Vitamin D Deficiency

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Introduction

Vitamin D, which is present in two forms called cholecalciferol (D_3) and ergocalciferol (D_2), is an essential micronutrient and in the bioactive form plays a key role in maintaining bone health [1]. Vitamin D_3 is predominantly derived from skin production by the direct action of ultraviolet light on skin. Alternative sources of D_3 and D_2 are oral intake from natural foodstuffs, fortified foodstuffs and supplements. Although the principal source is sunlight, oral intake has primacy over sunlight exposure in both the prevention and correction of privational vitamin D deficiency [2]. Sunlight exposure can be a cause of skin cancer and for this reason cannot be advocated as a means to prevent vitamin D deficiency. In determining the oral intake that is required to meet the needs both to prevent and to correct vitamin D deficiency one must take into account inadvertent and intentional exposure to sunlight. In other words, the recommended daily allowance for vitamin D as an oral nutrient need only be specified for those who are sun-deprived; those who are not sun-deprived have lower oral intake requirements [3].

Vitamin D is activated by two metabolic steps: first, hydroxylation to 25OHD in the liver that is substrate dependent on sources of parent vitamin D; then, further hydroxylation by 1α-hydroxylase in the kidney to the hormonal or active form, 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$) that is tightly regulated by PTH and FGF23 [4]. The hormonal form then circulates to remote sites of action and binds to the vitamin D receptor (VDR), principally at the intestine promoting absorption of calcium and phosphorus. The mineral-product of calcium and phosphorus is essential for the mineralization of newly formed bone matrix at all stages of life. The final activation step occurs also in extrarenal tissues followed by local binding to VDR, which is termed the paracrine/intracrine effect. This intracrine effect is not regulated by calciotropic hormones but by tissue-specific cytokines and is substrate dependent [5]. This is a more complicated aspect of vitamin D action, which is the subject of much basic and clinical research over the past two decades.

Severe vitamin D deficiency leads to rickets in the growing skeleton and osteomalacia in the adult skeleton. In adults, it also predisposes to low bone mass and contributes to bone fragility fractures in the elderly. Deficiencies in the intracrine action may account for associations between vitamin D deficiency and infections, autoimmune disease, cardiovascular disease, diabetes mellitus, falls and cancer, but according to a recent report from the Institute of Medicine

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(IOM), which was commissioned for the governments of Canada and the USA, the evidence for causality is inconsistent and inconclusive [3, 6]. On the contrary, the IOM report concluded that there was a well-established causal link between vitamin D intake and skeletal health [3].

Key Points

Definition of Vitamin D Deficiency

It is probably best for clinicians to divide vitamin D deficiency into two groups: those who are sun-deprived; and those who have intestinal, liver or kidney disorders. The correct term for the former is "privational" not "nutritional" vitamin D deficiency. Privational encompasses the role of both sources of vitamin D: sunlight exposure and oral intake. It is incorrect to apply the terms "deficiency" or "insufficiency" based on 25OHD levels. Although measuring 25OHD level has a prime role in assessing vitamin D status (see later); it is not a clinical outcome; it is merely a measure of risk of disease [3, 6, 7].

There has been a double paradigm shift since the 1990s: first, the term hypovitaminosis D was replaced by the terms "deficiency" and "insufficiency" implying the presence of a disease state; and, second, the 25OHD thresholds have steadily increased from 25 nmol/L (10 ng/ml) to 75 nmol/L (30 ng/ml). The recent IOM report states that 25OHD is an estimate of risk of clinical outcomes, and that risk of skeletal disease reaches a plateau at 30–40 nmol/L (12–16 ng/ml) (see below and Table 23.1) [3, 6–8].

Privational vitamin D deficiency is best defined as a clinical, biochemical, radiologic, densitometric or histomorphometric abnormality that is corrected and prevented by low dose vitamin D supplementation [9]. The natural history of vitamin D-related bone disease at the bone level is a phase of secondary hyperparathyroidism (SHPT) with accelerated irreversible bone loss culminating in a mineralization defect (rickets or osteomalacia). Once the entire surface of bone is

Table 23.1 Implications for clinical practice of the 2011 IOM report on dietary reference intakes

Sun-deprivation	The vitamin D specifications apply to individuals with minimal or no sunlight exposure. This encompasses housebound individuals especially the frail elderly, those who practice concealment for cultural or religious reasons, those with darker skin, those that apply high factor sunscreen, and those residing in high-latitude countries during the months when there is absent skin generation of vitamin D. These otherwise healthy individuals are at risk of reduced vitamin D synthesis.
Dietary reference intakes (DRIs)	Estimated average requirement (EAR): meets the needs of 50 % of the population. The EAR is an appropriate estimate when considering intake for groups or persons. The recommended daily allowance (RDA) meets the needs of over 97.5 %. The RDA is likely an overestimate of need for any particular individual; but since the true requirement of an individual may not be known, the clinician may aim for this higher intake level.
Vitamin D status as judged by serum or plasma 25OHD level	25OHD is considered a "biomarker of exposure" (namely, the best measure of vitamin D supply) but it is not a "biomarker of effect" (namely, it is not a clinical outcome). The plateau of skeletal benefit is reached at 30–40 nmol/L (12–16 ng/ml). The EAR corresponds to a 25OHD level of 40 nmol/L (16 ng/ml). The RDA corresponds to a 25OHD level of 50 nmol/L (20 ng/ml).
Current vitamin D status in USA	In the USA, the median oral intake of vitamin D is less than 400 IU/d but the mean 25OHD levels are above 50 nmol/L. The 25OHD level is higher than expected for vitamin D intake; this suggests, not surprisingly, that supply from sun-light exposure either inadvertent or intentional contributes substantially to vitamin D status. This reinforces the point that the EAR and RDA apply to sun-deprived individuals.
Safe vitamin D intake level and safe 25OHD level	The tolerable upper intake level is defined by the IOM report as the upper level of vitamin D intake beyond which harm could be expected to increase for the general population. The IOM specified that this threshold is 4,000 IU daily, and also specified that this not to be considered as a target intake. Furthermore, IOM specified that a 25OHD level of 125 nmol/L (40 ng/ml) corresponds with this upper intake level.
Calcium intake	The clinician must also consider the EARs and RDAs for calcium intake.

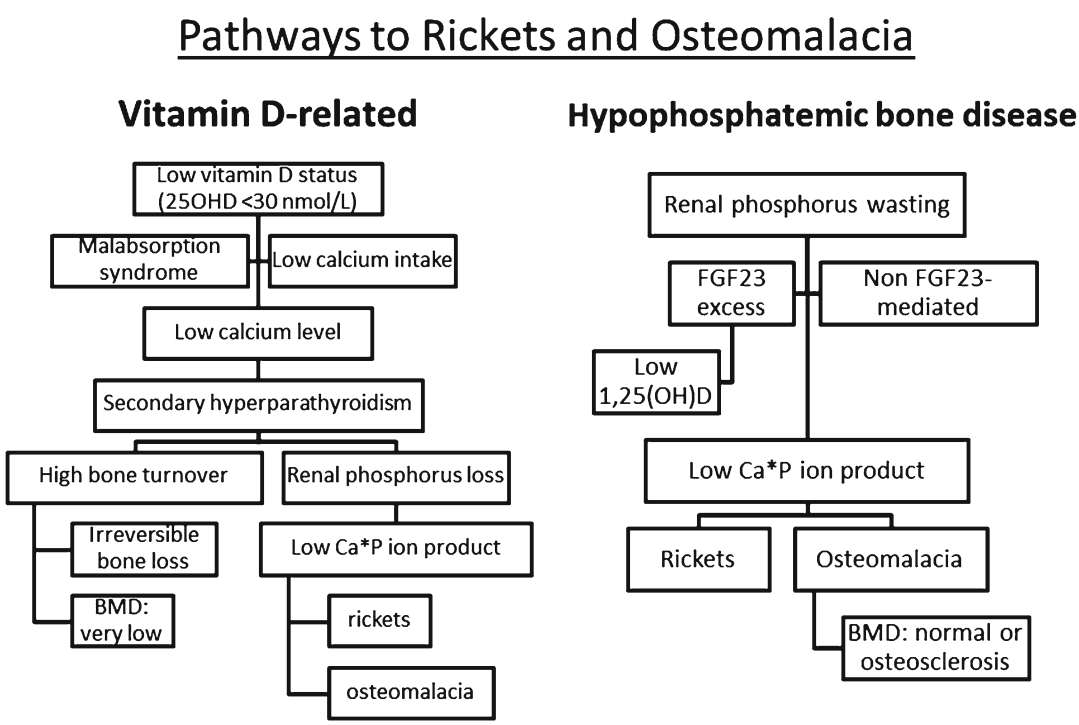

Fig. 23.1 BMD = bone mineral density; FGF23 = fibroblast growth factor 23; Ca = calcium; P = phosphorus; 25OHD = 25-hydroxyvitamin D; $1,25(OH)_2D$ = 1α,25-dihydroxyvitamin D

covered in unmineralized bone matrix (osteoid), irreversible bone loss ceases [10]. On the contrary for hypophosphataemic bone disease, the natural history is one of progressive mineralization defect [11]. This understanding is important in addressing differential diagnosis (Fig. 23.1).

Measuring 25OHD

Serum or plasma 25OHD is the best measure of vitamin D status because its synthesis is substrate dependent and it has a long half-life of about 2 weeks [12]. There are two types of assay for detecting total 25OHD, $25OHD_3$ and $25OHD_2$: (1) immunoassays and automated immunoassays for total 25OHD; and (2) high pressure liquid chromatography (HPLC) liquid chromatography tandem mass spectrometry (LC-MS/MS) and isotope dilution liquid chromatography tandem mass spectrometry (ID-LC-MS/MS) for $25OHD_3$ and $25OHD_2$.

One of the major factors contributing to analytical uncertainty in 25OHD testing is the lack of standardization of 25OHD methods [13–16]. Intermethod variability should improve following the introduction in 2009 of Standard Reference Materials (SRM 972) and solvent-based primary calibrators (SRM 2972) by the American National Institute of Standards and Technology (NIST), and also following the acceptance by the Joint Committee for Traceability in Laboratory Medicine (JCTLM) of the NIST and University of Ghent assays (ID-LC-MS/MS and ID/LC/MS) as reference measurement procedures (RMPs) [17]. However, 3 of the 4 SRM 972 reference materials are either spiked with exogenous metabolites (Level 3 with 25-hydroxyvitamin D_2, and Level 4 with 3-epi-25-hydroxyvitamin D_3) or diluted in horse serum (Level 2) which makes these levels unsuitable for many immunoassays. Only the SRM 972 Level 1 pool should be used for standardization purposes in immunoassays [18]. A new generation of human serum-based

SRMs are due to be released that should further improve assay standardization.

Many of the automated immunoassays, which do not have preliminary solvent extraction or protein precipitation to free 25OHD from vitamin-D-binding proteins (DBPs), are subject to DBP matrix interferences [16]. Also for immunoassay techniques, a measure of total metabolite concentration and equivalent detection of both $25OHD_2$ and $25OHD_3$ is challenging, because binding proteins show a higher affinity for $25OHD_3$ than $25OHD_2$ [19]. All immunoassays have a high cross-reactivity with the metabolite 24,25-dihydroxyvitamin D, which can be present in serum at concentrations of up to 12 nmol/L [20]. LC-MS/MS methods have been shown to suffer from two interferences: the C-3 epimer of 25OH D_3, and isobaric substance 7-α-hydroxy-4-cholesten-3-one [21, 22]. The NIST standard containing 3-epi-$25OHD_3$ (SRM 972 Level 4) allows laboratories to check whether or not their method suffers from interference from this metabolite. The isobaric substance has been separated by a novel LC-MS/MS method [21].

It is challenging for clinicians to assess multiple 25OHD results for a given patient if performed at different laboratories using different methods of measurement [23]. It is important for clinicians to be provided by their 25OHD service providers with their assay limitations with regard to traceability, specificity, imprecision and limit of detection. Their participation in a proficiency testing scheme such as the International Vitamin D External Quality Assessment Scheme (DEQAS) is essential [24]. Clinicians should be alerted to any change of methodology as this could have a significant impact on results, patient classification, and treatment recommendations. Finally, clinicians need to ignore reference ranges for 25OHD from commercial laboratories that quote inordinately high levels for vitamin D status [7].

IOM and Defining Vitamin D Status

Vitamin D status should be considered in the light of the recent IOM report, which revised the dietary reference intakes (DRIs) for the USA and Canada (Table 23.1). The 2011 IOM report is now the standard on vitamin D requirement and on vitamin D status because it examined the totality of evidence with respect to harms and benefits for both calcium and vitamin D for the entire population [8]. Using a risk assessment framework they specified the estimated average requirement (EAR) that meets the need of approximately 50 % of the population, and the recommended daily allowance (RDA) that meets the need of 97.5 % of the population (Table 23.2). They specified that a 25OHD level of 40 nmol/L (16 ng/ml) corresponded to the EAR and that a level of 50 nmol/L (20 ng/ml) corresponded to the RDA [3, 7, 25].

The implications of the IOM report for clinical practice are summarized in Table 23.1. The IOM report avoided using the terms "vitamin D deficiency" and "vitamin D insufficiency" when defining vitamin D status. Appropriate terms included "hypovitaminosis D" or "low vitamin D status" for a result below 30 nmol/L (12 ng/ml); and "vitamin D adequacy" or "vitamin D sufficiency" for levels 30–50 nmol/L (12–20 ng/ml). Just as there is a range of requirement for vitamin D intake, so is there a corresponding range of adequacy or sufficiency for 25OHD [7]. The RDA and the corresponding 25OHD of 50 nmol/L (20 ng/ml) is likely an overestimate of the need for any particular individual; but since the true requirement of an individual may not be known, the clinician may aim for this higher 25OHD level in defining adequacy or sufficiency [7, 8]. The IOM report expressed concern about levels above 125 nmol/L (50 ng/ml) based on emerging evidence about risks that could not be defined in the usual terms of vitamin D toxicity.

Secondary Indices of Vitamin D Deficiency (Fig. 23.2)

If 25OHD is below 30 nmol/L (12 ng/ml), then the practitioner should encourage an augmented oral intake (see treatment section below), but does not necessarily need to embark on additional investigations. Much lower levels may be associated with clinical features including proximal myopathy and diffuse bone pain. Secondary biochemical indices include hypocalcaemia and hypophosphataemia.

Table 23.2 Dietary reference intakes for calcium and vitamin D as specified by 2011 IOM report

	Calcium mg/d			Vitamin D IU/d		
Life stage group	EAR	RDA	UL	EAR	RDA	UL
Infants 0–6 months	*	*	1,000	**	**	1,000
Infants 0–12 months	*	*	1,500	**	**	1,500
1–3 years old	500	700	2,500	400	600	2,500
4–8 years old	800	1,000	2,500	400	600	3,000
9–13 years old	1,100	1,300	3,000	400	600	4,000
14–18 years old	1,100	1,300	3,000	400	600	4,000
19–30 years old	800	1,000	2,500	400	600	4,000
31–50 years old	800	1,000	2,500	400	600	4,000
51–70 years old	800	1,000	2,000	400	600	4,000
51–70-year-old females	1,000	1,200	2,000	400	600	4,000
71+ years old	1,000	1,200	2,000	400	600	4,000
14–18 years old, pregnant/lactating	1,100	1,300	3,000	400	600	4,000
19–50 years old, pregnant/lactating	800	1,000	2,500	400	600	4,000

*For infants, adequate intake is 200 mg/d for 0–6 months of age and 260 mg/d for 6–12 months of age. The adequate intake is used when an EAR/RDA cannot be developed; it is the average intake level based on observed or experimental intakes; and it is likely greater than the needs of most infants
**For infants, adequate intake is 400 IU/d for 0–12 months of age
EAR = estimated average requirement that meets the needs of 50 % of the population
RDA = recommended daily allowance that meets the needs of 97.5 % of the population
UL = upper intake tolerable level

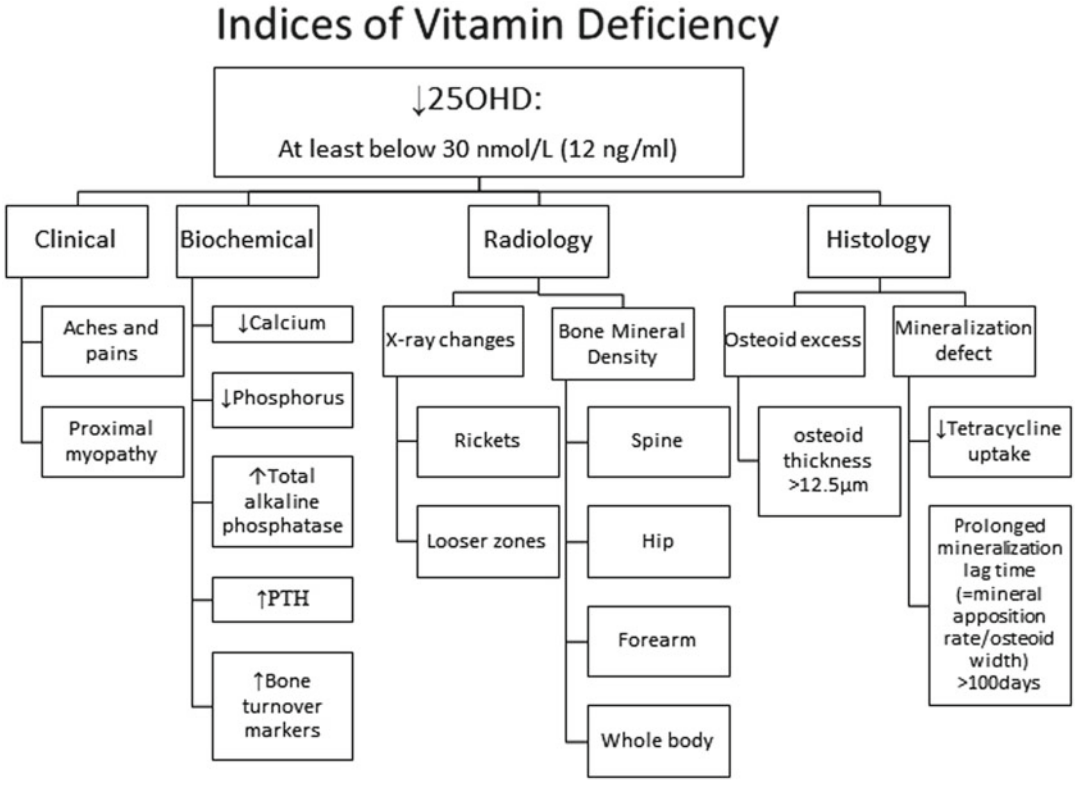

Fig. 23.2 25OHD = 25-hydroxyvitamin D; PTH = parathyroid hormone

Although not calculated in clinical practice, the calcium–phosphorus ion product is a measure of the degree of deficiency that links directly with the consequence of a mineralization defect in bone. Another simple measure that is routinely available is serum total alkaline phosphatase; in the absence of liver disease it is a direct marker of bone disease.

Serum PTH should be measured as part of the assessment. Secondary hyperparathyroidism (SHPT) occurs in response to hypocalcaemia. This results in an increase in bone turnover as part of the effort to restore calcium homeostasis. In addition, 1α-hydroxylase activity is augmented such that $1,25(OH)_2D$ levels may be elevated in vitamin D deficiency; this metabolite is not a measure of vitamin D status. Renal tubular effects of SHPT such as renal phosphorus wasting and renal bicarbonate wasting may hasten the onset of the mineralization defect in bone. Other factors influence PTH status such as calcium intake, renal function, age, ethnicity, body composition and geographic location [8]. There is no single threshold level of 25OHD that prevents secondary hyperparathyroidism [3, 8, 26].

An array of bone turnover markers is available for assessing bone status [27]. An increase in bone formation markers may reflect either an increase in bone remodelling activity due to SHPT or a defect in mineralization, or both. They are serum-based and should be collected in the fasting state (bone specific alkaline phosphatase, procollagen type I aminopropeptide and osteocalcin), whereas increased resorption markers only reflect SHPT. They include: (1) fasting serum-based tests such as beta-C-terminal cross-linking telopeptide of type I collagen (β-CTX), N-terminal cross-linking telopeptide of type I collagen (S-NTX), and tartrate-resistant acid phosphatase 5b (TRAP5b); and (2) either a timed-fasting urine or fasting second void urine or a 24-h urine collection for urinary NTX (U-NTX). Clinicians should obtain protocols from their laboratory service provider for instructions on specimen type required. It should be noted that reduced renal function may lead to reduced urinary excretion of β-CTX and a consequent increase in the apparent serum β-CTX concentration. Urinary markers of bone metabolism should be omitted in patients with renal insufficiency and a creatinine clearance of <20 ml/min [28]. In vitamin D deficiency both formation and resorption markers are increased, but in hypophosphataemic bone disease only formation markers are increased.

Specific radiographic changes occur late in the course of vitamin D deficiency. Rickets is a disease of the growing skeleton with radiographic changes being most pronounced at the growth plates in those bones that are growing fastest such as around the knee, the wrist especially the distal end of the ulna, the middle ribs, the proximal femur and the distal tibia. Initially the growth plate widens as a consequence of defective mineralization between epiphysis and metaphysis [29]. Then the metaphyseal surfaces become cupped and irregular. This is accompanied by splaying of the metaphyses and widening of the growth plates that accounts for the classical clinical signs of swelling at the wrists, knees and anterior ends of the ribs (rickety rosary). Bone deformities occur principally in lower extremities in weight-bearing bones resulting in knock knees, bow-legs, wind-swept legs [29, 30].

Insufficiency-type stress fractures in the setting of osteomalacia are referred to by the eponymous term, Looser zones [29]. They are often incorrectly called "pseudofractures". It has been recommended for many years that this term is of no further value [31]. Looser zones are stress fractures. They are usually multiple in origin and are often symmetric in occurrence. They occur at typical sites in both weight-bearing bones (such as pubic rami, medial aspects of the femur and tibia, and metatarsal bones) and non-weight bearing bones (such as ribs, and medial border of the scapula). Appearances are characteristic in that the fracture appears as a broad rather than a narrow band, margins are parallel, marginal sclerosis is minimal, callus is usually present, but healing is delayed (Fig. 23.3). Typically, they only occur late as a manifestation of osteomalacia. Traditionally, they were considered to be pathognomic of osteomalacia, but rarely insufficiency-type stress fractures with appearances of Looser zones are described [29, 31].

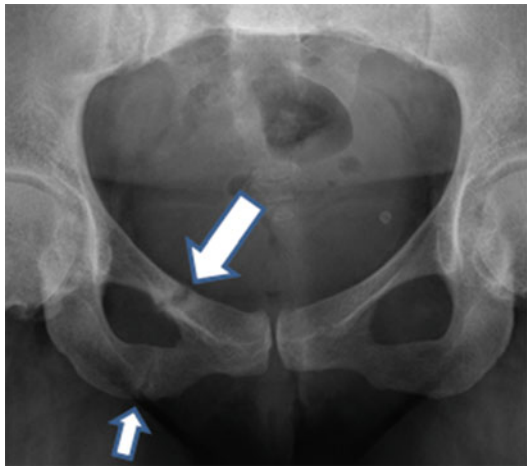

Fig. 23.3 Image of Looser zones in osteomalacia in right superior pubic ramus demonstrating all of the characteristics of broad band, minimal callus, transverse and marginal sclerosis in patient with hypophosphataemia due to tumour-induced osteomalacia with elevated FGF23 level. There is also a Looser zone in the right inferior pubic ramus

Bone mineral density (BMD) should be measured at spine, hip and forearm (and whole body for those under 20 years) using dual-energy X-ray absorptiometry. While this does not have any discriminant value in diagnostic terms, BMD is a measure of the risk of fragility fracture and is also a baseline measurement to assess the response to treatment. While correcting vitamin D deficiency in severe cases will result in an improvement in BMD, there is also an irreversible component to the bone loss especially cortical bone that is related to the prolonged phase of SHPT with high bone turnover prior to the onset of the mineralization defect [10]. Hypophosphataemic bone disorders, not having a phase of SHPT, do not have irreversible PTH-mediated bone loss. In some inherited hypophosphataemic disorders, BMD is increased [32].

Bone histology is rarely performed and rarely needed especially with the advance in the above-mentioned biochemical indices. That aside, it is still the gold standard for diagnosing osteomalacia. There are two principal findings: first, accumulation of unmineralized bone matrix called osteoid; second, impaired mineralization as measured using tetracycline-based histomorphometry. It is not sufficient to base a diagnosis on osteoid indices alone; any condition that increases bone turnover will also increase the surface extent of osteoid. An osteoid seam width >12.5 μm coupled with a prolonged mineralization lag time >100 days is diagnostic of osteomalacia [11, 33].

Differential Diagnosis (Table 23.2)

Intestinal, Hepatic and Renal Diseases

Malabsorption of calcium due to disease must be considered and excluded in all cases. Mucosal disorders most notably celiac disease should be considered. Measurement of antibodies to the enzyme tissue transglutaminase and to endomysium is the best screening test. Diagnosis is confirmed by small bowel histology. Dietary factors should be considered in certain ethnic groups such as Asian immigrants residing in high-latitude countries who ingest unleavened bread, chapati, which impairs calcium absorption. Pancreatic insufficiency and cholestatic liver disease such as primary biliary cirrhosis are less likely to cause vitamin D-related bone disease. Chronic kidney disease in early stages probably has a higher requirement for substrate vitamin D due to progressive impairment in 1α-hydroxylase; at later stages it may manifest with osteomalacia but it is a mixed bone disease including osteitis fibrosa cystica, adynamic bone disease and osteosclerosis.

Hypophosphataemic Bone Disease (Table 23.3)

Chronic hypophosphataemia also causes rickets and osteomalacia. Chronic hypophosphataemia is usually due to a sustained increase in renal phosphorus excretion, but may also be a consequence of impaired absorption and intake. FGF23 regulates renal phosphorus handling by reducing the expression of sodium–phosphorus cotransporters, and it inhibits 1α-hydroxylase activity. Hypophosphataemic bone disease is now divided into two categories: FGF23-mediated and non-FGF23 mediated [32].

Table 23.3 Differential Diagnosis of Causes of Rickets and Osteomalacia

1. Vitamin D-related
(a) Privational vitamin D deficiency (combined sun-deprivation and inadequate oral intake)
(b) Disease-specific
• Malabsorption
– Mucosal disorders such as celiac disease
– Pancreatic insufficiency
– Post-gastrectomy
– Gastric bypass
• Primary biliary cirrhosis
• Chronic kidney disease
(c) Inherited
• 1α-hydroxylase deficiency (pseudo-vitamin D deficiency)
• Vitamin D receptor defect (hereditary vitamin D resistant rickets)
2. Deficient calcium intake coupled with high phytate intake
(a) In Africa and India, and in Asian immigrants
3. Hypophosphataemic bone disease due to renal phosphorus wasting
(a) FGF23-mediated
• Inherited
– X-linked hypophosphataemia
– Autosomal dominant hypophosphataemic disease
– Autosomal recessive hypophosphataemic disease
• Acquired
– Tumour induced osteomalacia
– Post renal transplant hypophosphataemia
(b) Non-FGF23-mediated
• Fanconi's syndrome
– Drug induced:
Oral iron chelators
Antiretrovirals

See Imel (ref. [12]) and Lips (ref. [14]) for more details

In childhood, the commonest cause of inherited renal phosphorus wasting is X-linked hypophosphataemia due to inactivating mutations in the PHEX gene that is associated with increased bone expression of FGF23 (OMIM 307800). In adulthood, mesenchymal tumours of mixed connective tissue type that produce an excess of FGF23 higher than seen in the inherited conditions leads to severe tumour-induced osteomalacia (TIO). A number of drugs enhance renal excretion of phosphorus resulting in non-FGF23-mediated rickets or osteomalacia. Of recent interest is the effect of oral iron chelators for treating iron overload on renal phosphorus handling; they cause phosphaturia without increasing FGF23 and lead to both rickets and osteomalacia [34].

Diagnosis of renal phosphorus wasting is straightforward, but it requires measurement of the renal tubular maximum reabsorption of phosphorus per unit of glomerular filtrate: TmPO4/GFR. This is conducted by collecting a timed fasting urine and simultaneous blood sample for estimation of phosphorus and creatinine in both serum and urine, and then by calculating TmPO4/GFR according to a nomogram or an equation [35]. Hypophosphataemia with a low TmPO4/GFR in the absence of hypocalcaemia gives a diagnosis of renal phosphorus wasting. Serum $1,25(OH)_2D$ levels should be inappropriately low. FGF23 levels can now be measured in specialized laboratories. In childhood, genetic testing for the known mutations should be conducted. In adult patients, acquired causes should be sought including TIO but some of the inherited forms may not present until later in life [32].

Rare Conditions

A number of conditions may mimic privational vitamin D deficiency. In childhood rare congenital disorders in the metabolism and action of vitamin D should be considered such as: non-functioning 25-hydroxylase (OMIM 600081), non-functioning 1α-hydroxylase called pseudo-vitamin D deficiency (vitamin D-dependent rickets type 1, OMIM 264700) and non-functioning vitamin D receptor called hereditary 1,25-dihydroxyvitamin-D-resistant rickets (HVDRR, or vitamin D-dependent rickets type 2, OMIM 277440) [36]. These conditions are extremely rare and should only be considered in cases where there is failure to respond to standard intervention (see below).

Calcium deficiency of a severe degree, alone, is now considered to be a cause of rickets that is consistent with the known interdependence of calcium and vitamin D. This has been reported in African children in Nigeria and South Africa who

have abundant exposure to sunlight but have extremely low dietary calcium intakes at less than about 200 mg daily on a sustained basis. Intake of foods high in phytate and oxalate that chelate calcium may be confounding factors [30]. Similarly, in India where calcium intake is very low and phytate intake is high rickets and osteomalacia is reported, despite with what would be considered satisfactory vitamin D status in regions where calcium intake is much higher [37, 38].

Hypophosphatasia (OMIM 146300) is a rare heritable form of rickets and osteomalacia that is caused by sub-normal activity of tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). It may manifest in different clinical forms: perinatally with a fatal form, in infancy with severe rickets, in childhood with milder bone disease accompanied by premature loss of teeth, and in adulthood with poorly healing metatarsal stress fractures. Serum total alkaline phosphatase is low, while calcium, phosphorus, 25OHD and PTH levels are normal. In fact there is a tendency to hypercalcaemia and hyperphosphataemia. So standard treatment for rickets should be avoided; in fact a restricted calcium intake may be needed to avoid hypercalcaemia [39].

Chronic metabolic acidosis can cause a mineralization defect. This is seen with renal tubular acidosis as a consequence of renal bicarbonate-wasting. This is a direct effect of the acidotic state on bone, which functions as part of the buffering response in the body. Urinary diversion techniques may result in chronic metabolic acidosis, especially uretero-sigmoidostomy that was performed in the past and to a lesser extent the extant procedure of uretero-ileostomy. A simple indicant on routine testing is the presence of a normal anion gap metabolic acidosis accompanied by hyperchloremia.

Present and Future Therapies

Vitamin D and Calcium Supplementation

Privational vitamin D deficiency is corrected and prevented safely and efficaciously by low-dose vitamin D supplementation. The intake requirements for both vitamin D and calcium as specified by the recent IOM report should be followed (Table 23.3) [3, 6]. Vitamin D_3 is favoured over D_2 due to the greater potency of the former [12, 40].

The IOM report has made an invaluable contribution to clinical practice (Table 23.1). Foremost, it directs clinician to distinguish between two different at-risk populations: (1) those who are at risk as a consequence of sun-deprivation with resultant inadequate vitamin D synthesis, which includes all those, by definition, with privational vitamin D deficiency worldwide; and (2) those at risk for disease-specific reasons [8]. The former group only need to augment oral intake of vitamin D and calcium as specified by IOM. The latter group require clinical evaluation. For instance, an individual may have a higher intake requirement of both calcium and vitamin D in order to achieve the same optimal level of vitamin D status as the healthy population—the best example being patients with chronic malabsorption. Here, the clinician is guided by the secondary indices, in addition to 25OHD levels, in order to assess the success of supplementation doses of vitamin D and calcium. Alternatively, the patient may have a higher 25OHD threshold for adequacy—the best example being the patient with progressive chronic kidney disease, who needs a higher substrate concentration of 25OHD for activation in the kidney as consequence of declining 1α-hydroxylase activity. If higher doses of vitamin D are needed, then patients will need frequent monitoring of 25OHD and other indices such as PTH levels both to assess efficacy and to avoid toxicity.

In view of the interdependence of calcium and vitamin D, the adequacy of calcium intake must be considered in all clinical situations of privational vitamin D deficiency [3]. This is particularly important in regions were dietary calcium intake is very low and phytate intake is high [37, 38]. One recent guideline failed to mention at all about ensuring satisfactory calcium intake [41] but instead promoted vitamin D intakes that were threefold to fivefold higher than IOM specified intakes for preventing privational hypovitaminosis D [8, 42].

High-Dose Vitamin D Therapy

High-dose vitamin D therapy is often advocated both for the treatment and prevention of privational vitamin D deficiency. Suggested doses range from 50,000 to 500,000 units, are administered either orally or intramuscularly, and are prescribed at intervals ranging from once weekly to yearly. As a preventative strategy for at-risk populations, it is often recommended as a means of overcoming poor adherence. Clinicians should be cautious about this approach for a number of reasons: (1) for cases of rickets and osteomalacia, one must understand that one is dealing with a chronic disorder that evolved slowly over a long time, and is not possible to correct acutely at the bone level; (2) one may unwittingly omit to consider calcium supplementation when prescribing a very high dose vitamin D; (3) risk of toxicity. High dose therapy is harmful; it should be considered a pharmacologic agent, and it should not be considered equivalent to an average daily dose [12]. Two recently published high dose trials demonstrated harm unexpectedly in their pre-specified outcomes. One study of elderly over 70 years were assigned to receive placebo or 500,000 D_3 orally once yearly for 5 years to test whether there was a reduction in falls and fractures. There was a significant increase in falls and a trend towards an increase in fractures [43]. Another study of infants aged 1–11 months in Kabul were assigned to receive placebo or 100,000 IU D_3 orally every 3 months for 18 months to test whether it reduced the incidence and severity of pneumonia. No benefit was observed but they recorded a significant excess of repeat episodes of pneumonia, which was a pre-specified secondary outcome [44].

Activated Vitamin D Analogues

Rather than opting for high dose parent vitamin D in cases of chronic malabsorption, one should consider use of activated vitamin D: 1,25 $(OH)_2D$ or its monohydroxylated analogue 1α-hydroxyvitamin D, which is slightly less potent. Usually, the starting dose is about 0.25 μg twice daily increasing until resolution of the biochemical abnormality. Additional calcium supplementation is usually warranted. Parent vitamin D_3 should also be administered in an effort to try and improve vitamin D status both for endocrine and intracrine effects. Careful monitoring of calcium status, both in serum and urine, is advised for patients on activated forms of vitamin D in view of the risk of hypercalcaemia and hypercalciuria.

Future Therapies

An intractable problem that is rarely encountered in patients with prolonged malabsorption is refractory secondary hyperparathyroidism that persists despite restoring calcium status to normal. In time, these patients progress to autonomous hyperparathyroidism with hypercalcaemia. They tend to have marked increases in bone turnover markers, both resorption and formation, and have accelerated bone loss on densitometry. They may even progress to osteitis fibrosa cystica. One cannot increase the dose of activated forms of vitamin D because of the risk of hypercalcaemia. Some patients may need total parathyroidectomy with remnant implantation. A new alternative is to use a calcimimetic agent such as Cinacalcet. This is licensed for use in the treatment of primary hyperparathyroidism and secondary hyperparathyroidism in the setting of chronic kidney disease. Use in the setting of refractory secondary hyperparathyroidism would be off-label. Early introduction of calcimimetic therapy may halt the progress towards requiring parathyroid surgery.

Conclusion

Privational vitamin D deficiency is common in groups at risk of sun-deprivation. It is straight forward to investigate using standard biochemical tests. It is effectively and safely corrected by following IOM specified intakes. More severe and refractory cases should be investigated for other causes of vitamin D-related deficiency and for hypophosphataemic bone disease; these conditions are likely to need expert evaluation and pharmacologic intervention with regular supervision of response to intervention.

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