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ROLE OF IMAGING IN BONE DISORDERS

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Abstract:

Introduction: *The term 'metabolic diseases of bone' refers to the group of conditions where abnormalities occur to the bony mass, hemostasis of bone-related substance, the turnover of bone tissue, or the growth of bones. The most common disease in this group is osteoporosis which leads to a generalized bony mass loss along with destruction and degeneration of the microarchitecture of the bone tissue. In cases where impairment occurs during the development of chondrocytes, which is usually associated with growth plate cartilage mineralization failure, the clinical picture of rickets manifest by the development of widening of the growth plates along with fraying of the metaphyses at greatest growth rates areas. When mineralization of the new bone tissue is impaired, this will lead to the development of osteomalacia which is characterized by the presence of Looser zones. Another metabolic condition in the bone is hypophosphatemia which is a hereditary condition that also cause impairment in the mineralization of bones and is associated with several clinical phenotype.****Aim of work:*** *In this review, we will discuss the most recent evidence regarding imaging in bone disorders.****Methodology:*** *We did a systematic search for the role on imaging in bone disorders using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked for recent advances in the radiographical diagnosis of bone disorders All relevant studies were retrieved and discussed. We only included full articles.****Conclusions:*** *The term 'Metabolic conditions of the bone' refers to a wide range of diseases that lead to the development of abnormalities in the mass of bones, mineralization of bones, turnover of bones, and/or growth of bones. The most common condition of metabolic bone diseases is osteoporosis which usually affects postmenopausal women. Osteoporosis lead to the development of abnormal microarchitecture of bones which results from the loss of bone mass. Osteomalacia and rickets, on the other hand, are a result of abnormal or failed mineralization of bones. Other diseases include endocrinal dysfunctions like hypothyroidism, hyperthyroidism, hyperpituitarism, and hyperparathyroidism. It is crucial to understand exact mechanisms of these diseases to be able to correctly and early diagnose the disease and treat properly. Further studies are still required to further understand these conditions and develop better therapies that will prevent the development of severe skeletal complications.*

Key words: *Imaging, radiology, bone disorders*

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INTRODUCTION:

The term 'metabolic diseases of bone' refers to the group of conditions where abnormalities occur to the bony mass, hemostasis of bone-related substance, the turnover of bone tissue, or the growth of bones. The most common disease in this group is osteoporosis which leads to a generalized bony mass loss along with destruction and degeneration of the microarchitecture of the bone tissue. In cases where impairment occurs during the development of chondrocytes, which is usually associated with growth plate cartilage mineralization failure, the clinical picture of rickets manifest by the development of widening of the growth plates along with fraying of the metaphyses at greatest growth rates areas. When mineralization of the new bone tissue is impaired, this will lead to the development of osteomalacia which is characterized by the presence of looser zones. Another metabolic condition in the bone is hypophosphatemia which is a hereditary condition that also cause impairment in the mineralization of bones and is associated with several clinical phenotypes.

In cases of hyperparathyroidism, the pathology also affects the bone tissue by causing higher bone resorption leading resorption of the subperiosteal tissue of the hand. In patients with chronic kidney disease, secondary hyperparathyroidism can lead to the development of renal osteodystrophy where the patient will have a syndrome of osteosclerosis, osteopenia, and the presence of a 'rugger jersey spine'. Hypoparathyroidism, on the other hand, is usually a result of iatrogenic damage, but can sometimes occur due to other etiologies. In patients with chronic hypoparathyroidism, an increase in the mass of bone tissue is usually observed.

Other causes of bone metabolism conditions include thyroid hormone dysregulations as thyroid hormone is generally responsible for the regulation of endochondral formation of bones. For example, in cases of congenital hypothyroidism that are left untreated, patients will be found to have delayed age of bone and irregular or even absent distal femoral bone. Moreover, hands and feet could show thyroid acropachy and proliferation of soft tissues. Acromegaly, on the other hand, is associated with excess amounts of growth hormone which will lead to excessive proliferation of both soft tissues and bones. Nutritional deficiencies can also affect bone metabolism. For example, the deficiency of vitamin C, which is known as scurvy, leads to impairments of the posttranslational modification of collagen, which will eventually cause pathological fractures and hemorrhages.

In this review, we will discuss the most recent evidence regarding imaging in bone disorders.

METHODOLOGY:

We did a systematic search for the role on imaging in bone disorders using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). Our search also looked for recent advances in the radiographical diagnosis of bone disorders All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: imaging, radiography, x-rays, CT scan, MRI, bone diseases, and bone pathology.

Osteoporosis:

The definition of osteoporosis states that it is a pathology where bone is diminished but is normal otherwise. The state of osteoporosis usually develops in cases where the formation of bone is insufficient or when the resorption of bone tissue is higher than the formation. Osteoporosis is most likely generalized but can be local in some cases like disuse osteoporosis. Imaging can be helpful and detect changes of osteoporosis, which correlate with the rate and degree of the disease.

Osteoporosis is considered to be the single most common cause of metabolic abnormalities of bone tissue. It is estimated to be prevalent in up to 18% of elderly females and up to 4% of elderly males [1-2]. Prior to the development of techniques that can detect and estimate the mass of bone tissue, the diagnosis of osteoporosis was only made when a patient develops a pathological fracture with minimal or no trauma. However, this was changed when imaging techniques were later developed leading to providing accurate estimates of bone mass. These imaging modalities include CT scan, dual-energy photon absorptiometry, and more recently, dual-energy x-ray absorptiometry [3].

Significant morbidities and complications are usually associated with osteoporosis. The most important complication in patients with osteoporosis is pathological fractures, which were estimated to occur around the world as frequent as a fracture every three seconds, leading to more than nine million fractures annually [4]. Moreover, it is estimated that over 35% of elderly females and 20% of elderly males will develop a pathological fracture related to osteoporosis at least once during their lifetime[5]. Most common sites of pathological fractures in patient with

osteoporosis are the hip, the spine, and the forearm [6]. Patients with severe advanced osteoporosis may suffer from the inability to detect fractures that are not associated with displacement. In these cases, CT or MRI imaging modalities can assist the diagnosis and detection of the fracture, especially if X-ray shows normal findings but the patients suffers from severe pain.

As we previously stated, clinical picture of osteoporosis result from the state of decrease mass of bone tissue leading to a significant deterioration of the microarchitectural bone structure ad resulting in fragility of bone tissue and pathological fractures. In the year 1994, the WHO released their statement where they defined osteoporosis as having a density of bone that is 2.5 less than a normal adult. This correlates with a dual-energy x-ray absorptiometry giving T score that is less than -2.5. this diagnosis is most likely found in postmenopausal females and elderly men [7]. This definition was made as they observed more accurate diagnosis and prediction of fractures when the threshold score was set to be -2.5. however, in some cases, an individual could have osteoporosis while still having a normal score. This is defined as osteopenia by the WHO and is indicative of the underlying presence of a mild early osteoporosis.

The pathophysiology of primary osteoporosis can differ between both sexes. Generally, primary osteoporosis is categorized into type I and type II. However, this distinction is only theoretical and does not have clinical impacts, which make it not routinely used in clinical practice. When studying osteoporosis in females, estrogen usually decreases dramatically following menopause leading to the initiation of a phase with acceleration of loss in bone tissues. This mainly manifests in trabecular bone tissue[8]. Males, on the other hand, develop the pathology more gradually and less dramatically than females. When reaching the age of eighty years, both sexes will usually have similar rates of the disease.

Secondary osteoporosis, on the other hand, can have different pathophysiologies according to the underlying etiology. For example, the presence of hypogonadism in hyperprolactinemia can lead to more rapid resorption of bone, and the presence of anorexia nervosa or other eating disorders can lead to imbalance in energy that will worsen bone resorption. Other causes of secondary osteoporosis include gonadal failure, Klinefelter syndrome, hypothalamic dysfunctions, Turner syndrome, and pituitary dysfunctions. Hyperparathyroidism and hyperthyroidism are also considered to be important causes of osteoporosis due to the bone resorption that results of them. the deficiency of growth hormone, on the other hand, acts by a different mechanism which is the interference of proper formation of bone tissue leading to the development of osteoporosis. In Cushing disease, regardless of its etiology, low density of bone tissue will result in osteoporosis [9].

All these mentioned mechanisms have been associated with generalized osteoporosis. On the other hand, regional (or localized) osteoporosis is generally less common and is associated with disuse atrophy. However, it can also be a result of arthropathies, large-joints osteoporosis, and complex regional pain syndrome [10].

In areas of the body where bones have little cortical component like the vertebral body bones (which only consists of five percent cortical bone), horizontal trabecular bone is usually thin leading to the early development of osteoporosis symptoms in susceptible patients. Recent studies have concluded that the strength of bone tissue is directly correlated with both the structure and mineral density [11]. Therefore, the presence of thin horizontal trabeculae in the vertebral body bones is associated with the development of osteoporosis more early than other bones in the body. This can be clearly clarified and early detected using newer advanced techniques in CT and MRI imaging [11].

Rickets and Osteomalacia:

Rickets is defined as the presence of an interruption of organized bone development due to dysfunctional mineralization within the growth plates. Osteomalacia, on the other hand, is the presence of an insufficient mineralization of cortical and trabecular osteoid. Before the fusion of the growth plate occurs, osteomalacia and rickets can occur simultaneously. Rickets results from the presence of a hypophosphatemic status, while osteomalacia can occur as a result of any dysfunction during the pathway of bone mineraliztion, including hypocalcemia, hypophosphatemia, pH abnormalities, and mineralization inhibition [12].

Clinical manifestations of rickets are generally more obvious in sites that have the highest growth rates like the knee, the distal part of the tibia, the proximal part of the humerus, the distal part of the radius, the distal part of the ulna, and the anterior end of the middle ribs. These changes are usually present in the metaphyseal part of the growth plate. The presence of failing mineralization process will result in the

development of disorganized growth of chondrocytes, which will, in the presence of hypophosphatemia, cause hypertrophied chondrocytes to undergo abnormal apoptosis, eventually resulting in abnormally long cartilage tissue that will cause the observed radiological findings of cupping and frying [13].

Osteomalacia is generally associated with a reduction in the mass on bone tissue. However, this is not necessarily present in all patients and is not required for the diagnosis of osteomalacia. The reason behind this is that losing the ability of new osteoid mineralization does not necessarily mean the presence of skeleton with low mass of bone tissue.

Another pathognomonic characteristic of osteomalacia is the presence of Looser zones which appear in late osteomalacia and result from the abnormal accumulation of unmineralized bone in the sites of vessels or tress. The development of these zones is not associated with trauma, and can occur in bilateral symmetric pattern leading to the appearance of horizontal radiolucent bands. Looser zones had previously been called pseudofractures, but they are considered a subtype of fractures that is associated with deficiencies and are usually painful. Looser zones occur usually at the same sites where stress fractures occur. These include the femoral neck inner margin, and the pubic rami. However, in some cases, looser zones can develop in bones that do not bear weight and where a stress fracture is usually rare. These sites include the femoral shaft lateral border near the lesser trochanter, the ischium, and lateral aspect of the scapula, and the iliac wing.

Hypophosphatasia:

Hypophosphatasia is a hereditary disorder that has a relatively low incidence and is a result of genetic mutations in the genes responsible for tissue-nonspecific alkaline phosphatase transcription. These mutations will lead to the abnormal accumulation of pyrophosphate, which acts as a bone mineralization inhibitor. Hypophosphatemia leads to the development of clinical manifestations that are similar to osteomalacia or rickets, with a wide variation of clinical picture according to the phenotype and the severity. Four main categories of hypophosphatemia are present, and these are: perinatal, infantile, childhood, and adult, with the perinatal subtype being the most severe phenotype, and the adult subtype being the least severe phenotype [14]. The mineralization process is generally extremely poor in patients with the perinatal subtype, which will lead to the possible absence of entire spinal segments on the obtained radiographic images. On the other hand, the childhood and the infantile subtypes are associated with craniosynostosis. Following the use of enzyme replacements of asfotase alfa, skeletal manifestations can potentially improve. This agent has been recently developed to treat patients with congenital hypophosphatemia [15].

Hyperparathyroidism:

The state of hyperparathyroidism is defined as having pathological increase in the levels of the parathyroid hormone that will lead to an increase in the resorption of bones. Hyperparathyroidism can be either primary or secondary. Primary hyperparathyroidism results from the secretion of the parathyroid hormone from autonomously from the parathyroid glands with the absence of negative feedback, that usually occurs from elevated calcium levels in the serum. The etiology of primary hyperparathyroidism is usually adenoma, but can results in some cases from the hyperplasia of the four parathyroid glands. In very rare cases, parathyroid cancer can lead to the development of primary hyperparathyroidism [16].

Secondary hyperparathyroidism, on the other hand, is more common than primary hyperparathyroidism and results from abnormally decreased levels of calcium in the serum. Secondary hyperparathyroidism occurs most commonly as a result of late chronic kidney disease, leading to hyperplasia of the parathyroid chief cells. Moreover, the presence of a kidney disease will decrease the rates of metabolism of the parathyroid hormone leading to further increases in its levels. The nutritional deficiency of calcium or vitamin D can also cause the development of secondary hyperparathyroidism. Clinical manifestations of secondary hyperparathyroidism vary based on the underlying etiology [17].

In more than 90% of hyperparathyroidism cases, the earliest and most obvious skeletal findings will be seen in hands [18], where the resorption of the subperiosteal bone starts from the middle phalanges of the middle fingers forming irregular laces and at the distal phalanges forming acro osteolysis. Later throughout the progression of the disease, scalloping resorption can appear leading the appearance of pseudoperiostisis. Generally, the presence of subperiosteal bone resorption on radiological images is pathognomonic or hyperparathyroidism (30). Apart from the hand, subperiosteal bone resorption can be observed in the lamina dura around the teeth, the humerus, the ribs, the upper medial part of the tibia, and the femur. Resorption can also sometimes occue

within the endosteal bone, trabecular bone, intracortical bone, subligamentous bone, and subchondral bone. When occurs in the skull, hyperparathyroidism-associated bone resorption is said to have 'salt and pepper' pattern. On the other hand, a 'smudgy' pattern is associated with trabecular bone resorption and a 'cortical tunneling' appearance is associated with intracortical bone resorption.

Renal Osteodystrophy:

The term 'Renal osteodystrophy' is used to describe the presence of the complex findings associated with secondary hyperparathyroidism due to chronic kidney disease. These findings include both the findings of hyperparathyroidism and osteomalacia (or rickets when it occurs in the pediatrics population). Radiographic investigations in these patients usually show increased density of the bone especially in the axial skeleton due to the predominance of trabecular bone tissue.

It's not well-understood how this generalized osteosclerosis exactly occurs in these patients. However, some studies suggest that it may be a result of the anabolic activity of the parathyroid hormone, which is usually elevated in these patients. Despite the presence of osteosclerosis, bones are usually weak and these patients have significantly higher risk of developing fractures [19]. A 'striped' pattern, which is also called the rugger jersey appearance, is seen in images of the spine in these patients.

Hypoparathyroidism:

Hypoparathyroidism is usually acquired following iatrogenic damage of the glands during surgeries to the neck. Other less common causes of hypoparathyroidism include autoimmune causes or genetic diseases like DiGeorge syndrome [20]. On the other hand, pseudohypoparathyroidism refers to the peripheral resistance of organs against the parathyroid hormone. Despite being theoretically similar, hypoparathyroidism and pseudohypoparathyroidism can have different findings on radiological imaging [21].

Hypothyroidism:

Hypothyroidism can have many etiologies. When it is congenital, hypothyroidism is associated with severe abnormalities in the skeletal system which will lead to impaired growth. Acquired hypothyroidism, on the other hand, is associated with relatively milder skeletal impairments. Causes of acquired hypothyroidism are many and include iatrogenic injury, thyroiditis (with all its causes), atrophy, amyloidosis, lymphoma, drug-induced, iodine insufficiency, and pituitary hormones deficiency [22].

Scurvy :

Scurvy is the condition where vitamin C is deficient leading to the production of abnormal collagen molecules. This abnormal collagen will cause fragility of the blood vessels along with abnormalities in the matrix of the bone, especially when it affects sites of highest growth rates. Generally, bones appear to be osteopenic with thin cortices.

CONCLUSION:

The term 'Metabolic conditions of the bone' refers to a wide range of diseases that lead to the development of abnormalities in the mass of bones, mineralization of bones, turnover of bones, and/or growth of bones. The most common condition of metabolic bone diseases is osteoporosis which usually affects postmenopausal women. Osteoporosis lead to the development of abnormal microarchitecture of bones which results from the loss of bone mass. Osteomalacia and rickets, on the other hand, are a result of abnormal or failed mineralization of bones. Other diseases include endocrinal dysfunctions like hypothyroidism, hyperthyroidism, hyperpituitarism, and hyperparathyroidism. It is crucial to understand exact mechanisms of these diseases to be able to correctly and early diagnose the disease and treat properly. Further studies are still required to further understand these conditions and develop better therapies that will prevent the development of severe skeletal complications.

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