The importance of bone health in end-stage renal disease: out of the frying pan, into the fire?

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Abstract

In the early stages of renal failure, hyperparathyroidism develops as a compensatory mechanism to control serum levels of calcium, phosphorus and calcitriol. As kidney disease progresses, this ability to maintain mineral homeostasis is lost, leading to the development of renal osteodystrophy (ROD). Over the past decade, the pattern of ROD seen in patients with chronic kidney disease (CKD) has changed. Previously, the majority of patients had mixed uraemic osteodystrophy or aluminium-related osteomalacia. The decreased use of aluminium-based phosphate binders, coupled with improvements in the management of hyperphosphataemia, led to a reduction in the prevalence of these types of ROD. Since the mid-1990s, there has been an increase in the prevalence of adynamic bone disease as a result of increased suppression of parathyroid hormone through the use of calcium-based phosphate binders and calcitriol therapy. Adynamic bone disease is also associated with several clinical factors, such as older age, use of continuous ambulatory peritoneal dialysis and the presence of diabetes mellitus, as well as the use of calcitriol therapy. Studies of calcium metabolism in patients with CKD have shown that adynamic bone disease is a distinct clinical condition that leads to hypercalcaemia via mechanisms different from that seen in high-turnover bone disease. As high calcium × phosphorus product has been associated with soft tissue and vascular calcifications, and increased mortality, optimizing bone health may be an important way of reducing cardiovascular risk in patients with CKD. To do this, novel, effective, non-calcium, non-aluminium phosphate binders will be necessary.

Keywords: adynamic bone disease; bone turnover; calcitriol; extraosseous calcification; hyperparathyroidism; parathyroid hormone; renal bone disease

Introduction

Patients with chronic kidney disease (CKD) experience a progressive reduction in glomerular filtration rate (GFR) as their condition advances. When the GFR falls to < 15 ml/min/1.73 m², the patient will require treatment for renal failure, either by dialysis or by renal transplantation. It has been known for many years that, as GFR declines, levels of parathyroid hormone (PTH) increase; PTH levels start to rise when GFR falls to ~60 ml/min/1.73 m² [1]. In these patients, however, serum phosphorus and calcium levels are generally in the normal range. Levels of calcitriol (1,25-dihydroxyvitamin D₃) are also normal. Research in nephrectomized dogs has suggested that the increase in PTH levels is an adaptive response to the need for increased phosphorus excretion per remaining nephron that is seen in patients with CKD [2,3]. The dogs were 5/6th nephrectomized and, after 2 weeks, the remaining kidney was removed. Biochemical parameters, including calcium, phosphorus, PTH and calcitriol were assessed at 1, 2, 3, 8 and 28 days after nephrectomy. The earliest changes seen were a significant decrease in serum calcitriol levels, an increase in serum phosphorus levels and a mild rise in serum calcium levels after 1 day (Figure 1). By day 2, serum phosphorus levels rose further, serum calcitriol levels fell further, and PTH levels started to go up.

Calcium levels were maintained in the high-normal range (Figure 1) [4]. Thus, hyperparathyroidism develops in response to abnormal phosphorus and calcitriol levels in the early stages of renal failure [2,3]. It appears that this allows the body to maintain normal serum phosphorus and calcitriol levels by stimulating the remaining neurons to increase phosphorus excretion.
and calcitriol production [2,5,6]. With the rise in PTH, phosphorus and calcitriol levels return to the normal range until GFR declines to $\sim 40 \text{ml/min/1.73 m}^2$ [1]. As PTH and calcitriol play a pivotal role in the regulation of bone turnover [7–9], the altered mineral and hormone metabolism that accompanies renal failure leads to significant changes in bone [renal osteodystrophy (ROD)]. These changes begin to occur in patients with a moderate GFR [10,11], long before dialysis is required.

**Changes in the pattern of bone disease in the late 20th century**

In the past, the increase in PTH and decrease in calcitriol seen in patients with CKD was associated with a type of ROD known as mixed uraemic osteodystrophy in a high percentage of patients. Smaller proportions of patients presented with more severe forms of ROD: predominant hyperparathyroid bone disease or aluminium-related osteomalacia [12]. The use of aluminium-based phosphate binders decreased rapidly in the early 1990s when the toxic effects of aluminium (low-turnover bone disease, dialysis encephalopathy and anaemia [13,14]) became widely known. Thus, the levels of stainable bone aluminium detectable in the bone of patients with CKD began to decrease (Figure 2). This led, in turn, to a lower prevalence of adynamic bone disease and the near disappearance of osteomalacia (<2% of patients) by 1995 (Figure 3). After 1995, however, there was an increase in the prevalence of adynamic bone disease (Figure 3) without evidence of aluminium toxicity [12,15,16]. This rise coincided with the shift from aluminium-based phosphate binders to calcium-based agents: increased serum calcium levels lead to suppression of PTH, particularly when calcium salts are used together with calcitriol supplementation. Today, there is a ‘polarization’ between adynamic bone disease and hyperparathyroid bone disease in patients with CKD, with a decreasing prevalence of mixed uraemic osteodystrophy (Figure 3). The challenge for nephrologists is to distinguish between these two major types of ROD, as the management strategies are different for each type.

**Identifying adynamic bone disease**

Histologically, adynamic bone disease is characterized by very low bone formation rates with no osteoid accumulation and PTH levels in the low to low–normal range [17]. The pathogenic processes underlying adynamic bone disease are not fully understood, although a number of clinical characteristics have been identified that are closely associated with the occurrence of adynamic bone (Table 1). Excessive...
phosphorus levels do not appear to be directly linked to an increased risk of dynamic bone disease, but excessive intake of aluminium-based or calcium-based phosphate binders may increase the risk of adynamic bone [16,17]. Clinical studies have shown that calcitriol treatment in patients with advanced renal insufficiency who are not on dialysis can lead to adynamic bone disease as a result of oversuppression of PTH levels. In a trial of 16 patients with CKD, patients who received calcitriol had decreased lamellar osteoid volume as a percentage of bone volume, decreased osteoid thickness and decreased osteoblast number, compared with those who had received placebo [18]. In an open-label trial of children and adolescents who were receiving calcitriol treatment for secondary hyperparathyroidism, the rate of bone formation was significantly decreased in all patients (P<0.001) [19]. In half of the patients (6/12), however, bone formation decreased to the subnormal range and adynamic lesions developed. Thus, it is essential that suppression of PTH levels and control of serum phosphorus are balanced against the need to maintain sufficient PTH levels for normal bone turnover to occur.

**Is adynamic bone a disease or just a histological entity?**

Although adynamic bone disease clearly exists in the form of histological changes in bone, it previously has been unclear whether the different forms of ROD lead to different clinical consequences, such as abnormalities in calcium homeostasis. We assessed derangements in calcium metabolism in 43 patients on dialysis, 16 with low-turnover bone disease, 7 with predominant hyperparathyroid bone disease and 20 with mixed uraemic osteodystrophy [20]. Intestinal calcium absorption was the same in each of the three histological groups (Figure 4a). Calcium efflux from serum was normal in patients with low-turnover bone disease and in those with mixed uraemic osteodystrophy, and significantly higher than normal in patients with hyperparathyroid bone disease (P<0.001; Figure 4b). Calcium accretion in bone was also significantly higher than normal in patients with hyperparathyroid bone disease (P<0.001). Calcium accretion was within the normal range in patients with mixed uraemic osteodystrophy and was below normal in patients with low-turnover bone disease (Figure 4c). Significant positive correlations were seen between plasma calcium efflux and bone calcium accretion (P<0.001), and there was no significant correlation between these parameters and intestinal calcium absorption. Thus, the various forms of ROD are accompanied by different alterations in calcium metabolism. Patients with low-turnover bone disease showed low to normal plasma calcium efflux and low bone calcium accretion. When subjected to high calcium loads, these patients are unable to incorporate the extra calcium into the bone matrix, increasing the risk of hypercalcaemia and soft tissue deposition. It has also been shown that patients treated with calcium carbonate are at increased risk of hypercalcaemia when serum markers of bone turnover, such as PTH, osteocalcin and alkaline phosphatase, are low [21]. Thus, administration of calcium-based phosphate binders or vitamin D therapy may lead to calcium overload, with an increased risk of hypercalcaemia. Adynamic bone disease is, therefore, a genuine condition, characterized by a very low capacity for buffering calcium levels and an inability to handle an increased calcium load. Identifying states of low bone turnover is of great importance in the decision to use vitamin therapy or calcium salts in the treatment of patients with CKD.

**Bone disease and metastatic calcification**

In recent years, it has become increasingly clear that increased phosphorus levels and hypercalcaemia are important risk factors in the development of vascular and other soft tissue calcifications, which lead, in turn, to increased mortality rates in patients with CKD [22]. Thus, patients with low-turnover bone disease and hyperparathyroid bone disease are at increased risk of metastatic calcification, although the mechanisms underlying the hypercalcaemia in each case are different. In the past decade, with the reduction in the use of aluminium salts and the increased use of calcium-based phosphate binders, the focus of treatment in

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**Table 1. Clinical factors that are significantly different in patients with adynamic bone disease, compared with those with hyperparathyroid bone disease [12]**

<table>
<thead>
<tr>
<th></th>
<th>Adynamic bone disease</th>
<th>Hyperparathyroid bone disease</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56±0.7</td>
<td>46±1*</td>
</tr>
<tr>
<td>Age at onset of dialysis (years)</td>
<td>53±0.9</td>
<td>40±0.7*</td>
</tr>
<tr>
<td>Duration on dialysis (years)</td>
<td>3.9±0.2</td>
<td>5.5±0.2*</td>
</tr>
<tr>
<td>Patients receiving CAPD (%)</td>
<td>27.2</td>
<td>13.4*</td>
</tr>
<tr>
<td>Aluminium accumulation (SBA &gt;30%) (% of patients)</td>
<td>75.5</td>
<td>26.1*</td>
</tr>
<tr>
<td>Prevalence of diabetes mellitus (% of patients)</td>
<td>24.2</td>
<td>6.0*</td>
</tr>
<tr>
<td>Intact PTH level (pg/ml)</td>
<td>406±233</td>
<td>1958±848*</td>
</tr>
</tbody>
</table>

CAPD, continuous ambulatory peritoneal dialysis; PTH, parathyroid hormone; SBA, stainable bone aluminium.

*Significantly different from adynamic bone disease, P<0.05.
patients with CKD and hyperphosphataemia has moved away from bone health and towards the issue of calcification. It now appears that the best way of reducing the risk of metastatic calcification and the associated increase in mortality may be to focus on optimizing bone turnover. If the extremes of ROD, i.e. adynamic bone disease and hyperparathyroid bone disease, can be avoided, it seems likely that the incidence of metastatic calcification in dialysis patients will be reduced. To achieve this goal, novel, effective, non-calcium, non-aluminium phosphate binders will be necessary. It is hoped that these agents will lead to a reduction in mortality rates in this patient group, although this remains to be seen.

**Summary**

In recent years, the spectrum of bone disease in patients with CKD has changed, with a reduction in the prevalence of mixed uraemic osteodystrophy and osteomalacia. These reductions have been accompanied by an increase in the prevalence of adynamic bone disease. Adynamic bone disease is an important clinical condition, which leads to soft tissue and vascular calcifications via mechanisms different from the calcification seen in patients with high-turnover bone disease. The focus for treating patients with CKD and hyperphosphataemia has changed from bone health to calcifications. It now seems that an emphasis on optimal bone turnover will be essential to combat the issue of calcification.

**References**