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PERSPECTIVE

Pathogenesis and diagnostic criteria for rickets and osteomalacia—proposal by an expert panel supported by the Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral Research, and the Japan Endocrine Society

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Abstract Rickets and osteomalacia are diseases characterized by impaired mineralization of bone matrix. Recent investigations have revealed that the causes of rickets and osteomalacia are quite variable. Although these diseases can severely impair the quality of life of affected patients, rickets and osteomalacia can be completely cured or at least respond to treatment when properly diagnosed and treated according to the specific causes. On the other hand, there are no standard criteria to diagnose rickets or osteomalacia nationally and internationally. Therefore, we summarize the definition and pathogenesis of rickets and osteomalacia, and propose diagnostic criteria and a flowchart for the differential diagnosis of various causes of these diseases. We hope that these criteria and the flowchart are clinically useful for the proper diagnosis and management of these diseases.

Keywords Vitamin D · Hypophosphatemia · Hyopcalcemia · Fibroblast growth factor 23

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Introduction

Rickets and osteomalacia are diseases characterized by impaired mineralization of bone matrix [1, 2]. Although rickets and osteomalacia have the same causes, rickets develops before the closure of the growth plates. These diseases have been classified as metabolic bone diseases, and endocrinologists have not considered them as endocrine diseases. Historically, nutritional vitamin D deficient rickets and osteomalacia were clinically very important [3]. Studies of these vitamin D deficient diseases led to the identification of 25-hydroxyvitamin D [25(OH)D] and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Since then, many causes of rickets and osteomalacia have been identified. Especially, recent studies have established that fibroblast growth factor 23 (FGF23) is a phosphotropic hormone produced by bone and that excessive actions of FGF23 cause several kinds of hypophosphatemic rickets and osteomalacia [4]. These results have led to at least some kinds of hypophosphatemic rickets and osteomalacia now being considered to be endocrine diseases. Furthermore, it has been proposed that FGF23 measurement is useful for the differential diagnosis of hypophosphatemic diseases [5]. Therefore, it may be possible to newly classify causes of rickets and osteomalacia on the basis of the pathophysiology with use of these new findings.

There are no standard criteria to diagnose rickets or osteomalacia nationally and internationally. Since rickets

and osteomalacia are not common lifestyle diseases, it may be difficult for general health professionals to properly diagnose and manage these diseases. As impaired mineralization results in low bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry, osteomalacia must be discriminated from osteoporosis, a much commoner disease. Bone deformities observed in patients with rickets may lead to a wrong diagnosis, such as skeletal dysplasia. On the other hand, rickets and osteomalacia can severely impair the quality of life of affected patients without proper diagnosis and management. From this background, it is clinically important to establish diagnostic criteria for rickets and osteomalacia that can be easily used by health professionals. In this review, we briefly summarize the definition and pathogenesis of rickets and osteomalacia, and propose diagnostic criteria and investigation methods for the differential diagnosis of various causes of these diseases.

Definition and clinical presentations

Bone is a hard tissue created by deposition of hydroxyapatite crystals [$Ca_{10}(PO_4)_6(OH)_2$] on matrix proteins produced by osteoblasts. Because of the impairment of this mineralization of matrix proteins, the amount of unmineralized bone matrix (osteoid) increases in rickets and osteomalacia [1, 2]. Rickets develops in children, and osteomalacia is a disease in adulthood. Patients with rickets present with several symptoms and signs, including growth retardation, bone deformities such as genu valgum, genu varum, spinal curvature, craniotabes, open fontanels, rachitic rosary, and joint swelling [1, 2]. Patients with osteomalacia may have bone pain, muscle weakness, pigeon chest, spinal curvature, and pseudofractures (Looser's zone) [1, 2].

Pathogenesis and causes

Several drugs such as aluminum and etidronate directly inhibit mineralization of bone matrix proteins. In most other cases of patients with rickets or osteomalacia, chronic hypophosphatemia, chronic hypocalcemia, or both are present (Table 1). Hydroxyapatite crystals are formed in matrix vesicles produced by osteoblasts from calcium ion and phosphate. Hypophosphatemia or hypocalcemia is believed to impair mineralization by decreasing the calcium and phosphate product.

Serum phosphate level is maintained by intestinal phosphate absorption, renal phosphate handling, and phosphate movement between extracellular fluid and bone or intracellular fluid. Chronic hypophosphatemia resulting in rickets and osteomalacia is usually caused by impaired intestinal phosphate absorption and/or renal phosphate wasting. Phosphate is abundant in food, and phosphate deficiency does not occur in healthy people eating usual food. Phosphate deficiency may be observed in some patients with malnutrition or malabsorption syndrome.

Table 1 Causes of rickets and osteomalacia

Hypophosphatemia
Impaired actions of vitamin D metabolites
Vitamin D deficiency
Drugs (diphenylhydantoin, rifampicin, etc.)
Vitamin D-dependent rickets type 1[a]
Vitamin D-dependent rickets type 2[b]
Renal tubular dysfunction
Hereditary hypophosphatemic rickets with hypercalciuria[c]
Fanconi syndrome
Dent disease[d]
Renal tubular acidosis
Drugs (ifosfamide, adefovir dipivoxil, valproic acid, etc.)
FGF23-related hypophosphatemic rickets/osteomalacia (see Table 2)
Phosphate depletion
Phosphate deficiency
Malabsorption
Hypocalcemia
Some cases of vitamin D deficiency
Vitamin D-dependent rickets type 1[a]
Vitamin D-dependent rickets type 2[b]
Impaired mineralization from other causes
Drugs (aluminum, etidronate, etc.)

FGF23 fibroblast growth factor 23

[a] Mutations in the *CYP27B1* gene, autosomal recessive

[b] Mutations in the *VDR* gene, autosomal recessive

[c] Mutations in the *SLC34A3* gene, autosomal recessive

[d] Mutations in the *CLCN5* gene, X-linked recessive

$1,25(OH)_2D$ enhances intestinal phosphate and calcium absorption, and impaired actions of vitamin D metabolites can result in hypophosphatemia and/or hypocalcemia. Drugs such as diphenylhydantoin and rifampicin may cause impaired actions of vitamin D metabolites by altering vitamin D metabolism. Vitamin D-dependent rickets type 1 is caused by mutations in *CYP27B1*, encoding 25-hydroxyvitamin D-1α-hydroxylase [6]. This enzyme converts 25(OH)D into $1,25(OH)_2D$. *VDR*, which encodes vitamin D receptor, is mutated in patients with vitamin D-dependent rickets type 2 [7]. In patients with these vitamin D-dependent rickets, both hypophosphatemia and hypocalcemia are observed. Because hypocalcemia causes secondary hyperparathyroidism resulting in reduced renal tubular phosphate reabsorption, both impaired intestinal phosphate absorption and increased renal phosphate excretion contribute to

Table 2 FGF23-related hypophosphatemic rickets and osteomalacia

X-linked dominant hypophosphatemic rickets/osteomalacia (XLH): mutations in the *PHEX* gene
Autosomal dominant hypophosphatemic rickets/osteomalacia (ADHR): mutations in *FGF23* gene
Autosomal recessive hypophosphatemic rickets/osteomalacia 1 (ARHR1): mutations in the *DMP1* gene
Autosomal recessive hypophosphatemic rickets/osteomalacia 2 (ARHR2): mutations in the *ENPP1* gene
Hypophosphatemic disease with dental anomalies and ectopic calcification: mutations in the *FAM20C* gene
McCune–Albright syndrome/fibrous dysplasia
Linear sebaceous nevus syndrome
Tumor-induced rickets/osteomalacia
Hypophosphatemic rickets/osteomalacia caused by saccharated ferric oxide or iron polymaltose

DMP1 dentin matrix acidic phosphoprotein 1, *ENPP1* ectonucleotide pyrophosphatase/phosphodiesterase 1, *FAM20C* family with sequence similarity 20, member C, *FGF23* fibroblast growth factor 23, *PHEX* phosphate-regulating endopeptidase homolog, X-linked

the development of hypophosphatemia in these patients. Vitamin D deficiency is diagnosed by low serum 25(OH)D levels. Some patients with vitamin D deficiency also present with secondary hyperparathyroidism. Because parathyroid hormone stimulates conversion of 25(OH)D to $1,25(OH)_2D$, patients with vitamin D deficiency can present with various levels of $1,25(OH)_2D$. Therefore, vitamin D deficiency cannot be diagnosed by $1,25(OH)_2D$ levels.

Gastrectomy or enterectomy can cause osteomalacia [8]. It is possible that after these surgical procedures, osteomalacia is not properly diagnosed and treated in patients. The causes of osteomalacia in these patients may be multifactorial, including vitamin D deficiency and impaired mineral absorption. Although liver cirrhosis or chronic liver disease was described as one of the causes of osteomalacia, osteoporosis seems to be much commoner than osteomalacia in these patients [9].

There are many causes of renal phosphate wasting. About 80–90 % of phosphate filtered from glomeruli is absorbed in renal proximal tubules. Type 2a and 2c sodium–phosphate cotransporters mediate physiological phosphate reabsorption in proximal tubules [10]. Renal phosphate wasting can be observed in patients with Fanconi syndrome and some form of renal tubular acidosis. In addition, hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in *SLC34A3*, which encodes type 2c sodium–phosphate cotransporter [11, 12]. Dent disease is characterized by low molecular weight proteinuria, hypophosphatemia, and nephrolithiasis. This disease is caused by mutations in *CLC5*, which encodes a chloride channel [13]. In addition to these intrinsic renal tubular defect, excessive actions of FGF23 cause hypophosphatemia with enhanced renal phosphate excretion. FGF23 suppresses renal tubular phosphate reabsorption by reducing the expression of type 2a and 2c sodium–phosphate cotransporters [14]. In addition, FGF23 decreases serum $1,25(OH)_2D$ levels by altering the expression levels of vitamin D-metabolizing enzymes [14]. Therefore, FGF23 reduces serum phosphate level by suppressing renal phosphate reabsorption and inhibiting intestinal phosphate absorption through lowering $1,25(OH)_2D$ levels.

After the identification of FGF23, it became clear that patients with some kinds of hypophosphatemic rickets and osteomalacia, such as X-linked hypophosphatemic rickets (XLH) and tumor-induced osteomalacia (TIO), a rare paraneoplastic syndrome, show high circulatory levels of FGF23 [15, 16]. In contrast, FGF23 levels in patients with rickets or osteomalacia from other causes, including vitamin D deficiency, were rather low [5]. Together with the biological activities of FGF23 mentioned above, these results indicated that FGF23 is the humoral factor that causes hypophosphatemia in patients with several diseases, including XLH and TIO. Since then, other hypophosphatemic diseases have also been shown to be associated with high FGF23 levels [17] (Table 2). It is believed that FGF23 production in bone is enhanced in most patients with these FGF23-related hypophosphatemic diseases except for TIO. However, the precise mechanisms of overproduction of FGF23 and the actions of the gene products responsible for genetic FGF23-related hypophosphatemic diseases are largely unknown.

Diagnostic criteria

Because the clinical presentations of rickets and osteomalacia are quite different, it is not practical to prepare one kind of diagnostic criteria for both of these diseases. Therefore, we propose the following diagnostic criteria (Table 3). Rickets is basically diagnosed by the presence of rachitic changes of bones such as cupping and fraying of the metaphysis, and widening of the epiphyseal plate observed by X-ray. In addition, high alkaline phosphatase level is characteristic of diseases with impaired mineralization. We believe that these two laboratory findings are essential to make a diagnosis of rickets or suspect the presence of this

Table 3 Diagnostic criteria for rickets and osteomalacia

Rickets	Osteomalacia
(a) Rachitic changes by X-ray (cupping and fraying of the metaphysis, widening of the epiphyseal plate)	(a) Hypophosphatemia or hyocalcemia[a]
(b) High alkaline phosphatase level	(b) High bone alkaline phosphatase level
(c) Hypophosphatemia or hypocalcemia[a]	(c) Clinical symptoms: muscle weakness or bone pain
(d) Clinical signs: bone deformities such as genu varum and genu valgum, abnormal spinal curvature, craniotabes, open fontanels, rachitic rosary, joint swelling	(d) Low BMD: less than 80 % of YAM
Definite rickets: patients who have (a)–(d)	(e) Abnormal imaging findings: multiple uptake by bone scintigraphy or Looser's zone by X-ray
Possible rickets: patients who have (a), (b), and 1 of (c) or (d)	Definite osteomalacia: patients who have (a)–(e)
	Possible osteomalacia: patients who have (a), (b), and 2 of (c)–(e)

BMD bone mineral density, *YAM* young adult mean

[a] Does not apply to patients with inhibitors of mineralization

Table 4 Diseases that need to be discriminated form rickets and osteomalacia

Symptoms	Diseases
Low BMD	Osteoporosis, renal osteodystrophy, primary hyperparathyroidism
Bone deformity	Skeletal dysplasia
Bone pain	Polymyalgia rheumatica, ankylosing spondylitis
Muscle weakness	Neuromuscular diseases
Multiple uptake by bone scintigraph	Multiple metastases
Rachitic change	Hypophosphatasia
High bone alkaline phosphatase level	Primary hyperparathyroidism, renal osteodystrophy, multiple metastases

BMD bone mineral density

disease. In addition, patients with rickets usually show hypophosphatemia or hypocalcemia, and some clinical signs. However, it is possible that patients show no clinical signs especially when the diagnosis of rickets is established in the early phase of the disease. This can happen in family members of affected patients with rickets from genetic causes. Therefore, we propose that patients with all four of these findings (a–d for rickets in Table 3) are regarded as definitely having rickets, and patients who lack either hypophosphatemia or hypocalcemia, or clinical signs (c or d for rickets in Table 3) are regarding as possibly having rickets.

In contrast to rickets, there is no single laboratory test which strongly suggests the presence of osteomalacia. However, patients with osteomalacia usually show either hypophosphatemia or hypocalcemia. High alkaline phosphatase level is also seen in patients with osteomalacia. Although almost all alkaline phosphatase activity in blood derives from bone in children, there is a significant contribution from the liver and other organs in adults. We believe that either hypophosphatemia or hypocalcemia, and high bone alkaline phosphatase level are essential to diagnose osteomalacia or suspect this disease. In addition, patients with osteomalacia may show some clinical symptoms, low bone mineral density (BMD), multiple uptake by bone scintigraphy, or Looser's zone. However, patients may not show these findings when osteomalacia is suspected early in the course of the disease as in the case of rickets. Therefore, we propose that patients with all five of these findings (a–e for osteomalacia in Table 3) are regarded as definitely having osteomalacia, and patients who lack clinical symptoms, low BMD, or abnormal imaging findings (c–e for osteomalacia in Table 3) are regarding as possibly having osteomalacia.

Drugs that inhibit mineralization can induce rickets or osteomalacia without changing serum calcium or phosphate levels. In addition, several diseases need to be discriminated from rickets and osteomalacia (Table 4). The diseases listed in Table 4 can mimic some features of rickets or osteomalacia. On the other hand, most of these diseases cannot be diagnosed as rickets or osteomalacia with use of the diagnostic criteria given in Table 3. The exceptions are multiple metastases, primary hyperparathyroidism, and renal osteodystrophy. Osteoblastic bone metastases can cause either hypocalcemia or hypophosphatemia, high bone alkaline phosphatase level, bone

pain, and multiple uptake by bone scintigraphy. This possibility needs to be considered before the diagnosis of osteomalacia is finalized. Patients with primary hyperparathyroidism may also show hypophosphatemia, high bone alkaline phosphatase level, bone pain, low BMD, and multiple uptake by bone scintigraphy. However, hypercalcemia, which is rare in patients with osteomalacia, is usually present in patients with primary hyperparathyroidism. Patients with renal osteodystrophy may show hypocalcemia, high bone alkaline phosphatase level, bone pain, low BMD, and multiple uptake by bone scintigraphy. On the other hand, hyperphosphatemia rather than hypophosphatemia is usually observed in patients with renal osteodystrophy.

Hypophosphatasia is caused by mutations in *ALPL* (also known as *TNSALP* and *TNAP*), which encodes tissue-nonspecific alkaline phosphatase [18]. This disease is also characterized by impaired mineralization because alkaline phosphatase converts pyrophosphate, with potent inhibitory effects on mineralization, to phosphate. In this sense, hypophosphatasia can be regarded as one cause of rickets. However, patients with hypophosphatasia show low alkaline phosphatase levels, in contrast to those with rickets from other causes. Therefore, hypophosphatasia was treated as a disease that should be discriminated from rickets rather than a cause of rickets to avoid confusion in this proposal.

Differential diagnosis of causes of rickets and osteomalacia

After rickets or osteomalacia has been diagnosed, it is necessary to find the exact cause of these diseases. Table 5 summarizes typical biochemical changes observed in patients with rickets and osteomalacia from various causes. Vitamin D deficiency is defined by low 25(OH)D levels as mentioned before. Therefore, patients with low 25(OH)D levels are theoretically considered to have vitamin D deficient rickets or osteomalacia. However, vitamin D deficiency or insufficiency is quite common even in the general population [19], and it is possible that low 25(OH)D levels can be observed in patients with rickets or osteomalacia from other causes. Investigation of 25(OH)D levels in patients with vitamin D deficient rickets and XLH indicated that there was overlap of serum 25(OH)D levels in these patients. In contrast, FGF23 levels completely discriminated patients with vitamin D deficient rickets and XLH [20]. From these results, we propose a flowchart for differentiating various causes of rickets and osteomalacia (Fig. 1). In patients with hypophosphatemic rickets or osteomalacia, high FGF23 levels indicate FGF23-related hypophosphatemic diseases (Table 2). Vitamin D deficient rickets or osteomalacia is diagnosed after FGF23-related hypophosphatemic diseases, phosphate depletion, and other causes of renal tubular phosphate wasting have been ruled out. Vitamin D-dependent rickets type 1 and type 2 can be differentiated by $1,25(OH)_2D$ levels. Hereditary hypophosphatemic rickets with hypercalciuria is also characterized by high $1,25(OH)_2D$ levels. In normophosphatemic patients, use of drugs that inhibit mineralization and vitamin D deficiency should be considered. Patients with vitamin D deficiency may not show frank hypophosphatemia or hypocalcemia. It is possible that serum phosphate and calcium levels remain in the low normal range in these patients.

Discussion

Rickets and osteomalacia are not common diseases. However, quality of life of the affected patients can be severely compromised. For example, some untreated patients with TIO can become completely bedridden because of severe

Table 5 Typical biochemical findings in patients with rickets or osteomalacia from various causes

	Serum calcium	Serum phosphate	TmP/GFR	BAP	$1,25(OH)_2D$	25(OH)D	FGF23
FGF23-related hypophosphatemic disease	↓→	↓	↓	↑	↓→	→	⇧
Phosphate depletion	→	↓	↑	↑	→↑	→	↓→
Fanconi syndrome	→	↓	↓	↑	↓→	→	↓→
Vitamin D-dependent rickets type 1	↓	↓	↓	↑	↓	→	↓→
Vitamin D-dependent rickets type 2	↓	↓	↓	↑	↑	→	↓→
HHRH	→	↓	↓	↑	↑	→	↓→
Vitamin D deficiency	↓→	↓→	↓→	↑	→↑↓	⇩	↓→
Drugs that inhibit mineralization	→	→	→	↑	→	→	→

These thick down and up arrows indicate the specific laboratory tests for each category

BAP bone alkaline phosphatase, *25(OH)D* 25-hydroxyvitamin D, *1,25(OH)$_2$D* 1,25-dihydroxyvitamin D, *FGF23* fibroblast growth factor 23, *HHRH* hereditary hypophosphatemic rickets with hypercalciuria, *TmP/GFR* tubular maximum transport of phosphate per unit glomerular filtration rate

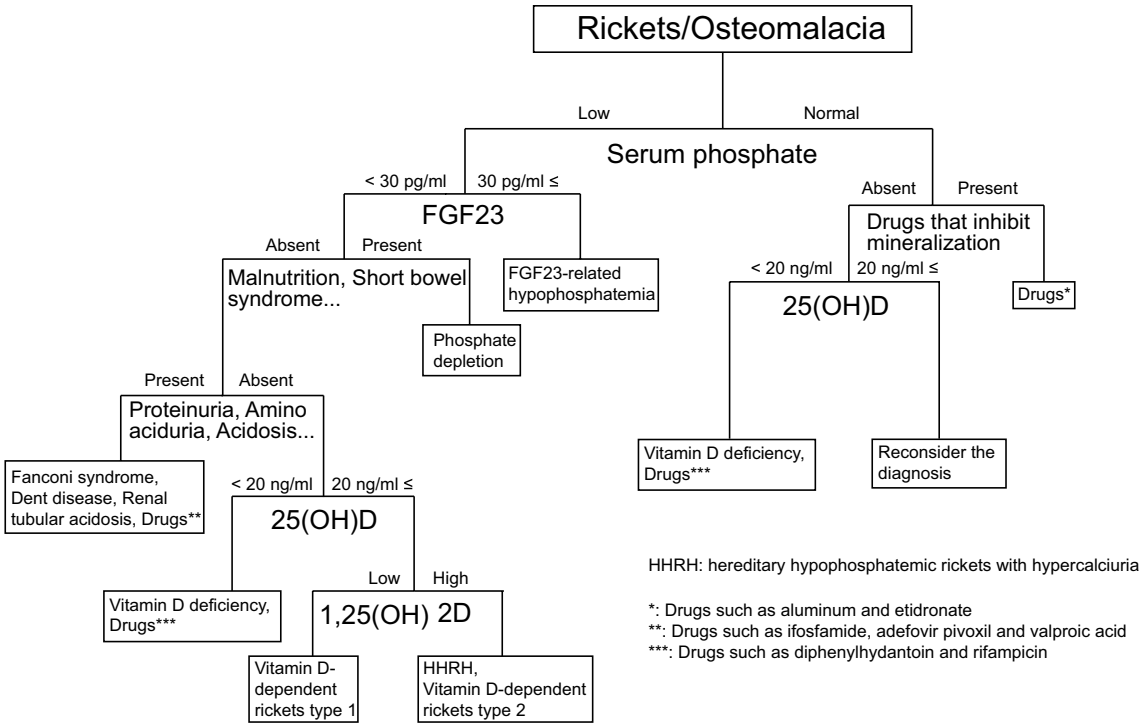

Fig. 1 Flowchart for the differential diagnosis of causes of rickets and osteomalacia. The causes of rickets and osteomalacia can be identified by several clinical findings and laboratory tests. *25(OH)D* 25-hydroxyvitamin D, *1,25(OH)$_2$D* 1,25-dihydroxyvitamin D, *FGF23* fibroblast growth factor 23

muscle weakness and bone pain. Short stature and bone deformities are big problems for patients with rickets. However, patients with rickets or osteomalacia can be completely cured or at least respond to treatment when rickets or osteomalacia is properly diagnosed and treated according to the specific causes. Therefore, we have listed causes of rickets and osteomalacia, and proposed diagnostic criteria and a flowchart for the differential diagnosis of various causes of these diseases.

There are several limitations to the proposed diagnostic criteria. These criteria were not created by retrospective review of clinical presentations of a large number of patients, but were proposed by several researchers and clinicians on the basis of their experiences. Therefore, the validity of these criteria and the flowchart needs to be examined in further studies. However, without any diagnostic criteria, it would be difficult for general medical professionals to correctly diagnose not-so-common illnesses. We hope that this proposal will become momentum for propagation of proper knowledge of rickets and osteomalacia, and for accumulation of more clinical data for revision of the criteria. In addition, there was a discussion about hypophosphatasia among us. This disease can be considered to be one cause of rickets. However, if hypophosphatasia is included in the causes of rickets, high alkaline phosphatase level cannot be used as one of the criteria for the diagnosis of rickets, and the flowchart for the differential diagnosis of various causes needs to be more complex. Because hypophosphatasia is rarer than other causes of rickets, such as vitamin D deficiency and XLH, and the easily usable diagnostic criteria for rickets and osteomalacia were planned, hypophosphatasia was not included as a cause of rickets in this proposal. Finally, measurements of FGF23 and 25(OH)D levels are not covered by medical insurance in Japan and are not included in routine laboratory tests. In contrast, these measurements are done by several commercial and research laboratories. We hope that this proposal will contribute to some extent to the future coverage of these measurements by medical insurance in Japan.

In summary, we have created diagnostic criteria and a flowchart for the differential diagnosis of various causes of rickets and osteomalacia. We hope that these criteria and the flowchart are clinically useful for the proper diagnosis and management of patients with rickets and osteomalacia.

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