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PATHOGENETIC ROLE OF CALCIUM AND VITAMIN D INSUFFICIENCY IN OSTEOPOROSIS

INTRODUCTION

Vitamin D insufficiency is a state where the intake of vitamin D falls below basic requirements leading to the development of secondary hyperparathyroidism in an attempt to maintain calcium homeostasis [1, 2]. This in turn will increase the initiation of new bone remodelling units and amplify any existing deficit between the rates of bone formation and bone resorption.

CALCIUM HOMEOSTASIS

Extracellular fluid (ECF) calcium is tightly regulated by the parathyroid hormone (PTH) – vitamin D endocrine system. As vitamin D intake begins to fall, there will be a decrease in proximal intestinal active calcium transport leading to a small reduction in the ECF calcium. This fall will be detected by the parathyroid gland, which will respond by increasing PTH secretion. The relationship between PTH and (ionised) serum calcium is sigmoid in shape with the steepest portion around the 'set point' [3]. This is the value of (ionised) calcium around which homeostasis is regulated and varies between individuals. The increased level of PTH will stimulate the renal 1α hydroxylase to increase the production of calcitriol ($1,25\text{ OH}_2\text{D}$), which is the major regulator of active calcium absorption and thereby maintain calcium homeostasis.

Although lack of vitamin D can occur at any age it is a particular problem in the elderly (Figure 1).

Most of our vitamin D comes from sunshine where the ultraviolet light converts pro-vitamin D (7 dehydrocholesterol) into vitamin D_3 (cholecalciferol) in the skin. Much smaller amounts of vitamin D, mainly D_2 (ergocalciferol), come from the diet.

BONE REMODELLING

Both men and women lose bone after the age of 50 and this is increased after the menopause in women due to oestrogen deficiency. However, the development of secondary hyperparathyroidism will increase the activation frequency of new bone remodelling units [4] and amplify the existing negative bone balance of ageing or oestrogen deficiency.

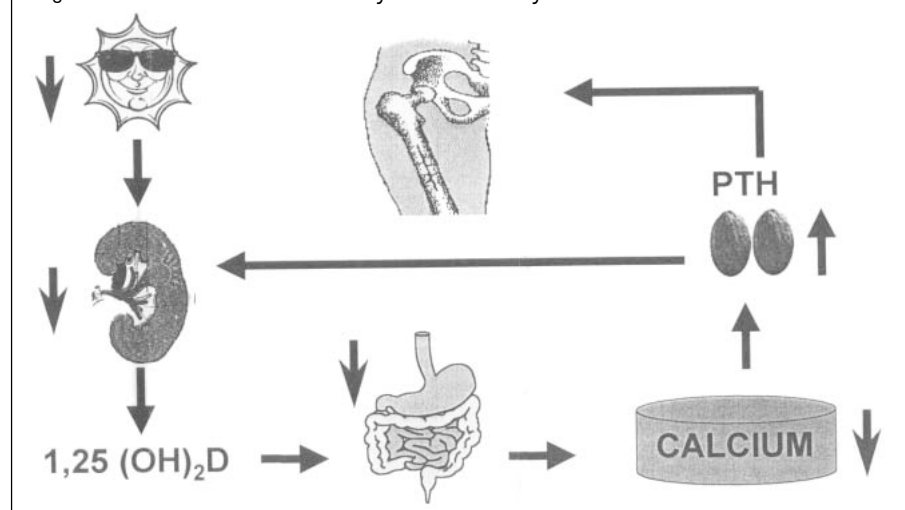
DIAGNOSIS

Vitamin D insufficiency is common in those over the age of 65 years [5] and may affect nearly 20 % of this age group referred to

an osteoporosis clinic [6]. Definitions are important and the central issue is the level of 25 hydroxy vitamin D (25 OHD) below which there will be a rise in PTH. There is a general consensus that this occurs at a 25 OHD concentration $< 25\text{ nmol/L}$ and is termed vitamin D insufficiency [2, 7]. This has to be distinguished from vitamin D deficiency with a lower 25 OHD ($< 15\text{ nmol/L}$) at which point bone mineralisation becomes impaired and osteomalacia develops. This contrasts with vitamin D insufficiency where the maintenance of normocalcaemia and adequate levels of $1.25\text{ OH}_2\text{D}$ preserves normal bone mineralisation. Measurement of 25 OHD is therefore important in the evaluation of the elderly osteoporotic patient.

Serum calcium is not a good discriminant for the presence of vitamin D insufficiency because the essential feature of the condition is maintenance of normal "set point" calcium by secondary hyperparathyroidism. Since there is such a range of set point calciums, vitamin D insufficiency may oc-

Figure 1: Vitamin D insufficiency in the elderly



cur with a serum calcium in the upper or lower part of the reference range.

Measurement of 25 OHD is essential and reliance should not be placed on calcium and PTH alone since they will not separate those with mild primary hyperparathyroidism (where the serum calcium may be in the upper part of the normal range at some time points) from vitamin D insufficiency. Treatment of mild primary hyperparathyroidism with calcium and vitamin D often leads to hypercalcaemia with little fall in PTH. This contrasts with treatment of vitamin D insufficiency where the serum calcium changes only slightly while PTH falls back into the reference range.

Our current practice therefore is to measure calcium and 25 OHD in all our elderly patients presenting to the osteoporosis clinic and to add a PTH measurement in all of those with a 25 OHD < 30 nmol/L.

TREATMENT

The importance of identifying patients with vitamin D insufficiency is that treatment is often cheaper than many of the alternative drugs. Vitamin D and calcium are generally well tolerated and have been shown to reduce the incidence of hip and other non-vertebral fractures [8, 9].

Vitamin D therapy reverses two important pathogenetic mechanisms, which result in a gain in bone mineral density. The first relates to the reversal phase of the bone remodelling cycle, which

separates the initial phase of resorption from the final phase of formation. During the reversal phase there is a finite time when the resorption cavity remains empty while it is prepared for bone formation. The number of cavities waiting to be filled in is termed the 'remodelling space' and its size (and therefore the deficit of bone) depends largely on the rate of bone remodelling. As the rate of bone remodelling falls with the decrease in PTH there will be reduction in size of the remodelling space and a net gain of bone. At the same time the amplification of the basic deficit between formation and resorption will also be reduced. Both of these processes will decrease the rate of bone loss as long as normal vitamin D nutrition is maintained [10].

VITAMIN D SUPPLEMENTATION WITH A LOW PTH

In some patients with vitamin D insufficiency, PTH is not increased and calcitriol is low. This raises the possibility of an additional defect of mild hypoparathyroidism. The intriguing question is whether such hypoparathyroidism might be protective in that increased bone turnover would not develop and there would be no amplification of the imbalance between formation and resorption. It might, in fact, minimise the age related bone loss because of a general decline in bone turnover.

A similar situation may arise in vitamin D replete subjects where the ambient PTH concentration is normally about twice the basal secretion rate [3]. Vitamin D

therapy in such patients has little potential for further suppression of PTH and may be less effective in improving bone mineral density.

The recent advances in our understanding of the vitamin D – PTH endocrine system may help us target treatment with vitamin D and calcium more appropriately. In this respect the limited studies of fracture prevention are encouraging.

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