Paget's disease of bone - causes and treatments

Paget’s disease of the bone, also known as Osteitis Deformans (Paget 1877) is a chronic inflammatory condition that results in the proliferation and softening of the bone that may affect any or all parts in the skeleton (Mann, 1990). It is characterised by increased bone remodelling, bone hypertrophy and abnormal bone structure. It is rarely present before the age of 55, therefore is found in increasing prevalence with advancing age. Overall mortility is low. Paget’s disease is the second most common bone disease in the Anglo-Saxon descent (Kuriara et al, 2007) affecting about 3% of the above 55 in the UK.

Before any ability in recognising the disease is acquired, the knowledge of normal should be understood. The normal human skeleton comprises of 206 bones. Bone is a living tissue consisting of 92% mineral or solids and 8% water (Mann, 1990). The solid matter is mainly collagen matrix hardened by impregnation with calcium salts (Thomas, 1985). Bones develop from either small cartilage models in the eight-week-old embryo or from condensed embryonic tissue known as mesenchyme that forms a dense membrane. The exquisite assembly of functionally distinct cell population is required to support both the structural, biochemical and mechanical integrity of this mineralised tissue and its central role in mineral homeostasis. Mechanical forces and metabolic regulatory signals that accommodate the requirement for maintaining serum calcium and phosphate levels are functioning throughout life (Mann et al, 1990). Bone forms along the path of invading blood vessels. Chondrocytes enlarge (hypertrophy) and proliferate (hyperplasia) about the blood vessels becoming osteocytes as the cartilaginous matrix becomes mineralised. Enchondral ossification is a well

ordered sequential process of converting the cartilaginous model into bone. It is present under the perichondrium which develops within the bone. This process is referred to as modelling (Mann et al, 1990). And any subsequent changes requiring resorption of pre-existent bone followed by deposition of new bone is remodelling. Thus modelling is an early process while remodelling occurs during normal growth and continues until death. Remodelling of bone involves the actions of two principle cells; the osteoclasts and osteoblasts. During remodelling, osteoclasts are recruited to a site on bone surface and the removal of bone mineral and matrix, creating a resorption matrix. As the osteoclasts moves away osteoblasts move in and fill in the pit osteoid, which is then mineralised. In other words, bone is laid down by osteoblasts and resorption occurs as a result of osteoclast action. Bone remodelling is essential in the maintenance of healthy bone and to repair fractures (Grubb, B, 2010)

Paget’s disease can be monostic or polystotic. In most cases, it is monostotic and asymptomatic occurring in the skull, femur, tibia, vertebra or pelvis. This can lead to pain, deformality, fratures, osteoarthritis, nerve compression syndromes and neoplastic transformations. Paget’s disease is a particularly common condition characterised by focal areas of greatly increased bone turnover. Hyperphosphatasia is a comparatively rare but possibly closely related condition. Osteitis Deformans is a disease of patchy distribution throughout the skeleton and is characterised by a great increase in the activity of osteoclasts, which frequently have many more nuclei(up to 100) than do the osteoclasts of e. g hyperparathyroidism. This leads to great increase in bone resorption, thus resulting in corresponding increase in

osteoblastic activity, contributing to an enormous local increase in bone turnover. Consequentially, leading to disorganized (haphazard) laying down of new bones (National Association for the Relief of Paget’s disease). The outcome is that the lamellar bone is replaced by woven bone, there is a loss of Haversian systems and bone architecture is uncoordinated. Due to great increase in bone turnover, increased volume of osteiod is frequently noted, with a normal calcification front (metabolic).

Osteitis Deformans is a common disorder of bone and often familial. Based on demographics of Paget’s disease and awareness of the presence of Paget’s disease in multiple members of the families, Grauer et al suggests that “ genetic, infectious or environmental factors play an important role in its aetiology”. Previously proposed by Hocking et al, mutations in the sequestosome1 (SQSTM1) was confirmed as the main cause of familial and sporadic Paget’s disease. Three different mutations were identified that affected the ubiquitin-binding domain., the most important mutation being at loci p392L. Sequestosome 1 encodes a component of the RANK-NF{kappa}B signalling pathway (Hocking et al). The member of the TNF receptor family RANK is a receptor activator of the NF{kappa}B ligand is involved in osteoclast differentiation. The binding of ligand to RANK also known as osteoprotegerin-ligand activates downstream signalling pathways that suppresses osteoclast activity and therefore helps to control bone remodelling. Kurihara and collegues(2007) proposed that mutation of sequestosome 1 (p62) gene alone is insufficient to induce Paget’s disease. It is also possible that the ubiquitin-binding domain is a mediator of p62 which causes protein-protein interaction to control the NF{kappa}B signalling in

osteoclasts production in reaction to the release of cytokines during inflammation. Any loss of this interaction may cause an amplification of the signalling pathway that leads to increased activation of this pathway (Kurihara et al, 2007). Furthermore in every case of Paget’s disease an additional component “ measles virus nucleocapsid protein (MVNP)” was present in bone biopsy. In contrast to these findings, it can be deduced that p62 mutation alone does not alone to cause Paget’s disease but additional factors are also required for the full phenotype to be expressed (Kurihara et al, 2007).

Typical features of Paget’s disease can be divided into three categories; bone pain, enlarging bones and impaired hearing (Seibel et al, 1999):

- Bone pain is caused by hypervascularity due to disease activity while joint dysfunction due to secondary osteoarthritis evokes the pain pathways. In some patients bone pain can also be associated with bowing that is the result of mechanical incompetence.
- Enlarging of bones can be a sign of danger of nerve compression symptoms, if the base of the skull or vertebral column is affected.
- Impaired hearing is predominately due to sensineural hearing loss and can be rarely due to the involvement of internal auditory canal.

Other features include patient becoming prone to fractures due to decrease in bone strength in the affected regions. These clinical features are present only in small subset of patients and patients can suffer from this disease for years without being diagnosed (Roodman et al).

Serum calcium and phosphate levels usually remain normal in Paget’s disease. Therefore calcium homeostasis is mostly achieved as a result of high bone turnover. This can be monitored through the detection of high urinary calcium. When there is a removal of part of the stimulus to bone formation, hypercalcaemia can develop. Calcitonin can influence significantly by increasing bone turnover (in normal adults it is hypocalcaemic).

A more accurate diagnosis is based on either radiographic abnormalities observed in bone scans and by identifying the elevation of bone formation marker alkaline phosphatase (AP). Serum alkaline phosphatase is elevated as a result of increased osteoblastic activity and therefore serves as an index of bone formation in Paget’s disease (Roodman et al). Nevertheless, high serum AP can also be associated with other symptoms and not all sufferers will have raised serum AP (NIAMS). Radiography is therefore the best diagnosis tool for this disease. Bone areas will show localised enlargement of the bone, cortical thickening, sclerotic changes, osteolytic areas such as V-shaped lesions in long bones and osteoporosis circumscripta in the skull (Grauer et al, 1996). The “ mosaic” structure appearance in bone biopsy can also confirm Paget’s disease when all other methods are not clear indicators (Langston et al).

Unfortunately, Paget’s disease is incurable and therefore once affected; the patients can only alleviate its symptoms by administration of drugs or surgery. Bisphosphonates a class of pyrophosphate are potent inhibitors of bone remodelling. Two types exists that act on osteoclasts via two mechanisms. One is by elevating programmed cell death of osteoclasts by disturbing the production of ATP and the other is by directly binding to

osteoclasts and disrupts its ability to bind to the bone. (Dale et al, 2004). Administration is orally, ideally empty stomach as these drugs have a low absorption rate. Calcitonin is a potent hormonal inhibitor of bone resorption. It has the ability to inhibit osteoclastic bone resorption in patients resulting in a return of bone turnover to normal. On the other hand calcitonin is also good at reliving pain in Paget’s disease. In most cases bisphosphonates are used as they provide a better overall decrease in bone turnover. Where a patient experiences high levels of pain, in addition to the above mentioned drugs, aspirin and Ibuprofen can be prescribed (Langston et al). Dickkopf-1 (DKK-1) that inhibits the Wnt signalling pathways has recently been identified as the therapeutic target for Paget’s disease (McCarthy et al, 2010). Wnt signalling is important in the regulation of healthy bone mass. Over-expression of DKK-1 can lead to bone loss as it inhibits the Wnt pathway. Thus patients with Paget’s disease therapeutically can be treated to elevate DKK-1 levels. This is the potential treatment for PDB, while the research into this is ongoing. Occasionally, patient’s may undergo surgeries to treat internal fractures caused by this disease. Once developed, the management of this disease is very important. Drugs taken in combination can suppress the pathologically increased bone turnover for prolonged period of time

Due to its unknown aetiology, the root cause of this disease remains to be discovered and thus management relies solely on drugs. While ongoing research is being carried out, optimism still arises for the ideal therapy for Paget’s disease of bone.

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