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Skeletal Disorders and Metabolic Bone Disease

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ABSTRACT

A healthy skeletal system with strong bones is essential to overall health and quality of life. Skeletal system being the framework of the human body, any problem affecting it can bring about great changes in the functioning of body systems. Bone and joint disorders are common and represent a major burden on health economics costs. For exam¬ple, osteoporosis and related fractures are the leading cause of hospital admission in women over the age of 50 years, and >80% of adults over 55 years of age will suffer from osteoarthritis. Treatments of some metabolic disorders have been greatly improved by an increased understanding of bone and joint biology that has been facilitated by advances in unraveling underlying genetic contributions. The features of Metabolic Bone Disease (MBD) include decreased linear growth, skeletal deformity, radiological changes such as osteopenia, fractures and changes of rickets, and biochemical abnormalities such as raised alkaline phosphatase, hypophosphatemia and hypocalcemia. These interactions between bone and joint biology, physiology and genetics have also greatly enhanced the understanding of normal bone function as well as the molecular pathogenesis of meta¬bolic bone disorders.

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INTRODUCTION

Bone is a critical component of the human musculoskeletal system. It not only provides strength to the legs, but also acts as the foundation for cartilage in the moveable joints. Bone diseases are conditions that result in the impairment of normal bone function and can make bones weak. Metabolic bone disease is most often diagnosed by a combination of radiological features, clinical signs and symptoms and biochemistry for serum calcium, phosphate and alkaline phosphatase. Metabolic bone diseases are a heterogeneous group of disorders characterized by abnormalities in calcium metabolism and/or bone cell physiology. They lead to an altered serum calcium concentration and/or skeletal failure. The most common type of metabolic bone disease in developed countries is osteoporosis. Because osteoporosis is essentially a disease of the elderly, the prevalence of this condition is increasing as the average age of people in developed countries rises. Osteoporotic fractures may lead to loss of independence in the elderly and is imposing an ever-increasing social and economic burden on society. It is now recognized that osteoporosis can be of a 'high-turnover' type or a 'low-turnover' type and a bone biopsy is often the only way to definitely establish which kind of osteoporosis is present. The rest of the metabolic conditions are relatively rare and again are often diagnosed without resorting to biopsy.

Bone is a metabolically active tissue that is continually changing in response to the physical stress placed upon the skeleton. This process, known as remodeling, is carefully regulated by parathyroid hormone (PTH) and locally active chemokines and requires adequate blood levels of vitamin D, calcium, magnesium and phosphorus. At a cellular level, osteoblasts are responsible for new bone deposition while osteoclasts are necessary for bone breakdown. During childhood and adolescence, bone mass gradually increases and peaks during early adulthood (age~30), then gradually declines as part of the aging process. However, certain disease processes accelerate mineral loss or the formation of abnormal bone that leads to an increased risk of bone fracture. Metabolic bone disease (MBD) is a term used to describe these abnormalities of bone metabolism.

Bone anatomy and physiology:

Bones are individual organs composed of multiple tissues including bone, cartilage, fat, connective tissue, hematopoietic tissue, nerves and vessels. The human skeleton is composed of 206 bones and is divided into the axial skeleton that includes the skull, hyoid, sternum, ribs and vertebrae and the peripheral skeleton that includes the bones of the limps and the pelvis. The acral skeleton is part of the peripheral skeleton and consists of the

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bones of the hands and feet [16]. Bone formation and function involves a complex coordination among multiple cell types. Additionally, bones are dynamic structures that are constantly remodeled during life in response to various mechanic and hormonic stimuli. This process requires a tightly regulated interplay among the various cell types of bone.

Bones are classified according to their shape and size in cuboid bones (i.e., carpal and tarsal bones), flat bones (bones of the skull, ilium) and tubular bones. The latter are further subdivided into long (i.e., humerus, radius, ulna, femur, tibia, fibula) and short (i.e., metacarpal and metatarsal bones) tubular bones [16]. Additionally, bones are classified according to the manner of embryological development. Thus, membranous bones are formed de novo from undifferentiated connective tissue (intramembranous ossification) whereas enchondral bones are formed by enchondral ossification in which undifferentiated mesenchymal cells differentiate into chondrocytes and form a cartilaginous anlage that will subsequently be replaced by bone [16,17].

Bone Functions:

Bones along with the muscles, tendons and ligands attached on them are responsible for movement and standing [17]. Bone development was critical for the evolution of our species, since it facilitated locomotion and bipedalism (Rodan 2003). Additionally, bones surround cavities in which critical organs are protected from external mechanical forces [17]. For example, skull bones form the cranial cavity where the brain resides. Pleura and thoracic vertebrae form the thoracic cage which is important for the protection of the heart and lungs. The spinal cord is located in the spinal tube. In between the trabeculae of cancellous bone resides the hematopoietic bone marrow.

Apart from their protective role, bone cells have the ability to respond to signals that regulate hematopoiesis. Bone resorption increases diameter of medullary cavity when needed for example in high altitudes. Apart from the obvious structural functions mentioned above, bones are more than a rigid inactive organ and exert various metabolic functions in the body, since they are critically involved in mineral homeostasis. Bones deposit and store minerals, especially calcium and phosphate, which are released when needed. Thus, bone tissue responds to changes in blood calcium and phosphate levels and is involved in restoration of their levels within normal limits [17]. Additionally, bones' large surface absorbs toxins and heavy metals, minimizing their deleterious effects on other tissues.

Additionally, bones play a critical role in the regulation of hematopoiesis. Bone microenvironment provides a supportive microenvironment for the development of mature blood cells from hematopoietic stem cells, known as the stem cell niche.

Interactions between progenitor cells and their microenvironment determine the maturation process, providing both permissive and instructive signals for stem cell differentiation. The hematopoietic stem cell niche is composed of the osteoblasts located along the endosteal surface and the bone marrow blood vessels. It has been proposed that osteoblastic niche provides a quiescent microenvironment for stem cells whereas the vascular niche drives proliferation and further differentiation of hematopoietic stem cells.

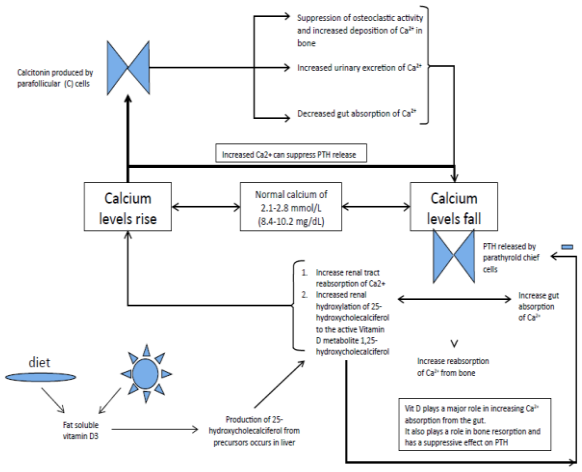

Fig. 1: Calcium homeostasis

Bone metabolism:

Ninety-nine per cent of the body's calcium is contained within bone. These stores are not static and through formation and resorption, bone plays a vital role in calcium homeostasis. Calcium has a number of important roles beyond bone formation. It is involved in signal transduction during synapse function, muscle contractility

and cell division; it also maintains excitable cell membranes. It is a co-factor for many enzymes, particularly those involved in cell death and coagulation. Calcium homeostasis is maintained, principally, by the actions of three hormones, the active metabolite of vitamin D3, 1, 25-dihydroxycholecalciferol, parathyroid hormone (PTH) and calcitonin. The complex control of calcium homeostasis is illustrated in figure 1 and highlights the importance of the alimentary canal in maintaining homeostasis through endocrine and absorptive mechanisms.

Vitamin D and calcium intake:

Hypocalcaemia has been observed in some obese individuals; however this may be due to poor diet [8]. Up to 60-90% of the obese are known to have vitamin D deficiency, even without surgery [20,4] and an inverse correlation between serum vitamin D levels and obesity has been documented [23,5]. Despite this, the deficiency does not seem to translate to clinically relevant consequences such as osteoporosis. Bone health and obesity have a complicated relationship and obesity has been shown to exert a protective effect against osteoporosis. This is likely a result of Wolff's law that states bone is laid down in response to the stresses placed upon it, in this case the skeletal loading that obesity generates. Meanwhile the interplay of osteokines and adipokines has shown homeostatic feedback between bone and the adipose tissue [19]. Leptin, produced by adipose tissue, increases trabecular bone though reduces overall bone mass [10]. Hyper-insulinaemia also seems to plays a role, as mice osteoblasts respond by increasing osteocalcin secretion and subsequently bone turnover and mass [7]. In humans, although weight loss has been shown to reduce insulin, it is unclear whether it is an additional factor [3].

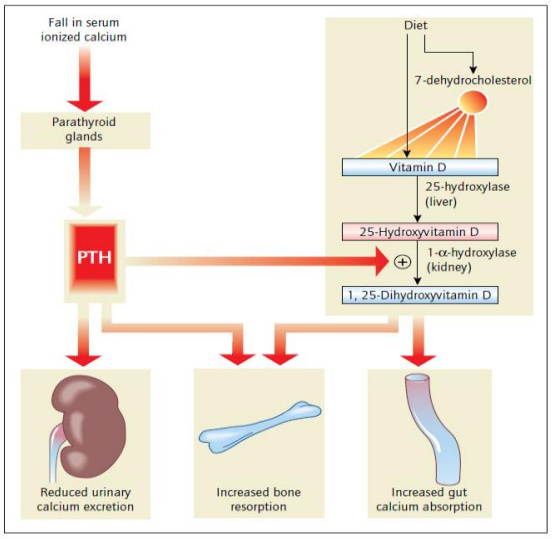

Fig. 2: Regulation of calcium metabolism by parathyroid hormone (PTH) and vitamin D. PTH and vitamin D are the principal hormones responsible for calcium homoeostasis.

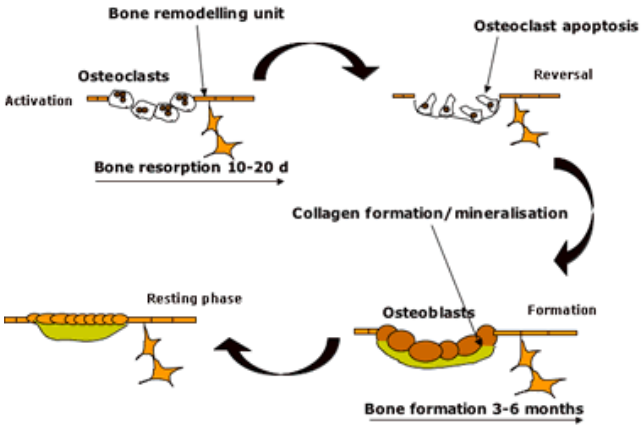

Fig. 3: Bone turnover cycle.

Methods for Assessing Metabolic Bone Changes

Several methods/techniques have been used to quantify bone changes particularly in the context of osteomalacia. Bone biopsy is considered as the gold standard for confirming a suspected diagnosis of osteomalacia [21], but can be unpractical for routine follow up and is not widely practiced. Plain radiographs are useful in identifying osteomalacia as it can cause some typical features. These relate to the softening of bone and include kyphosis, Looser's zones (pseudofractures),

amyloid deposition and osteopaenia. Dual-energy x-ray absorptiometry (DEXA) is also useful and frequently shows reduced bone mineral density (BMD) throughout the skeleton, reflecting the osteopaenia seen in plain radiographs. Radionuclide uptake displays more widespread patterns; these can be diffuse (a super scan) or be discrete (hotspots) [18,15]. However, these changes can frequently be mistaken for metastatic disease, limiting its use in isolation [18,9]. Biochemical studies are routinely used in the identification of metabolic bone disease and whilst hypocalcaemia and

hypophosphatemia can be characteristic of osteomalacia, an increase in the levels of serum alkaline phosphatase (ALP) is the most common biochemical sign. Levels can rise to more than eight times the normal value [1]. Secondary hyperparathyroidism is also characteristically seen; as vitamin D levels fall, its ability to suppress PTH levels fall too.

This rise in PTH increases osteoclastic activity and bone turn over, resorbing calcium from bone. Serum calcium, however, is an unreliable marker, as although total body calcium maybe reduced, serum calcium is often maintained by the action of PTH. Bone turnover can also be measured using markers such as osteocalcin, which in surgically induced weight loss is significantly raised [1,6].

Table 1: Causes of Secondary Metabolic Bone Disease

Osteoporosis	Osteomalacia
Endocrine disease Hyperthyroidism Hypogonadism Hyperparathyroidism Insulin dependent diabetes mellitus	Gastrointestinal and hepatobiliary disease Crohn's disease Radiation enteritis Short bowel syndrome Post-gastrectomy syndrome Pancreatic insufficiency Primary biliary cirrhosis Sclerosing cholangitis Cirrhosis
Gastrointestinal disease Crohn's disease Radiation enteritis Short bowel syndrome Post-gastrectomy syndrome Pancreatic insufficiency	Disorders of vitamin D metabolism Renal disease Liver disease Disorders of vitamin D metabolism Renal disease Liver disease Vitamin D dependant and resistant rickets
Hepatobiliary disease Primary biliary cirrhosis Sclerosing cholangitis Cirrhosis	Drugs that inhibit bone mineralization Anticonvulsants Fluoride Etidronate Aluminum
Malignancy Chemo and radiation therapy Oopherectomy Paraneoplastic syndromes	Other unusual causes Renal tubular acidosis Hypophosphatemia Hypophosphatasia
Drugs and toxins Glucocorticoids Anticonvulsants Therapeutic doses of heparin Excess thyroxine Alcohol Tobacco	Inadequate sun exposure thyroxine Institutionalized patients Higher latitudes Excessive sun screen use Use of clothing that covers entire skin surface
Other Decreased mobility	

Metabolic Bone Disease:

MBD in long-term parenteral nutrition (PN) was first described in the early 1980's when studies from large home parenteral nutrition (HPN) programs began to report that many of their patients developed debilitating bone pain, weakness, hypercalciuria and hypercalcemia. Some of these studies described bone biopsies with increased osteoid formation, defective bone mineralization and decreased bone turnover, which is consistent with OM, while other studies found a reduction in both osteoid and bone mineralization, a picture consistentwith OP [12]. Many of the patients with OM probably had aluminum toxicity, since formulas at that time were made with amino acids derived from casein hydrolysates that contained high concentrations of aluminum. Aluminum was subsequently found in significant amounts in the plasma, urine and bone of these patients [23]. Casein

hydrolysates were eventually replaced with crystalline amino acids, which eliminated most of the aluminum in PN solutions and thus avoided the development of OM in a majority of these patients.

Today the development of MBD is still a concern in HPN patients and may be related to a number of factors including the various components of the PN solution and the conditions for which the PN is prescribed. In this paper we will discuss the prevalence of MBD in patients on long-term PN, the effect of PN on bone metabolism, and finally the evaluation and management

Osteoporosis and Osteomalacia:

The two major forms of MBD are osteoporosis (OP) and osteomalacia (OM). Osteoporosis affects over 28 million individuals in the Unites States, 80% of which are women, and will lead to 1.5 million fractures each year. It occurs when there is a decrease in the total amount of bone with a normal ratio of bone osteoid (the protein matrix of bone made predominantly of collagen) to bone mineral content. Osteomalacia, which means soft bones, is characterized by defective calcification of bone osteoid and leads to a paradoxical increase in bone volume. It is usually caused by vitamin D deficiency and poor calcium absorption. Conditions that lead to MBD are outlined in Table 1. It should be noted that screening tests used to identify an individual with MBD cannot differentiate OP from OM.

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