NDT Plus (2008) 1 [Suppl 1]: i2–i6
doi: 10.1093/ndtplus/sfm037

NDT PLUS
Nephrology Dialysis Transplantation

The pathophysiology of secondary hyperparathyroidism and the consequences of uncontrolled mineral metabolism in chronic kidney disease: the role of COSMOS

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Abstract

The development of secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease. SHPT develops as a consequence of mineral metabolism disturbances and is characterized by elevated serum parathyroid hormone (PTH) and parathyroid hyperplasia. Evidence suggests that SHPT contributes to the development of vascular calcification and cardiovascular disease, as well as to the development of renal osteodystrophy. The elevated serum calcium, phosphorus, calcium–phosphorus product and PTH that accompany SHPT have been independently associated with an increased relative risk of mortality. Despite the danger that these risks represent, achieving control of mineral metabolism in SHPT is difficult. Recent evidence from the Current Management of Secondary Hyperparathyroidism: Multicentre Observational Study has shown that fewer than 1 in 10 haemodialysis patients simultaneously meet their National Kidney Foundation Kidney Disease Outcomes Quality Initiative targets for serum calcium, phosphorus, calcium–phosphorus product and PTH with standard treatments. There is therefore an urgent need for new strategies and novel pharmacologic therapies that improve control of mineral metabolism and PTH secretion in SHPT and thus reduce the mortality associated with this condition.

Keywords: calcium; haemodialysis; kidney; phosphorus; secondary hyperparathyroidism

Introduction

Phosphorus levels increase and active vitamin D (calcitriol) synthesis decreases in direct response to declining kidney function, triggering a cascade of sequelae including decreased calcium absorption and increased production of parathyroid hormone (PTH) [1–3]. Elevations in serum PTH concentration are observed early in the development of chronic kidney disease (CKD) [4]. As CKD progresses, serum PTH continues to rise [4] and patients typically develop secondary hyperparathyroidism (SHPT) [5]. Consequently, most of the patients receiving dialysis have persistently elevated serum PTH [6]. Prolonged hypocalcaemia, hyperphosphataemia and low vitamin D concentrations all contribute to the increased PTH synthesis and secretion and parathyroid gland hyperplasia that are the hallmarks of SHPT [7,8]. Prevention and treatment of SHPT are critical because these mineral metabolism imbalances are independently associated with increased morbidity and mortality in CKD patients [9] and add to the development of extraosseous calcification, particularly in the vasculature [10,11], and bone disorders such as renal osteodystrophy [12]. This review discusses the pathophysiology of SHPT, the various clinical complications of uncontrolled mineral metabolism and the need for new strategies for SHPT treatment in CKD patients.

Pathophysiology of SHPT

Alterations in both phosphorus and calcium metabolism play critical roles in the development of SHPT. The kidney's ability to remove phosphorus from circulating plasma is reduced in CKD, resulting in an accumulation of phosphorus in the serum [3]. One consequence of this increase in serum phosphorus is increased PTH synthesis and secretion, and parathyroid cell proliferation [1,13]. The kidney plays an equally important role in mineral metabolism through a second mechanism. The final step in the synthesis of 1,25-dihydroxyvitamin D_3 occurs in the kidney [14], and it is this active D_3 metabolite that is required for efficient absorption of calcium from the small intestine [15]. Calcium and 1,25-dihydroxyvitamin D_3 levels regulate a variety of processes, including bone morphogenesis and turnover in conjunction with PTH [15], calcium channel–mediated processes [16] and gene transcription at the subcellular level [17]. In CKD, the reduction in 1,25-dihydroxyvitamin D_3 and serum calcium triggers the release of PTH [18], which in turn promotes intestinal calcium absorption,

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reabsorption of calcium in the kidney and the release of calcium from bone.

The calcium-sensing receptor (CaR), located on the surface of the chief cells of the parathyroid gland, plays a central role in the regulation of PTH secretion and synthesis, making it an important regulator of calcium homeostasis. In CKD, lowered serum calcium levels result in ongoing inactivation of the CaR, reduced signalling through the CaR and increased PTH synthesis and secretion [3,19]. As PTH secretion increases, calcium is released from bone tissue, enhancing phosphate excretion in the presence of a functioning kidney [20]. This response of the parathyroid gland depends on the rapidity and duration of the hypocalcaemic stress [21,22]. PTH release in response to calcium occurs within seconds to minutes following signalling through the CaR [22,23], chronic hypocalcaemic stress and hyperphosphataemia stimulate PTH gene expression and subsequent PTH synthesis within hours to days [24] and proliferation of parathyroid cells occurs over days to weeks [13].

The mechanisms governing the synthesis of PTH in the parathyroid gland are complex and still not fully understood. Although the nuclear vitamin D receptor (VDR) can suppress PTH gene transcription [18,25], PTH is also regulated post-transcriptionally by the binding of stabilizing RNA-binding proteins to the 3′ untranslated region of the PTH transcript [26,27]. Interestingly, the PTH transcript has a greater stability under conditions of low calcium and high phosphorus [19].

As CKD progresses towards stage 5, SHPT increases in severity, resulting in the proliferation of parathyroid cells and the development of diffuse hyperplasia [3]. This is accompanied by a decrease in CaR and VDR expression [28–30]. Because vitamin D is a potent inhibitor of PTH synthesis [18,31], a reduction in VDR expression might also inhibit the vitamin D–mediated signals that suppress PTH synthesis and release, although this has not yet been demonstrated experimentally. It is the hyperplastic nodules of the parathyroid gland that show the greatest decrease in both CaR and VDR expression [28,30], rendering them less responsive to circulating calcium. As parathyroid cells are transformed into a severe nodular hyperplastic state, a decline in VDR expression reduces the efficiency of vitamin D receptor activators in up-regulating the transcription of the CaR gene and in inhibiting parathyroid cell proliferation.

Clinical complications of uncontrolled mineral metabolism

Evidence suggests that the alterations in serum PTH and mineral metabolism in SHPT have important consequences for haemodialysis patients. Increased calcium and phosphorus concentrations are key contributors to SHPT-associated all-cause and cardiovascular (CV) mortality [9,32] and bone disease [12]. It is less recognized, but of equal importance, that PTH levels also significantly correlate with CV mortality risk. In a study of the correlation between the degree of deviation from National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI^{TM})

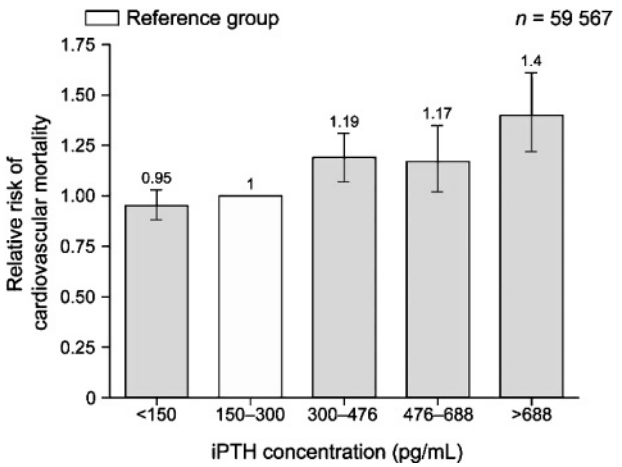

Fig. 1. Risk of cardiovascular death according to iPTH levels in a cohort of North American haemodialysis patients ($n = 59\,567$). Intact PTH level was assessed during a 6-month baseline period and cardiovascular mortality was determined during an 18-month follow-up period. Error bars represent 95% confidence interval. Data from Belozeroff *et al.* [33].

targets (intact PTH [iPTH] 150–300 pg/mL) and the risk of CV death in patients undergoing dialysis ($n = 59\,567$), Belozeroff *et al.* [33] demonstrated that increased PTH concentrations were significantly correlated with increased CV mortality risk (Figure 1). In another large study ($n = 19\,388$) of CKD patients undergoing dialysis, Naves *et al.* [34] showed that the risk of CV death increased proportionally with increasing PTH concentrations, with a relative risk (RR) of 1.34 for 300–600 pg/mL and 1.52 for >600 pg/mL compared with the reference group of 150–300 pg/mL. Block *et al.* [9] reported a similar relationship between PTH levels and all-cause mortality in patients with stage 5 CKD.

Uncontrolled mineral metabolism also increases the risk of mortality. Naves *et al.* [34] documented that elevated mean serum concentrations of phosphorus (>5.0 mg/dL), calcium (>11 mg/dL) and calcium–phosphorus product (Ca × P; >50 mg^2/dL^2) were positively and significantly associated with increased RR of CV death. In contrast with data from other studies evaluated by Block *et al.* [35], serum calcium concentrations <8.5 mg/dL were also significantly associated with increased RR of CV death (RR = 1.87). In a study of a large cohort ($n = 24\,803$) of haemodialysis patients, failure to achieve any KDOQI^{TM} targets for serum PTH (150–300 pg/mL), calcium (8.4–9.5 g/dL) and phosphorus (3.5–5.5 g/dL) was associated with an increased RR of death (RR = 1.51) compared with patients who achieved all three targets [36]. Achievement of either one or two KDOQI^{TM} targets was associated with proportional increases in the RR of death. Block *et al.* [37] have shown that the highest mortality rates are found in patients who have not achieved KDOQI^{TM} targets for Ca × P and PTH (Figure 2) [9,37].

Consistent with their contribution to CV mortality, increased serum phosphorus and Ca × P are associated with the development of vascular calcification [38,39]. Both calcium and phosphorus have been shown to directly promote mineralization in cultured smooth muscle cells [40,41]. Furthermore, phosphorus may contribute to

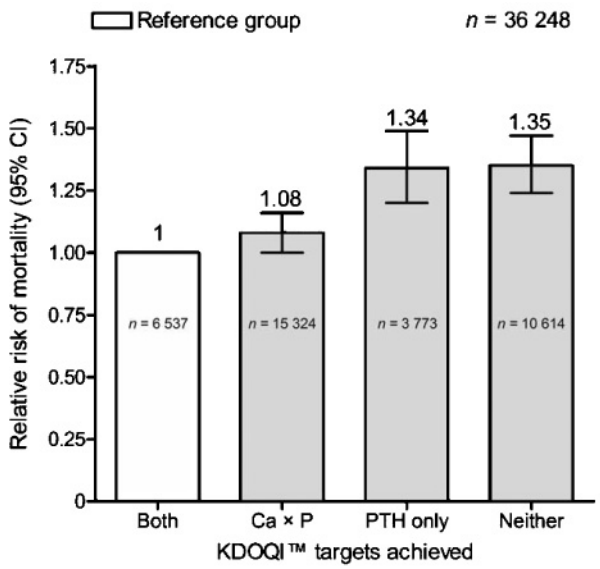

Fig. 2. Relative risk of death associated with not achieving KDOQI[TM] targets for serum PTH (150–300 pg/mL) and Ca × P (<55 mg^2/dL^2) concentrations. The relative risk of mortality is highest among patients not achieving either target. Error bars represent 95% confidence interval, $n = 36\,248$. Adapted with permission from Block *et al.* [37].

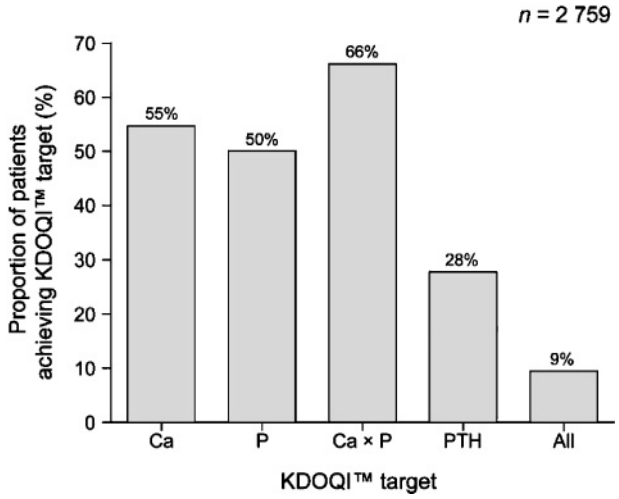

Fig. 3. Achievement of KDOQI[TM] guidelines at baseline in COSMOS study. Data are baseline values from a subset of 2759 patients. Adapted with permission from Fernández-Martín *et al*. [49].

calcification by promoting increased PTH synthesis and secretion and parathyroid gland hyperplasia [42]. Arterial calcification results in stiffness and increased atherosclerotic load in the arteries [43], each of which increases the risk of a myocardial infarction and surgical complications. The risk of aortic calcification has been shown to be significantly higher in both men and women undergoing dialysis compared with age-matched patients in the general population (RR = 7.7 for men and RR = 9.0 for women) [44].

Another serious consequence of uncontrolled mineral metabolism is fracture [9,45]. In a cohort of patients from the European Vertebral Osteoporosis Study [44], the presence of vascular calcifications was positively and significantly associated with a higher risk of vertebral fractures (aortic calcification, RR = 1.9; femoral calcifications, RR = 3.2; uterus-spermatic calcifications, RR = 3.9) [44]. In addition, a significant increase (more than fivefold) in peripheral bone fractures was observed in patients undergoing dialysis compared with age-matched patients in the general population [44]. After 8 years of follow-up, mortality was directly correlated with severe vascular calcification in men (RR = 4.2) and bone fractures in women (RR = 2.2) [44].

Challenges meeting recommended targets

National Kidney Foundation KDOQI[TM] guidelines were developed as recommendations based on a patient's degree of kidney function [46]. For stage 5 CKD, the KDOQI[TM] guidelines specify strict target concentrations of serum iPTH (150–300 pg/mL), calcium (8.4–9.5 mg/dL), phosphorus (3.5–5.5 mg/dL) and Ca × P (<55 mg^2/dL^2). Meeting the KDOQI[TM] targets is, however, difficult and challenging. In fact, <10% of dialysis patients achieve combined targets for PTH, calcium, phosphorus and Ca × P [47–49]. In the international Dialysis Outcome Practice Patterns Study (DOPPS), Young *et al.* [50] investigated the associations between altered mineral metabolism and mortality in haemodialysis patients ($n = 17\,236$). DOPPS, which was conducted before publication of the KDOQI[TM] guidelines, demonstrated that the phosphorus and PTH levels in the majority of patients were outside the KDOQI[TM] recommended ranges, and Ca × P exceeded the upper limit of the range in >40% of patients. In addition, all-cause and CV mortality were significantly associated with serum phosphorus, calcium and Ca × P concentrations.

To increase the knowledge of the impact of SHPT management strategies on outcomes, the Current Management of Secondary Hyperparathyroidism: Multicentre Observational Study (COSMOS) was initiated in February 2005 [49]. In this 3-year pan-European prospective observational cohort study, primary objectives include the association between clinical events and the achievement of KDOQI[TM] and European best practice guidelines targets in patients undergoing haemodialysis [49,51]. The association between achievement of these targets and mortality, overall CV hospitalization, type of dialysis, type of centre and time on dialysis will be investigated. Secondary objectives include the association of targets with parathyroidectomy, manifest bone disease (including fractures), hospitalizations and vascular access, as well as the value of albumin and haemoglobin assessments in addition to bone mineral markers as predictors of mortality and clinical events.

This pan-European prospective study is currently enrolling with a target of 5700 haemodialysis patients from 20 countries in 285 centres into a web-based database [52]. Preliminary baseline data from 2759 patients indicate that <30% of patients had PTH concentrations within KDOQI[TM] targets; 55% attained goal serum calcium, 50% attained goal serum phosphorus and 66% of patients were within Ca × P target limits [49]. Only 9% of patients simultaneously met all KDOQI[TM] targets (Figure 3).

Future directions in the management of SHPT

Once the COSMOS study is completed, these data will allow for a better understanding of the consequences of SHPT and the potential advantages of maintaining patients within therapeutic targets. Nevertheless, the available evidence from both COSMOS and DOPPS demonstrates the challenge of meeting KDOQI™ targets with current standard care for SHPT in haemodialysis patients and emphasize the need for new strategies and the development of new treatments for the management of bone and mineral disorders. Recent advances in our understanding of the pathophysiology of SHPT in CKD have resulted in new therapeutic targets, in particular the CaR. Such new treatment options may improve the management of SHPT and outcomes in this patient population.

Acknowledgements. The authors wish to thank Dylan Harris and Ali Hassan for providing medical writing assistance in the preparation of this manuscript, and Cristina Riesgo for invaluable editorial assistance. This supplement and online open access are sponsored by Amgen Inc.

Conflict of interest statement. Jorge B. Cannata-Andía has been a member of international steering committees and scientific advisory boards of Amgen, Abbott, Shire and Roche. Fernando Carrera is a scientific consultant, a member of steering committees for international clinical trials and/or a member of international advisory boards for the following companies: Amgen (Europe), Roche (International) and Shire (International).

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Received for publication: 17.7.07
Accepted in revised form: 10.9.07