Metabolic Bone Disease — Recent Developments

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SUMMARY

Advances made in the management of generalised osteoporosis and Paget's disease are described and, in addition, the emergence of a 'new hormone', vitamin D, and its therapeutic implications, are mentioned.

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THERAPY OF OSTEOPOROSIS

Osteoporosis is a disorder of bone characterised by the progressive loss of bone mass until the skeleton is inadequate in providing mechanical support to the body. The chemical composition of the remaining bone is normal.

By far the commonest form of osteoporosis is that occurring in postmenopausal women where several factors such as lack of oestrogens, decreased calcium absorption, and dietary insufficiency have been held responsible. Osteoporosis occurring in the relatively young patient poses an even greater aetiological puzzle and the term 'idiopathic' has been reserved for such patients. Osteoporosis is a common disease causing a vast amount of disability and pain, especially from bone fractures, vertebral distortion and compression. The basic disease process is unknown and treatment has usually hinged upon attempting to strengthen existing bone to prevent further rarefaction, since true healing of bone seems to be difficult or even impossible.

Treatment has included such medications as oestrogens, anabolic steroids and calcium supplementation.

Oestrogen Therapy

Oestrogens, which have enjoyed a chequered career in the treatment of postmenopausal osteoporosis, appear to prevent progression of the disease. Until recently there had been no evidence that it increased bone mass. Aitken *et al.*[1] have shown that oestrogens provided an increase in bone mineral content when given within 3 years of the menopause. Oestrogens may therefore turn out to be the keystone in the treatment of postmenopausal osteoporosis.

Calcium Therapy

Calcium supplements have been universally used, usually with poor success, probably because with the dose of oral calcium supplements employed, significant hypercalcaemia was not achieved.[2,3] With the discovery of thyrocalcitonin (TCT) another calcium-regulating hormone, apart from parathyroid hormone, appeared important in the pathogenesis of osteoporosis. It was speculated that osteoporosis might represent a subtle imbalance between the secretion of these two hormones, so that osteoporotic patients may in fact have subclinical hyperparathyroidism. This non-autonomous hyperparathyroidism, it was reasoned, could be suppressed by exogenous hypercalcaemia and thus correct the balance. To achieve this, calcium infusions 15 mg/kg body mass were given intravenously in 1 litre 5% dextrose water for 12 consecutive days by Pak *et al.*[4] The results in 6 patients (although relatively young) were most encouraging, an increase in calcium balance and an improvement in symptoms being found.

We have employed this form of treatment in some of our osteoporotic patients with gratifying improvement of pain in the majority, including the elderly and those with steroid-induced osteoporosis. Improvement may last from 3 to 6 months. Its disadvantage is that it requires daily intravenous infusion for 12 days, usually necessitating hospital admission, and that repeated future admissions may be required.

Fluoride Therapy

In 1964 Rich *et al.*[5] proposed the use of fluoride in the treatment of osteoporosis, as fluoride ingestion produces osteosclerosis. Although it stimulates new bone formation, the newly-formed bone is poorly mineralised and osteomalacia and secondary hyperparathyroidism frequently occur. To overcome this problem Jowsey *et al.*[6] suggested the addition of vitamin D and calcium to strengthen the osteoid tissue. Biopsy specimens from 11 patients on this treatment showed new bone formation without evidence of fluorosis or osteomalacia. This therapeutic regimen appears to be encouraging, and although the relief of pain is not as dramatic as with calcium infusions, we now have a number of osteoporotic patients on this more convenient form of therapy. It is too early to be certain of its efficacy as yet.

Thyrocalcitonin

In recent years this hormone has been found to be important in calcium homeostasis, besides parathyroid hormone. To date 9 calcitonins have been isolated: 3 from salmon, 1 bovine, 1 ovine, 1 porcine, 1 human, 1 dogfish and 1 Japanese eel. Thyrocalcitonin (TCT) has its main action on bone, causing inhibition of bone resorption and to a much lesser extent increasing new bone formation, and thus appears ideal for the treatment of osteoporosis. Results to date have been variable, with the greatest

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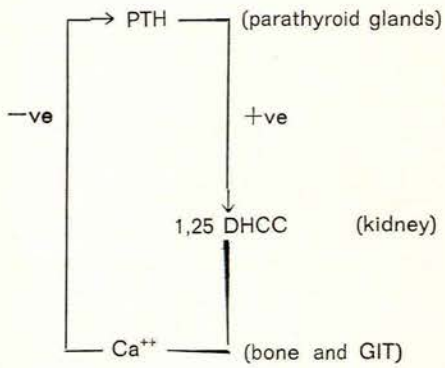
Vitamin D_3 (cholecalciferol), obtained mainly by ultraviolet irradiation of the skin (although there is a similar pathway for ingested vitamin D), undergoes specific hydroxylation in the liver to a metabolically active form called 25-hydroxycholecalciferol (25-HCC). This compound enters the circulation and is carried by specific binding proteins to the kidneys, where further specific hydroxylation to the final most active metabolite 1,25-dihydroxycholecalciferol (1,25-DHCC) occurs.[22] This pathway can be summarised as follows:

Vitamin D_3	(skin)
↓	
25-HCC	(liver)
↓	
1,25-DHCC	(kidney)

It is now believed that 1,25-DHCC carries out the function of calcium mobilisation from bone and enhances intestinal calcium absorption. However, it has a strong feedback mechanism regulated by serum calcium or some factor responsive to serum calcium.[23] Thus, as serum calcium drops below normal, the synthesis of 1,25-DHCC increases, which in turn makes calcium available from intestine and bone, thereby completing a feedback loop system. Therefore, 1,25-DHCC is a calcium-mobilising hormone with the kidney as the endocrine gland.[24]

Since the parathyroid glands are sensitive to serum calcium levels, it appears that they may regulate the synthesis of 1,25-DHCC and act as a secretor of the trophic hormone PTH.[25] The completed feedback loop can be schematically depicted, thus:



However, this may be an oversimplification as recent work has shown that besides hypocalcaemia, a reduced renal cell level of inorganic phosphorus stimulates the production of 1,25-DHCC.[26] Furthermore, Galante *et al.*,[27] in contradistinction to other authorities,[28] have demonstrated that parathyroid hormone is not an essential trophic hormone for the production of 1,25-DHCC. The therapeutic benefit of this new active vitamin D metabolite will apply particularly to the treatment of bone disease occurring in uraemic patients. In these patients progressive renal parenchymal tissue destruction has prevented the synthesis of 1,25-DHCC and resulted in a negative calcium balance with bony sequelae. Administration of 1,25-DHCC has already been shown to be of benefit in these patients.[29] Other vitamin D-resistant states, where large amounts of the less active cholecalciferol have been used previously, often with toxic effects, will also benefit from this new treatment.

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