THE RELATIONSHIP BETWEEN DISTURBED METABOLISM OF VITAMIN D AND BONE DISEASE IN CHRONIC RENAL FAILURE

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Summary

Following the discovery that the kidney is involved in the metabolism of vitamin D, a causal relationship has been sought between defective production of 1,25-dihydroxy vitamin D$_3$ and bone disease in chronic renal failure. This paper reviews some of the clinical evidence for and against such a relationship, and considers the possible role of other vitamin D metabolites in the pathophysiology of renal bone disease.

Vitamin D

It has been recognised for a long time that large doses of vitamin D may increase the intestinal absorption of calcium, and heal osteomalacia and osteitis fibrosa in patients with renal failure. The bone disease in renal failure can be considered as 'vitamin D-resistant' in the sense that the doses of vitamin D required to produce a biological response are greater than the amounts required to satisfy physiological requirements. There is now considerable evidence that this resistance is due to a defect in the metabolism of vitamin D [1, 2].

25-Hydroxy Vitamin D$_3$ (25-OHD$_3$)

The first step in the metabolism of vitamin D$_3$ is its conversion to 25-OHD$_3$, which occurs mainly in the liver. Is renal bone disease due to defective production, accelerated metabolism, or impaired action of this metabolite? Certainly plasma levels of 25-OHD (D$_2$ and D$_3$) may be low in patients with the nephrotic syndrome [3] and be associated with bone disease [4]. Certain drugs such as anti-convulsants and barbiturates, induce hepatic microsomal enzymes and might be expected to increase the metabolism of 25-OHD, but there is no evidence for this [5]. These drugs may also have adverse effects by blocking the action of
vitamin D metabolites on gut and bone [6]. Apart from this exception, there is no convincing evidence that low levels of 25-OHD$_3$ are due to defects in vitamin D metabolism despite suggestions to the contrary. Low levels, when present, may therefore be due to inadequate diets or reduced exposure to sunlight. The usual experience, in common with ours [7] is that, when anticonvulsants are avoided and patients allowed to eat normal diets (for example on dialysis treatment), plasma 25-OHD levels are normal.

It has recently been suggested that patients with advanced renal failure and bone disease have low levels of 25-OHD and that ‘physiological’ doses of this metabolite improve skeletal lesions [8, 9]. These observations are subject to a number of interpretations, and we have been unable to find any correlation between plasma 25-OHD levels and the presence or absence of bone disease [10] in patients with renal failure. Moreover, the general experience is that pharmacological, not physiological, amounts of 25-OHD$_3$ are required to treat renal bone disease [10, 11]. This suggests that in advanced renal failure, the level of 25-OHD seen in untreated patients (i.e. not given pharmacological amounts of vitamin D or 25-OHD$_3$) may be irrelevant to bone disease, and that any defect lies in its further metabolism.

**1,25-Dihydroxy Vitamin D$_3$ (1,25(OH)$_2$D$_3$)**

It is commonly thought that most of the actions of vitamin D$_3$ are mediated by metabolism of 25-OHD$_3$ to 1,25(OH)$_2$D$_3$. Since the kidney is the sole site of synthesis of 1,25(OH)$_2$D$_3$ [1, 12], the development of renal bone disease and its resistance to vitamin D and to 25-OHD$_3$ may result from impaired production of 1,25(OH)$_2$D$_3$, due perhaps in part to loss of renal tissue and in part to the inhibitory effects of hyperphosphataemia on the kidney 1α-hydroxylase.

The evidence for a causal relationship between vitamin D resistance, defective 1α-hydroxylation, and renal bone disease is based on several observations. Firstly, plasma levels of 1,25(OH)$_2$D$_3$ and its formation rate decrease when the glomerular filtration rate is less than 40ml/min, and 1,25(OH)$_2$D$_3$ is usually undetectable in end-stage chronic renal failure [1, 12]. Secondly, x-ray and histological appearances of bone in renal osteodystrophy have features resembling those found in nutritional vitamin D deficiency. The administration of 1,25(OH)$_2$D$_3$, or its synthetic analogue 1α-hydroxy vitamin D$_3$, in renal bone disease reverses many of its biochemical and radiographic features. Moreover, the doses of 1,25(OH)$_2$D$_3$ required to maintain remission (0.25–0.5µg daily) are close to its estimated daily endogenous production rate in health suggesting that, unlike 25-OHD$_3$, target organs are sensitive to physiological amounts of 1,25(OH)$_2$D$_3$ [2, 13, 14].

The view that lack of 1,25(OH)$_2$D$_3$ causes bone disease may be an oversimplification. Thus, although radiographic and histological appearances may be improved by treatment with 1α-hydroxylated metabolites, this is not invariable and healing is commonly incomplete [13–15]. It could be that responses to treatment identifies those patients in whom other factors operate to give rise to bone disease. Also, bone disease does not affect all patients with severe chronic renal failure and its incidence does not invariably increase with time on dialysis [15]. The possibility that the end-stage kidney still produces adequate though
barely detectable amounts of $1,25(OH)_2D_3$ seems unlikely since the prevalence of osteomalacia and osteitis fibrosa is not increased in anephric patients, and in some patients the rates of mineralisation and bone formation are quite normal [15–17]. These data suggest that normal skeletal homeostasis is not necessarily dependent on production of $1,25(OH)_2D_3$.

24,25-Dihydroxy Vitamin D₃ ($24,25(OH)_2D_3$)

The kidney has an enzyme system capable of converting 25-OHD₃ to 24,25(OH)₂D₃. There is controversy as to whether this 24-hydroxylase is exclusive to renal tissue [18, 19]. Unlike some centres we have been unable to detect 24,25(OH)₂D₃ in plasma from anephric patients [20] suggesting that the kidney is the major site of synthesis of 24,25(OH)₂D₃. One reason for divergent results between centres may be the variable practice of giving patients supplements of vitamin D₂, the metabolites of which may interfere with the assay for 24,25(OH)₂D₃ [19]. Nevertheless, extra-renal production of 24,25(OH)₂D₃ probably does occur in experimental animals [18, 21]. Even if this also occurred in man it need not contribute to plasma concentrations. For example, one of the putative extra-renal sites of production is cartilage which itself may be a target organ for 24,25(OH)₂D₃ [22].

In states of vitamin D sufficiency 24,25(OH)₂D₃ is the major circulating dihydroxymetabolite, and plasma concentrations generally correlate with circulating 25-OHD₃ [20]. The production rate of 24,25(OH)₂D₃ in animals is, however, also governed by factors such as calcium and phosphate. In man, its synthesis is augmented by 1,25(OH)₂D₃ repletion as well as by giving 25-OHD₃ [19] a phenomenon which may complicate considerably the assessment of the effects of metabolites in vivo. Thus some of the reported effects of 1,25(OH)₂D₃ may in fact be mediated by the increased endogenous synthesis of 24,25(OH)₂D₃.

With respect to renal bone disease, plasma levels of 24,25(OH)₂D₃ in a proportion of patients with end-stage renal failure appear to be lower than would be predicted for 25-OHD₃ levels. Preliminary observations suggest that those patients with osteomalacia have the lower levels of 24,25(OH)₂D₃ (Figure 1) but more

![Figure 1](image.png)

Figure 1. Plasma levels of 24,25(OH)₂D₃ and 25-OHD₃ in 17 patients with end-stage chronic renal failure. The line denotes the normal relationship between metabolite levels [20]. Patients with osteomalacia alone (●) or in combination with osteitis fibrosa (▼) had lower levels of 24,25(OH)₂D₃ than patients with osteitis fibrosa alone (○) or other forms of bone disease (★)
patients need to be studied. 24,25(OH)$_2$D$_3$, given to patients with renal failure in
doses which restore plasma levels to normal, increase skeletal calcium retention in
patients with and without kidneys [10, 23]. The longer term effects of treatment
of renal bone disease with 24,25(OH)$_2$D$_3$ include a rise in plasma alkaline phos-
phatase, but without a change in plasma hydroxyproline, suggesting that bone
formation is stimulated [24]. This response is quite unlike the changes noted
after treatment with 1,25(OH)$_2$D$_3$ or 25-OHD$_3$ [11, 13, 14]. These biological
effects of 24,25(OH)$_2$D$_3$, together with the studies on plasma levels, might
suggest a causal relationship between renal bone disease and defective synthesis of
24,25(OH)$_2$D$_3$. In this context the crucial question remains of whether the kid-
ney is the sole site of production of 24,25(OH)$_2$D$_3$ in man since it is probably
significant that nephrectomy does not aggravate bone disease [16].

25,26-Dihydroxy Vitamin D$_3$

There is evidence from biochemical and tracer studies that other metabolites of
25-OHD$_3$ may be produced in anephric patients [18, 25] some of which may be
relevant to renal bone disease. Thus far the extra-renal metabolite 25,26(OH)$_2$D$_3$
is the only one yet to be evaluated in man. Preliminary clinical studies suggest that
its administration reduces secretion of parathyroid hormone [26] but the physi-
ological importance of this observation and its relevance to renal bone disease has
yet to be explored.

Other Factors

Although the oldest known manifestation of vitamin D deficiency is rickets, it is
still uncertain whether vitamin D metabolites directly promote skeletal mineralisa-
tion. This is partly because it is difficult to study mineralisation in vitro, while
interpretation of the effects of vitamin D metabolites in vivo have to take account
of concurrent changes in calcium, phosphate, parathyroid hormone and vitamin
D metabolism.

In many clinical situations and in renal failure, the level of plasma phosphate
appears to be an important determinant of osteomalacia. Levels of plasma phos-
phate in dialysis-treated patients correlate inversely with the degree of osteomal-
acia such that those patients with normal amounts of osteoid have the higher
plasma phosphate levels [15]. It may be relevant that levels of phosphate in such
patients are considerably higher than the upper limit of normal in health. It is
thus possible that high levels of phosphate protect the patient from osteomalacia
despite defective vitamin D metabolism. A similar mechanism may occur in hypo-
parathyroidism where low levels of 1,25(OH)$_2$D$_3$ exist but mineralisation is
usually normal — perhaps due to hyperphosphataemia. The converse argument
would be that rickets arising from nutritional deficiency of vitamin D is due pri-
marily to the hypophosphataemia secondary to hyperparathyroidism rather than
to D deficiency itself. If such mechanisms do exist it becomes important to ident-
ify them clearly so that the pathophysiological role of disturbed vitamin D meta-
bolism in renal bone disease can be objectively evaluated.
Acknowledgments

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References


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Open Discussion

MADSEN Have you any data on the combined use of 24,25(OH)\(_2\)D\(_3\) and 1,25(OH)\(_2\)D\(_3\) in patients with renal osteodystrophy?

KANIS No, the reason for that is that we would like to know what 24,25(OH)\(_2\)D\(_3\) alone is doing.

MALLUCHE (Los Angeles) Let me add two comments: First a word of warning not to base the diagnosis of osteomalacia merely on osteoid accumulation. As you know the total amount of osteoid depends on three factors: 1. the activation frequency of bone formation sites i.e. the birth rate of osteoid; 2. the rate of matrix formation and 3. the disappearance rate i.e. mineralisation of osteoid. Any one of these factors or a combination might have been operative in your patients. Thus tetracycline double labelling is desirable to assess presence or absence of osteomalacia. My second comment supports your data. In a prospective study in 40 Vit-D deficient chicks supplemented with 24,25(OH)\(_2\)D\(_3\) and/or 1,25(OH)\(_2\)D\(_3\) we found that osteoid accumulation and endosteal fibrosis was avoided by either metabolite alone.

KANIS The work on animals is very interesting. I think it is difficult however to apply data from these animal experiments to man, mainly because these experiments are usually in the developing skeleton. In end-stage chronic renal failure in adult man the processes of mineralisation are quite different. Regarding the diagnosis of osteomalacia I would agree with your comments.

FOURNIER (Amiens) In what percentage of uraemic patients have you observed an increase in plasma 24,25(OH)\(_2\) vitamin D\(_3\) when giving them either 1,25(OH)\(_2\)D\(_3\) or 25(OH)D\(_3\)? What was the effect of chronic administration of 24,25(OH)\(_2\)D\(_3\) on bone resorption as assessed by histomorphometry?

KANIS We do not have a lot of histological data. The limited information indicates two things: Firstly, we are not curing osteomalacia and secondly, bone resorption does not increase. With respect to the effects of 1,25(OH)\(_2\)D\(_3\) on the endogenous production of 24,25(OH)\(_2\)D\(_3\), so far this has been a consistent phenomenon.

WINNEY (Edinburgh) Would you comment on the mechanism and site of production of 24,25(OH)\(_2\)D\(_3\) in response to 25(OH)D\(_3\). Is it possible to manipulate 1,25(OH)\(_2\)D\(_3\) production in a similar manner? Finally have you found any relation between plasma phosphate and 24,25(OH)\(_2\)D\(_3\) in patients with chronic renal failure?

KANIS The last point: no we have not really looked at this area yet though I agree that it would be interesting to look at what might stimulate 24,25(OH)\(_2\)D\(_3\). There are very little data that I am aware of trying to stimulate the residual activity of 1α-hydroxylase in end-stage renal failure. Perhaps others in the audience have data? Dr Peacock, a number of years ago phosphate depleted patients with end-stage chronic renal failure and could not see an increase in calcium absorption, suggesting that 1,25(OH)\(_2\)D\(_3\) production was not increased. With respect to the site of synthesis of 24,25(OH)\(_2\)D\(_3\), this is a very difficult area since there have
been conflicting reports about $24,25(\text{OH})_2\text{D}_3$ levels in anephric patients. Haddad has reported normal levels in their anephric patients. A number of other investigators report reduced but detectable levels. Carol Taylor recently presented evidence that the administration of Vit $\text{D}_2$ in many may complicate interpretation of assays in the sense that $25,26(\text{OH})_2\text{D}_3$ co-chromatographs with $24,25(\text{OH})_2\text{D}_3$. The giving of vitamin $\text{D}_2$ supplements to some patients may account for some of the confusing data. On the other hand there is ample evidence in animal studies that 24-hydroxylation may occur in extra-renal sites such as gut and cartilage. To what extent these might contribute to plasma levels is unknown.