Regular Review

Therapeutic applications of vitamin D analogues

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In the sunnier parts of the world a dietary intake of vitamin D is unnecessary,* but for most of us it is a true vitamin. Its dihydroxylated metabolite 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is, however, a hormone synthesised in the kidney and borne by the bloodstream to distant target organs (gut, bone, and possibly the parathyroid glands) with a complex feedback mechanism regulating its rate of production.[1] None of the other vitamin D metabolites has yet been confidently assigned a hormonal role in man.

The unravelling of the interrelationships between vitamin D and its metabolites is one of the triumphs of recent medical research, and the stage has now been reached when treatment with synthetic metabolites of vitamin D is beginning to be available for several disorders. The major functional categories of endocrine disease are all represented among defects in the metabolism of $1,25(OH)_2D_3$. Hormone deficiency may occur from failure of tubular cell function; impairment of feedback control may result in subnormal or excessive production; or the disorder may be due to unresponsiveness in the target organs.

Physiological considerations—Cholecalciferol (D_3) is formed in the skin under the influence of ultraviolet light.[2] Its precursors remain in situ because they are insoluble in water and do not bind to the circulating D-binding globulin[3]; but, once formed, D_3 is taken up into the circulation and is converted to its 25-hydroxylated form—($25(OH)D_3$)—in the liver. This conversion is restricted, and the proportion of D_3 hydroxylated declines as more becomes available, so that production of $25(OH)D_3$ is increased only 4-fold and 20-fold in response to increases in D_3 supply of 10-fold and 100-fold respectively.[4] The result is a weak, but not negligible, inbuilt defence against overdosage with vitamin D.

$25(OH)D_3$ is, then, the principal circulating form of the vitamin, with a normal turnover of between three and four weeks.[5] When given by mouth to patients with chronic renal failure $25(OH)D_3$ has a weak direct action on calcium absorption of its own, roughly one-hundredth that of its metabolite $1,25(OH)_2D_3$ and one-tenth that of $24,25(OH)_2D_3$.[6] Nevertheless, since $25(OH)D_3$ circulates in concentrations about 30 times greater than those of $1,25(OH)_2D_3$ and ten times greater than that of $24,25(OH)_2D_3$, this action may be physiologically important. $25(OH)D_3$ may also promote mineralisation of bone independently.[7]

The further metabolism of $25(OH)D_3$ to $1,25(OH)_2D_3$ and to $24,25(OH)_2D_3$ occurs in the kidney. Neither metabolite is formed by any other tissue,[8 9] except in pregnancy.[10] The production rate of $1,25(OH)_2D_3$ is closely regulated, not only by its own concentration in the plasma, but also by the plasma concentrations of parathyroid hormone and calcium and by intracellular levels of phosphate.[1] $1,25(OH)_2D_3$ is a potent stimulator of calcium absorption in physiological dosage and of bone resorption in slightly supraphysiological dosage.[11] Its turnover time in the plasma is about one day. The physiological function of $24,25(OH)_2D_3$ is uncertain.[12] Its turnover time is much the same as that of $25(OH)D_3$.[13] When $1,25(OH)_2D_3$ is given to normal man the production of $24,25(OH)_2D_3$ increases.[9]

Some portion of the plasma D_3 may be metabolised through pathways other than the ones outlined above or excreted unchanged. There may be an enterohepatic recirculation of D_3 and its metabolites,[14] though more recent studies have not confirmed this.[15] Since in many patients with steatorrhoea absorption of vitamin D is only moderately impaired,[16] the osteomalacia sometimes associated with malabsorption of fat has not been fully explained.

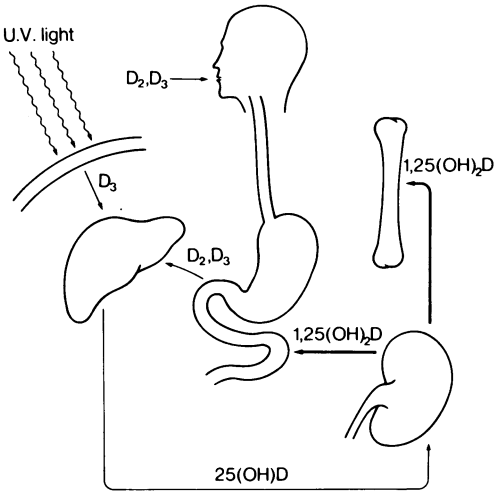
Vitamin D metabolites and analogues—For many years foods such as margarine have been fortified with ergocalciferol (vitamin D_2). The first available analogue of potency greater than the natural vitamin was dihydrotachysterol (DHT), though even this compound is 50-500 times less potent than $1,25(OH)_2D_3$. DHT has a swifter onset and end of action than D_3 or $25(OH)D_3$, and since it does not require a hydroxylation in the 1 position like $25(OH)D_3$, treatment of "D-resistant" states became possible with dose levels of DHT little higher than those required to heal D-deficiency rickets or osteomalacia.

The elucidation over the last 10 years of the metabolic transformations undergone by D_3 has been followed by the synthesis of several of its metabolites.[1] $25(OH)D_3$ may become available in the United States (approved name calcifediol), and $1,25(OH)_2D_3$ is already available in the United States and some European countries (approved name calcitriol). In addition, the more easily synthesised analogue of $1,25(OH)_2D_3$, $1\alpha(OH)D_3$ (approved name alfacalcidol), is available in Britain and some other countries. Alfacalcidol depends for its biological activity on its hydroxylation in the liver to $1,25(OH)_2D_3$.

Substrate deficiency—Several disorders lead to substrate deficiency, which for preference should be treated with precursors of $1,25(OH)_2D_3$, though theoretically effective treatment could be given with vitamin D, $25(OH)D_3$, or $1,25(OH)_2D_3$. Nevertheless, when the two former compounds are used the normal intrinsic mechanisms for regulating the rate of production of $1,25(OH)_2D_3$ are activated, so automatically bringing the effectiveness of treatment to an optimum.

The most common cause of substrate deficiency in Britain is the combination of inadequate exposure to sunlight and a low intake of vitamin D in the diet. This combination is most prevalent among persons of Asian origin and among the elderly

*Vitamin D_3 is the naturally occurring form, cholecalciferol. Vitamin D_2, ergocalciferol, is simpler to manufacture and is used in the fortification of foodstuffs and some pharmaceutical preparations. They are biologically equivalent.



Outline of vitamin D metabolism in normal man. Only a small fraction of circulating vitamin D is eventually converted into $1,25(OH)_2D_3$ in conditions of sufficiency, the remainder being converted into 24, $25(OH)_2D_3$ and other less active metabolic products, or excreted. Factors regulating $1,25(OH)_2D_3$ production rate are described in the text.

and housebound. There is no place for treating these simple forms of vitamin D deficiency with anything other than the vitamin itself, in doses ranging from 10 to 100 μg (400 to 4000 IU) daily. This dosage may be partially achieved with dietary advice (margarine in the United Kingdom contains about 4 μg ergocalciferol in a normal daily ration of 50 g); by using a daily oral preparation (Ca and vitamin D tablets BPC, each containing 12·5 μg vitamin D_2); or by giving infrequent injections of calciferol (300 000 IU, 7·5 mg every three months). Epileptics receiving drug treatment seem to provide too little $25(OH)D_3$ to the kidney and they may require larger doses, in the range 50-250 μg daily.

Patients with liver disease are said to convert D_3 to $25(OH)D_3$ at a reduced rate. Current evidence suggests that this is not the mechanism for the osteomalacia associated with primary biliary cirrhosis, but reduced hydroxylation rates have been observed in some cases of alcoholic liver disease.[17]

Much work remains to be done on the indications for management of treatment with vitamin D and its metabolites in gastrointestinal disease, but the appropriate dose level of D is usually in the range of 100-300 μg (4000-12 000 IU) daily.[18] Treatment with $1,25(OH)_2D_3$, while of clinical interest,[19] should become unnecessary as well as illogical in liver disease when $25(OH)D_3$ becomes available for the management of those patients who cannot adequately hydroxylate D in the 25 position.

"Gland" failure—By far the most common cause of inadequate production of $1,25(OH)_2D_3$ is chronic renal failure. Even so, as with other endocrine systems, a hereditary deficiency of the capacity to synthesise this hormone has been described.[20] In early chronic renal failure any tendency toward raised plasma concentration of phosphate and parathyroid hormone and a lowered one of calcium will produce a complex interaction of influences on the remaining tubular cells. Concentrations of $1,25(OH)_2D_3$ begin to decline when the glomerular filtration rate falls below about 30 ml/min.[21] There is no evidence that the vitamin D metabolites benefit the osteomalacia presumed to be caused by aluminium or other toxins.[22]

Treatment of renal osteodystrophy with $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ will usually provide an encouraging response in symptomatic patients whose $1,25(OH)_2D_3$ deficiency is accompanied by evidence of secondary hyperparathyroidism and a reduced plasma calcium concentration before treatment.[23-25] In these "responsive" patients plasma concentrations of alkaline phosphatase and parathyroid hormone fall gradually to normal, though histological changes (osteitis fibrosa and thickened osteoid seams) respond less dramatically.[24]

What are the advantages of this form of hormone replacement treatment? The response in patients with symptoms is often gratifying, particularly in children.[25] Similar responses were, of course, seen before the advent of treatment with $1\alpha(OH)D_3$ and $1,25(OH)_2D_3$, but large doses of vitamin D had to be used and their effects were probably secondary to the weak actions of 25(OH)D in mimicking $1,25(OH)_2D_3$. Overdosage was associated with prolonged episodes of hypercalcaemia, which probably adversely affected the remaining renal function.[26] Dihydrotachysterol overdosage was associated with less prolonged episodes of hypercalcaemia than with treatment with D_3, but $1,25(OH)_2D_3$ and its analogue $1\alpha(OH)D_3$ have the advantage over both. Nevertheless, reports have appeared implicating treatment with $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ in the accelerated decline of renal function.[27]

Treatment with these compounds should therefore be reserved for those who have symptomatic osteodystrophy. Given facilities for frequent monitoring of the plasma calcium concentration (not less than once a month and preferably up to once weekly), treatment with 2·0-2·5 μg of $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ daily will usually obtain the best response.[24] Hypercalcaemia may occur early during treatment, particularly in adults with histologically pure osteomalacia who were normocalcaemic beforehand. The dose usually has to be reduced as the biochemical indices return towards normal.

Since $1,25(OH)_2D_3$ increases the absorption of phosphate from the gut[1] the restoration of the plasma calcium concentration to normal carries with it the risk of metastatic calcification and a more rapid decline in remaining renal function[29] if the plasma phosphate concentration is not kept below 2·4 mmol/l by giving oral phosphate-binding agents. Any existing metastatic calcification should be reviewed radiologically at intervals to ensure that it is not increasing.

Inappropriate $1,25(OH)_2D_3$ production rates—Almost certainly, the renal tubular cell has a subsidiary role to the parathyroids, so that in hypoparathyroid patients the production of $1,25(OH)_2D_3$ is subnormal and calcium absorption falls as a consequence. This aggravates the risk of hypocalcaemia from reduced renal calcium conservation.

Recent studies have shown that $1,25(OH)_2D_3$ and its analogue $1\alpha(OH)D_3$ given in "replacement" doses can restore the plasma calcium concentration to normal and may be used instead of the large doses of D_3 used hitherto.[29-31] Whether this substitution confers practical advantages remains to be determined[31] and may depend on how much the patient's requirements for D fluctuate with the two modes of treatment.

Interestingly, the opposite biochemical picture—inappropriately high $1,25(OH)_2D_3$ secretion rates—may be seen in the hypercalcaemia associated with sarcoidosis.[32]

Target organ resistance—There are two main target cells for $1,25(OH)_2D_3$—enterocytes and osteoclasts. Target organ resistance is far more common in the enterocytes: in coeliac disease, for example, the balance between calcium absorption and its endogenous faecal excretion is disturbed.[33] In such circumstances treatment should be directed at the primary disorder, but enough substrate must also be made available for the potentially raised production of $1,25(OH)_2D_3$.

Several cases have now been described[34 35] of inherited target organ resistance to $1,25(OH)_2D_3$. These patients have raised serum concentrations of $1,25(OH)_2D_3$ and are resistant to treatment with it. Some have alopecia.

Miscellaneous disorders—Vitamin D and its metabolites have been used to treat conditions in which there is less clear

evidence of disordered vitamin D metabolism. One example is the various forms of hypophosphataemic vitamin-D-resistant rickets. Traditional treatment has been phosphate supplements with or without large doses of vitamin D. When $1\alpha(OH)D_3$ or $1,25(OH)_2D_3$ is substituted for vitamin D, large doses (up to 6 μg/day) are required.[36] The only obvious advantage of such a switch is that biochemical abnormalities in the plasma may be brought back to normal more quickly.

Moderate reductions in plasma concentrations of $1,25(OH)_2D_3$ have been found in primary osteoporosis. The simplest explanation is that this is a secondary feedback response to the imbalance between bone formation and resorption. Trials of treatment with $1\alpha(OH)D_3$ and $1,25(OH)_2D_3$ in osteoporosis have given mixed results.[11 37–40] Overall, the effect on mineral balance seems so slight as to be of negligible benefit unless treatment is continued for many years. The combination of $1\alpha(OH)D_3$ and oestrogen replacement therapy looks more promising,[40] but further results are awaited with interest.

In conclusion, it is worth re-emphasising that $1,25(OH)_2D_3$, $1\alpha(OH)D_3$, DHT, and vitamin D in large doses are hormones or hormone substitutes; whereas vitamin D and $25(OH)D_3$ in daily doses of up to 200 μg require further well-regulated metabolic transformations for them to become active biologically, so that they may still be viewed as vitamins. Many of us are content for our patients happily and harmlessly to consume a range of vitamins far above their minimum requirements, because the "therapeutic ratio" for most vitamins is high. On the other hand, we are accustomed to prescribing replacement doses of hormones with care, taking every precaution to avoid producing the iatrogenic counterparts of the various diseases associated with hormone excess—which in the case of vitamin D given in large "hormonal" doses is still an all-too-common problem.[41]

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