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OSTEOPOROSIS, OSTEOPENIA AND OSTEOMALACIA

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Abstract:

Osteomalacia, osteopenia, and osteoporosis are distinct bone diseases each with characteristic pathogenesis, risk factors, and aetiologies. Osteomalacia is a disease of defective bone mineralization of osteoid and impaired remodelling at sites of bone turnover. It occurs chiefly due to vitamin D deficiency, inadequate serum and extracellular levels of essential minerals for bone growth (particularly calcium and phosphate), alteration in pH (such as in renal tubular acidosis, chronic kidney disease, and metabolic acidosis), or administration of direct mineralization inhibitors such as etidronate, aluminium, or fluorides. Osteoporosis is characterized by reduced bone mass either due to decreased remodelling or excessive resorption. The main pathogenesis of osteoporosis is defective development of normal bone density due to reduction of the sex hormone influence on bone development. The main causes of osteoporosis are hypogonadism, androgen insensitivity syndromes, and delayed puberty. Other risk factors include excessive alcohol consumption, heavy smoking, low body mass index, low levels of physical activity, vitamin D deficiency, hypercalciuria, diabetes mellitus, cerebrovascular stroke, history of bone fractures, hemochromatosis, anorexia nervosa, growth hormone deficiency, chronic steroid use, and antiepileptic drugs (e.g. phenytoin). Osteopenia is considered a precursor to osteoporosis or a less severe form of osteoporosis. It has almost the same pathogenesis, aetiology, and risk factors of osteoporosis. This article will address the differences between osteomalacia, osteoporosis, and osteopenia as regards the pathogenesis, risk factors, and causes.

Keywords: *Osteomalacia, osteopenia, osteoporosis.*

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INTRODUCTION:

Several bone diseases are prevalent among different age groups. Three distinct diseases exist namely osteomalacia, osteoporosis, and osteopenia. Though the three diseases are sometimes confused together, each of them represents a distinct disease with peculiar pathogenesis, aetiology, and risk factors. The clinical presentation of the three diseases is similar. They may be asymptomatic, or may present with diffuse bone pains and aches, bone tenderness, muscle weakness, difficulty walking, or even pathological fractures [1-3]. On physical examination, proximal muscular weakness, generalized or localized bone tenderness, waddling gait, and hypotonia can be revealed. Asymptomatic cases can be diagnosed on radiological basis [1,2].

Though the clinical presentation is similar, the three diseases are distinct diseases. Osteomalacia is a disease of defective bone mineralization of osteoid and impaired remodelling at sites of bone turnover [3]. Osteoporosis and osteopenia are diseases characterized by reduced bone mass either due to decreased remodelling or excessive resorption [1,2]. The main pathogenesis of osteomalacia is defective bone mineralization due to vitamin D deficiency, inadequate serum and extracellular levels of essential minerals for bone growth (e.g. calcium), alteration in pH (e.g. renal tubular acidosis), or administration of direct mineralization inhibitors (e.g. etidronate) [4,5]. The pathogenesis of osteoporosis and osteopenia, on the other hand, implies defective development of normal bone density due to reduction of the sex hormone influence on bone development [1,2]. The aim of this article is to enlighten the differences between osteomalacia, osteoporosis, and osteopenia as regards the pathogenesis, risk factors, and causes.

OSTEOMALACI:

Osteomalacia is a bone disorder characterized by reduction of bone mineralization of the newly synthetized bones at areas of regenerating bones (or bone turnover) [6]. It is to be noted that osteomalacia is not a synonym for rickets. Risks is also a bone disorder of impaired mineralization, but the defective mineralization occurs at the cartilage not the bones at epiphyseal growth plates. Therefore, both rickets and osteomalacia may occur simultaneously in children. However, adults experience only osteomalacia as the epiphyseal growth plates close [7].

Regarding the pathogenesis of osteomalacia, appropriate understanding of normal physiology of bone formation and resorption. On a continuous basis, about 7% of the Haversian and trabecular surfaces of the bone undergo remodeling and formation of new bone. The first step of remodeling is excavating the surface of bone followed by recruitment of osteoblasts. When activated, osteoblasts lay organ matrix referred to as “osteoid” which mature over about two weeks under action of several enzymes. After maturation, mineralization starts. Amorphous calcium phosphate is deposited on bone surface, converted to hydroxyapatite, and then taken up by mitochondria to be transported to matrix vesicles where phosphate is available [8]. The process of bone remodeling can be clinically measured by radiological histo-morphometric study utilizing double tetracycline labelling techniques. Labelled tetracycline antibiotic is administrated in two courses separated by a couple of days. The tetracycline is deposited in the form of bands in front of mineralization bands, and can therefore by easily visualized using a fluorescence microscope. The site and pattern of deposition of the two separated courses of the antibiotic will give an approximate estimate of the bone growth rate. In iliac crest, the normal distance between the two tetracycline bands deposited should be around 0.6 microm/day [9]. In osteomalacia, histomorphometry double tetracycline labelling studies reveal reduced distance between the two deposited tetracycline bands, and characteristic widened osteoid seam appearance of the unmineralized matrix. The distance between tetracycline bands is usually below 0.6 microm/day, and the osteoid volume is usually more than 10 percent [5]. It is essential that both of these features exist simultaneously to reliably diagnose osteomalacia because many other disorders may reveal one of these features [5].

For appropriate mineralization to occur, there should be healthy adequate newly-formed osteoid, normal serum and extracellular levels of essential minerals for bone growth (particularly calcium and phosphate), normal quantity and quality of active enzymes necessary for the mineralization process to proceed (particularly alkaline phosphatase), and normal tissue pH for the reactions to occur. Lack of one or more of these factors can result in defective mineralization [4]. Furthermore, mineralization may be impaired in the presence of various substances that inhibit calcifications such as aluminum, fluorides, or etidronate [10].

Osteomalacia occurs as a result of various diseases and conditions that cause hypocalcaemia, impaired

mineralization, or hypophosphatemia. One of these conditions is vitamin D deficiency particularly among adults. Recently, the prevalence of vitamin D deficiency is increasing, and considerable reduction in active forms of vitamin D (i.e. levels of 25-hydroxy-vitamin D below 25 nmol/L) are associated with hypocalcemia, hypophosphatemia, and consequently osteomalacia [11]. The main mechanisms that result in deficiency of vitamin D include Hence, vitamin D deficiency and osteomalacia are particularly common among individuals who are inadequately exposed to sun ultraviolet rays (lack of photoisomerization), and those with malabsorption such as ulcerative colitis, Crohn's disease, gastrointestinal bypass surgeries, … etc.) [3]. Other mechanisms of vitamin D deficiency include impaired hydroxylation at the 25-hydroxylation site in the hepatic tissue, impaired hydroxylation at the one alpha site in renal tissue, or insensitivity of the end organs to the active form of vitamin D (1,25 di-hydroxy-vitamin D) [3].

As calcium is one of the essential minerals for the process of bone remodeling, hypocalcemia is a common cause of osteomalacia. Inadequate dietary calcium intake can contribute in the pathogenesis and development of both rickets and osteomalacia, even with adequate exposure to ultraviolet sun rays. Phosphate is also necessary for bone remodeling and, along with vitamin D deficiency and hypocalcemia, hypophosphatemia is a third important cause of osteomalacia. Vitamin D deficiency leads to reduction of serum calcitriol level, reduction in intestinal absorption of calcium, hyperparathyroidism secondarily, and subsequent increased phosphate excretion in urine. Other less common causes of hypophosphatemia and osteomalacia exist such as tumor-induced osteomalacia (which results in renal phosphate wasting), hereditary hypophosphatemia, drug-induced Fanconi syndrome (associated with wasting of phosphate from proximal renal tubules), and paraneoplastic renal phosphate wasting syndrome [6,12-14].

Impairment of renal parenchyma pH, such as the case in renal tubular acidosis, can result in osteomalacia. In this setting, phosphate and calcium wasting are increased resulting in secondary hyperparathyroidism and defective bone mineralization [15]. Chronic kidney disease is another important and multifactorial cause of osteomalacia. In chronic kidney disease, the defective bone remodeling occurs as a result of decreased activation of vitamin D at the one alpha site, associated metabolic acidosis, and administration of aluminum [16].

Lastly, several medications that possess a direct inhibitory effect on the mineralization process can result in osteomalacia. Bisphosphonates (particularly etidronate) are the prototype of these medications. Bisphosphonates are structurally similar to a natural inhibitor of mineralization called 'pyrophosphate'. Therefore, continuous use of some forms of bisphosphonates (e.g. etidronate) can result, on a long-term basis, in defective bone mineralization, impaired remodeling, and subsequently osteomalacia. However, the newly developed nitrogen-containing bisphosphonates (such as risedronate and alendronate) have a low potential of mineralization inhibition and, thus, do not cause osteomalacia [17,18]. Less common inhibitors of mineralization include fluoride and aluminum [19,20].

OSTEOPOROSIS:

Osteoporosis is another common bone disorder associated with considerable morbidity and mortality, particularly among elderly. Osteoporosis is more prevalent among males than females, and it is estimated to be a contributing factor for about 40-60% of fractures in elderly. Men at age of 60 years have a 25% risk for developing an osteoporotic fracture, and the risk increases with age that above the age of 90, one in each seven men are vulnerable to osteoporotic fractures [21,22].

Osteoporosis is characterized by reduced bone mass either due to decreased remodelling or excessive resorption [2]. Under normal physiological conditions, the peak bone mass occurs after puberty through the effect of sex hormones. Sex hormones increased levels, noted after puberty, result in a marked increase in bone mineral density (BMD) particularly at the cortical bones [23,24]. Thus, the main determinants of peak bone mass and bone mineral index are sex hormones and timing of puberty. Other less common but equally important determinants include chronic illnesses, genetic predisposition, and drugs with direct inhibitory effect on bone density accrual [25,26].

Both estrogen and testosterone are fundamental for acquisition of normal bone density. Testosterone level was reported to be significantly correlated with bone mineral density, and men with total testosterone level below 200 ng/dL had a triple hip osteoporosis and hip fracture rate in comparison with men with high testosterone levels (more than 200 ng/dL) [27].

Estrogen association was bone density was reported to be stronger than testosterone and androgen [28]. Many literature studies reported a strong positive correlation with serum estradiol levels and bone density [28]. Moreover, fracture rates were reported to be significantly higher among men with low estradiol levels than those with low testosterone levels [29]. Though the role of sex hormones in the development of normal bone density is well-stablished, their role in age-related diminution of bone mineral density remains controversial [29]. Other hormones are also implicated in the development of normal bone density and are thought to play a role in age-related reduction in bone density. Those hormones include parathormone (PTH), active forms of vitamin D (i.e. 25-hydroxy vitamin D and 1,25 di-hydroxy vitamin D) and insulin-like growth factor-1 (IGF-1) [30].

Many diseases and conditions can result in osteoporosis. Prototypic examples include idiopathic hypogonadotropic hypogonadism, complete androgen insensitivity, and delayed puberty. Patients with idiopathic hypogonadotropic hypogonadism have significant reductions in both cortical and trabecular bone mineral density. They have a notable higher prevalence of osteoporosis even before puberty [31]. Patients with complete androgen insensitivity have reduced shaft bone density than their healthy counterparts [32,33]. Men with history of delayed puberty were also found to have reduced bone mineral density in several bones (e.g. radius, femur, and lumbar spine) [34].

Assessment of reduced bone mineral density for diagnosis of osteoporosis can be carried out via multiple measurement techniques. The most common of which are quantitative computer tomography and dual energy X-ray absorptiometry. Quantitative computer tomography can be used to measure trabecular bone density of vertebral bodies. Dual energy X-ray absorptiometry (DEXA) is another sensitive technique for measurement of bone mineral density, particularly the degenerative changes in the posterior-anterior projections of the vertebral spine [2].

Many risk factors are associated with an increased vulnerability to osteoporosis. These risk factors include excessive alcohol consumption, heavy smoking, low body mass index, low levels of physical activity, vitamin D deficiency, hypercalciuria, diabetes mellitus, cerebrovascular stroke, history of bone fractures, hemochromatosis, anorexia nervosa, growth hormone deficiency, chronic steroid use, and antiepileptic drugs (e.g. phenytoin) [2,35,36].

OSTEOPENIA:

Osteopenia is, like osteoporosis, a bone disease characterized by reduction in bone density. Osteopenia and osteoporosis are considered diseases of the same spectrum, with osteopenia representing a milder or less severe form of osteoporosis. In several literature reports, osteopenia is considered a precursor to osteoporosis [1,37].

As aforementioned, bone mineral density can be measured by quantitative computer tomography and dual energy X-ray absorptiometry. Representation of bone mineral density is expressed by many scores such as T-score, Z-score, and areal density. The T-score has a cut off value below which defective bone mineralization is diagnosed. In normal individuals, Z-score should be -1 or more. Scores between -1 and -2.5 indicate osteopenia, and scores below -2.5 indicate osteoporosis [38].

Osteopenia has the same pathogenesis of osteoporosis. It results mainly from reduced sex hormones (i.e. estrogen and testosterone) on bone mineralization, and it is prevalent among men with hypogonadism and women with low estrogen levels. Physical activity, body weight, smoking, alcohol overuse, inadequate dietary intake of calcium, vitamin D deficiency, and chronic medical conditions (e.g. diabetes mellitus, hypercalciuria, malabsorption syndrome, cerebrovascular strokes ...etc.), history of previous fractures, history of fall, and chronic steroid use are established risk factors for osteopenia [37-39].

CONCLUSION:

Osteomalacia, osteopenia, and osteoporosis are distinct bone diseases each with characteristic pathogenesis, risk factors, and aetiologies. Osteomalacia is a disease of defective bone mineralization of osteoid and impaired remodelling at sites of bone turnover. It occurs chiefly due to vitamin D deficiency, inadequate serum and extracellular levels of essential minerals for bone growth (particularly calcium and phosphate), alteration in pH (such as in renal tubular acidosis, chronic kidney disease, and metabolic acidosis), or administration of direct mineralization inhibitors such as etidronate, aluminium, or fluorides. Osteoporosis

is characterized by reduced bone mass either due to decreased remodelling or excessive resorption. The main pathogenesis of osteoporosis is defective development of normal bone density due to reduction of the sex hormone influence on bone development. The main causes of osteoporosis are hypogonadism, androgen insensitivity syndromes, and delayed puberty. Other risk factors include excessive alcohol consumption, heavy smoking, low body mass index, low levels of physical activity, vitamin D deficiency, hypercalciuria, diabetes mellitus, cerebrovascular stroke, history of bone fractures, hemochromatosis, anorexia nervosa, growth hormone deficiency, chronic steroid use, and antiepileptic drugs (e.g. phenytoin). Osteopenia is considered a precursor to osteoporosis or a less severe form of osteoporosis. It has almost the same pathogenesis, aetiology, and risk factors of osteoporosis.

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