General Overview of Rickets: A Review Article

Author: Abba Musa Abdullahi

INTRODUCTION

Rickets is a disease of growing bone that is unique to children and adolescents and when occurs in adults, it is referred to as Osteomalacia. It is mainly caused by a failure of osteod (organic bone matrix) to calcify/mineralize in a growing person (Steven et al., 2017).

Put simply, Rickets is the term signifying a failure in mineralization of growing bone or osteoid tissue. Thus, the bone become less rigid, twist and bend easily.The defective or inadequate mineralization is related to lack of Vitamin D (VitD), Alkaline Phosphatase, calcium or phosphate. However, imbalance between calcium and phosphate could also lead to defective mineralization of osteod tissue (Hameed et al., 1998).

The fact that Rickets is a disease of bone resulting from defective mineralization due to abnormality of VitD metabolism, calcium or phosphate, an overview of bone anatomy, VitD metabolism and Parathyroid hormone is vital before making a discussion on Rickets for better understanding (Holick, M.F., 1996).

Therefore, the aim of this review is to provide general overview of Rickets from bone structure to vitD metabolism, epidemiology, aetiology, pathophysiology, clinical presentation, diagnosis, treatment, complication and prognosis of Rickets.

BONE ANATOMY/GROWTH

A bone is a rigid organ that constitutes part of vertebral skeleton. It protects various organs of the body like heart and lungs, produces red and white marrow, store minerals, provide structure and support for the body and enable motility. It has two compartments: the outside cortical/compact bone which make up 80% of bone mass and the resident bone cells here are called osteocysts. Within the cortical bone lies the other compartment, the trabecular or cancellous bone which make up the remaining 20% of bone mass and it harbors the bone marrow (Marx et al., 1992).

Bone is actively remodelled throughout life, which begin before birth and continues till death, by special bone cells known as osteoblasts and osteoclasts. Bone remodelling occurs in an orderly cycles in which old bone is first removed and a new bone is deposited (Marx et al., 1992). In some bones remodelling occurs every week, while in others every 6-12months. The aim of bone remodelling is to maintain bone strength and mineral homeostasis (Clarke et al., 2008).

The remodelling cycle consists of five phases: Activation, Resorption, Reversal, Formation, and Quiescence. Activation Phase involve recruitment of preosteoclasts from the circulation to the remodelling site and subsequent activation of the preosteoclasts to the multinucleated Osteoclasts. This activation requires parathyroid hormone, PTH and vitD. Resorption Phase: here osteoclasts align on bone surface and seal off an area by forming adhesive ring in which cellular integrins bind tightly to bone matrix proteins. Osteoclasts then secrete lysosomes, collagenases and proteases which dissolve and break down the bone matrix. Here calcium is released into the circulation (Clarke et al, 2008).

Reversal Phase: here osteoclasts disappear and osteoblasts pre-cursors are recruited from the mesenchymal stem cells which then proliferate and differentiate into osteoblasts. Formation Phase: here mature osteoblasts start laying down bone matrix called Osteod, consisting of proteins and proteoglycans, which is a new non-mineralized matrix. The osteoblasts then mineralize the Osteod by depositing hydroxyapatite crystals in the presence of adequate supply of calcium and phosphate. Quiescence Phase: this is just a period of rest before commencement of next remodeling (Marx et al.,1992).

VITAMIN D METABOLISM

Vitamin D is a fat soluble vitamin that acts very much like a hormone in the control of calcium and phosphorus homeostasis. It is one of the derivatives of cholesterol. Natural nutritional sources of vitD include fatty fish and fortified diary product. Human milk contain little vitD, generally less than 20-40iu/l. Thus, exclusively breastfed infants are at risk of rickets especially those with darkly pigmented skin (Steven et al., 2017).

It comprises a group of sterols; the most important of which are Cholecalciferol (vitD3) and Ergocalciferol (vitD2). Unlike vitD2 which is synthesize by plants, humans only synthesize vitD3 which can also be obtained from diet. Although vitD3 is more active than vitD2, but current series suggest that both can be use by human and are both hydrolyzed in the liver and kidney to active vitD (Bikle et al., 2015).

VitD3 (cholecalciferol) is produced in the skin (in both epidermis and dermis) from cholesterol molecule, 7-dehydrocholesterol. When an UV light falls on the skin, the 7-dehydrocholesterol is activated to cholecalciferol, vitD3 (Strewler et al., 1995). The vitD3 then undergo hydroxylation in 2 steps. The first occurs at the liver at carbon-25 by an enzyme called 25-hydroxylase forming 25-hydroxycholecalciferol. This cholecalciferol which circulates in the plasma as the most abundant of the vitD metabolite, is thought to be a good indicator of overall vitD status and it is also a storage form of vitD and is called pro-vitD (Schwarz et al., 2017).

The second hydroxylation occurs in the kidney at proximal convoluted tubule, PCT where hydroxylation occurs at carbon-1 by an enzyme 1-alpha hydroxylase forming 1,25-dihydroxycholecalciferol which is the active form of vitD known as calcitriol (Strewler, 1995; Steven et al 2017). This cholecalciferol which circulates in the blood stream in minute amounts, is not technically a vitamin but a hormone (Strewler et al, 1995).

The active vitD acts at 3 known sites to tightly regulates calcium metabolism: it promotes absorption of calcium and

phosphorus from the intestine, it increases reabsorption of calcium and phosphates from the kidney and it acts on bone to cause release of calcium and phosphate. These actions result in an increase in the concentrations of calcium and phosphate in the ECF which then leads to the mineralization of Osteod (Schwarz et al., 2017).

Not only bone mineralization, adequate vitD has many important clinical applications. A meta-analysis of a number of randomized control trials demonstrated a positive dose-response relationship between vitD supplementation and osteoporosis/fracture prevention (Bischoff-Ferrari et al., 2009). Supplemental active vitD was successfully shown to be an effective treatment of Psoriasis (Bikle et al., 2012). Clinical trials in individuals with Diabetes Mellitus, DM or prediabetics suggest a benefit from vitD administration with respect to improving or preventing the development of frank DM (Mitri et al., 2011; Pittas et al., 2007).

The data from animal and cell culture studies are very promising that active vitD or its analog can prevent cancer development or retard its progress/metastasis once developed (Bikle et al., 2004). The vitaminD receptor, VDR and CYP27B1 are expressed in the heart, both in the myocytes and fibroblasts (Chen et al.,2008). Therefore, active vitD were shown to supress markers of cardiac hypertrophy, thus preventing cardiomyopathy. Also, deletion of VDR specifically from the heart results in hypertrophy (Chen and Gardner, 2013).

PARATHYROID HORMONE (PTH)

Parathyroid hormone is a hormone secreted by the Chief cells of parathyroid gland. Secretion is stimulated by low serum level of calcium and high serum level of phosphate (Arnold et al., 1993). PTH acts on bone and facilitate resorption of calcium from bones by stimulating osteoclasts. It acts on kidney where it increases renal reabsorption of calcium along with magnesium ions and hydrogen ions but causes renal excretion of phosphate, hence called Phosphate Trashing Hormone. It also increases formation of active vitD from pro-vitD by stimulating 1-alpha hydroxylase enzyme (Arnold et al., 1993).

EPIDEMIOLOGY

The frequency of rickets has been increasing internationally. There are wide geographical variations in the frequency of rickets among children world-wide (Sakr et al., 2016). In developed countries, rickets is a rare disease, incidence of less than 1 in 200,000 were reported (NHS England., 2010). In the USA, vitD deficiency rickets does not generally occur in infants fed proprietry infant formulas, nearly all cases occur in breastfed infants who have dark skin and receive no vitD supplementation (Steven et al., 2017). The incidence of rickets in Europe is similar to that in the USA, in 2013/2014, there were fewer than 700 cases in England (NHS England, 2017).

Middle East is a region that registers some of the highest rates of rickets world-wide (Sakr et al., 2016). In Egypt the prevalence of rickets were found to be about 10.6% (Najada et al, 2004). In Qatar, the prevalence of about 23.9% was reported among <5yr children (Bener et al., 2010). In Saudi Arabia the prevalence rate of rickets was 3.5% in all rachitic compared with 17.3% in non-rachitic infants (Khalil et al., 2014).

In Africa about 30% of outpatients were found to have clinical rickets in Addis Ababa of Ethiopia. In South Africa, 9.3% of children in a rural community have leg signs, 6.8% have hypocalcemia plus elevated ALP, and 41.5% have elevated ALP (Pettifor et al, 1978).

AETIOLOGY

Rickets can be caused by a variety of factors which can be divided into two main groups. The first one is the deficiency of vitamin D as a result of either inadequate exposure to sunlight or limited dietary intake (Hameed et al., 1998). Skin pigmentation was also shown to have effect in the absorption of ultraviolet light, the darker the skin the less absorption. Therefore dark skin can cause vitamin D deficiency (Henderson et al., 1987). The second group of aetiological factors include fat malabsorption from chronic diarrhoear, increased degradation of vitamin D, hepatobiliary diseases, renal diseases and some drugs like anticonvulsants such as phenobarbitone and phenytoin (Hameed et al.,1998).

VARIANTS/CLASSIFICATION

There are many forms of classification of rickets but the commonest and widely acceptable classification is the nutritional and non-nutritional rickets. Nutritional is mainly due to low levels of vitamin D (cholecalciferol or ergocalciferol) in the diet, low levels of serum calcium, poor exposure to sunlight. It is the commonest form of rickets in developing countries but very rare in developed countries due to fortification of diary milk and adequate exposure to sunlight.

Non-nutritional rickets is either due to abnormal vitamin D metabolism such as vitamin D dependent rickets, autosomal recessive disease due to deficiency of 1 alpha hydroxylase, chronic renal disease causing renal osteodystrophy with reduced 1 alpha hydroxylase, chronic liver disease causing reduced absorption of vitD, chronic anticonvulsant therapy with phenobarbitone or phenytoin causing increased metabolism of 25 hydroxycholecal leading to rickets. Also non-nutritional rickets include rickets caused by mineral deficiency, X- linked hypophosphataemia (familial) and rickets of prematurity (Atapattu, 2013).

PATHOPHYSIOLOGY

The pathology produced and the consequent clinical features in rickets result from deficiencies of vitD, of serum calcium, of phosphate or from agents that have adverse effects on bone (Hutchison et al., 1992). In vitD deficiency state, hypocalcemia develops, which stimulate excess secretion of PTH. In turn, renal phosphorus loss is enhanced further reducing deposition of calcium in the bone (Steven et al., 2017).

VitD appears to have direct and indirect effect in bone development and remodelling for prevention of rickets, so deficiencies of vitD result in osteoporosis and fractures as it renders the bone fragile (Bikle et al., 2015).

Intestinal malabsorption of fat and diseases of the liver or kidney may produce the clinical and secondary biochemical picture of nutritional rickets. In such cases, disturbances in calcium homeostasis may be the consequence of renal excretion or may result from intestinal losses, as dietary calcium forms insoluble soaps with malabsorbed fats. Due to increased bone resorption from hypocalcaemia, osteoblast become overactive which produces alkaline phosphatases, ALP that leaks into the extracellular fluid, ECF so that its concentration will significantly raised (Steven et al., 2017).

Anticonvulsants drugs like phenobarb, phenytoin accelerate metabolism of calcidiol which may lead to insufficiency and rickets particularly in children who have darkly pigmented skin and those who are kept primarily indoors. Seizure and tetany can result from the hypocalcemia. All other bony features result from the poor bone mineralization (Schwarz et al., 2017).

CLINICAL PRESENTATION

Generalized muscular hypotonia of unknown mechanism and Craniotabes, which is a thinning and softening of the skull are the early features. If rickets occur at a later age, thickening of the skull develops which lead to frontal bossing and delayed closure of fontanelles. In the long bones, laying down of uncalcified osteod at the metaphyses lead to spreading of those areas producing knobby deformities visualized on radiograph as cupping and flaring of the metaphyses (Atapattu N, 2013).

Weight bearing produces deformities such as bowlegs and knock-knees. In the chest, knobby deformity results in rachitic rosary along the chostochondral junctions. The weakened ribs pulled by the muscles also produce flaring over the diaphragm known as Harrison groove. The sternum is consequently pulled into a pigeon breast deformity (Rajah et al., 2011).

In more severe instances in children older than 2yr, vertebral softening leads to kyphoscoliosis. At the ankles palpation of tibial malleolus gives the impression of double epiphyses (Marfan sign). Because the softened long bones may bend, they may fracture on one side of the cortex, greenstick fracture (Jan et al,2011; Siddiqui et al, 2005).

DIFFERENTIAL DIAGNOSIS

Rare metabolic bone diseases like hypophosphatasia are good differentials for rickets. Others include Jansen syndrome, which is a rare autosomal dominant form of short-limbed deformity in which infant present with metaphyseal chondroplasia, and hypophosphatemic vitD-resistant rickets, which is a hereditary disorder of VitD metabolism. Severe calcium deficiency can also cause a syndrome that is confused with vitD deficiency rickets (Steven et al., 2017).

DIAGNOSTIC WORK-UP

Early diagnostic approach include:

1) Serological Tests: The serum level of calcium is normal or slightly reduced, phosphorus is reduced, ALP is elevated, PTH is elevated, 25-hydroxy vitD and 1,25-dihydroxyvitD are both reduced (Chandna P et al., 2017).

2) Radiography: The best single radiographic view for infants and children less than 3yr is an anterior view of the knee that reveals the metaphyseal end and epiphysis of the femur and tibia. This site is best because growth is most rapid in these location, thus the changes are accentuated.

The metaphysis exhibit widening and cupping because of their exagerated normal concavity and irregular calcification. Along the shaft, the uncalcified osteod causes the periosteum to appear separated from the diaphysis (Steven et al., 2017).

Generally, X-rays may show bending of shaft of long bones, cupping(concavity of the metaphysis), splaying(widening of the metaphyseal end of the bone) and fraying(widening and irregularities of the growth plate) of the metaphysis, widening of epiphysial plate (Chandna P et al., 2017).

TREATMENT

Treatment for rickets may be administered gradually over several months or may be a single day dose of 15,000mcg (600,000iu) of vitD, Cholecalciferol (Patel et al., 2017). If the gradual method is chosen, 125-250mcg (5000-10000iu) is given daily for 2-3months until healing is fully established and the ALP is approaching reference range (Steven et al., 2017). Success of this method depends on compliance. If the vitD is administered in a single day, it is usually divided into 4 or 6 oral doses. An IM injection is also available.

A daily calcium intake of 1000mg or 2000mg result in more rapid radiographic healing than 500mg. Complete healing of nutritional rickets may take some children longer than 24weeks (Thacher et al, 2004). If severe deformities have occurred, orthopaedic correction may be required after healing. A consultation with paediatric endocrinologist is also required (Steven et al., 2017).

COMPLICATIONS

Rickets as a metabolic disease causes serious morbidity ranging from poor growth, motor developmental

abnormality, hypocalcaemic convulsion, short stature, skeletal deformities and dental defects (Behman et al., 2000). Other complications include mental disorders like schizophrenia and respiratory diseases like pneumonia (Muhe et al., 1997).

PROGNOSIS

Rickets has a very good prognosis, with sufficient vitamin D administration healing begins. Deformities disappear after 2-3years of treatment (Behman et al, 2000).

PREVENTION

There are three level of prevention: primary, secondary and tertiary. Primary prevention is the best method of prevention. It entails public enlightment about the importance of vitamin D supplementation for breastfed infants (Spence et al., 2004). The recommendation of vitamin D supplementation is 400i.u/l for infants and 600i.u/l for children above 12months (Craig et al., 2016). Adequate exposure to sunlight is an important primary preventive strategy, however it should be cautious and should be avoided in infants less than 6months due to fear of skin cancer (Lawrence et al., 2003). Many studies have link low maternal nutrition and low vitamin D status during pregnancy and lactation with risk of rickets. Therefore, adequate maternal nutrition and maternal vitamin D supplementation of 6000i.u/d during pregnancy and lactation is also an important primary preventive strategy (Mahon et al., 2010).

When primary preventive strategy failed, then secondary and tertiary prevention become paramount. Secondary prevention means to identify and curtail subclinical rickets before it become clinical rickets (Spence et al., 2004). To detect subclinical rickets, Alkaline Phosphate should be measured in a high risk individuals and high level should prompt further investigation such as wrist radiograph and serum 25-hydroxyvitaminD (Joiner et al., 2000). Presence of radiographic changes that are consistent with rickets and low serum 25-hydroxyvitaminD is a confirmation of subclinical rickets (Pettifor et al., 1980). Patient with subclinical rickets should be given higher doses of vitamin D rather than the 400iu/l (Spence et al., 2004).

Tertiary prevention simply means treating individual with clinical rickets to prevent development of complications (Spence et al., 2004).

CONCLUSION

This review demonstrates that Rickets is still prevalent in many part of the world and is ranked among the 5 most prevalent diseases of young children in developing countries which are frequently found in African, Asian, and Middle Eastern settings. It is also evident from the review that Rickets can be caused by a wide variety of underlying nutritional deficiencies, systemic diseases or genetic defects. There is significant overlap in the clinical presentations of the various forms of rickets and the risk for misdiagnosis is great. Therefore, high index of suspicion is required in all patients with features resembling Rickets.

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