; Hoorn, E.J.; Hoenderop, J.G.J.; Bindels, R.J.M. Effects of a high-sodium/low-potassium diet on renal calcium, magnesium, and phosphate handling. Am. J. Physiol. Ren. Physiol. 2018, 315, F110–F122.
18. Blackwood, A.M.; Sagnella, G.A.; Cook, D.G.; Cappuccio, F.P. Urinary calcium excretion, sodium intake and blood pressure in a multi-ethnic population: Results of the Wandsworth Heart and Stroke Study. J. Hum. Hypertens. 2001, 15, 229–237.
19. Timio, F.; Kerry, S.M.; Anson, K.M.; Eastwood, J.B.; Cappuccio, F.P. Calcium urolithiasis, blood pressure and salt intake. Blood Press. 2003, 12, 122–127.
20. DiNicolantonio, J.J.; Mehta, V.; Zaman, S.B.; O'Keefe, J.H. Not salt but sugar as aetiological in osteoporosis: A review. Mo. Med. 2018, 115, 247–252.
21. Ericsson, Y.; Angmar-Månsson, B.; Flores, M. Urinary mineral ion loss after sugar ingestion. Bone Miner. 1990, 9, 233–237.
22. Douard, V.; Sabbagh, Y.; Lee, J.; Patel, C.; Kemp, F.W.; Bogden, J.D.; Lin, S.; Ferraris, R.P. Excessive fructose intake causes 1,25-(OH)(2)D(3)-dependent inhibition of intestinal and renal calcium transport in growing rats. Am. J. Physiol. Endocrinol. Metab. 2013, 304, E1303–E1313.
23. Terada, M.; Inaba, M.; Yano, Y.; Hasuma, T.; Nishizawa, Y.; Morii, H.; Otani, S. Growth-inhibitory effect of a high glucose concentration on osteoblast-like cells. Bone 1998, 22, 17–23.
24. Merlotti, D.; Gennari, L.; Dotta, F.; Lauro, D.; Nuti, R. Mechanisms of impaired bone strength in type 1 and 2 diabetes. Nutr. Metab. Cardiovasc. Dis. 2010, 20, 683–690.
25. Wyshak, G.; Frisch, R.E. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. J. Adolesc. Health 1994, 15, 210–215.
26. Wyshak, G. Teenaged girls, carbonated beverage consumption, and bone fractures. Arch. Pediatr. Adolesc. Med. 2000, 154, 610–613.
27. Ma, D.; Jones, G. Soft drink and milk consumption, physical activity, bone mass, and upper limb fractures in children: A population-based case-control study. Calcif. Tissue Int. 2004, 75, 286–291.
28. Petridou, E.; Karpathios, T.; Dessypris, N.; Simou, E.; Trichopoulos, D. The role of dairy products and non alcoholic beverages in bone fractures among schoolage children. Scand. J. Soc. Med. 1997, 25, 119–125.
29. Sorensen, M.D.; Chi, T.; Shara, N.M.; Wang, H.; Hsi, R.S.; Orchard, T.; Kahn, A.J.; Jackson, R.D.; Miller, J.; Reiner, A.P.; et al. Activity, energy intake, obesity, and the risk of incident kidney stones in postmenopausal women: A report from the Women's Health Initiative. J. Am. Soc. Nephrol. 2014, 25, 362–369.
30. Booth, F.W.; Roberts, C.K.; Thyfault, J.P.; Ruegsegger, G.N.; Toedebusch, R.G. Role of inactivity in chronic diseases: Evolutionary insight and pathophysiological mechanisms. Physiol. Rev. 2017, 97, 1351–1402.
31. Khan, S.R. Stress oxidative: Nephrolithiasis and chronic kidney diseases. Minerva Med. 2013, 104, 23–30.

32. Manolagas, S.C. Birth and death of bone cells: Basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr. Rev. 2000, 2, 115–137.

33. Yoon, V.; Maalouf, N.M.; Sakhaee, K. The effects of smoking on bone metabolism. Osteoporos. Int. 2012, 23, 2081–2092.

34. Cusano, N.E. Skeletal Effects of Smoking. Curr. Osteoporos. Rep. 2015, 13, 302–309.

35. Ralston, S.H.; Uitterlinden, A.G. Genetics of osteoporosis. Endocr. Rev. 2010, 31, 629–662.

36. Howles, S.A.; Thakker, R.V. Genetics of kidney stone disease. Nat. Rev. Urol. 2020, 17, 407–421.

37. Di Nisio, A.; Rocca, M.S.; Ghezzi, M.; Ponce, M.R.; Taglianetti, S.; Plebani, M.; Ferlin, A.; Foresta, C. Calcium-sensing receptor polymorphisms increase the risk of osteoporosis in ageing males. Endocrine 2018, 61, 349–352.

38. Holick, M.F. Vitamin D deficiency. N. Engl. J. Med. 2007, 357, 266–281.

39. Amrein, K.; Scherkl, M.; Hoffmann, M.; Neuwersch-Sommeregger, S.; Köstenberger, M.; TmavaBerisha, A.; Martucci, G.; Pilz, S.; Malle, O. Vitamin D deficiency 2.0: An update on the current status worldwide. Eur. J. Clin. Nutr. 2020, in press.

40. Hagenau, T.; Vest, R.; Gissel, T.N.; Poulsen, C.S.; Erlandsen, M.; Mosekilde, L.; Vestergaard, P. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: An ecologic meta-regression analysis. Osteoporos. Int. 2009, 20, 133–140.

41. Cashman, K.D. Vitamin D in childhood and adolescence. Postgrad. Med. J. 2007, 83, 230–235.

42. Wray, N.R.; Wijmenga, C.; Sullivan, P.F.; Yang, J.; Visscher, P.M. Common disease is more complex than implied by the core gene omnigenic model. Cell 2018, 173, 1573–1580.

43. Wang, Y.B.; Guo, J.J.; Liu, Y.J.; Deng, F.Y.; Jiang, D.K.; Deng, H.W. The human calcium-sensing receptor and interleukin-6 genes are associated with bone mineral density in Chinese. Yi Chuan Xue Bao 2006, 33, 870–880.

44. Vezzoli, G.; Terranegra, A.; Aloia, A.; Arcidiacono, T.; Milanesi, L.; Mosca, E.; Mingione, A.; Spotti, D.; Cusi, D.; Hou, J.; et al. Decreased transcriptional activity of calcium-sensing receptor gene promoter 1 is associated with calcium nephrolithiasis. J. Clin. Endocrinol. Metab. 2013, 98, 3839–3847.

45. Ranieri, M. Renal Ca2+ and Water Handling in Response to Calcium Sensing Receptor Signaling: Physiopathological Aspects and Role of CaSR-Regulated microRNAs. Int. J. Mol. Sci. 2019, 20, 5341.

46. Christakos, S.; Dhawan, P.; Verstuyf, A.; Verlinden, L.; Carmeliet, G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol. Rev. 2016, 96, 365–408.

47. González-Castro, T.B.; Blachman-Braun, R.; Hernández-Díaz, Y.; Tovilla-Zárate, C.A.; Pérez-Hernández, N.; Moscardi, P.R.M.; Alam, A.; Borgonio-Cuadra, V.M.; Reyes-López, P.A.; Juárez-Rojop, I.E.; et al. Association of vitamin D receptor polymorphisms and nephrolithiasis: A meta-analysis. Gene 2019, 711, 143936.

48. Rendina, D.; De Filippo, G.; Gianfrancesco, F.; Muscariello, R.; Schiano di Cola, M.; Strazzullo, P.; Esposito, T. Evidence for epistatic interaction between VDR and SLC13A2 genes in the pathogenesis of hypocitraturia in recurrent calcium oxalate stone formers. J. Nephrol. 2017, 30, 411–418.

49. Rendina, D.; Mossetti, G.; Viceconti, R.; Sorrentino, M.; Castaldo, R.; Manno, G.; Guadagno, V.; Strazzullo, P.; Nunziata, V. Association between vitamin D receptor gene polymorphisms and fasting idiopathic hypercalciuria in recurrent stone-forming patients. Urology 2004, 64, 833–838.

50. Mossetti, G.; Rendina, D.; Viceconti, R.; Manno, G.; Guadagno, V.; Strazzullo, P.; Nunziata, V. The relationship of 3′ vitamin D receptor haplotypes to urinary supersaturation of calcium oxalate salts and to age at onset and familial prevalence of nephrolithiasis. Nephrol. Dial. Transplant. 2004, 19, 2259–2265.

51. Mossetti, G.; Vuotto, P.; Rendina, D.; Numis, F.G.; Viceconti, R.; Giordano, F.; Cioffi, M.; Scopacasa, F.; Nunziata, V. Association between vitamin D receptor gene polymorphisms and tubular citrate handling in calcium nephrolithiasis. J. Intern. Med. 2003, 253, 194–200.

52. Palsson, R.; Indridason, O.S.; Edvardsson, V.O.; Oddsson, A. Genetics of common complex kidney stone disease: Insights from genome-wide association studies. Urolithiasis 2019, 47, 11–21.

53. Arita, K.; Nanda, A.; Wessagowit, V.; Akiyama, M.; Alsaleh, Q.A.; McGrath, J.A. A novel mutation in the VDR gene in hereditary vitamin D-resistant rickets. Br. J. Dermatol. 2008, 158, 168–171.

54. Weiss, M.J.; Henthorn, P.S.; Lafferty, M.A.; Slaughter, C.; Raducha, M.; Harris, H. Isolation and characterization of a cDNA encoding a human liver/bone/kidney-type alkaline phosphatase. Proc. Natl. Acad. Sci. USA 1986, 83, 7182–7186.

55. Peris, P.; González-Roca, E.; Rodríguez-García, S.C.; Del Mar López-Cobo, M.; Monegal, A.; Guañabens, N. Incidence of mutations in the ALPL, GGPS1, and CYP1A1 genes in patients with atypical femoral fractures. JBMR Plus 2018, 3, 29–36.

56. Alonso, N.; Larraz-Prieto, B.; Berg, K.; Lambert, Z.; Redmond, P.; Harris, S.E.; Deary, I.J.; Pugh, C.; Prendergast, J.; Ralston, S.H. Loss-of-function mutations in the ALPL gene presenting with adult onset osteoporosis and low serum concentrations of total alkaline phosphatase. J. Bone Miner. Res. 2020, 35, 657–666.

57. Zurutuza, L.; Muller, F.; Gibrat, J.F.; Taillandier, A.; Simon-Bouy, B.; Serre, J.L.; Mornet, E. Correlations of genotype and phenotype in hypophosphatasia. Hum. Mol. Genet. 1999, 8, 1039–1046.

58. Ogbureke, K.U.; Fisher, L.W. Renal expression of SIBLING proteins and their partner matrix metalloproteinases (MMPs). Kidney Int. 2005, 68, 155–166.

59. Xie, Y.; Sakatsume, M.; Nishi, S.; Narita, I.; Arakawa, M.; Gejyo, F. Expression, roles, receptors, and regulation of osteopontin in the kidney. Kidney Int. 2001, 60, 1645–1657.

60. Gleberzon, J.S.; Liao, Y.; Mittler, S.; Goldberg, H.A.; Grohe, B. Incorporation of osteopontin peptide into kidney stone-related calcium oxalate monohydrate crystals: A quantitative study. Urolithiasis 2019, 47, 425–440.

61. Reinholt, F.P.; Hultenby, K.; Oldberg, A.; Heinegård, D. Osteopontin—A possible anchor of osteoclasts to bone. Proc. Natl. Acad. Sci. USA 1990, 87, 4473–4475.

62. Safarinejad, M.R.; Shafiei, N.; Safarinejad, S. Association between polymorphisms in osteopontin gene (SPP1) and first episode calcium oxalate urolithiasis. Urolithiasis 2013, 41, 303–313.

63. Gao, B.; Yasui, T.; Itoh, Y.; Li, Z.; Okada, A.; Tozawa, K.; Hayashi, Y.; Kohri, K. Association of osteopontin gene haplotypes with nephrolithiasis. Kidney Int. 2007, 72, 592–598

64. Gong, Y.; Hou, J. Claudins in barrier and transport function-the kidney. Pflugers Arch. 2017, 469, 105–113.

65. Thorleifsson, G.; Holm, H.; Edvardsson, V.; Walters, G.B.; Styrkarsdottir, U.; Gudbjartsson, D.F.; Sulem, P.; Halldorsson, B.V.; de Vegt, F.; d'Ancona, F.C.; et al. Sequence variants in the CLDN14 gene associate with kidney stones and bone mineral density. Nat. Genet. 2009, 41, 926–930.

66. Tang, R.; Wei, Y.; Li, Z.; Chen, H.; Miao, Q.; Bian, Z.; Zhang, H.; Wang, Q.; Wang, Z.; Lian, M.; et al. A Common variant in CLDN14 is associated with primary biliary cirrhosis and bone mineral density. Sci. Rep. 2016, 6, 19877.

67. Zhang, L.; Choi, H.J.; Estrada, K.; Leo, P.J.; Li, J.; Pei, Y.F.; Zhang, Y.; Lin, Y.; Shen, H.; Liu, Y.Z.; et al. Multistage genome-wide association meta-analyses identified two new loci for bone mineral density. Hum. Mol. Genet. 2014, 23, 1923–1933.

68. Fukumoto, S.; Yamashita, T. FGF23 is a hormone-regulating phosphate metabolism—Unique biological characteristics of FGF23. Bone 2007, 40, 1190–1195.

69. Mossetti, G.; Rendina, D.; De Filippo, G.; Zampa, G.; Strazzullo, P. Phosphatonins: Novel insights and clinical perspectives. G. Ital. Nefrol. 2009, 26, 171–180.

70. Rendina, D.; Mossetti, G.; De Filippo, G.; Cioffi, M.; Strazzullo, P. Fibroblast growth factor 23 is increased in calcium nephrolithiasis with hypophosphatemia and renal phosphate leak. J. Clin. Endocrinol. Metab. 2006, 91, 959–963.

71. Prié, D.; Beck, L.; Silve, C.; Friedlander, G. Hypophosphatemia and calcium nephrolithiasis. Nephron Exp. Nephrol. 2004, 98, e50–e54.

72. Rendina, D.; Esposito, T.; Mossetti, G.; De Filippo, G.; Gianfrancesco, F.; Perfetti, A.; Magliocca, S.; Formisano, P.; Prié, D.; Strazzullo, P. A functional allelic variant of the FGF23 gene is associated with renal phosphate leak in calcium nephrolithiasis. J. Clin. Endocrinol. Metab. 2012, 97, E840–E844.

73. Ferraro, P.M.; Minucci, A.; Primiano, A.; De Paolis, E.; Gervasoni, J.; Persichilli, S.; Naticchia, A.; Capoluongo, E.; Gambaro, G. A novel CYP24A1 genotype associated to a clinical picture of hypercalcemia, nephrolithiasis and low bone mass. Urolithiasis 2017, 45, 291–294.

74. Murer, H.; Hernando, N.; Forster, I.; Biber, J. Proximal tubular phosphate reabsorption: Molecular mechanisms. Physiol. Rev. 2000, 80, 1373–1409.

75. Schlingmann, K.P.; Kaufmann, M.; Weber, S.; Irwin, A.; Goos, C.; John, U.; Misselwitz, J.; Klaus, G.; Kuwertz-Bröking, E.; Fehrenbach, H.; et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N. Engl. J. Med. 2011, 365, 410–421.

76. Labuda, M.; Lemieux, N.; Tihy, F.; Prinster, C.; Glorieux, F.H. Human 25-hydroxyvitamin D 24-hydroxylase cytochrome P450 subunit maps to a different chromosomal location than that of pseudovitamin D-deficient rickets. J. Bone Miner. Res. 1993, 8, 1397–1406.