Editorial

OSTEOMALACIA

Osteomalacia is a metabolic bone disease of multifactoral etiology, all factors leading to a defect in mineralization of mature lamellar bone. Most important is deficiency of Vitamin D.

Vitamin D has a number of metabolites, the naturally occurring one is Vitamin D or cholecalciferol (Frame et al., 1978). The skin has 7-dehydrocholesterol which is acted upon by ultraviolet light and converted with clevage of C9 - C10 bond in steroid ring into cholecalciferol (D_3). This D_3 is carried via blood to the liver and converted into 25-hydroxy-cholecalciferol (25 (OH) D_3) which on reaching kidney under-goes a second hydroxylation to form 1,25 dihydroxy cholecalciferol (1,25 $(OH)_2$ D_3). Renal 1-hydroxylation is stimulated by many factors, important of which are, parathyroid hormone and hypophosphatemia. 1,25 dihydroxy cholecalciferol, is the most active metabolite (Frame et al., 1978) and is considered by some as a hormone as its synthesis is controlled by hemostatic demand (Haussler and McCain, 1977). It stimulates intestinal calcium absorption (Haussler and McCain, 1977) and rate of parathormone mediated bone resorption thereby increasing the mineral ion product of extra-cellular fluids (Haussler and McCain, 1977; Mankin, 1974; Glorieux et al., 1972).

25, hydroxy cholecalciferol (25, (OH) D_3), another metabolite of Vitamin D, acts on proximal renal tubules decreasing the excretion of both calcium and phosphate, and thus raising serum phosphate concentration and later serum calcium (Bordier et al., 1978). The combined effect of above two metabolites is an increase in serum phosphate concentration. This alongwith direct action of 1,25 $(OH)_2$ D_3 on bone enhances bone mineralization (Haussler and McCain, 1977), abnormality of Vitamin D metabolism will therefore, lead to osteomalacia. In osteomalacia total mineral content in a given volume of bone is less than normal, as in this condition replacement of bone of normal content, removed by usual process of bone resorption, is by non-mineralized or poorly mineralized osteoid occupying the same volume, giving a radiographic appearance of demineralization or better stated as "reduced radiodensity" as mineral content of the bone is also reduced in osteitis fibrosa, where replacement is by fibrous tissue and more loosely textured woven bone, and in osteoporosis where replacement is by a lesser volume of bone of normal composition. Osteoporosis and osteomalacia frequently co-exist and decreased radiodensity may be equally due to pre-existing osteoporosis and osteomalacia or both. Sometimes in osteomalacia more osteoid accumlates than mineralized bone is lost. Partly mineralized osteoid has greater radiodensity than marrow tissue and therefore roentgenograms reveal bone to be of normal or even of increased density (Haussler and McCain, 1977; Mankin, 1974).

Osteomalacia because of disturbance in Vitamin D metabolism may be due to Vitamin D deficiency, Vitamin D malabsorption, impaired hepatic 25-hydroxylation, impaired renal 1-hydroxylation, and refractoriness to the action of Vitamin D associated with hypophosphatemia and phosphate depletion. Factors unrelated to Vitamin D metabolism such as accumulation of mineralization inhibitors for example pyrophosphate (Fleisch 1973) especially its synthetic analogue Diphosphonates and sodium flouride in excess; and local defects in mineralization as in Fibrogenesis imperfecta osium (Oreopoulos 1973) and axial osteomalacia (McCance et al., 1956) may also result in osteomalacia.

Osteomalacia has also been observed in patients with certain mesenchymal tumours of blood vessel (hemangiopericytomas) and giant cell tumour of bone, called tumorigenic osteomalacias (Linovitz et al., 1976).

Patients of osteomalacia usually present with vague skeletal pains and tenderness in the region of spine, ribs, pelvis and lower extremities. Waddling gait or a limp may result from muscle weakness, or pain in lower extremities or pelvis. Long standing cases in areas where Vitamin D deficiency is endemic may develop gibbus, pigeon chest, or protrusio acetabuli, bowing, narrowing of birth canal, scoliosis, Kyphosis, shortening of spine resulting in changes in height because of vertebral compression, vertebral fractures are quite uncommon. If osteomalacia and osteoporosis co-exist patient will have little skeletal pain as compared to spinal deformity and Kyphosis (Frame et al., 1978).

Biochemical changes in osteomalacia depend on the etiological factor and stage of the disease and are not very conclusive. Hypophosphatemia is more significant and a better clue for the under-lying osteomalacia than

hypocalcemia as alkaline phosphatase may be normal or raised. The cause of raised alkaline phosphatase is not known. Previous explanation of increased, osteoblastic activity does not hold good as in Vitamin D deficiency each osteoblast is making less bone matrix than normal. Recent suggestion is that some chemical processes in the osteoblast involving alkaline phosphatase may be increased, although the cell is unable to carry out its normal function (Frame et al., 1978).

The exact role of alkaline phosphatase in normal bone formation and mineralization is not known. It probably destroys inhibitors of mineralization such as pyrophosphate or ATP (Felix and Fleisch, 1977).

The diagnostic radiographic feature in osteomalacia is Looser zone or pseudo fractures in the ribs, public rami outer borders of scapulae and near the end of long bones. They are really stress fractures not treated properly due to mineralization defects. They appear as symmetrical radiolucent bands adjacent and usually perpendicular to the periosteal surface (Frame et al., 1978). Other features of osteomalacia, like decreased radiodensity or demineralization, defective trabecular pattern, coarsened in some or replaced by a homogenous ground glass appearance in others are non-specific. Vertebral biconcavity, which is regularly distributed in osteoporosis, follow a definite pattern in osteomalacia affecting adjacent vertebrae and upper and lower border of same vertebrae (Frame et al., 1978).

Clinically, biochemically and radiographically suspected cases of osteomalacia have to be confirmed by bone biopsy. Undermineralized section shows increase in number and surface extent of osteoid seams as compared to age and sex matched controls (Frame et al., 1978).

Previous labelling of bone with tetracycline shows decrease in mineralization from about 5 per cent to 50 per cent (Frame et al., 1978).

Osteoblast function is impaired in osteomalacia as indicated by reduced appositional rate, reduced matrix appositional rate, increased mineralization lag time and increase osteon formation time. These disturbances are present from the outset. Abnormalities of osteoblast function may also be seen in osteoporosis, but here they are confined to terminal phase of bone formation resulting in thin seams which in cortical bone have small circumference or perimeter (Parfitt, 1976; Villanueva et al., 1966). These mini seams have reduced fractional labelling with tetracycline and reduced mineral appositional rate. However mineral lag time is normal with no indication of mineralization defect (Frame et al., 1978). The mineralization lag time (MLT) represent the length of time between extracellular assembly of bone matrix and its mineralization, and it is normally 10 days (Baylink et al., 1970).

Excess osteoid is also seen in increased bone turnover, as in hyperparathyroidism and paget's disease but mineralization and osteoblast function are normal.

Prognosis of osteomalacia if treated properly is good. Patients with incapacitating skeletal symptom become asymptomatic within 2-3 months and if not associated with osteoporosis. With better understanding of Vitamin D metabolism and availability of its various metabolites in recent years, treatment of different forms of osteomalacia has improved considerably although the desirable treatment would still be the removal of underlying cause.

References

Baylink, D., Stauffer, M., Wergedal, J., Rich, C. (1970) Formation, mineralization and resorption of bone in vitamin D deficient rats. J. Clin. Invest., 49:1122.

Bordier, P., Rasmussen, H., Marie, P., Miravet, L., Gueris, J., Ryckwaert, A. (1978) Vitamin D metabolites and bone mineralization in man. J. Clin. Endocrionol. Metab., 46:284.

Felix, R., Fleisch, H. (1977) Pyrophosphatase and ATPase of isolated cartilage matrix vesicles. Calcif. Tissue Res., 22:1.

Fleisch, H. (1973) Diphosphonates, an overview, in Clinical Aspects of Metabolic Bone Disease, International Congress Series No. 27, Amsterdam. Excerpta Medica, pp. 501-505.

Frame, B., Parfitt, A.M., Michigan, D. (1978) Osteomalacia: current concept. Ann. Intern. Med., 89:966.

Glorieux, F.H., Scriver, C.R., Reade, T.M., Goldman, H., Roseborough, A. (1972) Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hyphosphatemia. N. Eng. J. Med., 287:487.

Haussler, M.R., McCain, T.A. (1977) Basic and clinical concepts related to vitamin D metabolism and action. N. Engl. J. Med., 297:983, 1041-1050.

Linovitz, R.J., Resnick, D., Keissling, P., Kondon, J.J., Sehler, B., Nejdl, R.J., Rowe, J.H., Deftos, L.J. (1976) Tumor-induced osteomalacia and rickets; a surgically curable syndrome. Report of two cases. J. Bone Joint Surg., 584:419.

Mankin, H.J. (1974) Rickets, osteomalacia and renal osteodystrophy. J. Bone Joint Surg. (Am), 56:101, 352.

McCance, R.A., Fairweather, D.V.I., Morrison, A.B.

(1956) Genetic, clinical, biochemical and pathological features of hypophosphatasia. Q.J. Med., 25:532.

Oreopoulos, D.G., Rabinovich, S., Meema, H.E., Lloyd, G.J., Rappoport, A., Deverber, G.A. Contrasting bone changes in patients on chronic haemodialysis and chronic peritoneal dialysis in clinical aspects of metabolic bone disease. Edited by Frame, B., Parfitt, A.M., Duncan, H. Amsterdam Excerpta Medica 1973, pp. 628-633.

Parfitt, A.M. (1976) The actions of parathyroid hormone on bone. Relation to bone remodelling and turnover, calcium homeostasis and metabolic bone disease. III. PTH and osteoblasts, the relationship between bone turnover and bone loss, and the state of the bones in primary hyperparathyroidism. Metabolism, 25:1033.

Villanueva, A.R., Ilnicki, I., Duncan, H. and Frosh, H.M. (1966) Bone cell dynamics in osteoporosis: A review of measurement by tetracycline bone labelling. Clin. Orthop., 49:135.