Use and indication of vitamin D and vitamin D analogues in patients with renal bone disease

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Abstract

Vitamin D plays a pivotal role in the pathogenesis and treatment of renal bone disease. Vitamin D levels decline in the early phase of renal failure, however, through a compensatory mechanism parathyroid hormone (PTH) stimulates the production of 1,25-dihydroxyvitamin D3 (1,25(OH)2D3, calcitriol) to return it to normal circulating concentrations. Nevertheless, resistance to calcitriol is observed and may be related to the decreased presence of the heterodimeric, DNA-binding partner for the vitamin D receptor protein. In end-stage kidney disease (ESKD) the circulating levels of calcitriol are invariably low. The indications of vitamin D therapy are the replacement of the missing hormone vs suppression of hyperparathyroidism (HPT) requiring daily low-dose oral vs intermittent ‘pulse’ or oral administration. However, this therapy must be accompanied by careful patient monitoring to avoid hypercalcaemia and low bone turnover. Low bone turnover is not merely a histologic entity, but a clinical condition associated with a high risk of extraosseous calcifications, in particular in the cardiovascular system, leading to increased morbidity. Thus, determination of bone turnover in patients with ESKD is essential. Bone biopsy is the gold standard to assess bone turnover, however, it is not always available and nephrologists rely on PTH levels. The intact PTH assay measures PTH(1–84) and large C-PTH fragments, which may antagonize the PTH(1–84) effects on bone. An assay that measures exclusively PTH(1–84) has recently become available and a calculated PTH(1–84)/C-PTH fragment ratio has been shown to be the best predictor of bone turnover in patients with ESKD not treated with vitamin D or with other medications known to affect bone metabolism. 1,25-dihydroxy-22-oxavitamin D3 (22-oxacalcitriol, OCT) is a vitamin D analogue that could control serum PTH concentrations without deleterious effects on bone.

Keywords: bone turnover; calcitriol; OCT; parathyroid hormone; renal failure; vitamin D analogues

Introduction

Vitamin D is an important hormone for mineral homeostasis and the proper formation and maintenance of bone. The vitamin is converted through a series of hydroxylations in the liver and kidney to its active, hormonal form, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3, calcitriol). The hormone acts by binding to an intracellular, nuclear receptor protein, the vitamin D receptor (VDR) [1]. The hormone–receptor complex binds with high affinity to specific DNA sequences, termed vitamin D response element (VDRE) to alter transcriptional events within target cells. Furthermore, data indicate that the VDR requires an accessory nuclear protein, termed the retinoid X receptor (RXR), to bind with high affinity to VDRE. Similar to other members of the nuclear receptor superfamily, the VDR has been shown to interact with several types of transcription factors and co-activator proteins [2]. VDR has been identified in numerous target tissues associated with mineral homeostasis such as the bone, intestine, kidneys, and parathyroid glands, but has also been found in non-classical target cells such as the cardiovascular system, brain, and immune cells, suggesting a wider role in the actions of the circulating hormone [3,4]. Progressive loss of kidney function is accompanied by disturbances in the delicate balance of calciotropic hormones and mineral homeostasis that ultimately affects bone [5].
Role of vitamin D in the pathogenesis of renal bone disease

With the progressive loss of excretory kidney function, secondary hyperparathyroidism (2HPT) typically develops early on. Even though a variety of factors have been identified as influencing the hyperparathyroid state in advanced renal failure, there remain controversies over the sequence of early events leading to increased circulating levels of PTH. Induced renal failure in 5/6 nephrectomized dogs was used to study early time-dependent changes in serum calcium, phosphate, calcitriol, and PTH [6]. At day 1 there was a decrease in calcitriol concentrations with an increase in serum calcium and phosphate. PTH rose after the fall in 1,25(OH)\textsubscript{2}D\textsubscript{3} while calcium and phosphate levels were elevated. This is followed by a normalization of serum phosphate and calcitriol while serum calcium remained elevated. This result suggests that the elevation of PTH secretion represents an adaptive compensatory mechanism to overcome calcitriol deficiency.

This is in keeping with the observation that many patients with mild chronic renal failure have 2HPT with normal levels of serum calcium, phosphorus, and calcitriol. However, these patients exhibit signs of end-organ resistance to calcitriol such as reduced intestinal calcium absorption, and altered calcicuriic response to oral calcitriol supplementation. A rat model of mild renal failure (2/3 nephrectomy) was used to examine early changes in VDR expression and DNA-binding activity [7]. PTH increased significantly 3 days after nephrectomy and peaked after 2 weeks, despite a mild reduction in the glomerular filtration rate (GFR). Consistent with the results in experimental dogs [6], PTH levels remained elevated but there was no difference in serum calcium, phosphorus, and calcitriol concentrations between nephrectomized and control animals [7]. Histomorphometric analysis of bone revealed significant increases in parameters of bone turnover, including osteoid thickness, osteoblast number, erosion surface with osteoclasts, and erosion depth consistent with the development of hyperparathyroid bone disease. There was no difference in VDR content in the kidneys of the two groups of animals as measured by hormone-binding assays; however, protein extracts prepared from nephrectomized animals exhibited a reduced capacity to specifically bind to a known VDRE. Further analysis revealed a marked decline in the expression of RXR proteins from the same extracts, suggesting that one of the early events leading to resistance to the actions of the vitamin could involve a reduction in the requisite DNA-binding partner for the VDR.

However, with progression of renal failure the compensatory effect of PTH on calcitriol deficiency is overcome and a relative and, thereafter, absolute deficiency in calcitriol exists as suggested by the direct relationship between the decrease in GFR and circulating levels of calcitriol [8].

Indications for treatment with vitamin D

Replacement of the deficient vitamin D hormone seems a logical step to avoid HPT and renal bone disease. In a prospective, double blind placebo-controlled study the efficacy of calcitriol treatment on the development of 2HPT and bone disease was assessed in patients with mild to moderate renal failure (creatinine clearance 20–59 ml/min) [9]. Patients received calcitriol at a dose of 0.25–0.5 μg/day or placebo. Bone biopsies were obtained at baseline and 1 year thereafter. PTH decreased to levels not significantly different from placebo in the calcitriol-treated group and there were few episodes of associated hypercalcemia. In contrast, bone histology at 1 year showed significant suppression in bone turnover in the hormone-treated group, which reached levels lower than the normal range and significantly lower than placebo in a non-negligible number of patients. The data showed that calcitriol is efficient in controlling 2HPT in pre-dialysis patients; however, it runs the risk of inducing adynamic bone disease. Alternative strategies may avoid the potential for this unwanted side effect of calcitriol treatment.

In advanced renal failure serum calcitriol levels are invariably low. In a study of nephrectomized and thyroparathyroidectomized dogs it was shown that administration of calcitriol increased the activity, but not the number of bone cells irrespective of circulating PTH levels and, in contrast, administration of PTH increased the number of bone cells, but not their activity [10]. Thus, the combination of high PTH and low vitamin D would lead to an unexpected bone histology that is a combination of varying degrees of 2HPT with mineralization defects leading to mixed uraemic osteodystrophy. However, in a recent survey of more than 500 patients on dialysis, bone histology showed normal to high bone turnover in only 60% of the patients while low bone turnover was evident in 40% of the patients [11]. Pulse i.v. or oral vitamin D treatment is indicated for suppression of parathyroid gland activity in patients with high bone turnover. Treatment is not indicated and might also prove dangerous in patients with low bone turnover because of the risk of high Ca × P product and development of extrasosseous calcifications [12,13], including cardiovascular calcium deposits and potentially life-threatening consequences.

Determination of bone turnover is essential for the proper management of patients on dialysis. Bone biopsy is the ‘gold standard’ for the determination of the severity of 2HPT [14]. However, this procedure is not widely employed. Therefore, nephrologists rely on the assessment of circulating PTH levels to determine the need for calcitriol treatment. Intact PTH concentrations below 100 pg/ml are diagnostic for low bone turnover and concentrations greater than 500 pg/ml are frequently associated with high turnover bone disease. However, for the majority of patients on dialysis whose circulating PTH concentrations are
between 100 and 500 pg/ml the likelihood of low vs high turnover bone disease is 60:40, or essentially a ‘toss-up’ [11]. More recently, it has been shown that the intact PTH assay measures not only the PTH molecule, but also a large C-PTH fragment [15]. Thus, the intact assay overestimates the circulating concentration of the true PTH(1–84) peptide. In addition, this C-PTH fragment may possess antagonistic activity with regards to the actions of the PTH(1–84) peptide [16,17]. The availability of a new assay that purportedly measures just the PTH(1–84) molecule has renewed interest in assessing the association between bone turnover and PTH. We have found that a calculated ratio of the PTH(1–84)/large C-PTH fragment greater than 1 is predictive of high bone turnover with 100% sensitivity; whereas a ratio of less than 1 indicates a high probability (~87.5%) of low turnover bone disease in a selected cohort of patients with end-stage kidney disease (ESKD) not treated with vitamin D or other medications known to affect bone metabolism [11].

The administration of calcitriol is a standard therapy in the management of hyperparathyroid bone disease in patients with ESKD. Although daily oral calcitriol suppresses serum levels of PTH, it has numerous therapeutic drawbacks, including hypercalcemia and marked suppression of bone turnover, which can lead to adynamic bone disease. Intermittent oral or i.v. administration of the hormone is efficient in suppressing parathyroid over-activity, but still produce episodes of hypercalcemia and adynamic bone disease. Therefore, there has been a pronounced interest in developing analogues of calcitriol that maintain the ability to suppress parathyroid gland over-activity while not adversely affecting bone turnover. Two analogues approved for use in the US market include Zemplar® and Hectorol®. They have demonstrated a capacity to suppress PTH serum concentrations, however, their effects on bone are presently unknown. Another analogue that has been extensively studied and has received regulatory approval for use in Japan is 1,25-dihydroxy-22-oxavitamin D₃ (22-oxacalcitriol, OCT). To study the effects of OCT on bone a prospective, placebo-controlled study was initiated in 5/6 nephrectomized vs sham-operated dogs [18]. Bone biopsies were performed at baseline and 60 weeks, together with serum measurements for calcium, phosphate, PTH, calcitriol, and osteocalcin. OCT administration was initiated at 0.01 µg/kg body weight three times a week. The amount of OCT administered was increased to a maintenance dose that was limited to the highest amount of OCT that did not induce hypercalcemia in the individual dogs. In nephrectomized dogs, OCT prevented the rise in serum PTH concentrations, but some episodes of hypercalcemia were observed. In nephrectomized dogs, OCT reversed abnormal bone formation such as woven osteoid and fibrosis, but did not significantly alter the level of bone turnover, indicating that it is less likely to induce adynamic bone disease. OCT also improved mineralization parameters in both nephrectomized and sham dogs.

**Conclusions**

The management of patients with ESKD still represents a formidable challenge for the nephrologist. This involves controlling a variety of factors concerned with the maintenance of mineral homeostasis, including among others serum calcium, phosphate, and PTH. Often overlooked in this regard is the impact that therapeutic measures taken by the nephrologist will have on bone. The decision to start vitamin D therapy, the route of administration, the dose, and the duration is complex and should be adapted to the individual patient. Careful monitoring of serum calcium and PTH levels is required to avoid hypercalcaemic episodes. Further studies will determine whether following the calculated PTH(1–84)/C-PTH fragment ratio may help in monitoring vitamin D therapy in patients with ESKD. In addition, caution should be taken in the use of vitamin D therapy so as to not over-suppress bone turnover in an overzealous effort to control HPT. The complications of low bone turnover are extraosseous calcification, particularly with regard to cardiovascular calcifications that may increase morbidity, and potentially a higher risk of bone fractures. These concerns have fostered interest in the development of analogues of vitamin D that are able to suppress HPT without inducing hypercalcemia and low bone turnover. Among several candidate compounds, OCT still can produce episodes of hypercalcemia in a canine model of renal insufficiency; however, it exhibits considerable promise as it relates to bone turnover.

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