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EXECUTIVE INDEX

Rickets in the 21st century

Introduction

Rickets may have been thought to be a "thing of the past". In fact at the beginning of the 20th century, it has been estimated that 85% of children living in northern hemisphere urban industrialised cities had rickets. Major public health initiatives were then introduced to tackle this problem.

In "sunny Australia" rickets has not been considered a significant health problem until the last decade or so, when a rising incidence of Vitamin D deficiency rickets occurring in southern states in particular, has been observed, however as yet there has been no systematic approach to prevention. This article will outline both the pathophysiology and clinical features of rickets, highlighting recognition of infants and children at risk.

Rickets is broadly defined as undermineralised bone, particularly at the metaphyseal growth plates, in growing children. The skeleton is a complex structure comprising mineral ions which precipitate on a predominantly collagen framework of bone matrix proteins, to form the rigid, strong structure characteristic of normal bone. Reinforced concrete may be considered an analogy of bone structure, as the steel provides tensile strength, analogous with the bone collagen and the concrete provides rigidity analogous with bone mineral ion deposition. In growing infants and children, bone growth, involving laying down of a collagen framework, which is subsequently mineralised, predominantly occurs at the metaphyseal growth plates, within the long bones. Unmineralised osteoid, as occurs in rickets in children, results in soft, pliable bones.

Causes and risks factors

World-wide the most common cause of rickets is due to Vitamin D deficiency. Individuals at risk for Vitamin D deficiency include those with:
1. limited sunlight exposure,
2. highly pigmented skin, or
3. malabsorption syndromes.

Specific social and cultural settings that may predispose individuals to Vitamin D deficiency include:

- reduced sun exposure in institutionalised and "house bound" individuals, especially the chronically disabled,
- the practice of *Hajjab* in the Islamic tradition, where women are almost entirely covered for reasons of modesty,
- highly pigmented individuals who are socially isolated, particularly apartment dwellers, who spend minimal time exposed to direct sunlight.

Vitamin D metabolism (see Figure 1) involves multiple organ systems, namely the skin, liver, kidney, placenta, gut and bone. For this reaction to take place there must be direct exposure to sunlight or other sources of UV B, as this wavelength of UV radiation is not transmitted through glass or clothing. Both dietary Vitamin D_2 and D_3, and skin synthesized Vitamin D_3 are hydroxylated in the liver to form 25 hydroxyvitamin D_3 (25OH D_3), which is the storage form of Vitamin D, and this hydroxylation step is largely unregulated. Further hydroxylation of 25OH D_3 to form 1,25 dihydroxyvitamin D_3 (1,25$(OH)_2D_3$), occurs in the kidney, through the stimulation of 1 alpha hydroxylase by parathyroid hormone (PTH), hypocalcaemia (probably indirectly via PTH)

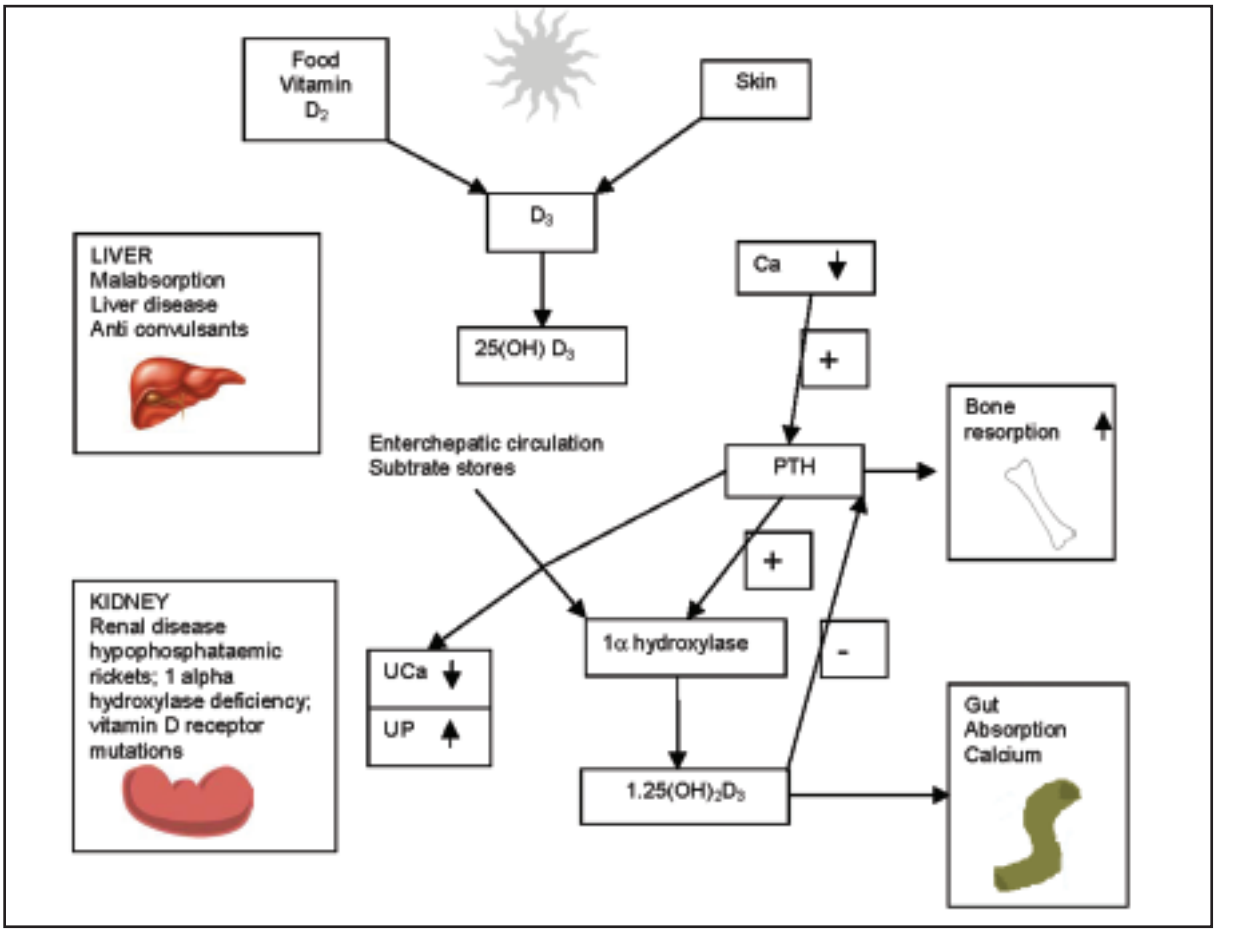


Figure 1: Vitamin D/calcium metabolism – PTH: parathyroid hormone, produced by the parathyroid glands; [Ca]: serum calcium; [P]: serum phosphate; UCa: urinary calcium; UP: urinary phosphate

and hypophosphataemia, with feedback inhibition of PTH secretion by $1,25(OH)_2D_3$.

Skin pigmentation also influences the efficiency of Vitamin D_3 production from sunlight exposure, and Vitamin D production in the skin is inversely proportional to melanin production, as melanin competes with 7DHC for UV B protons. Consequently black skinned individuals need approximately 6 times the sunlight exposure compared with fair skinned individuals, to maintain equivalent Vitamin D status. The amount of UV B exposure from sunlight is also inversely proportional to latitude, so that UV B exposure is greater in equatorial regions compared with that in regions at higher latitudes. Furthermore, UV B exposure is greater during summer than winter at higher latitudes, so that the greatest risk for Vitamin D deficiency in such regions is late winter and early spring. For lightly pigmented individuals, just 10 – 20 minutes direct sun exposure of face and forearms every day or so over summer should prevent the development of Vitamin D deficiency.

In Australia, sun avoidance is increasing due to the development of the "ozone hole" in the earth's atmosphere, resulting in increased exposure to ultraviolet light and consequent increased risk of skin melanoma due to exposure to UV B. This has prompted the development of "broad spectrum" sunscreens which block both UV A and UV B from sunlight, and when used assiduously, these may also reduce skin exposure to UV B sufficiently to cause Vitamin D deficiency, raising the issue that very fair skinned individuals at highest risk of melanoma and other skin cancers may more safely maintain their Vitamin D stores through long term supplementation.

In populations where there is no Vitamin D supplemented foodstuffs, approximately 90% of Vitamin D is obtained from Vitamin D_3 synthesised in the epidermis from 7-dehydrocholesterol (7DHC), in a reaction catalysed by ultraviolet B light with a wave-length of 288nm. The remaining 10% of Vitamin D is derived from dietary sources such as cod liver oil, eggs or oily fish.

To maintain normal mineral ion homeostasis, particularly in growing children, the Recommended Daily Intake (RDI) of both calcium and Vitamin D (Table 1) must be met. However, the RDI for Vitamin D remains controversial given the wide variation in direct sun exposure around the world due to both latitude and lifestyle factors. In Australia there are no national RDI's for Vitamin D, as it is assumed that Australians have adequate sunlight exposure for their Vitamin D requirements. The RDI's for Vitamin D cited are based on a number of published recommendations by other authors.

Table 1: Recommended Daily Intake (RDI) for calcium for women and children *(Australian National Health and Medical Research Council 1991)* and RDI for iron (from other published reports)

Category and age	Australian RDI for calcium	RDI for Vitamin D
Children 1 – 3 yrs 4 – 7 yrs	700mg 800mg	400iu 400iu
Women 19 – 54 yrs	800mg	200iu
Pregnant women	1100mg	800iu
Lactating women	1200mg	800iu

In the absence of Vitamin D fortified foods or Vitamin D supplements, individuals living in polluted cities, at high latitudes are at increased risk of Vitamin D deficiency, and child bearing women and infants and young children are at greatest risk. In industrially developed countries today, rickets most commonly occurs in exclusively breast fed infants born in industrialised cities at high latitudes, to mothers who are also at risk of Vitamin D deficiency due to poor sunlight exposure, unfortified food sources (such as milk), social isolation, increased skin pigmentation, or cultural clothing practices, independently or in combination. *In utero,* the foetus receives 25 OHD_3 from transplacental transfer from the maternal circulation. Hence neonatal 25 OHD_3 levels reflect maternal stores. Premature infants and infants of Vitamin D deficient mothers are at high risk of Vitamin D deficiency, if Vitamin D supplementation is not instituted routinely in the neonatal period.

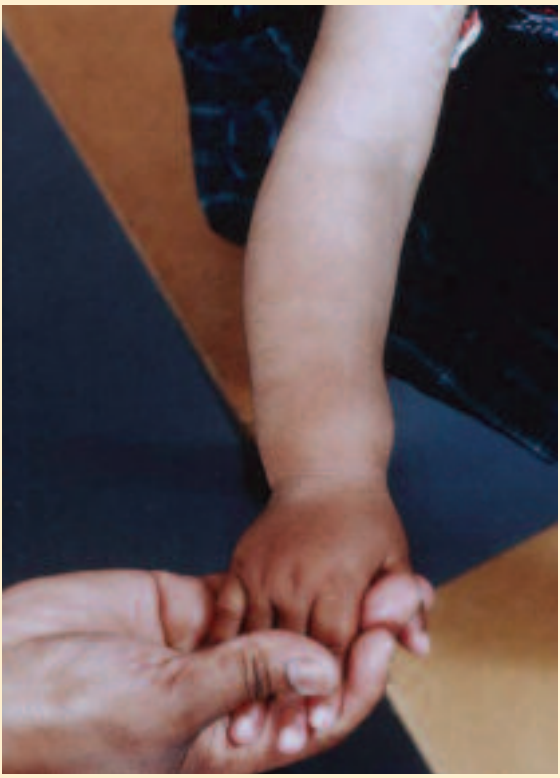
Clinical characteristics

The clinical characteristics of rickets include:

- hypocalcaemic seizures
- slowing of linear growth
- rachitic rosary
- wrist and ankle swelling
- craniotabes (softening of the skull bones)
- a widely patent anterior fontanelle
- frontal bossing
- reluctance to weight bear/delayed walking

Hypocalcaemic seizures are a common presenting feature of rickets in infants aged less than 9 months, but are seen less frequently in older infants and toddlers. Older infants and toddlers tend to present with gross motor delay, leg bowing, or occasionally fragility fractures. However, the diagnosis may be made incidentally on biochemical testing or on chest X-ray performed for other reasons, such as investigation for failure to thrive or fever of unknown origin.

Rachitic bones are characteristically soft and pliable, as a result of growth of unmineralised bone osteoid. Consequently, wrist and ankle swelling, and leg bowing become more marked as infants start weight bearing through crawling, cruising and walking. Rachitic rosary corresponds to the flaring of the costochondral junctions seen radiologically, and almost invariably may be palpated anteriorly along the "nipple line" in infants and young children with rickets, and is sometimes also visible on the anterior chest wall in infants and children in the setting of failure to thrive. It is important also to be aware that other dietary deficiencies may co-exist in prolonged, essentially exclusively breast fed infants and toddlers through the second and into the third year of life, including iron deficiency anaemia, and if the mother is a vegan, consuming no dairy products, Vitamin B_{12} deficiency may also be present. Older infants and children may also have abnormal dentition, due to enamel hypoplasia.



An 18 month old boy with vitamin D deficiency rickets, showing moderate skin pigmentation and wrist swelling.

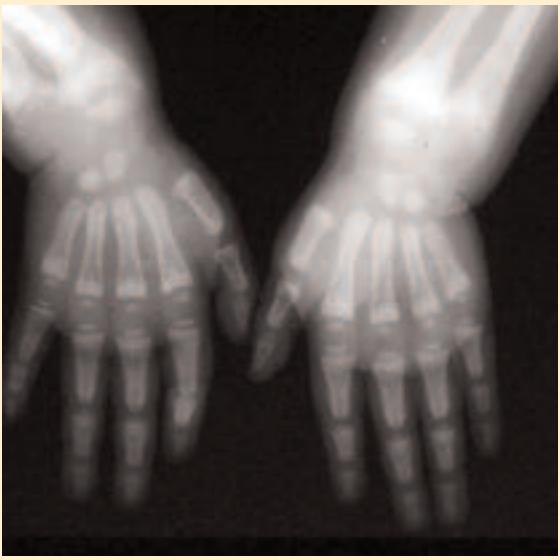


Figure 2: Wrist X-rays of an 18 month old boy with vitamin D deficiency rickets. Note the expanded metaphyses particularly of the radius and ulnar at the wrist, and generalised osteopaenia.

Rachitic X-ray changes include flaring of the costochondral junctions and frayed, cupped long bone metaphyses, with generalised osteopaenia. The typical radiological appearances of rickets are shown in Figure 2. These radiological changes represent ongoing osteoid being laid down in bone that is then poorly mineralised. Radiologically gross metaphyseal changes are frequently not seen in infants under 3 months of age, however generalised osteopaenia remains characteristic, and occasionally "periosteal reactions" are also seen in the long bone X-rays, giving rise to the radiological differential diagnosis of osteomyelitis or scurvy, which may be excluded on clinical grounds.

Characteristic biochemical features include:

- raised alkaline phosphatase (bone specific alkaline phosphatase, BSAP), due to increased bone turnover
- raised parathyroid hormone, in response to hypocalcaemia
- low or undetectable 25 OHD_3

Other biochemical changes such as serum 1,25 OHD_3, calcium and phosphate levels are variable, and dependent on the course of the disease. 1,25 $(OH)_2D_3$ may often be within the upper end of the reference range or frankly elevated. Both serum calcium and serum phosphate may be low or within the normal range, hence measurement of these parameters is unhelpful in diagnosis. Serum phosphate is characteristically decreased in long standing rickets, due to the phosphaturic action of PTH.

Sources and preparations of Vitamin D

Vitamin D preparations used for Vitamin D deficiency include **ergocalciferol** (D_2) and **cholecalciferol** (D_3) and either preparation is effective in restoring Vitamin D stores in Vitamin D deficiency. The active form of Vitamin D, 1,25 $(OH)_2$ Vitamin D_3 **(calcitriol)** should not be used to treat Vitamin D deficiency as it "bypasses" the regulating step of 1 alpha hydroxylation in the kidney, and may lead to hypercalcaemia. Furthermore, calcitriol does not build up hepatic stores of 25 OH Vitamin D.

Expectant and lactating mothers have an increased Vitamin D requirement, 2 to 4 times the RDI for healthy adults. Identification of pregnant mothers at risk for Vitamin D deficiency and providing Vitamin D supplementation during pregnancy, will protect both the mother and foetus from Vitamin D deficiency. Postnatal administration of Vitamin D to Vitamin D deficient lactating mothers needs to be approximately 6 times the adult RDI to correct their infants Vitamin D deficiency, indicating that it is preferable to give Vitamin D replacement to the mother and infant separately. Vitamin D deficiency may be prevented in at risk groups, by providing mothers with the RDI of Vitamin D 800iu during pregnancy and lactation, and 200iu at other times. Vitamin D supplementation of 400iu daily to exclusively breast fed "at risk" infants, or Vitamin D supplemented infant formula feeds totally prevents the development of Vitamin D deficiency rickets in otherwise normal infants. Currently the only commercially available preparation of Vitamin D syrup is the multivitamin preparation "Infant Pentavite" which contains 400iu Vitamin D per dose.

Food type	Vitamin D content – iu per 100gm
Cod liver oil	8,000 – 28,000
Oily fish (e.g. salmon, sardines)	200 – 480
Margarine	200 – 240
Eggs	40 – 80
Breast milk	12 – 60 iu/l
Infant formulas	400 iu/l

Conclusion

Although Vitamin D deficiency rickets almost exclusively occurs in a very small at risk group, it remains a major cause of morbidity in affected individuals, with hypocalcaemic seizures occurring in young infants, bone pain with or without gross motor delay in older children, and osteomalacia with bone pain and increased risk of osteoporotic fractures in at risk mothers. Cultural sensitivity towards and clinical awareness of this readily preventable medical condition is needed to ensure that Vitamin D deficiency rickets once again become "a disease of the past".

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Reflection Questions

1. *Are there any of the high risk groups for Vitamin D deficiency amongst the clients that you see?*
2. *Consider the issues that you would have to discuss with a very fair skinned mother about obtaining adequate Vitamin D for herself, and her equally fair skinned breast-fed infant.*
3. *What alternatives are available to those who do not get adequate exposure to sunlight to meet the requirements for the body to manufacture Vitamin D?*

Note from the Editor

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