

Genetic Causes of Rickets

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Abstract

Rickets is a metabolic bone disease that develops as a result of inadequate mineralization of growing bone due to disruption of calcium, phosphorus and/or vitamin D metabolism. Nutritional rickets remains a significant child health problem in developing countries. In addition, several rare genetic causes of rickets have also been described, which can be divided into two groups. The first group consists of genetic disorders of vitamin D biosynthesis and action, such as vitamin D-dependent rickets type 1A (VDDR1A), vitamin D-dependent rickets type 1B (VDDR1B), vitamin D-dependent rickets type 2A (VDDR2A), and vitamin D-dependent rickets type 2B (VDDR2B). The second group involves genetic disorders of excessive renal phosphate loss (hereditary hypophosphatemic rickets) due to impairment in renal tubular phosphate reabsorption as a result of FGF23-related or FGF23-independent causes. In this review, we focus on clinical, laboratory and genetic characteristics of various types of hereditary rickets as well as differential diagnosis and treatment approaches.

Keywords: Rickets, hereditary, genetic, vitamin D dependent, hypophosphatemic rickets

Introduction

Rickets is a disease of growing bone seen in children and adolescents due to deficiency in calcium, phosphate and/or vitamin D, leading to inadequate mineralization of osteoid tissue in the growth plate and bone matrix (1). The most frequent cause of rickets in Turkey, as well as in the rest of the world, continues to be nutritional vitamin D deficiency (1,2). Genetic causes of rickets (hereditary rickets) are rare: accounting for about 13 % of total rickets (3).

They can be divided into two groups: vitamin D-dependent rickets which is caused by mutations either in enzymes involved in the vitamin D biosynthesis or vitamin D receptor (4), and hypophosphatemic rickets (HR) which is caused by impaired renal tubular phosphate reabsorption or transport due to genetic disorders associated with phosphatonins or phosphate co-transporters (5).

Calcium is one of the most common minerals in the body and it is mainly derived from dietary sources (6). It is essential for bone metabolism and various biological functions (6). While more than 99 % of total calcium is stored in bone tissue as calcium-phosphate complex, less than < 1 % is distributed

between intracellular and extracellular compartments (7). Of the < 1 % calcium outside bone tissue, 40 % is bound to proteins, 9 % is contained in ionic complexes and the remaining 51 % is in the form of free Ca²⁺ ions that are the biologically active portion of body calcium (6,8). The ionized calcium balances the calcium pool in the intracellular-extracellular space and plays an important role in bone metabolism. This balance is achieved through the collective action of several hormones such as parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D [1,25(OH)₂D] and organs such as the kidney, bone and intestinal system (7,8). If serum calcium levels decrease, calcium-sensing receptors located on parathyroid cells mediate increased secretion of PTH, which binds to PTH 1 receptor (PTH1R, expressed in high levels in bone and kidney) to promote calcium resorption from bone and reabsorption from kidneys. PTH also activates 25-hydroxyvitamin D3-1 α -hydroxylase, leading to increased 1,25(OH)₂D synthesis, which promotes calcium absorption from intestines and reabsorption from proximal tubules of kidney (6,7,8).

Phosphorus is the most common anion in the human body. It is found in the form of inorganic phosphate and plays an important role in many biological processes such



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as bone mineralization, cell membrane integrity, nucleic acid and energy metabolism, signal transduction through phosphorylation of proteins and oxygen transport (9). In the adult male human, total body phosphorus is between 15 mol and 20 mol (12.0 g/kg), 80-90% of which is present in bone in the form of hydroxyapatite and the remaining 10-20% in soft tissue and extracellular spaces (9). Approximately two-thirds of dietary phosphate is absorbed via the sodium-dependent phosphate transporter 2B (NaPi-2b, encoded by the *SLC34A2* gene), the major transporter that mediates phosphate reabsorption in the small intestine, predominantly in the jejunum. The expression of NaPi-2b is regulated by 1,25(OH)₂D, which induces transcriptional up-regulation of NaPi-2b in the small intestine and low phosphate can activate 1 α -hydroxylase in the kidney (10). Phosphate in the circulation can be taken up into cells for various biological activities or can be stored in the bone tissue. Approximately 85% of phosphate is reabsorbed by the sodium-dependent phosphate transporter 2A (NaPi-2a, encoded by the gene *SLC34A1*) and the sodium-dependent phosphate transporter 2C (NaPi-2c, encoded by the gene *SLC34A3*) both of which are expressed in the proximal tubules of the kidney (5,11). 1,25(OH)₂D increases intestinal absorption of phosphate and tubular reabsorption, whereas PTH decreases tubular reabsorption of phosphate (TRP). In addition, other molecules that have phosphaturic effects, so-called phosphatonins, have significant impact on the balance of serum phosphate by reducing TRP (12,13).

Vitamin D is a group of biologically inactive, fat-soluble prohormones that exist in two major forms: ergocalciferol (vitamin D₂) produced by plants in response to ultraviolet irradiation and cholecalciferol (vitamin D₃) derived from animal tissues or 7-dehydrocholesterol in human skin by the action of ultraviolet rays present in sunlight with a wavelength of 270-290 nm (4). The main source of vitamin D is endogenous synthesis. Normally only 0.04% of 25-hydroxyvitamin D [25(OH)D] and 0.4% of 1,25(OH)₂D are free in plasma, the remainder being tightly bound to either a vitamin D transporter protein (85-88%; high affinity) or albumin (12-15%; low affinity) (14). Both forms need two-step hydroxylation for activation. The first step occurs in the liver where vitamin D is hydroxylated to the minimally active 25(OH)D by hepatic 25-hydroxylase. The second step occurs mainly in the kidney where 25(OH)D is further hydroxylated by 1 α -hydroxylase to become the biologically active hormone 1,25(OH)₂D (calcitriol), which binds to its nuclear receptor vitamin D responsive (VDR) to regulate gene transcription through heterodimerization with one of three retinoid X receptor (RXR) isoforms (RXR α , RXR β , RXR γ) and binds to cognate VDR elements

(VDREs) in the promoter region of target genes (14,15). The renal synthesis of 1,25(OH)₂D is stimulated by PTH and suppressed by calcium, phosphate and 1,25(OH)₂D itself with renal 1 α -hydroxylase being stimulated by PTH, hypophosphatemia or hypocalcaemia. Alternatively, 25(OH)D and 1,25(OH)₂D may be catabolized to 24,25(OH)₂D and 1,24,25(OH)₂D, respectively, through 24-hydroxylation by 25-hydroxyvitamin D 24-hydroxylase to maintain calcium homeostasis (4,14).

1. Vitamin D-Dependent Rickets

Disorders in the biosynthesis of vitamin D or its receptor activity result in vitamin D deficiency [vitamin D dependent rickets, type 1A (VDDR1A) and type 1B (VDDR1B)] or resistance [type 2A (VDDR2A) and type 2B (VDDR2B)]. All of them present similar clinical and biochemical manifestations of rickets such as findings related to hypocalcemia (irritability, fatigue, muscle cramps, seizures) and rickets (craniotables, delayed closure of fontanelles, frontal bossing, enlarged wrists, bowed legs, short stature, and bone pain) (Table 1) (1,4).

1.1. Vitamin D-Dependent Rickets Type 1A

This disease, also called hereditary pseudo-vitamin D deficiency, was first described by Prader et al in 1961 as an autosomal recessive, persistent infantile rickets that responded to high dose vitamin D (16). Fraser et al (17) later reported that this condition was caused by lack of the 1-alpha hydroxylase enzyme. It is now defined as VDDR1A, (MIM 264700). VDDR1A occurs as a result of mutations in the *CYP27B1* (cytochrome P450, family 27, subfamily B, polypeptide 1, MIM 609506) that encodes the 1-alpha hydroxylase enzyme (17,18). As a result, 25(OH)D cannot be converted to active 1,25(OH)₂D, leading to clinical findings of rickets and vitamin D deficiency. To date, over 100 patients with 72 different mutations have been described in the Human Gene Mutation Database (HGMD, <http://www.hgmd.cf.ac.uk/ac/index.php>, accessed Nov 13, 2017) (4,14,19,20,21). Strikingly, in a genetically isolated population of French-Canadians in Quebec, the disease is found with the highest global incidence (1/2700) (4). The most commonly reported mutation in this region is 958delG, the "Charlevoix mutation".

There is some genotype-phenotype correlation: milder phenotype is usually associated with mutations with residual enzyme activities (*E189G*, *G102E* and *L343F*) (22,23,24,25). Some milder cases may be missed and thus VDDR1A might be more common than is reported.

The disease is clinically similar to the phenotype of nutritional vitamin D-deficient rickets. The cases are usually normal at birth. However, growth retardation, skeletal

Table 1. Laboratory characteristics of rickets associated with vitamin D metabolism

Disease	Inheritance	Genetic defect	Protein	Serum calcium	Serum phosphate	ALP	PTH	25(OH)D	1,25(OH)2D	Urinary calcium/creatinine
Calcium deficiency rickets	-	-	-	↓ or N	N or ↓	↑	↑	N	↑ or N	↓
Nutritional vitamin D deficiency	-	-	-	↓ or N	N or ↓	↑	↑	↓	↓ or N or ↑	↓
Vitamin D dependent rickets Type 1A (VDDR1A)	Autosomal recessive	<i>CYP27B1</i> mutation	1-alpha hydroxylase	↓ or N	N or ↓	↑	↑	N or ↑	↓ or N	↓
Vitamin D dependent rickets Type 1B (VDDR1B)	Autosomal recessive	<i>CYP2R1</i> mutation	25-hydroxylase	↓ or N	N or ↓	↑	↑	↓	N or ↓	↓
Vitamin D dependent rickets Type 2A (VDDR2A)	Autosomal recessive	<i>VDR</i> mutation	Vitamin D receptor	↓ or N	N or ↓	↑	↑	N	↑	↓
Vitamin D dependent rickets Type 2B (VDDR2B)	unknown	<i>HNRNPC</i> overexpression	Heterogeneous nuclear ribonucleoprotein C	↓ or N	N or ↓	↑	↑	N	↑	↓

ALP: alkaline phosphatase, PTH: parathyroid hormone, N: normal, VDR: vitamin D responsive, HNRPC: heterogeneous nuclear ribonucleoprotein C, 1,25(OH)2D: 1,25-dihydroxyvitamin D, 25(OH)D: 25-hydroxyvitamin D

deformities, muscle weakness, bone pain, muscle spasms and hypocalcemic convulsions may occur in the first year of life. The first observed findings in bone and joints include deformities such as craniotabes, metaphyseal enlargement, prominence of costochondral joints (rachitic rosary), delayed closure of the anterior fontanel, Harrison's grooves and thoracic anomalies (1,26).

Similar to cases of nutritional rickets, typical cases with VDDR1A present with hypocalcemia, hypophosphatemia and increased serum levels of alkaline phosphatase (ALP) and PTH (Table 1). In contrast to nutritional rickets, levels of 25(OH)D are generally normal and 1,25(OH)2D are low (20). Some patients may be misdiagnosed as nutritional rickets and thus incorrectly treated with high dose vitamin D, leading to very high levels of 25(OH)D. Renal calcium excretion is low in these patients. In addition, hyperchloremic metabolic acidosis and hyperaminoaciduria secondary to PTH elevation can occur (4). Inappropriately normal 1,25(OH)2D levels in the presence of hypocalcemia can also be found in some patients with VDDR1A (20,27). Some cases might also be normocalcemic and a misdiagnosis of HR might be made before the detection of significantly elevated PTH levels (20).

Proper treatment of the disease includes administration of calcitriol, 1,25-dihydroxyvitamin D3 or alfacalcidol, 1 alpha-hydroxy-vitamin D3 in physiological doses (10-20 ng/kg/day, 2 doses), which will gradually improve clinical, biochemical and radiological findings (26). In addition, it is recommended to add 50-75 mg/kg/day of elemental calcium at the beginning of treatment. On follow-up, effective management should result in low-normal serum levels of calcium (8.5-9 mg/dL), normal phosphate levels and high-normal PTH values (4,26). High-normal levels of serum calcium might lead to hypercalciuria and subsequent development of nephrocalcinosis. Regular monitoring of 24-hour urinary calcium excretion and keeping the urine calcium excretion below 4 mg/kg/day is recommended (4,5,26). The degree of calciuria can also be assessed with spot urine calcium/creatinine ratios, for which varying normal ranges exist for different age groups: < 0.8 mg/mg (≤6 months of age), < 0.6 mg/mg (7-12 months), < 0.53 mg/mg (1-3 years), < 0.39 mg/mg (3-5 years), < 0.28 mg/mg (5-7 years) and < 0.21 mg/mg (> 7 years) (28).

1.2. Vitamin D Dependent Rickets Type 1B

VDDR1B (MIM 600081) is an extremely rare autosomal recessive disorder, due to 25-hydroxylase deficiency. This disease was first described in 1994 by Casella et al (29) in two Nigerian siblings of two and seven years old. Skeletal deformities compatible with rickets, hypocalcemia,

hypophosphatemia, markedly elevated ALP and PTH, normal 1,25(OH)2D and low 25(OH)D levels were present. These siblings were diagnosed with 25-hydroxylase deficiency and showed clinical and laboratory improvement after high-dose vitamin D2 treatment. The gene encoding 25-hydroxylase (*CYP2R1*, MIM 608713) was described by Cheng et al (30) in 2003 and a homozygous *CYP2R1* mutation (*L99P*) was identified in one of the first reported Nigerian siblings (31). Currently, only four *CYP2R1* mutations are listed in the HGMD (accessed Nov 13, 2017). Apart from *CYP2R1*, there are five other cytochrome P450 enzymes (*CYP27A1*, *CYP2J2/3*, *CYP3A4*, *CYP2D25* and *CYP2C11*) capable of catalyzing the initial 25-hydroxylation step (32). Indeed, a 20-month-old male patient has been described recently having hypocalcemic convulsions and rickets (33). His mother, maternal grandmother and aunt also have a history of hypercalcemic convulsion and skeletal deformities related with rickets in childhood. In all cases, hypocalcemia, hypophosphatemia, decreased 25(OH)D, markedly elevated ALP and PTH are present. Interestingly, a *CYP2R1* mutation has not been found in this kin, suggesting that another gene may be involved in 25-hydroxylation. Calcitriol is the only choice of treatment for the disease (10-20 ng/kg/day, 2 doses).

1.3. Vitamin D Dependent Rickets Type 2A

VDDR2A (MIM 277440), also known as hereditary vitamin D-resistant rickets, was first described by Brooks et al (34) in 1978 in a case who had skeletal findings suggesting rickets, short stature, hypocalcemia, elevated ALP, normal 25(OH)D, and very high 1,25(OH)2D. VDDR2A is an autosomal recessive disorder and is characterized by resistance to 1,25(OH)2D as a result of homozygous or compound heterozygous mutations in the vitamin D receptor gene (*VDR*, MIM 601769), which is located in 12q13.11 and consists of 11 exons. Patients with this disease usually present in infancy or early childhood, but patients with mild *VDR* defects may not be recognized until adolescence or adulthood (26). Clinical findings are similar to nutritional vitamin D deficiency or VDDR1A or VDDR1B except for high level of 1,25(OH)2D in VDDR2A (Table 1). Moreover, partial or total alopecia is present in many patients from birth or infancy (Figure 1) (35). The relationship between vitamin D and the hair follicle is not completely understood. However, *VDR/RXR α* heterodimer formation has been suggested to play an important role in the proliferation and differentiation of epidermal keratinocytes (36).

It is well known that active vitamin D mediates its biological functions by binding to its receptor *VDR*, which contains an N-terminal dual zinc finger DNA binding domain, a C-terminal ligand-binding domain and an extensive and

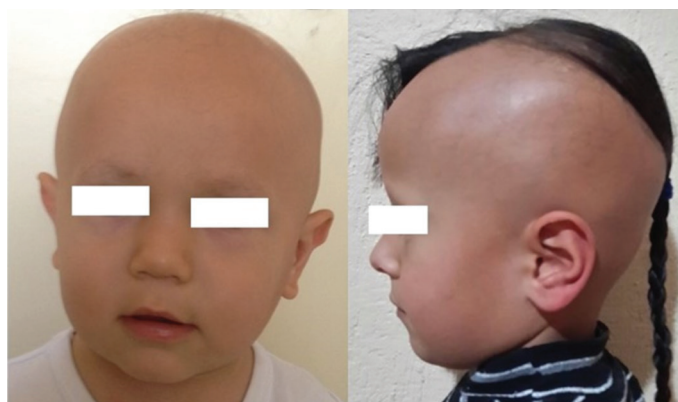


Figure 1. Near-total and partial alopecia in two children with VDDR2A (From the archives of Division of Pediatric Endocrinology, Dokuz Eylül University)

unstructured region that links the two functional domains together (15). After binding of vitamin D, *VDR* forms a ternary structure with *RXR α* , which binds to a VDRE in the promoter region of vitamin D-regulated genes to initiate transcription (37,38). Currently, there are 65 different mutations listed in HGMD (accessed Nov 13, 2017). Inactivating mutations that affect any domain of *VDR* would lead to disease development. Mutations in the DNA binding domain that lead to complete loss of function result in severe clinical presentations accompanied by alopecia, whereas mutations in the ligand binding domain usually cause partial loss of *VDR* functions and a milder phenotype without alopecia (35,38). In addition to the genotype-phenotype relationship, the clinical presentation of the disease may improve with age. Serum levels of calcium, phosphate and ALP may gradually normalize in some pubertal cases and calcitriol/calcium treatment would be unnecessary (39,40,41). Intestinal calcium absorption has been shown to become less vitamin D-dependent after the end of puberty (40).

Hypocalcemia, hypophosphatemia, increased serum levels of ALP and PTH, and normal serum levels of 25(OH)D are usually found. Hypocalcemia, hypophosphatemia and increased PTH lead to activation of 1-alpha hydroxylase and inhibition of 24-hydroxylase. Therefore, low levels of 24,25(OH)2D and high levels of 1,25(OH)2D (300-1000 pg/mL, normal range: 15-90 pg/mL) are generally present (4,26).

High doses of oral calcitriol (1-6 μ g/kg/day, 2 doses) and calcium (1-3 g/day elementary calcium) are the recommended treatment (26,39). Serum calcium, phosphate, ALP and PTH levels should be intermittently monitored and regular urine calcium excretion and renal ultrasonography are suggested because of the risk of nephrocalcinosis. Clinical presentation and response to

treatment varies depending on the location of mutations in the *VDR*: patients with alopecia and nonsense mutations in the DNA-binding domain frequently exhibit a poor response to treatment (35,38). Treatment response may also be poor in patients without alopecia (42).

Long-term, high-dose intracaval/intravenous calcium (0.4-1.4 g/m²/day) treatment is also effective (38,43,44). After successful response to the treatment regimen, it is recommended to continue with high dose oral calcium (3.5-9.0 g/m²/day) (26,45). On the other hand, parenteral calcium therapy requires long-term hospitalization and may be associated with a number of complications such as cardiac arrhythmia, hypercalciuria, nephrocalcinosis, catheter related sepsis and extravasation of calcium (45,46). A case of *VDDR2A* without alopecia has been successfully treated with enteral administration of elemental calcium (calcium chloride) via gastric tube (47). Prolonged serum calcium deprivation might lead to secondary hyperparathyroidism and, if not managed properly, tertiary hyperthyroidism. Cinacalcet is reported to be effective in cases with *VDDR2A* and tertiary hyperparathyroidism (48,49).

1.4. Vitamin D Dependent Rickets Type 2B

VDDR2B (MIM 600785) is an unusual form of rickets due to abnormal expression of a hormone response element-binding protein that interferes with normal function of *VDR*. The disease was first described by Hewison et al (50) in 1993 in a patient with alopecia, skeletal abnormalities and biochemical features classically associated with *VDRR2*, but without *VDR* mutations (4). The similar clinical and genetic features were also found in more than 200 affected children from a rural area of southwest Colombia in 1995 (51). In contrast to *VDDR2A*, functions of *VDR* and *VDR-RXR* heterodimer formation are normal in *VDDR2B* (52). The main pathology is the overexpression of heterogeneous nuclear ribonucleoproteins (hnRNPs) C1 and C2 proteins, members of the hnRNP family, that prevent *VDR-RXR* heterodimer binding to *VDRE* (52,53). Without genetic testing, the differential diagnosis cannot be made between *VDDR2A* and *VDDR2B* (Table 1). The same treatment approaches for *VDDR2A* are used for patients with *VDDR2B*.

2. Hypophosphatemic Rickets

Hereditary HR is a group of rare, renal phosphate wasting disorders with a prevalence of 3.9 per 100,000 live births and differential diagnosis often requires genetic testing (54,55). It is characterized by renal phosphate wasting, leading to subsequent hypophosphatemia and bone mineralization defects such as rickets and osteomalacia. Hypophosphatemia and normal serum calcium are typical biochemical findings (55).

Serum levels of phosphate are maintained in the main by vitamin D and PTH. 1,25(OH)₂D increases phosphate absorption from the intestine and suppresses the biosynthesis and secretion of PTH (5,56). PTH exhibits its phosphaturic effect by reducing the expression of *NaPi-2a* (*SLC34A1*) and *NaPi-2c* (*SLC34A3*) phosphate transporter in the renal tubules via *PTH1R*, a member of the G protein-coupled receptor family (5). In addition, several molecules [fibroblast growth factor 23 (FGF23), secreted frizzled related protein 4 (sFRP4), matrix extracellular phosphoglycoprotein, and FGF7], so-called phosphatonins, have been shown to reduce serum phosphate via direct inhibition of renal phosphate absorption in the proximal tubule (13). FGF23 and sFRP4 can also indirectly inhibit 25-OH vitamin D 1- α hydroxylase and thus intestinal phosphate absorption (57,58).

FGF23 is the most important phosphaturic agent and is produced from osteocytes and osteoblasts (57). There is a close relationship between serum phosphate and FGF23 levels. In response to elevated or decreased phosphate levels, serum FGF23 levels increase or decrease, respectively (5,58). FGF23 activates renal *klotho*/FGF receptor 1 (FGFR1) receptor heterodimers to inhibit renal phosphate reabsorption by down-regulation of *NaPi-2a* and *NaPi-2c* expression in the renal proximal tubules (58). FGFR3 and FGFR4 are also involved in mediating FGF23 activities (59). *Klotho*, a transmembrane protein, is required for FGF23 function and *klotho* knockout mice exhibit extremely high levels of serum FGF23, most likely due to end-organ resistance to FGF23 (60,61). In addition, FGF23 inhibits 25-OH vitamin D 1- α hydroxylase and activates 25-OH vitamin D 24-hydroxylase, resulting in decreased 1,25(OH)₂D and increased 24,25(OH)₂D levels (62).

Another molecule that plays a role in phosphate regulation is sodium-hydrogen exchanger regulatory factor 1 (NHERF1) (58). NHERF1 has been shown to have two different effects on phosphate reabsorption in the proximal tubules. The first is to bind to *PTH1R* to reduce the effect of PTH-induced cAMP synthesis and the second is to increase the activation of *NaPi-2a* by interacting with C-terminal region of the protein (58,62).

Serum phosphate levels normally vary according to age, which needs to be carefully considered when assessing whether hypophosphatemia is present or not. Normal ranges of serum phosphate are 4.8-8.2 mg/dL for 0-5 days of age, 3.8-6.5 mg/dL for 1-3 years of age, 3.7-5.6 mg/dL for 4-11 years of age, 2.9-5.4 mg/dL for 12-15 years of age and 2.7-4.7 mg/dL for 16-19 years of age (27). In addition to hypophosphatemia, decreased TRP, normal or mildly elevated serum levels of PTH and markedly elevated serum levels of ALP are typically detected. In a study comparing serum levels of ALP and PTH in HR, *VDDR* and nutritional

rickets, the highest serum levels of PTH and ALP have been found in patients with VDDR and the lowest levels in patients with HR (63).

Renal phosphate excretion can be evaluated using various parameters. The most widely used is the TRP defined by the formula: $1 - (\text{urine phosphate} \times \text{serum creatinine}) / (\text{serum phosphate} \times \text{urine creatinine})$. Various lower limits for TRP are generally used in daily practice ranging from 75-85%. However, in the presence of hypophosphatemia, fractional excretion of filtered phosphate should be less than 5% (TRP > 95%) (64). The ratio of tubular maximum reabsorption rate of phosphate per glomerular filtration rate (TmP/GFR) is a superior method for assessing phosphaturia, which can be assessed via the nomogram of Walton and Bijvoet or can be calculated as shown below:

For TRP \leq 86%: $\text{TmP/GFR} = \text{TRP} \times \text{serum phosphate}$

For TRP > 86%: $\text{TmP/GFR} = (0.3 \times \text{TRP}) / [1 - (0.8 \times \text{TRP})] \times \text{serum phosphate}$

Low TmP/GFR values in the setting of hypophosphatemia points to renal phosphate wasting (65). The normal ranges of TmP/GFR (mg/dL) vary with age: Birth, 3.6-8.6; 3 months of age, 3.7-8.25; 6 months of age, 2.9-6.5; 2-15 years of age, 2.9-6.1, and the normal adult range for TmP/GFR is 2.2 to 3.6 mg/dL (66).

Laboratory findings such as normal serum calcium, low serum phosphate and elevated serum ALP and PTH may not always be diagnostic of HR. These can also be seen in rickets (especially in stage 2) associated with vitamin D deficiency or disorders of vitamin D biosynthesis (20). The distinctive finding is that PTH is significantly higher in vitamin D-related rickets, whereas normal/mildly elevated PTH is expected in HR (26). To date, a variety of genetic causes leading to HR have been identified (Table 2) (5,58,62). Some of these genetic defects lead to an increase in serum FGF23 levels (FGF23-related or -dependent HR), while others affect phosphate transporters which does not affect serum FGF23 levels (FGF23-independent HR). Laboratory characteristics of several types of HR are summarized in Table 3.

2.1. FGF23-Related Hypophosphatemic Rickets

2.1.1. X-linked Dominant Hypophosphatemic Rickets

X-linked dominant HR (XLDHR, MIM 307800) is the most common type of HR with an incidence of approximately 1 in 20000 live births and is caused by inactivating mutations of *PHEX* (phosphate regulating gene with homologies to endopeptidases on the X chromosome, MIM 307800) (55,67). XLDHR affects both genders equally in terms of disease severity as a result of random X-inactivation in girls (62). Skeletal findings of the disease frequently appear in the late infantile period and are especially evident by the effect on

body weight in the period after starting to walk (5). *PHEX* encodes a membrane endopeptidase, which is expressed in mature osteoblasts and odontoblasts, and plays a role in down-regulation of FGF23 expression (68). Therefore *PHEX* mutations would lead to increased serum levels of FGF23 (69). Currently, there are 423 *PHEX* mutations listed in HGMD (accessed Nov 13, 2017).

In the Turkish population, *PHEX* mutation is also the most common cause of HR, accounting for 87% cases (55,70,71). *De novo* mutations are frequent and more often occur in female patients, likely resulting from mutagenesis of the X chromosome in paternal germ cells (70).

Typical clinical findings include short stature, wrist enlargement, rachitic rosary, bowed legs, frontal bossing, dental abscess and bone pain in children. Osteomalacia, bone pain, dental abscess and spinal canal stenosis are typical presentation in adult patients. Laboratory findings include low serum levels of phosphate, decreased TRP, normal/mildly elevated PTH and high levels of ALP with normal calcium and 25(OH)D, and inappropriately normal or low serum 1,25(OH)2D levels (Table 3). These clinical and laboratory findings suggest HR but confirmation of diagnosis requires genetic confirmation of *PHEX* mutations.

2.1.2. Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant HR (ADHR, MIM 193100) is caused by gain-of-function mutations in the proteolytic cleavage domain of FGF23 (R176XXR179, MIM 605380). Mutations that alter the arginine (R) residue at the position 176 or 179 would render the protein resistant to proteolytic cleavage and lead to increased serum levels of FGF23 and its activity, resulting in hypophosphatemia (61,71,72). It is less common than XLHR and 16 different mutations are reported in HGMD (accessed Nov 13, 2017).

ADHR exhibits similar clinical and laboratory findings as XLHR and also needs genetic testing for diagnosis. Differences in the age of onset, severity and a waxing and waning course of phosphate wasting (renal phosphate wasting can be spontaneously normalized) is related to serum FGF23 levels (73,74). This led to the discovery that iron deficiency is an environmental trigger, which stimulates FGF23 expression and thus hypophosphatemia in ADHR (75,76,77).

2.1.3. Autosomal Recessive Hypophosphatemic Rickets

2.1.3.1. Autosomal Recessive Hypophosphatemic Rickets Type 1

ARHR type 1 (ARHR1, MIM 241520) is due to inactivating homozygous mutations in the *DMP1* gene (dentin matrix acidic phosphoprotein 1, MIM 600980) (78). *DMP1* is an

Table 2. Genetic causes of hypophosphatemic rickets

Disease	Abbreviation	Gene	Protein	Inheritance	Clinical characteristics
FGF23-dependent HR					
X-linked dominant hypophosphatemic rickets	XLDHR	<i>PHEX</i>	Phosphate regulating endopeptidase	X-linked dominant	Increased FGF23; decreased renal phosphorous reabsorption
Autosomal dominant hypophosphatemic rickets	ADHR	<i>FGF23</i>	Fibroblast growth factor 23	AD	
Autosomal recessive hypophosphatemic rickets Type 1	ARHR1	<i>DMP1</i>	dentin matrix acidic phosphoprotein 1	AR	
Autosomal recessive hypophosphatemic rickets Type 2	ARHR2	<i>ENPP1</i>	Ectonucleotide pyrophosphatase / phosphodiesterase 1	AR	
Hypophosphatemic rickets with hyperparathyroidism	HRHPT	9:13 balanced translocation affecting <i>KL</i> gene	α -klotho	unknown	Increased alpha-klotho and FGF23 levels and beta-glucuronidase activity. Hypercalciuria, nephrocalcinosis, parathyroid hyperplasia
Osteoglyphonic dysplasia		<i>FGFR1</i>	Fibroblast growth factor receptor 1	AD	Craniofacial abnormalities, increased FGF23
McCune-Albright Syndrome		<i>GNAS</i>	Guanine nucleotide binding protein, alpha	Postzygotic somatic mutation	Fibrous dysplasia, increased FGF23
Raine syndrome		<i>FAM20C</i>	Family with sequence similarity 20, member c (FAM20C)	AR	Generalized osteosclerosis, increased FGF23
Opsismodysplasia		<i>INPPL1</i>	Inositol polyphosphate phosphatase-like 1	AR	Craniofacial abnormalities, increased FGF23
FGF23-independent HR					
Hereditary HR with Hypercalciuria	HHRH	<i>SLC34A3</i>	Sodium-dependent phosphate transport protein 2C	AR	Hypercalciuria, hypophosphatemia, nephrocalcinosis
Hypophosphatemic rickets with nephrolithiasis and osteoporosis type 1	NPHLOP1	<i>SLC34A1</i>	Sodium-dependent phosphate transport protein 2A	AD, AR	Hypercalciuria, hypophosphatemia, nephrocalcinosis, proximal tubulopathy
	HCINF2 FRTS2				
Infantile hypercalcemia Type 2; Fanconi renotubular syndrome Type 2					
Hypophosphatemic rickets with nephrolithiasis and osteoporosis type 2	NPHLOP2	<i>SLC9A3R1</i>	Sodium-hydrogen exchanger regulatory factor 1 (NHERF1)	AD	Hypercalciuria, nephrocalcinosis and decreased bone mineral density
Dent disease 1		<i>CLCN5</i>	Chloride Voltage-Gated Channel 5	X-linked, recessive	Hypercalciuria, hypophosphatemia, nephrocalcinosis, renal failure, proteinuria, and glucosuria
Dent disease 2 or Lowe syndrome		<i>OCRL1</i>	Inositol Polyphosphate-5-Phosphatase	X-linked recessive	Mild mental retardation, developmental delay, hypophosphatemia, hypercalciuria, nephrocalcinosis, amino aciduria, and proteinuria

AD: autosomal dominant, AR: autosomal recessive, *FGF23*: Fibroblast growth factor 23, *PHEX*: Phosphate regulating endopeptidase homolog x-linked, *XLDHR*: X-linked dominant hypophosphatemic rickets, *ADHR*: Autosomal dominant hypophosphatemic rickets, *ARHR1*: Autosomal recessive hypophosphatemic rickets Type 1, *DMP1*: Dentin matrix acidic phosphoprotein, *ENPP1*: Ectonucleotide pyrophosphatase/phosphodiesterase 1, *FGFR1*: Fibroblast growth factor receptor 1, *INPPL1*: Inositol polyphosphate phosphatase-like 1, *CLCN5*: Chloride voltage-gated channel 5

Tale 3. Laboratory characteristics of genetic causes of hypophosphatemic rickets

Disease	Gene	FGF23	TmP/ GFR	Serum calcium	Serum phosphate	ALP	PTH	1,25 (OH)2D	Urinary calcium/ creatinine
FGF23-dependent HR									
X-linked dominant HR	<i>PHEX</i>	↑ or N	↓	N	↓	↑	N or ↑	N or ↓	N
Autosomal dominant HR	<i>FGF23</i>	↑ or N	↓	N	↓	↑	N or ↑	N or ↓	N
Autosomal recessive HR Type 1	<i>DMP1</i>	↑ or N	↓	N	↓	↑	N or ↑	N or ↓	N
Autosomal recessive HR Type 2	<i>ENPP1</i>	↑ or N	↓	N	↓	↑	N or ↑	N or ↓	N
Osteoglophonic dysplasia	<i>FGFR1</i>	↑ or N	↓ or N	N	↓ or N	↑ or N	N or ↑	N or ↓	N
McCune-Albright Syndrome	<i>GNAS</i>	↑ or N	↓ or N	N	↓ or N	↑ or N	N or ↑	N or ↓	N
Raine syndrome	<i>FAM20C</i>	↑ or N	↓ or N	N	↓ or N	↑ or N	N or ↑	N or ↓	N
Opsismodysplasia	<i>INPPL1</i>	↑ or N	↓ or N	N	↓ or N	↑ or N	N or ↑	N or ↓	N
Hypophosphatemic rickets with hyperparathyroidism	9:13 balanced translocation affecting <i>KL</i> gene	↑	↓	N or ↑	↓	↑	↑	N	N
FGF23-independent HR									
Hereditary HR with Hypercalciuria	<i>SLC34A3</i>	↓ or N	↓	N	↓	N or ↑	N	↑	↑
Hypophosphatemic rickets with nephrolithiasis or osteoporosis Type 1	<i>SLC34A1</i>	↓ or N	↓	N or ↑	↓	N or ↑	N or ↓	↑	↑
Infantile hypercalcemia Type 2									
Fanconi renotubular syndrome Type 2									
Hypophosphatemic rickets with nephrolithiasis and osteoporosis Type 2	<i>SLC9A3R1</i>	↓ or N	↓	N	↓	↑	N or ↓	↑	↑
Dent Disease 1	<i>CLCN5</i>	↓ or N	↓	N	↓	↑	N or ↓	↑	↑
Dent Disease 2 or Lowe syndrome	<i>OCRL1</i>	↓ or N	↓	N	↓	↑	N or ↓	↑	↑

ALP: alkaline phosphatase, PTH: Parathyroid hormone, N: normal, *FGF23*: Fibroblast growth factor 23, *PHEX*: Phosphate regulating endopeptidase homolog x-linked, *DMP1*: Dentin matrix acidic phosphoprotein, *ENPP1*: Ectonucleotide pyrophosphatase/phosphodiesterase 1, *INPPL1*: Inositol polyphosphate phosphatase-like 1, *FGFR1*: Fibroblast growth factor receptor 1, *FAM20C*: Family with sequence similarity 20, member c, *CLCN5*: Chloride voltage-gated channel 5, 1,25(OH)2D: 1,25-dihydroxyvitamin D, *GFR*: Growth factor receptor

extracellular matrix protein expressed in osteoblasts and osteocytes and acts in the inhibition of FGF23 expression (62,68). Inactivating mutations of *DMP1* result in an increase in serum FGF23 levels and thus leads to HR. Clinical, laboratory and radiological findings are similar to those of XLHR and ADHR. There are 9 different mutations listed in the HGMD (accessed Nov 13, 2017). *DMP1* knockout mice have displayed increased serum levels of FGF23, hypophosphatemia, skeletal and dental anomalies and osteomalacia (79). Unlike other HR types, osteosclerosis in the base of skull and calvarial

bones may occur (62). Haploinsufficiency has been reported in heterozygous carriers: mild hypophosphatemia, low TRP and focal osteomalacia, without typical skeletal deformities of rickets (80).

2.1.3.2. Autosomal Recessive Hypophosphatemic Rickets Type 2

ARHR type 2 (ARHR2, MIM 613312) is caused by inactivating homozygous mutations in *ENPP1* (ectonucleotide pyrophosphatase/phosphodiesterase 1, MIM 173335) (81).

Interestingly, the majority of *ENPP1* mutations (49 mutations) have been reported in patients with idiopathic infantile arterial calcification or generalized arterial calcification of infancy, which is an autosomal recessive disorder and characterized by calcification of the internal elastic lamina of muscular arteries and stenosis due to myointimal proliferation (82). There are only eight mutations reported in patients with HR (HGMD, accessed Nov 13, 2017), suggesting a different pathway is involved in the generation of ARHR2 (83).

By generating inorganic pyrophosphate (PPi), ENPP1 plays an important role in the regulation of pyrophosphate levels, bone mineralization and soft tissue calcification. The mineral accumulation in the bones is determined by the ratio of phosphate and PPi that is balanced by ENPP1 (84). Enpp1 knockout mice show altered bone development and an increase in FGF23 expression (84). *ENPP1* mutations increase serum levels of FGF23. However, the mechanism of FGF23 elevation caused by ENPP1 mutation is not completely understood (82,83,84).

2.1.4. Hypophosphatemic Rickets with Hyperparathyroidism

HR with hyperparathyroidism (MIM 612089) is a very rare disease caused by a balanced translocation with breakpoints at 9q21.13 and 13q13.1, which is adjacent to the *KL* gene (85). Its product, alpha-Klotho, is implicated in aging and regulation of FGF signaling and calcium homeostasis (86). The translocation result in increased serum α -klotho, FGF23 levels and β -glucuronidase activity (85). The disease is characterized by hypophosphatemia and elevated serum PTH levels, with inappropriate renal phosphate wasting (85). Increased levels of FGF23 lead to decreased TRP, hypophosphatemia and rickets. Hyperparathyroidism due to diffuse parathyroid hyperplasia results in increased levels of PTH. It is not clear whether increased levels of α -klotho cause parathyroid hyperplasia. PTH levels in this disease are much higher compared to other causes of HR and are comparable with those in VDDR. Klotho knockout mice, deficient for α -klotho, display a phenotype comparable with human ageing and are characterized by a mild hypercalcemia, hyperphosphatemia, increased levels of serum 1,25(OH)2D, decreased PTH and bone abnormalities such as increased metaphyseal trabecular bone mass and soft tissue calcifications, which are different from the phenotype caused by the translocation [hypophosphatemia, high PTH, and normal 1,25(OH)2D7] (87,88). Treatment includes calcitriol with oral phosphate supplementation.

2.1.5. Other Genetic Causes

2.1.5.1. Osteoglophonic Dysplasia

Osteoglophonic dysplasia (MIM 166250) is caused by heterozygous gain-of-function mutations in *FGFR1*

(MIM 136350), a rare autosomal dominant disorder characterized by craniosynostosis, rhizomelic short stature, maxillary hypoplasia, depressed nasal bridge, mandibular pragmatism, dental anomalies, tower-shaped skull, vertebral anomalies and bone mineralization defects (metaphyseal radiolucent changes) (89). High levels of serum FGF23, low levels of serum phosphate and 1, 25(OH)2D, and low TRP are present in some patients (89). Increased FGF23 leads to renal phosphate wasting, hypophosphatemia and deterioration of bone mineralization. It has been suggested that FGF23 production is stimulated from bone tissue due to the effect of activating mutations in *FGFR1* (5). Among 197 mutations in *FGFR1*, only three are reported in patients with osteoglophonic dysplasia (HGMD, accessed Nov 13, 2017).

2.1.5.2. McCune-Albright Syndrome

McCune-Albright Syndrome (MAS, MIM 174800) is caused by post-zygotic activating mutations in the G α subunit of G proteins (encoded by *GNAS*, MIM 139320), leading to a mosaic distribution of cells bearing constitutively active adenylyl cyclase activity. The disease is characterized by the classic triad of polyostotic fibrous dysplasia, cafe-au-lait skin pigmentation and peripheral precocious puberty, but is clinically heterogeneous and usually include hyperfunctional endocrinopathies such as thyrotoxicosis, pituitary gigantism and Cushing syndrome due to autonomous hormonal hyper-production (90). There is an association between fibrous dysplasia of bone tissue and increase in serum FGF23 level. TRP is decreased in 50% of cases (91). Therefore, hypophosphatemic rickets/osteomalacia can be seen in these patients. More than 250 mutations are listed in the HGMD (accessed Nov 13, 2017) and most of them (221 inactivating mutations) are found in patients with resistance to PTH (pseudohypoparathyroidism or Albright hereditary osteodystrophy, which is different from the disease). In all patients reported to date, there are only two activating mutations (p.R201H or p.R201C and p.T55A) listed in the HGMD (accessed Nov 13, 2017) that is associated with McCune-Albright Syndrome.

2.1.5.3. Raine Syndrome

Raine syndrome (MIM 259775) is an autosomal recessive disorder first described in 1989 by Raine et al (92) in a case with generalized osteosclerosis of the periosteal bone formation and severe craniofacial dysmorphology. The disease is caused by mutations in the *FAM20C* (family with sequence similarity 20, member c, also called dentin matrix protein 4 DMP4; MIM 611061) and was initially reported to be lethal (93). Non-lethal cases have since been found (94). *FAM20C* is mainly expressed in osteoblasts, odontoblasts and ameloblasts in skeletal and dental tissues and is a

novel FGF23 regulator (95,96). Increased renal phosphate loss and hypophosphatemia due to increased serum FGF23 levels have been reported in Raine's syndrome (97,98,99). HR has been observed in *FAM20C* knockout mice (96). *FAM20C* can suppress FGF23 production by enhancing DMP1 expression and its inactivation causes FGF23-related hypophosphatemia by decreasing transcription of DMP1, resulting in increased FGF23 levels in patients with Raine's syndrome (98). There are 22 mutations listed in the HGMD (accessed Nov 13, 2017).

2.1.5.4. Opsismodysplasia

Opsismodysplasia (OPSM, MIM 258480) is a rare skeletal dysplasia involving delayed bone maturation first described by Zonana et al (100) in 1977 and later defined by Maroteaux et al (101) in 1982. It is an autosomal recessive disease and caused by mutations in the *INPPL1* gene (inositol polyphosphate phosphatase-like 1, MIM 600829) (102). Clinical signs observed at birth include short limbs, small hands and feet, relative macrocephaly with a large anterior fontanelle and characteristic craniofacial abnormalities such as a prominent brow, depressed nasal bridge, a small anteverted nose and relatively long philtrum. Abdominal protrusion, abnormalities of the extremities, progressive bone demineralization, delayed bone maturation and hypotonia are commonly reported (103). The main radiological features are severe platyspondyly, short long bones including squared metacarpals, delayed epiphyseal ossification, and metaphyseal flaring and cupping (103). In addition to these clinical and radiological findings, increased renal phosphate excretion and HR have been reported by Zeger et al (104). The serum level of FGF23 was high in one of the two patients at three years of age. Currently, there are 26 mutations listed in the HGMD (accessed Nov 13, 2017).

2.1.6. Treatment of FGF23-related Hypophosphatemic Rickets

There is no difference in the management of XLHR, ADHR, ARHR and other rare genetic causes of HR. It is a lifelong treatment of phosphate and calcitriol replacement to restore bone mineralization and improve skeletal deformities. Calcitriol is recommended at doses ranging from 25 to 70 ng/kg/day (2 doses) and elemental phosphate at 30 to 70 mg/kg/day (4-6 doses) (26). The main goal of treatment is to achieve low-normal serum phosphate and high-normal serum ALP levels (105). Treatment should not attempt to normalize serum phosphate levels by giving aggressive phosphate therapy as this might lead to side effects such as diarrhea, secondary hyperparathyroidism, increased FGF23 synthesis, nephrocalcinosis and renal insufficiency (105). In addition, serum phosphate levels should not be

used alone in evaluating response to treatment, due to rapid fluctuations in serum levels. Therefore, reduction in ALP levels, improvement in clinical findings and growth velocity after treatment are more useful indicators in assessing treatment response. Traditional calcitriol and phosphate therapy improves bone mineralization, skeletal findings of rickets and growth rate. However, despite these treatments, skeletal deformities may persist to varying degrees in some patients (105).

Phosphate salts (sodium phosphate, potassium phosphate) are generally used for phosphate replacement. It can be given in tablet or solution form both of which are equally effective. Tablet form (Phosphate-Sandoz®) contains a high dose of phosphate supplement, consisting of sodium phosphate monobasic. Each tablet provides elemental phosphate 500 mg (16.1 mmol phosphate), sodium 469 mg (20.4 mmol Na⁺), potassium 123 mg (3.1 mmol K⁺) and citric acid-anhydrous 800 mg. "Joulie's solution" can be used for children if the tablet form is not available. Prepared with 136 g of dibasic sodium phosphate, 58.8 g phosphoric acid and 1000 mL of distilled water, 1 mL of this solution contains 30.4 mg of elemental phosphate (106). More frequent dividing of phosphate dose avoids a profound drop in post-dose serum phosphate levels and reduces the frequency of diarrhea, the most common side effect of this treatment.

Patients should be monitored for clinical, anthropometric and laboratory characteristics at three month intervals. Laboratory assessments include serum calcium, phosphate, ALP and PTH levels, as well as urinary calcium and creatinine for hypercalciuria. In addition, renal ultrasonography should be performed annually, before and after treatment, to monitor the development of nephrocalcinosis (105). Skeletal X-ray is recommended to be performed annually before treatment and during treatment for monitoring of skeletal findings (5).

The dosage of calcitriol should be adjusted according to serum levels of PTH and the urine calcium/creatinine ratio. The main goal is to suppress PTH, maintain serum calcium in the normal range and prevent hypercalciuria. Twenty-four hours of urinary calcium excretion above 4 mg/kg/day indicates increased calcium excretion (hypercalciuria) (26). In addition, the ratio of calcium to creatinine in the spot urine can be used. The normal range varies with age: ≤6 months of age, <0.8; 7-12 months of age, <0.6; 1-3 years of age, <0.53; 3-5 years of age, <0.39; 5-7 years of age, <0.28; >7 years of age, <0.21 (28). In the presence of hypercalciuria, it is necessary to reduce calcitriol dosage. The evening dosage of calcitriol should be higher in order to suppress increased secretion of PTH at night (26).

There is a close relationship between high dose phosphate therapy and the development of nephrocalcinosis (107,108). The frequency of nephrocalcinosis in HR patients after calcitriol and phosphate combined therapy is between 33 % and 80 %, and usually occurs within the first 3-4 years of treatment (105,107,108,109). However, long-term follow-up of cases with nephrocalcinosis has been reported to have no significant impairment on renal function (110). On the other hand, long-term, high-dose phosphate therapy may result in secondary and tertiary hyperparathyroidism (105,111,112,113). Cinacalcet can be used in the treatment of tertiary hyperparathyroidism in children with HR (111). In brief, oral phosphate should be given at the lowest dose that is sufficient to improve rickets and patients should be monitored for the development of hyperparathyroidism and nephrocalcinosis.

Conventional treatment should gradually improve biochemical and skeletal abnormalities, however mild or moderate skeletal deformities may persist in some patients. For these patients, some devices, such as braces, are suggested to correct leg bowing. If such devices are not tolerated, surgical correction can be considered. In children younger than 10 years with XLHR, femoral and tibial hemiepiphyseodesis are recommended to correct lower extremity deformities, which is a relatively minor surgical procedure to allow appropriate growth (114). For children older than 10 years of age, osteotomy is suggested, a surgical procedure in which a surgeon removes a wedge of bone near a damaged joint (26).

Short stature is one of the major findings in the diagnosis of HR patients. With appropriate calcitriol and phosphate treatment, the skeletal and biochemical findings should improve and an increase in height velocity should be achieved. However, some patients with XLHR do not achieve the desired height velocity despite appropriate treatment (115,108). It is suggested that this may be related to delayed treatment or deficit in GH secretion (115,116). Recombinant human growth hormone (rhGH) treatment, especially in the pre-pubertal period, has been demonstrated to significantly increase height velocity and positively contributes to final height in these patients (117,118,119).

Recent progress in treatment has focused on the pathogenesis of HR. It has been shown that pharmacological inhibition of FGF receptor signaling ameliorates FGF23-mediated HR using NVP-BGJ398, a novel, selective, FGFR inhibitor that inhibits FGFR1, FGFR2, and FGFR3 with IC50 of 0.9 nM, 1.4 nM, and 1 nM, respectively (120). Similar results have been achieved using anti-FGF23 antibody (KRN23), a human monoclonal KRN23 (121). In a study of 28 adults with XLHR who received monthly KRN23, a significant increase in

serum phosphate, 1,25(OH)2D and maximum renal tubular threshold for phosphate reabsorption (TmP/GFR) has been observed after four or twelve months of treatment (121). The half-life is 8-12 days after intravenous administration and longer (13-19 days) after subcutaneous administration. The serum levels of phosphate remained higher than baseline level for four weeks (122,123). Therefore, it is recommended that KRN23 should be given at four weekly intervals. Finally, phase III studies of KRN23 in adults and children are still ongoing.

2.2. Hypophosphatemic Rickets Accompanied by Hypercalciuria (FGF23-independent Rickets)

2.2.1. Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary HR with hypercalciuria (HHRH, MIM 241530) is an autosomal recessive disease caused by inactivating mutations in the *SLC34A3* (solute carrier family 34, member 3, also known as NaPi-2c, MIM 609826) (124). *SLC34A3* plays a role in phosphate reabsorption in the kidney and its mutation results in increased renal phosphate loss and subsequent hypophosphatemia (5). FGF23 is not involved in the disease. The decrease in serum phosphate promotes biosynthesis of 1,25(OH)2D, which leads to increase in the absorption of intestinal calcium, suppressed PTH and development of hypercalciuria and nephrocalcinosis. Diagnosis can be made based on skeletal findings of rickets, hypophosphatemia, hypercalciuria and nephrolithiasis (124,125). There are 33 mutations listed in HGMD (accessed Nov 13, 2017) and genotype-phenotype correlation has not yet been established (125,126,127). Increased renal phosphate wasting, mild hypophosphatemia, increased 1,25(OH)2D and hypercalciuria without metabolic bone disease, can be present in patients with heterozygous *SLC34A3* mutations, indicating haploinsufficiency (124).

Oral phosphate alone is sufficient for patients with HHRH in contrast to patients with XLHR, ADHR or ARHP, who are usually treated with high doses of alphacalcidol or calcitriol and multiple daily doses of oral phosphate, low-sodium diet and hydration are recommended for the disease (5,26). The response to treatment is excellent. Phosphate treatment results in a decrease in serum levels of calcitriol and, consequently, urinary calcium excretion gradually returns to normal. The use of calcitriol is contradictory and harmful because it can increase hypercalciuria.

2.2.2. Hypophosphatemic Rickets with Nephrolithiasis and Osteoporosis Type 1

SLC34A1 (solute carrier family 34, member 1, MIM 182309) encodes NaPi-2a, which plays an important role in phosphate

reabsorption from proximal tubules and is down-regulated by PTH and FGF23 (128). Inactivating mutations in *SLC34A1* can cause three different diseases: HRs with Nephrolithiasis and Osteoporosis type 1 (NPHLOP1, MIM 612286) (129,130), Fanconi Renotubular Syndrome type 2 (FRTS2, MIM 613388) (131) and Infantile Hypercalcemia type 2 (HCINF2; MIM 616963) (132). NPHLOP1 was originally reported as an autosomal-dominant disease. However, multiple groups later questioned a single heterozygous mutation in the pathogenesis of the disease (131,133,134). The initial cases caused by heterozygous *SLC34A1* mutations are probably represent a milder phenotype characterized by increased renal phosphate wasting, hypercalciuria, osteoporosis and nephrolithiasis in adults. Currently, there are 25 different mutations listed in the HGMD (accessed Nov 13, 2017).

Similar to HHRH, NPHLOP1 is characterized by hypophosphatemia and decreased renal phosphate absorption with an appropriate elevation in serum 1,25(OH)2D. Laboratory findings include decreased TRP, hypophosphatemia, hypercalcemia, elevated serum 1,25(OH)2D, decreased serum PTH, hypercalciuria and nephrocalcinosis.

The original patients with FRTS2 were adults with clinical features of increased renal phosphate and other substance wasting (without loss of bicarbonate) and significantly increased 1,25(OH)2D leading to severe skeletal deformities (HR in children and osteomalacia in adults), bone pain, marked hypercalciuria, glycosuria, generalized aminoaciduria and tubular proteinuria without renal tubular acidosis (135).

HCINF2 is characterized by severe hypercalcemia with failure to thrive, vomiting, dehydration and medullary nephrocalcinosis. Laboratory findings include decreased TRP, hypophosphatemia, hypercalcemia, elevated 1,25(OH)2D, suppressed PTH, hypercalciuria, nephrocalcinosis, hyperuricosuria and low-molecular-weight proteinuria (136).

The main pathogenesis of all three diseases is increased phosphate wasting due to inactivated phosphate cotransporter NaPi-2a in the proximal tubules. They should be considered as one disease with different clinical presentations, probably caused by differences in severity of mutations. The mechanism for renal tubulopathy is unclear at present.

Treatment is the same as in HHRH. Oral phosphate replacement will result in improvement in bone pain, muscle strength and radiologic signs of rickets, with normalization of urinary calcium excretion and significant decrease in 1,25(OH)2D. However, the glomerular filtration rate, serum uric acid levels and rate of urinary excretion of glucose, protein and amino acids will remain unchanged.

2.2.3. Hypophosphatemic Rickets with Nephrolithiasis and Osteoporosis Type 2

HRs with Nephrolithiasis and Osteoporosis type 2 (Nephrolithiasis/osteoporosis, hypophosphatemic, 2, NPHLOP2, MIM 612287) is an autosomal dominant disease caused by mutations in the *SLC9A3R1* (MIM 604990). It encodes NHERF1, an adaptor protein that regulates several G protein-coupled receptors, including the PTH1R (58,137). It regulates phosphate reabsorption in the renal proximal tubules by binding to renal phosphate transporter NaPi-2a to maintain correct expression at the apical domain of proximal tubular cells and PTH1R leading to a decrease in PTH-induced cAMP synthesis and phosphate transport (128,138). Mutations in the *NHERF1* result in reduced NaPi-2a expression and hypophosphatemia due to increased renal phosphate loss. Characteristic clinical features include hypophosphatemia, hypercalcemia, elevated serum levels of 1,25(OH)2D, hypercalciuria, decreased TRP or low TmP/GFR value and nephrolithiasis, which cannot be distinguished from HHRH or NPHLOP1 without molecular testing. Serum levels of PTH and FGF23 are normal. Osteopenia has been demonstrated in patients with *NHERF1* mutations, although rickets has not yet been reported, probably reflecting late-onset and milder phenotype caused by the gene mutation. There are only four different mutations listed in the HGMD (accessed Nov 13, 2017).

2.2.4. Dent Disease

Dent disease can be divided into type 1 and type 2. Dent disease 1 (MIM 300009, also known as X-linked nephrolithiasis, X-linked nephrolithiasis type 2 (NPHL2), X-linked recessive nephrolithiasis with renal failure, or X-linked recessive nephrolithiasis type 1 (NPHL1), MIM 310468) is an X-linked recessive disease caused by mutations in the *CLCN5* gene which encodes chloride voltage-gated channel 5 (MIM300008) (139). It is characterized by proximal tubular dysfunction and 30-80% of patients can progress to chronic kidney disease or renal failure: low molecular weight proteinuria, hypercalciuria, glycosuria, phosphaturia, aminoaciduria, uricosuria, hematuria and nephrocalcinosis (140,141,142). More than 259 different *CLCN5* mutations are listed in the HGMD (accessed Nov 13, 2017). The presence of hypophosphatemic rickets in Dent disease is variable from 30-50% in patients from US and UK, to rare in Japanese patients (142,143,144). Clinical presentations and *CLCN5* mutations are heterogeneous and there is no genotype-phenotype correlation.

Dent disease 2 (MIM 300555, or Lowe syndrome or oculocerebrorenal syndrome, MIM 309000) is also an X-linked recessive disease caused by mutations in the *OCRL*

gene (MIM 300535) which encodes inositol polyphosphate-5-phosphatase (145). Clinical features are similar to Dent disease 1 and genetic testing is required to distinguish between them. There is a broad phenotypic spectrum of *OCRL* mutations and Dent disease 2 may be a mild variant of Lowe syndrome characterized by hydrophthalmia, cataract, mental retardation, HR, amino aciduria, proteinuria and phosphaturia (146).

There are 245 different *OCRL* mutations listed in the HGMD (accessed Nov 13, 2017). Approximately 50-60% of cases with Dent disease have *CLCN5* mutations, 15-20% have *OCRL* mutations and the remaining cases have no detectable mutation (140,146). Patients usually respond well to oral phosphate for the treatment of hypophosphatemia. In addition, some patients may need calcitriol, but it should be carefully used as it may increase urinary calcium excretion. A sodium-restricted diet to reduce urinary calcium excretion may be useful.

Conclusion

Calcium and phosphate, which play important roles in bone mineralization, are regulated by various molecules such as PTH, 1,25(OH)₂D and FGF23. Nutritional vitamin D deficiency is the most common cause of rickets due to low vitamin D in breast milk, social and economic conditions that prevent access to vitamin D from other sources, or climatic conditions preventing adequate ultraviolet light exposure. Various genetic causes of rickets should be considered to avoid delay in diagnosis and treatment. Rickets caused by calcium deficiency should also be considered, which usually occurs among older toddlers and children due to low dietary calcium intake. Although clinical presentations are usually similar, differential diagnosis of different types of rickets such as nutritional and VDDR (VDDR1A, VDDR1B, VDDR2A and VDDR2B) can be made by examining serum levels of 25(OH)₂D and 1,25(OH)₂D, and their responses to treatment (calcium, vitamin D or calcitriol) (Table 1).

The genetic causes of HR can be divided into two groups: FGF23-dependent and FGF23-independent groups (Table 2). The most common genetic cause of HR is *XLDHR* resulting from *PHEX* mutations. Although clinical presentations are similar, differential diagnosis between these two groups can be made by serum FGF23 levels. However, diagnosis of individual diseases within each group often require molecular testing to confirm diagnosis. The current treatment for FGF23-dependant HR is oral phosphate replacement and calcitriol which have potential treatment complications such as calciuria and nephrocalcinosis. Recent progress of targeted therapy against FGF23-mediated HR (NVP-BGJ398

and KRN23) has produced promising results and may offer better therapeutic outcome in the future. In the FGF23-independent HR group, hypercalciuria and nephrolithiasis are major clinical findings and oral phosphate replacement alone is sufficient in the treatment. Furthermore, there are some HR patients whose genetic defects remain to be identified.

Ethics

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Authorship Contributions

Concept: Sezer Acar, Korcan Demir, Yufei Shi, Design: Sezer Acar, Korcan Demir, Yufei Shi, Data Collection or Processing: Sezer Acar, Korcan Demir, Yufei Shi, Analysis or Interpretation: Sezer Acar, Korcan Demir, Yufei Shi, Literature Search: Sezer Acar, Korcan Demir, Yufei Shi, Writing: Sezer Acar, Korcan Demir, Yufei Shi.

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