RICKETS AND OSTEOMALACIA IN SAUDI ARABIA: THE NEED FOR A NATIONAL PREVENTIVE PROGRAM

[1]Nasir A. M. Al-Jurayyan MD
Professor and Head of Endocrine Division, Department of Pediatrics
[2]Abdullah N.A. Al Jurayyan Ph.D
Department of Pathology and Laboratory Medicine
[1]Rushaid N. A. Al Jurayyan, MD
Department of Radiology and Medical Imaging
[1]Abdulaziz N.A. Al Jurayyan MD
Department of Orthopedics
[1]College of Medicine & King Saud University, and
[2]King Fahad Medical City Riyadh, **SAUDI ARABIA**

ABSTRACT

Rickets and osteomalacia are two distinct clinical disorders of impaired bone mineralization. Rickets is arising throughout the growing skeleton, in infants and children, whilst osteomalacia is occulting after the growth plates have fused in adults. Rickets and osteomalacia are reported with increasing frequency in Saudi Arabia, with vitamin D deficiency, being the most common etiological cause. The major clinical features of rickets and osteomalacia include bone pain and tenderness, and fatigue, muscle weakness, skeletal deformities, and tetany, due to hypocalcemia, in infants. Hypocalcemia, hypophosphataemia, and raised alkaline phosphatase activity are often typically found together with radiological changes such as widening of growth plates in rickets and pseudofractures in osteomalacia. Serum concentration of 25-hydroxyvitamin D are usually low, however, it could be normal in chronic renal failure, or hereditary forms of rickets. Treatment with vitamin D, or its active metabolites and mineral supplementation will generally effective. Measures for prevention of rickets and osteomalacia at a nationwide level should be established.

Keywords: Bone mineralization, Rickets, prevention, Osteomalacia, Saudi Arabia.

INTRODUCTION

Rickets and osteomalacia are two disorders characterized by defective bone and cartilage mineralization. Therefore, children will have both rickets and osteomalacia while adults will have only osteomalacia.[1-3] Rickets and osteomalacia have several causes, table 1. [4-6]

The most common is vitamin D deficiency, either due to lack of sunlight exposure, poor dietary intake, or malabsorption. Abnormalities in Vitamin D metabolism can occur with liver and renal diseases, or as a side effect of drugs such as anticonvulsant medications. Some patients may have inherited disease with vitamin D or with functions of the osteoblasts. Renal tubular disorders leading to severe phosphate depletion can be a cause.

Rickets and osteomalacia are emerging as a major public health problem worldwide. [7-15] It has been estimated that more than one billion people suffer from vitamin D deficiency. In Saudi Arabia, it is reported with increasing frequency. [16-33]

In this review, rickets and osteomalacia are presented from the perspective of clinical characterization, radiological and biochemical investigations. Treatments and preventive measures at a nationwide level are suggested.

Vitamin D and Metabolism

The two main sources of vitamin D in humans are vitamin D3 (cholecalciferol) produced by the skin after ultraviolet (UV) radiation (290-320nm) and dietary intake of either vitamin D2 (ergocalciferol) or vitamin D3 – both forms of vitamin D have identical biological actions. Therefore, lack of sun exposure increased pigmentation of the skin, custom of the dress, poor dietary intake and malabsorption considered as major risk factors.

The initial step in metabolic activation processe in the introduction of hydroxyl group at the side chain at C- 25 by the hepatic enzymes. CYP 27 (a vitamin D – 25 - hydroxylase). The products of this reaction are 25(OH)D2 and 25(OH)D3 respectively.

Further hydroxylation of these metabolites occurs in the mitochondria of renal tissue, catalyzed by renal 5-*Hydroxyvitamin D*3 *1-alpha*-hydroxylase to produce 1 – alpha – 25 $(OH)_2$ D_2 (activated D2 or 1, 25 $(OH)_2$ D_2), the primary biologically active form of vitamin D2 and 1- alpha- 25 $(OH)_2$ D_3 (calcitriol or 1, 25$(OH)_2$ D_3) the biologically active form of vitamin D3.[34-36]

Pathophysiology

The ossification of osteoid cells depends on adequate levels of ionized calcium and phosphate in the extracellular fluids which influenced by metabolites of vitamin D. As the vitamin D deficient, ionized calcium depletion occurs, so does parathormone PTH – hypersecretion[37] leading to increase bone resorption and poor mineralization, hence, serum alkaline phosphatase (ALP) activity is elevated[38-40] and the typical radiological findings.[41-43] In rickets, anteroposterior radiography of the knees and posteroanterior radiography of the wrists show widening of growth plates, figure 1. Typically the metaphysics are splayed, ragged, and concave, and the epiphyses appear as a cup. In osteomalacia, the changes are best seen in the subperiosteum, with pseudofractures as a characteristic, figure 2. Bone scintigraphy is useful, but does not provide a diagnosis. Enhanced radioisotrope uptake occurs when osteodesis is present hence; rickets and osteomalacia can produce a "superscan", figure 3.

Risk factors

The pediatrician should be familiar with the risk factors associated with rickets and osteomalacia. With the realization of those, coupled with a high index of suspicion, the pediatrician should be able to diagnose rickets and osteomalacia. The major risk factors are:

- Dark skin ethnic population
- Exclusively breast – fed infants
- Children and those aged over 65 years
- Pregnancy
- Obesity
- Lactating mothers
- Malnutrition or low milk or dairy products intake
- Vegetarianism
- Cold environment
- Living in countries at high latitude or crowded high rise buildings

- Family history of vitamin D deficiency
- Routine covering of the face and body
- Housebound or institutional
- Prematurity or small for gestational age
- Medications such as steroids and anticonvulsant drugs

Clinical manifestation of rickets and osteomalacia:

Rickets and osteomalacia may manifests with a constellation of symptoms and signs of which muscle weakness and bone pains and tenderness among the commonest. Rickets manifests during growth and the signs are most prominent in areas where bone growth is most rapid, such as swollen wrists and ankles or bow legs. Short stature, bow – legs deformities, craniotabes, and hypocalcemic tetany are important features. While in osteomalacia in adolescents and adults may cause non-specific symptoms.

A high index of suspicion in the right clinical context is necessary for diagnosis. An underlying etiology is often suggested by detailed medical history.

Treatment

Once laboratory and radiologic tests confirm the diagnosis of vitamin D deficiency rickets or osteomalacia. Vitamin D supplementation, [45-55] table 2. Until serum alkaline phosphatase level and skeletal deformities return to normal. Calcium should also be supplemented. Additionally, recommending a diet rich in calcium is advisable.

Prevention

Currently, no clear recommendations whether or how to screen for vitamin D deficiency rickets or osteomalacia. Both patients and physicians need to be aware of the problem and the known risk factors.

Therefore, efforts to encourage exposure to sunlight in the appropriate time, and a diet rich in vitamin D and calcium can help to prevent vitamin D deficiency. Vitamin D is found in large amounts in fortified dairy products, such as milk and yogurt, cereals, bread, egg yolks and fish oils. Finally, patients on anticonvulsant medications or steroid should be screened periodically for osteomalacia and rickets and also if they are at a high risk should be started on vitamin D and calcium supplements as prophylaxis. Therefore, in summary educational measures, appropriate vitamin D and calcium supplement, and appropriate sun exposures are mandatory to prevent osteomalacia and rickets.[56-58]

Table 1, Causes of rickets and osteomalacia

- Primary vitamin D deficiency
  - Classic vitamin D deficiency – infants and puberty
  - Exclusively breast fed
  - Immigrant adults in industrialized countries
  - Decreased exposure to sunlight
  - Use of sunscreen
  - Elderly, housebound and institutionalized groups
  - Pregnancy and lactation

- Food faddists or reduced dietary intake
- Morbid obesity

- Secondary vitamin D deficiency
  - Partial gastrectomy
  - Small bowel malabsorption syndromes (e.g. coeliac disease)
  - Hepatobiliary disease
  - Pancreatic insufficiency
  - Chronic renal failure
  - Metabolic acidosis
  - Drugs and toxins
    - Anticonvulsants
    - Phosphate – binding antacids (e.g. aluminum hydroxide)
    - Bisphosphonate (etidronate sodium)
    - Steroid
    - Fluoride
- Miscellaneous forms
  - Calcium depletion
  - Magnesium depletion
  - Primary hyperparathyroidism
  - Oncogenic
- Hereditary forms
  - Hypophosphataemia (X-linked, autosomal dominant and recessive forms)
  - Vitamin D-dependent rickets type 1 and type 2
  - Proximal renal tubular disorders (Fanconi's dyndrome)
  - Distal renal tubular disorders (renal rickets with nephrocalcinosis and dwarfism)
  - Hypophosphatasia
  - Osteopetrorickets

Table 2: Pharmaceutical preparations of vitamin D and active metabolites

	Calciferol	**Dihydrotachysterol**	**Calcifediol**	**Calcitriol**	**Alfacalcidiol**
Drug	Vitamin D_3 and D_2	DHT	25-hydroxyvitamin D_3	1,25 $(OH)_2D_3$	1a$(OH)D_3$
Form and preparation	Capsules, 0.25 mg & 0.25 mg	Liquid,0.25 mg/ml	Capsules,20 & 50 µg	Capsules,0.25 & 0.50 µg Injection,1 µg/ml Liquid, 1 µg/ml	Capsules,0.25, 0.50 & 1 µg Liquid, 2 µg/ml Injection, 2µg/ml in propylene glycol
Time to maximum effect	4-10 weeks	2-4 weeks	4-20 weeks	0.5-1 week	0.5-1 week
Persistence of effect after cessation	6-30 weeks	2-8 weeks	4-12 weeks	0.5-1 week	0.5-1 week

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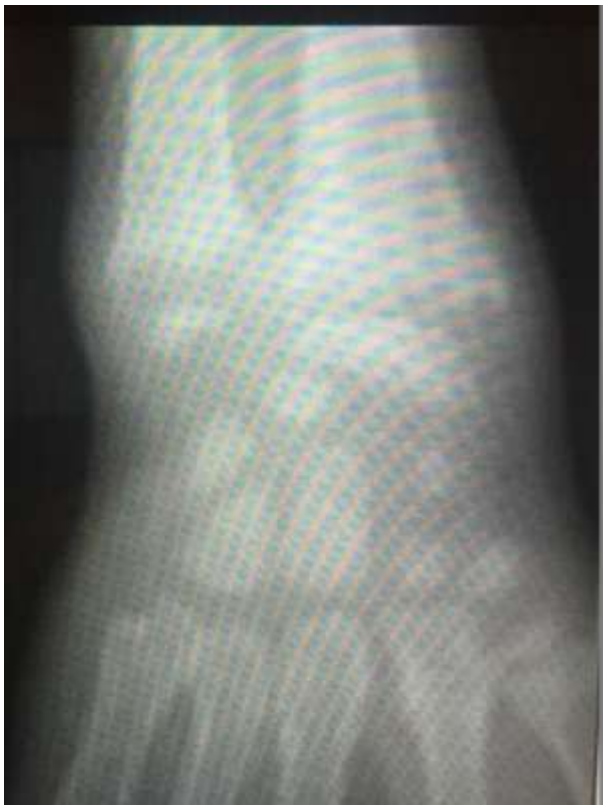
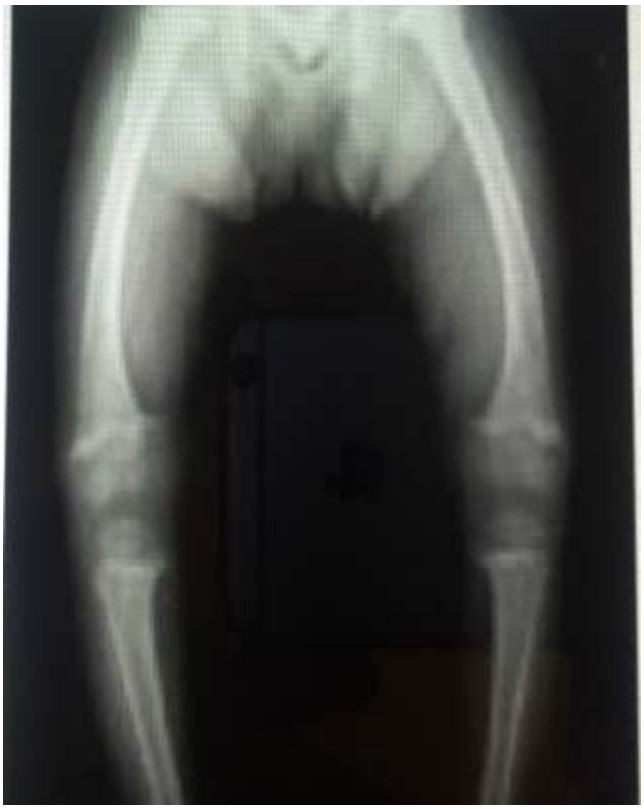
Legend to figure 1

Anteroposterior view of the wrist (A) showing, the classical signs of metaphysial splaying and concavity and the epiphyses showing the typical cupping appearance and (B), the lower limbs with bone bowing in a child with rickets.

A **B**

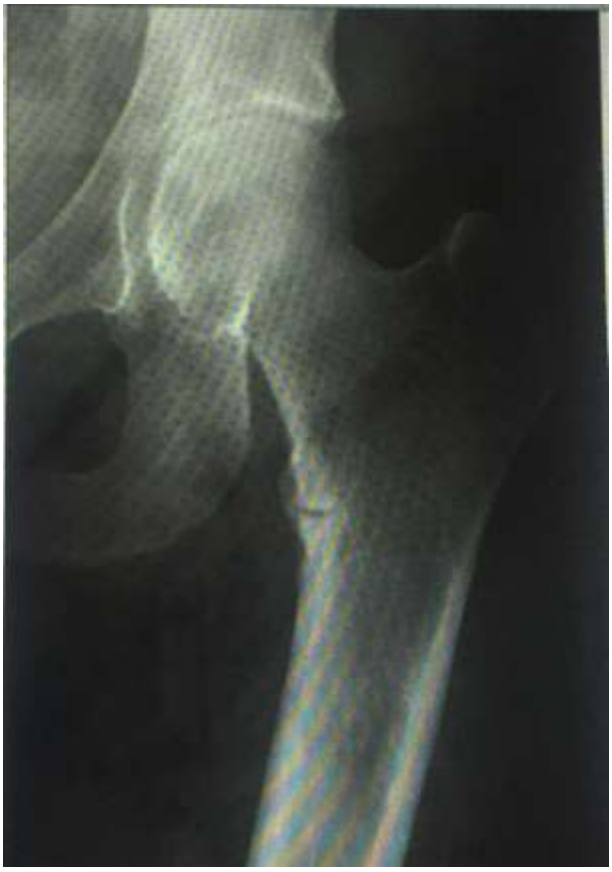


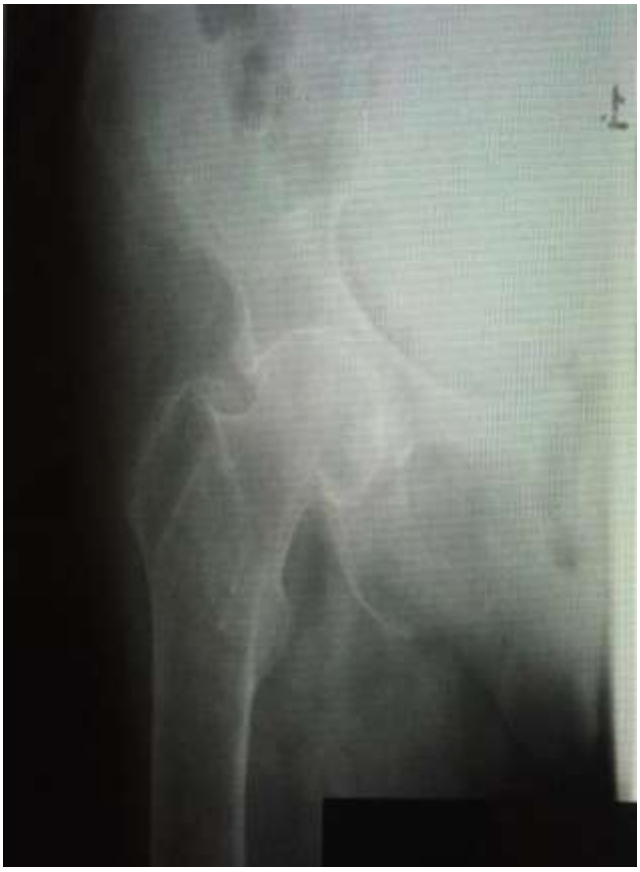


Legend to figure 2

Anteroposterior view of the pelvis, showing Looser's zone (pseudofracture) in the femur (A), and lytic lesion (brown tumor) (B) in a patient with osteomalacia.

A **B**





Legend to figure 3,

A whole body A Tc ^{99m} scan (A) and chest (B), in a patient with osteomalacia. Note, the multiple hot spots 'superscan' i.e. multiple stress fractures in various areas of the body.

A **B**