

## REVIEW ARTICLE

## Disordered minerals and disease of soft tissue and bones in chronic kidney disease

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### ABSTRACT

This article briefly reviews the mineral and bone disorder (MBD) found in patients with chronic kidney disease (CKD) and should provide a useful summary for trainees in nephrology and internal medicine. The storage of minerals is one of the principal roles of our bones, which are alive and are constantly being remodelled under the influence of vitamin D and parathyroid hormone (PTH), aided and abetted by calcium and phosphates. This occurs in a controlled fashion in healthy individuals. In patients with CKD, this control is lost and either an exaggerated, ineffectual remodelling takes place, resulting in the removal (in the case of high-turnover bone disease) or inadequate (in low-turnover bone disease) deposition of minerals. Vascular (and other soft tissue) calcification accompanies MBD, with phosphate and calcium playing major roles in the pathogenesis of the condition.

The development of MBD is insidious and evident by changes in blood PTH, calcium and phosphate levels seen as early as stage 3 CKD. Vascular calcification may also be observed at this early stage. Various reports have demonstrated associations between these abnormal blood levels and morbidity and mortality; however, randomised controlled studies are lacking that show definite proof of cause and effect.

In resource-limited countries, the control of PTH is restricted to the use of basic, inexpensive medicines, and patients with CKD can have inadequate means to afford blood tests. The use of vitamin D must be balanced between the use of natural vitamin D (a relatively cheap option) and active vitamin D. The cost of intravenous vitamin D analogues can be prohibitive. The more expensive phosphate binders (mostly non-calcium containing) too are unaffordable for most African patients. The surgical expertise to perform parathyroidectomies is limited to only certain major centres throughout the continent.

**Keywords:** CKD–MBD; klotho; FGF23; calcium; phosphate; PTH; renal osteodystrophy; vitamin D; parathyroidectomy; calcimimetics.

### INTRODUCTION

Controlling mineral and bone disorder (MBD) in patients with chronic kidney disease (CKD) is a priority for nephrologists. This stems from observational studies that show negative associations between abnormal concentrations of minerals (mainly serum calcium and serum phosphate) and of parathyroid hormone (PTH) with morbidity and mortality [1,2]. There are no published randomised controlled studies to show cause and effect or to reveal what target concentrations ought to be achieved to exert a positive influence on the outcome of the disorder.

### PATHOPHYSIOLOGICAL CHANGES IN CKD

The pathophysiological changes related to MBD in CKD have been well described and are illustrated in Figure 1 [3]. The decline in klotho, a gene involved in the ageing process through the regulation of phosphate homeostasis and the activity of members of the fibroblast growth factor (FGF) family, is an early event, which is followed by other changes as CKD progresses. These changes, which occur mainly after the start of stage 3 CKD, impact on the morbidity and mortality of patients with the disease. This has led to debates as to when to

institute therapy to try to prevent these changes and their associated repercussions. No consensus has been reached but this may change in the future. Evidence of earlier disease occurrence has been shown in a small study by El-Husseini et al., who reported that at an eGFR of 44 mL/min/1.73 m<sup>2</sup>, 84% of patients manifested low-turnover bone disease [4]. Most of the patients (>80%) demonstrated vascular calcification, which was positively correlated with phosphate levels. This research suggests that examining for vascular calcification – even in early CKD – may be a worthwhile exercise in addressing CKD–MBD.

### α-KLOTHO , SOLUBLE KLOTHO AND FGF23

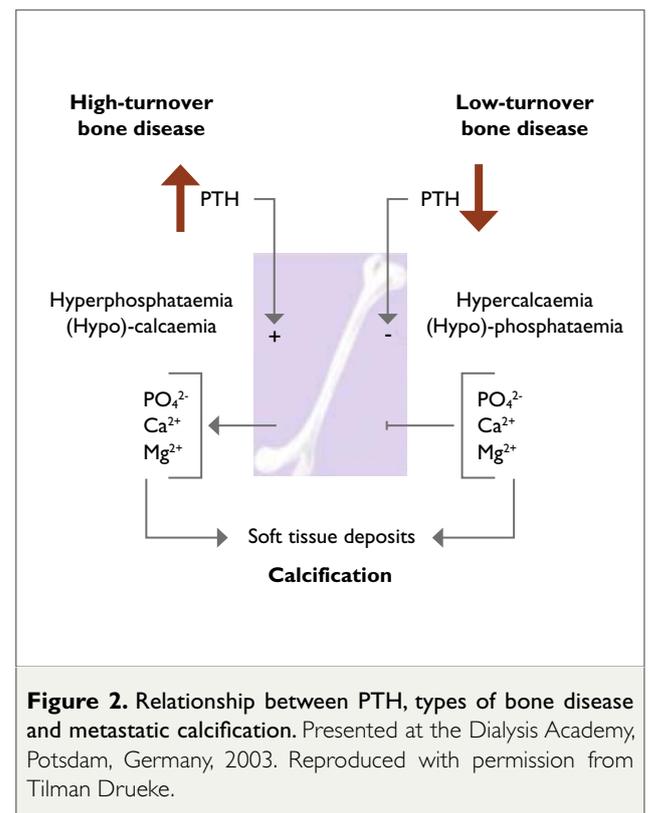
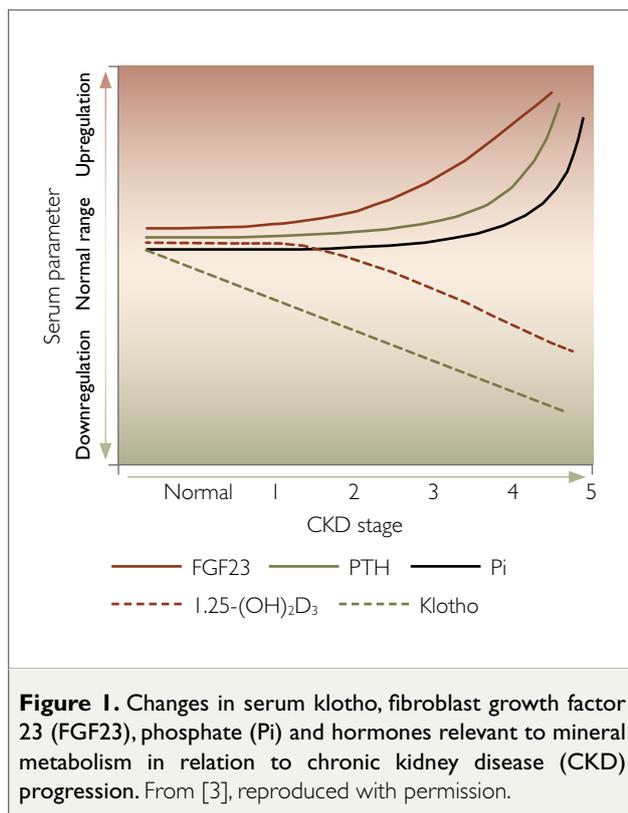
As a transmembrane protein expressed in kidney tubular epithelial cells, α-klotho acts as a co-receptor that binds fibroblast growth factor 23 (FGF23) to its receptor, fibroblast growth factor receptor 1 (FGFR1). Once bound to the receptor, the signalling that follows leads to reduced renal phosphate reabsorption and suppression of activation of vitamin D by 1-α hydroxylase [5]. Soluble klotho (s-klotho) is cleaved mainly from membrane α-klotho and, once in circulation, has FGF23-dependent and independent actions, which include the amelioration of cardiac hypertrophy [3].

The linear decrease in circulating s-klotho concentrations with the progression of CKD (Figure 1) has led to the call for its use to predict and anticipate the progressive decline of kidney function [3,5]. s-Klotho augmentation has been used successfully in animal studies either by its replacement or by upregulation of endogenous klotho. The replenishment of s-klotho protects the kidney from insults in acute kidney injury, inhibits renal fibrosis and reduces vascular calcification in CKD [3,5,6]. Its application in humans still faces many hurdles [7-9] and, to date, no studies of klotho administration in humans have been reported.

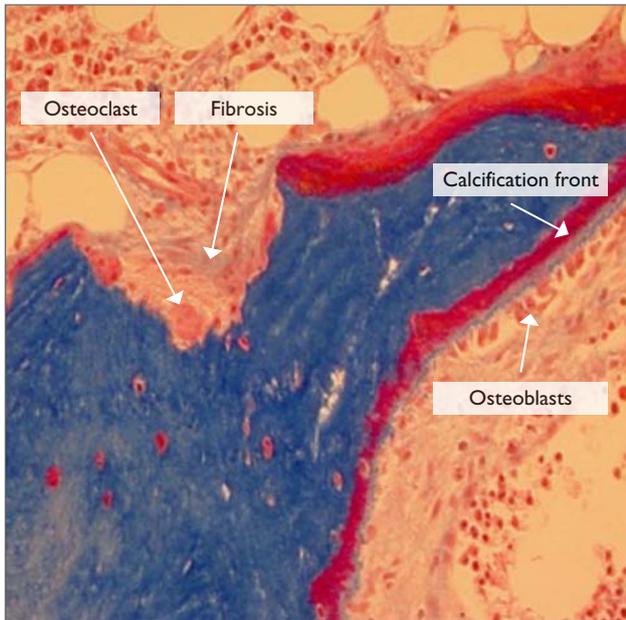
### DEVELOPMENT OF HIGH- AND LOW-TURNOVER BONE DISEASE

As CKD progresses, the initial mineral abnormalities include a decrease in renal phosphate clearance and then a fall in serum calcium concentration due to the FGF23-induced reduction in 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> production. These changes promote the secretion of PTH, with development of a high bone turnover state (Figures 2 and 3) and consequent mobilisation of calcium and phosphate from bone. In the absence of good kidney function to excrete this mobilised calcium and phosphate, the minerals are deposited in the soft tissues.

Overcorrection of the initial mineral disorders may result in low PTH levels with consequent low bone turnover,



causing either osteomalacia or adynamic bone disease. The normal deposition of calcium and phosphate into the bone is reduced and the minerals are deposited in the soft tissues (Figures 2 and 4). Both of these bone diseases may result in bone pain and increased risk of fractures [10,11].

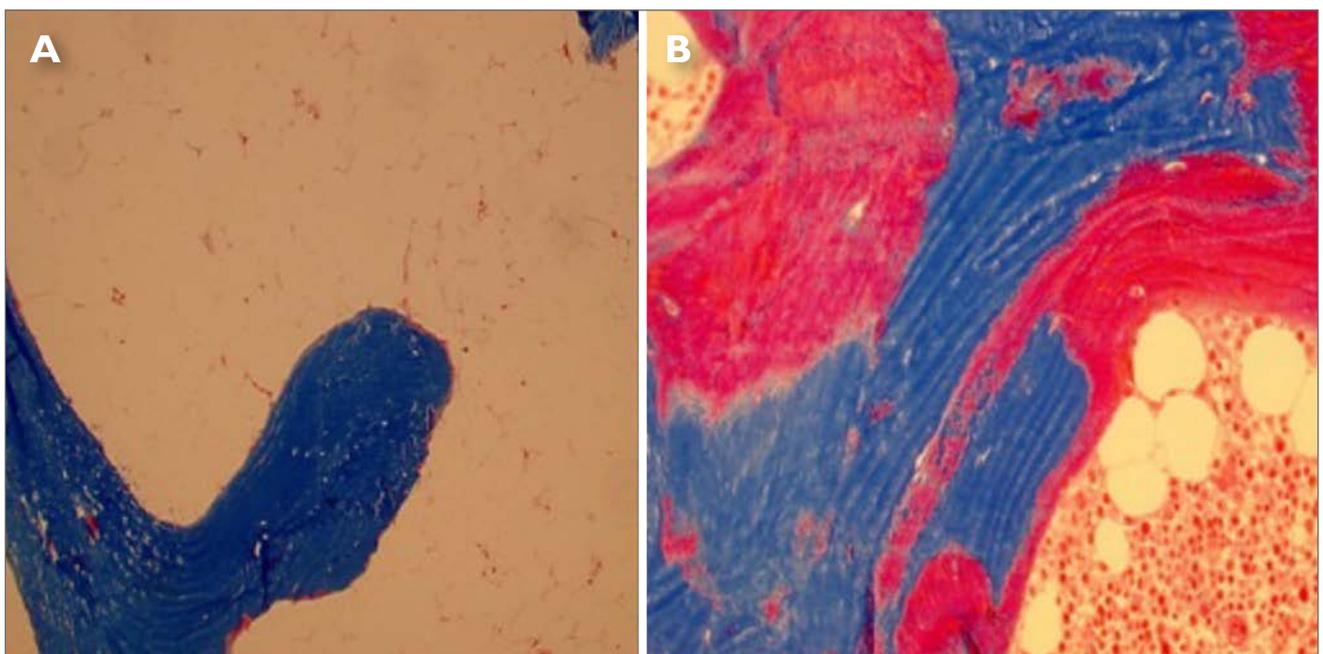


**Figure 3. Bone architecture in a patient with hyperparathyroidism.** The bone histomorphometry illustrates increases in both osteoblastic and osteoclastic activity. The dark blue staining is mineralised bone, whereas the red/pink is unmineralised osteoid with a calcification front. Fibrosis occurs following PTH stimulation of fibroblasts.

## CLINICAL ASSOCIATIONS WITH DERANGED CALCIUM AND PHOSPHATE METABOLISM

The exact ranges within which the abnormal PTH, calcium and phosphate levels should be adjusted are not known. The KDIGO clinical practice guideline update offers only recommendations based on observational studies and comments that the quality of supporting evidence is low and that KDIGO is unable to offer a stronger opinion than “suggest” [12]. The COSMOS study [13], an investigation of the association of MBD parameters with mortality in European patients, claims to provide the best available evidence (which meets Hill’s criteria [14]) to support cause and effect. For the blood levels of phosphate, calcium and PTH, a U-shaped relationship with mortality was demonstrated [13]. A comparison of recommendations from KDIGO [12], the COSMOS study [13], KDOQI [15] and GCC–DOPPS [16] is provided in Table 1.

Multiple studies have demonstrated an association between serum phosphate levels and vascular calcification in CKD. An increase in the former predisposes to the precipitation of calcium phosphate crystals in the walls of blood vessels [15,16]. In a study of the aortas of uraemic rats, Verberckmoes et al. used X-ray fluorescence to reveal deposits of calcium phosphate ( $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ), apatite [ $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ] and whitlockite [ $(\text{Mg},\text{Ca})_3(\text{PO}_4)_2$ ] [17]. Vervloet and Cozzolino have shown that phosphate uptake into vascular smooth muscle cells (VSMCs) through

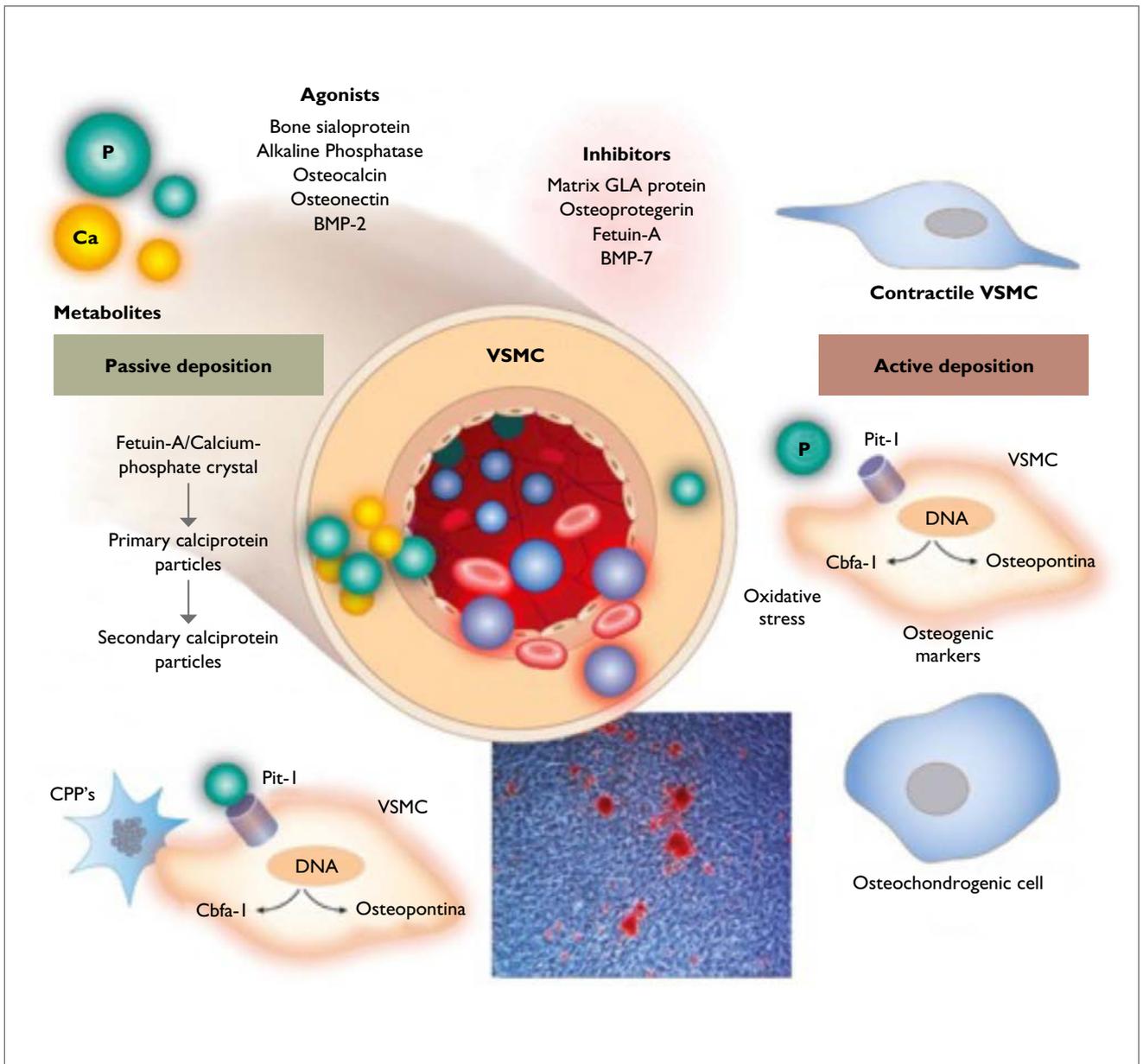


**Figure 4. Histomorphometric findings in two patients with low PTH levels.** Note the absence of cellular activity (no osteoclasts and osteoblasts) and no calcification (no new bone, nor mineralized osteoid) in either adynamic bone disease (A) or osteomalacia (B). In adynamic bone disease, there are minimal osteoid seams whereas in osteomalacia there are thick osteoid seams (stained red in panel B).

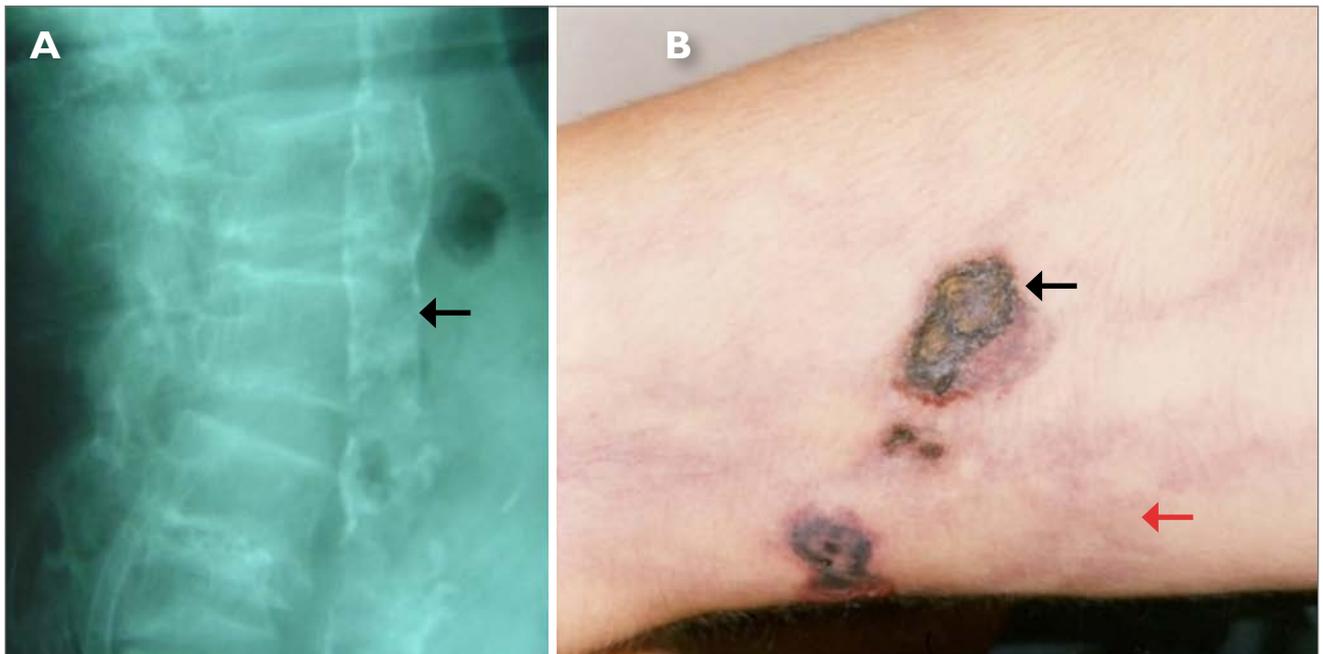
**Table 1.** Recommendations for the control of phosphate, calcium and PTH.

Source/Reference	Phosphate mmol/L (mg/dL)	Calcium mmol/L (mg/dL)	PTH pg/mL
KDIGO	Towards normal values	Avoid hypercalcaemia	2–9 times upper limit of assay
KDOQI	1.13–1.78 (3.5–5.5)	2.1–2.37 (8.4–9.5)	150–300
COSMOS study	1.16–1.68 (3.6–5.2)	1.97–2.37 (7.9–9.5)	168–674
GCC–DOPPS			300–450

Abbreviations: PTH, parathyroid hormone; KDIGO, Kidney Disease: Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; COSMOS, Gulf Cooperation Council–Dialysis Outcomes and Practice Patterns Study.



**Figure 5.** Schematic diagram of the cross section of a medium-sized artery. Calcium (yellow) and phosphate (green) ions are deposited in the vessel wall. Note the agonists and inhibitors of calcification. On the left, note the formation of calciprotein particles (CPPs), which evolve into secondary particles toxic to vascular smooth muscle cells (VSMCs). On the lower left and mid right, the entrance of phosphate into VSMCs through Pit-1 is shown. Abbreviations: BMP, bone morphogenetic protein; Cbfa-1, core-binding factor A1; CPP, calciprotein particle; VSMC, vascular smooth muscle cell. Reproduced from [18], with permission.



**Figure 6.** Vascular calcification in two patients on maintenance dialysis. Panel A shows aortic calcification (arrow) as an example of large vessel involvement; panel B demonstrates the skin infarcts (black arrow) and livedo reticularis (red arrow) of systemic calciphylaxis, which are related to small vessel calcification, inflammation and thrombosis.

the inorganic phosphate transporter 1 (Pit-1) is essential for phenotypic modulation of VSMCs and their calcification [18]. This is illustrated in Figure 5.

Calcification in the media of vessel walls (Mönckeberg's arteriosclerosis) causes the wall to be non-compliant, producing an increased pulse wave velocity and systolic hypertension. It is therefore not surprising to see patients on dialysis with high blood pressure readings due to "stiff" vascular walls. Figure 6 shows examples of both large (A) and small (B) vessel calcification in patients on haemodialysis.

Aortic valve calcification may also occur, most often in elderly patients, and will often result in a rapid reduction of the aortic valve area and consequent impairment of cardiac output. Ultrafiltration during dialysis may then result in steep falls in blood pressure.

### ETHNIC DIFFERENCES IN MINERAL METABOLISM

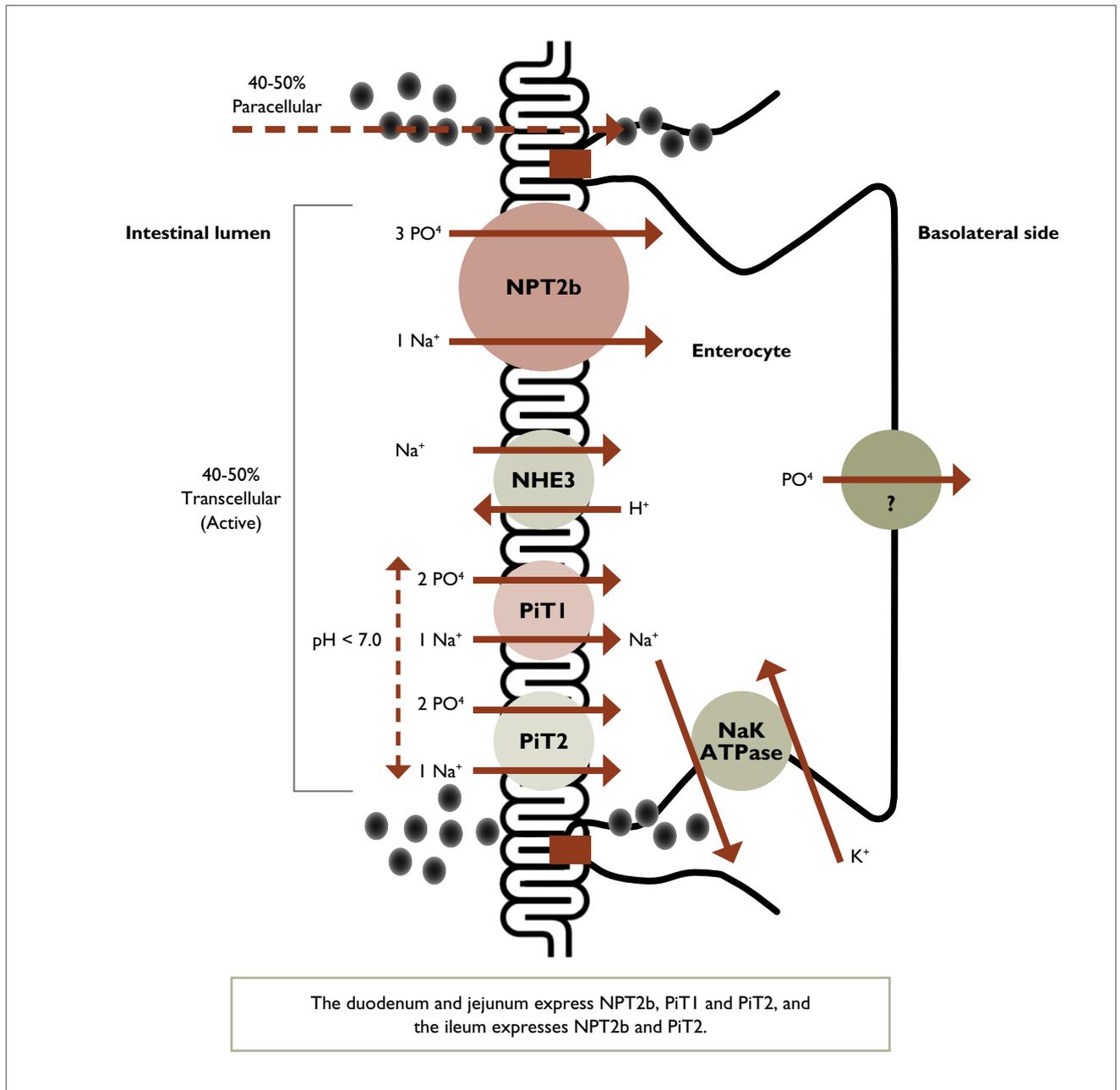
Freercks et al. assessed the extent and severity of vascular calcification in South African dialysis patients, according to ethnicity and known risk factors [19]. Black ethnicity remained a significant negative predictor for coronary calcification after adjustment. After five years of follow-up, and adjusting for increased parathyroidectomy rates, Freercks' group showed that there was a greater progression of vascular calcification among non-Blacks compared to Black patients [20]. The US Renal Data System report of 2009

similarly indicated that, among patients starting dialysis, Black persons demonstrated less cardiovascular calcification. Also, Black patients on dialysis recorded fewer hospitalisations for cardiovascular disease, fewer fractures and lower mortality rates [21].

### A MORE DETAILED LOOK AT PHOSPHATE CONTROL

The association of hyperphosphataemia with many of the problems in CKD–MBD makes it important to follow the consensus opinion that blood phosphate be controlled once levels become elevated. Phosphate is found in most foodstuffs including meats, dairy products and processed foods and beverages, so that a phosphate-restricted diet hardly ever succeeds as a means of lowering its presence in the body. Processed foods contain inorganic phosphate, which is rapidly absorbed from the gut. Vegetable diets are an advantage because their phosphate content is less bioavailable than that of animal products [22]. However, potassium ingestion may nevertheless be increased and close monitoring of serum potassium is required in patients on vegetable diets.

Figure 7 illustrates the absorption of phosphate in the gut. Note the significant paracellular absorption pathway, which is a passive process, relying on a concentration gradient. Phosphate's paracellular permeability extends along the entire length of the small and large intestines [23].



**Figure 7.** The absorption of phosphate in the gut.

Abbreviations: NHE3, sodium–hydrogen exchanger; NPT, sodium-dependent phosphate co-transporter; PiT, phosphate transporter. Figure kindly provided by Pablo Urefia-Torres.

Because of the difficulty in restricting dietary intake of phosphate completely, a phosphate binder in the gut is needed to limit absorption. Calcium carbonate binds phosphate well and supplies calcium, which is an advantage when calcium levels are low. The phosphate binder is given just before a meal, three times daily. An average daily dose of six tablets (equivalent to elemental calcium of 500 mg per tablet or less) is usually sufficient to control the blood phosphate level. A metabolic balance study, by Hill et al., demonstrated that the use of calcium carbonate produced a positive net calcium balance [24]. Using calcium kinetics – with a <sup>45</sup>Ca radiotracer – they recorded a positive

bone balance which was less than the overall calcium balance, suggesting calcium deposition in soft tissue. This implies that binders with the lowest calcium content necessary to control phosphate levels should be prescribed.

The more expensive non-calcium containing binders are particularly useful for patients with severe vascular calcification and in the setting of low PTH levels, as any extra calcium may suppress PTH further. Sucroferric oxyhydroxide [Fe(III)-oxyhydroxide] is a calcium-free phosphate binder with a high phosphate-binding capacity [25], which has the added advantage of increasing serum ferritin levels without additional iron administration [26].

Isaka et al. conducted a randomised study, in dialysis patients, to compare the effects on the progression of coronary artery calcification with sucroferric oxyhydroxide and lanthanum carbonate (another non-calcium containing phosphate binder), using two different phosphate target ranges [27]. The percentage change in calcification score over 12 months in the strict phosphate control group (target 3.5–4.5 mg/dL) was significantly lower than that in their standard phosphate control group (5.0–6.0 mg/dL). The two phosphate binders did not differ in their effects on calcification progression. Although the small sample size was a limiting factor, it appears that strict phosphate control delayed coronary artery calcification progression in patients on haemodialysis.

Sevelamer hydrochloride (or sevelamer carbonate) and lanthanum carbonate are also effective non-calcium containing phosphate binders [28,29]. When compared with calcium carbonate, lanthanum carbonate induced higher bone turnover after one year and greater bone volume after two years.

Tenapanor is a new phosphate-lowering agent which blocks paracellular phosphate absorption in the gut (but is awaiting FDA approval for this indication). It operates via the sodium–hydrogen exchanger (NHE3) and closes paracellular tight junctions [30]. Pergola et al. proved the efficacy of tenapanor in the AMPLIFY study [31]. After four weeks of treatment, tenapanor plus standard phosphate binder reduced phosphate levels significantly when compared with placebo and standard phosphate binder.

## A MORE DETAILED LOOK AT CALCIUM CONTROL AND VITAMIN D USE

Vitamin D is a fat-soluble vitamin that exists in two main dietary forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 derives from animal products and vitamin D2 from plants (e.g. mushrooms). Both D2 and D3 are similarly hydroxylated in the liver and kidneys to produce the active 1,25-dihydroxyvitamin D. Sunlight and body heat convert skin 7-dihydroxycholesterol to vitamin D3, which then follows the same metabolic pathway as dietary vitamin D3 and vitamin D2.

Once phosphate has been corrected, the low serum calcium levels found in the later stages of CKD – due to the inhibition by FGF23 of the production of active vitamin D in the kidneys – will need attention. Calcium carbonate supplies calcium; however, if the calcium concentration remains low, vitamin D must then be prescribed to restore calcium to normal levels and reduce the PTH secretion to the recommended ranges. It is important to remember that vitamin D also increases the absorption of phosphate from

the gut. This may be a disadvantage when active vitamin D is prescribed. In a 12-week study, Westerberg et al. showed that the use of cholecalciferol had little adverse effect on phosphate or calcium levels in CKD stages 3 and 4 [32]. It also halted PTH levels from increasing when compared with placebo. It therefore seems safer in the early stages of CKD to use the natural vitamin D than the active form of 1,25-dihydroxyvitamin D or 1-alpha-hydroxyvitamin D3. The cost of intravenous vitamin D analogues is prohibitive [33].

## AUTONOMOUS HYPERPARATHYROIDISM

Uncontrollable secondary hyperparathyroidism (autonomous hyperparathyroidism) requires a parathyroidectomy. Calcimimetic agents (e.g. cinacalcet) may “switch off” PTH secretion in advanced hyperparathyroidism by sensitising the calcium-sensing receptors but do not cure the condition [34]. Its use is ideal in those unfit for surgery, and in the EVOLVE study it reduced parathyroidectomy rates. High cost is the limiting factor for its use in Africa.

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## Conflict of interest

The author has previously received sponsorship from Shire.

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