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The New Kidney and Bone Disease: Chronic Kidney Disease – Mineral and Bone Disorder (CKD–MBD)

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1. Introduction

Kidney is one of the most important organs in the regulation of mineral metabolism (Fukagawa et al., 2006). Chronic kidney disease (CKD) is a worldwide public health problem that affects 5% to 10% of the world population, with increasing prevalence and adverse outcomes, including progressive loss of kidney function, cardiovascular disease, and premature death (Eknoyan et al., 2004). Calcium and phosphorus are fundamentally important in a wide array of biological functions. Abnormalities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism (usually referred to as disordered mineral metabolism) are common in patients with (CKD) (Block et al., 1998). Cardiovascular disease is the leading cause of death in patients with CKD (London et al., 2003). It has been shown that in individuals with kidney failure on maintenance dialysis who are younger than 65 years, cardiovascular mortality is 10 to 500 times higher than in the general population, even after adjustment for sex, race, and presence of diabetes (Foley RN et al., 1998). Disturbances in mineral metabolism are common complications of CKD and an important cause of morbidity and decreased quality of life. Importantly, increasing evidence suggests that these disturbances are associated with changes in arterial compliance, cardiovascular calcification, bone disorders and all-cause and cardiovascular mortality (Palmer SC et al., 2005, Drueke et al., 2010). Traditionally, when defining bone diseases in CKD patients, this group of disorders has been usually termed renal osteodystrophy. However, beside strictly defined, the term renal osteodystrophy means only bone abnormalities. Recently, the KDIGO (Kidney Disease: Improving Global Outcomes) conference group agreed that the definition of renal osteodystrophy should be only specific to bone pathology found in patients with CKD (Moe S. et al., 2006). It has been concluded that renal osteodystrophy is one component of the mineral and bone disorders that occur as a complication of CKD. It has been proposed that the evaluation and definitive diagnosis of renal osteodystrophy requires performing a bone biopsy. Histomorphometry is not essential for clinical diagnosis, but should be performed in research studies. There was an agreement that histomorphometric results are to be reported by use of the standard nomenclature

recommended by the American Society for Bone and Mineral Research (Parfitt et al., 1987), and investigators would supply primary measurements used to report any derived parameters. Based on all of this a new term has been proposed and coined "Chronic kidney disease – mineral and bone disorder (CKD-MBD)" willing to describe the systemic consequences of mineral metabolism disturbances in CKD patients which can no longer be considered restricted only to bone disease. CKD-MBD defines a triad of interrelated abnormalities of serum biochemistry, bone and the vasculature associated with CKD. The adverse effects of high serum phosphorus and an increase of serum calcium due to calcium overload which are present late in CKD are important component of CKD-MBD as well as vascular changes. Furthermore, to clarify the interpretation of bone biopsy results in the evaluation of CKD-MBD, it has been proposed to use three key histologic descriptors—bone turnover, bone mineralization, and bone volume (so called TMV system)— with any combination of each of the descriptors possible in a given specimen. The TMV classification scheme provides a clinically relevant description of the underlying bone pathology, as assessed by histomorphometry, which, in turn, helps to define the pathophysiology, and, thereby, probably to guide the therapy (Moe S. et al., 2006).

2. CKD – MBD and biochemical abnormalities

The initial evaluation of CKD-MBD should include laboratory for calcium (it has been proposed either ionized or total corrected for albumin), phosphorus, PTH, alkaline phosphatases (total or bone specific), bicarbonate, as well as imaging for soft-tissue calcification. Epidemiologic studies from the early 1990s have demonstrated that an increase in serum phosphorus and in calcium x phosphorus product are associated with poor outcomes in CKD patients. The association of elevated serum phosphorus and calcium and increased mortality in these patients has been confirmed in several recent studies. If inconsistencies exist in the biochemical markers (eg, high PTH but low alkaline phosphatases), unexplained bone pain, or unexplained fractures are present, a bone biopsy would be strongly indicated (London and Drueke, 1997; London *et al., 2003;* Neves et al., 2007; Bucay et al., 1998).

2.1 Calcium

Serum calcium is tightly controlled in healthy individuals, within a narrow range, usually 2.2–2.6 mmol/l, with a minimal, diurnal variation. In patients with CKD, serum calcium levels fluctuate more, because of altered homeostasis and concomitant therapies. Serum calcium levels are routinely measured in clinical laboratories using colorimetric methods in automated machines. In patients with CKD stage 5D, there are additional fluctuations in association with dialysis-induced changes, hemoconcentration, and subsequent hemodilution. Moreover, predialysis samples collected from dialysis patients after the longer interdialytic interval during the weekend, as compared with predialysis samples drawn after the shorter interdialytic intervals during the week, often contain higher serum calcium levels (Tentori et al., 2008). It has been shown that the serum calcium level is a poor reflection of overall total body calcium. Only 1% of total body calcium is measurable in the extracellular compartment while the most important part of calcium is stored in the bones. Serum ionized calcium, generally 40–50% of total serum calcium, is physiologically active, while non-ionized calcium is bound to albumin or anions such as citrate, bicarbonate, and

phosphate, and is therefore not physiologically active. In the presence of hypoalbuminemia, there is an increase in ionized calcium relative to total calcium; thus, total serum calcium may underestimate the physiologically active (ionized) serum calcium. The most commonly used formula for estimating ionized calcium from total calcium is the addition of 0.2 mmol/l for every 1 g decrease in serum albumin below 40 g/l. Unfortunately, recent data have shown that it offers no superiority over total calcium alone and is less specific than ionized calcium measurements. In addition, the assay used for albumin may affect the corrected calcium measurement.

2.2 Phosphorus

It has been shown that inorganic phosphorus is critical for numerous normal physiological functions, including skeletal development, mineral metabolism, cell-membrane phospholipid content and function, cell signaling, platelet aggregation, and energy transfer through mitochondrial metabolism. Owing to its importance, normal homeostasis maintains serum concentrations between 0.81–1.45 mmol/l. The terms, phosphorus and phosphate, are often used interchangeably, but strictly speaking, the term phosphate means the sum of the two physiologically occurring inorganic ions in the serum, and in other body fluids, hydrogenphosphate ($HPO4_2$) and dihydrogenphosphate ($H2PO_4$). However, most laboratories report this measurable, inorganic component as phosphorus. Unlike calcium, a major component of phosphorus is intracellular, and factors such as pH and glucose can cause shifts of phosphate ions into or out of cells, thereby altering the serum concentration without changing the total body phosphorus. Phosphorus is routinely measured in clinical laboratories with colorimetric methods in automated machines. Serum phosphorus levels reach the lowest level in the early hours of the morning, increasing to a plateau at the afternoon, and further increasing to a peak late in the evening (Portale et al., 1987).

Hyperphosphatemia occurs as a consequence of diminished phosphorus filtration and excretion with the progression of CKD. Decreased phosphorus excretion can initially be overcome by increased secretion of parathyroid hormone (PTH), which decreases proximal phosphate reabsorption (Slatopolsky and Delmez, 1994). Hence, phosphorus levels are usually within normal range until the GFR falls below approximately 30 ml/min, or stage IV. CKD according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF–K/DOQI) classification (National Kidney Foundation: K/DOQI). In more advanced stages of CKD, the blunted urinary excretion of phosphorus can no longer keep pace with the obligatory intestinal phosphate absorption, resulting in hyperphosphatemia. Therefore, it is not surprising that the majority of patients with CKD stage 4 and stage 5 have a significant hyperphosphatemia (Block et al., 1998). It has been shown that in patients with advanced CKD high serum calcium, phosphate, and calcium-phosphate product levels are associated with unaccountably high rates of cardiovascular disease (Ganesh et al., 2001; Stevens et al., 2004; Slinin et al., 2005). Moreover, it has been shown also that these derangements in mineral metabolism could occur as well during the early stages of CKD (Slatopolsky and Delmez, 1994).

2.3 Parathyroid hormone

The parathyroid gland plays an important role in the regulation of mineral homeostasis by effects trough other organs such as the kidney and bone. Fluctuation in extracellular calcium

ion levels is sensed by the parathyroid calcium-sensing receptors (CaSRs) and subsequently regulates the synthesis and secretion of parathyroid hormone (PTH) (Felsenfeld et al., 2007). PTH acts on the bone to increase the efflux of calcium and phosphate, and acts on the kidney to reduce urinary calcium excretion, inhibit phosphate reabsorption, and stimulate the production of 1,25-dihydroxyvitamin D (1,25(OH)2D). PTH is cleaved to an 84-amino-acid protein in the parathyroid gland, where it is stored with fragments in secretory granules for release. When it is released, the circulating 1–84-amino-acid protein has a half-life of 2–4 min. The hormone is cleaved both within the parathyroid gland and after secretion into the N-terminal, C-terminal, and middle region fragments of PTH, which are metabolized in the liver and in the kidneys. Enhanced PTH synthesis/secretion occurs in response to hypocalcemia, hyperphosphatemia, and/or a decrease in serum 1,25-dihydroxyvitamin D (1,25(OH)2D), whereas high serum levels of calcium or calcitriol—and, as recently shown, of Fibroblast growth factor 23 (FGF-23)—suppress PTH synthesis/secretion. The extracellular concentration of ionized calcium is the most important determinant of the minute-to-minute secretion of PTH, which is normally oscillatory.

In patients with CKD, this normal oscillation is somehow altered. Over the past few decades there has been a progress in development of sensitive assays in order to measure PTH. Initial measurements of PTH using C-terminal assays were inaccurate in patients with CKD because of the impaired renal excretion of C-terminal fragments (and thus retention) and the measurement of these probably inactive fragments. The development of the N-terminal assay was initially thought to be more accurate but it also detected inactive metabolites. The development of a second generation of PTH assays, the two-site immunoradiometric assay—commonly called an 'intact PTH' assay—improved the detection of full-length (active) PTH molecules. In this assay, a captured antibody binds within the amino terminus and a second antibody binds within the carboxy terminus. Unfortunately, recent data indicate that this 'intact' PTH assay also detects accumulated large C-terminal fragments, commonly referred to as '7–84' fragments; these are a mixture of four PTH fragments that include, and are similar in size to, 7–84 PTH (Gao and D'Amour 2005). In parathyroidectomized rats, the injection of a truly whole 1- to 84-amino-acid PTH was able to induce bone resorption, whereas the 7- to 84-amino-acid fragment was antagonistic, explaining why patients with CKD may have high levels of 'intact' PTH but relative hypoparathyroidism at the bone-tissue level (Slatopolsky et al., 2000; Malluche et al., 2003; Huan et al., 2006). Thus, the major difficulty in accurately measuring PTH with this assay is the presence of circulating fragments, particularly in the presence of CKD. Unfortunately, the different assays measure different types and amounts of these circulating fragments, leading to inconsistent results. More recently, a third generation of assays has become available that truly detect only the 1- to 84-amino-acid, full-length molecule: 'whole' or 'bioactive' PTH assays. There are differences in PTH results when samples are measured in plasma, serum, or citrate, and depending on whether the samples are on ice, or are allowed to sit at room temperature.

PTH and vitamin D have been shown to influence cardiac and vascular growth and function experimentally in human subjects with normal renal function. Because of increased prevalence of hyperparathyroidism and altered vitamin D status in CKD, these alterations have been considered to contribute to the increased prevalence of cardiovascular disease and hypertension seen in this patient population (Slinin Y et al., 2005).

2.4 Vitamin D (25(OH)D)

The parent compounds of vitamin D—D_3 (cholecalciferol) or D_2 (ergocalciferol)—are highly lipophilic. They are difficult to quantify in the serum or plasma. They also have a short half-life in circulation of about 24 h. These parent compounds are metabolized in the liver to 25(OH)D_3 (calcidiol) or 25(OH)D_2 (ercalcidiol). Collectively, they are called 25(OH)D or 25-hydroxyvitamin D. The measurement of serum 25(OH)D is regarded as the best measure of vitamin D status, because of its long half-life of approximately 3 weeks. In addition, it is an assessment of the multiple sources of vitamin D, including both nutritional intake and skin synthesis of vitamin D. There is a seasonal variation in calcidiol levels because of an increased production of cholecalciferol by the action of sunlight on skin during summer months. The gold standard of calcidiol measurement is high performance liquid chromatography (HPLC), but this is not widely available clinically. This is because HPLC is time consuming, requires expertise and special instrumentation, and is expensive. In early 1985, Hollis and Napoli developed the first radioimmunoassay (RIA) for total 25(OH)D, which was co-specific for 25(OH)D_2 and 25(OH)D_3. The values correlated with those obtained from HPLC analysis, and DiaSorin RIA became the first test to be approved by the Food and Drug Administration for use in clinical settings (Hollis and Napoli, 1985). Another method now carried out is liquid chromatography- tandem mass spectrometry (LC-MS/MS). Similar to HPLC, the LC-MS/MS method also has the ability to quantify 25(OH)D_2 and 25(OH)D_3 separately, which distinguishes it from RIA and enzyme-linked immunosorbent assay technologies. This method is very accurate and has been shown to correlate well with DiaSorin RIA (Saenger et al. 2006; Tsugawa et al., 2005). It has been suggested recently that the assays for 25(OH)D are not well standardized, and the definition of deficiency is not yet well validated. At best, clinicians should ensure that patients use the same laboratory for measurements of these levels, if carried out. The most appropriate vitamin D assays presently available seem to be those that measure both 25(OH)D_2 and 25(OH)D_3. Presently, approximately 20–50% of the general population has low vitamin D levels, irrespective of CKD status. However, the benefits from replacing vitamin D have not been documented in patients with CKD, particularly if they are taking calcitriol or a vitamin D analog.

2.5 Vitamin D (1,25(OH)$_2$D)

1,25(OH)$_2$D is used to describe both hydroxylated D_2 (ercalcitriol) and D_3 (calcitriol) compounds, both of which have a short half-life of 4–6 h. Furthermore, in patients with earlier stages of CKD and in the general population, mild-to-moderate vitamin D deficiency, or partly treated vitamin D deficiency, is frequently associated with increased levels of 1,25(OH)$_2$D. Thus, even accurate levels can be misleading. The serum levels of 1,25(OH)$_2$D are uniformly low in late stages of CKD–MBD, at least in patients not treated with vitamin D derivatives (Andress et al., 2006). It has not been recommend a routine measurement of 1,25(OH)$_2$D levels, as the assays are not well standardized, the half-life is short, and there are no data indicating that the measurement is helpful in guiding therapy or predicting outcomes (KDIGO).

2.6 Alkaline phosphatases

Alkaline phosphatases (ALP) are enzymes that remove phosphate from proteins and nucleotides, functioning optimally at alkaline pH. Measurement of the level of total ALP (t-

ALP) is a colorimetric assay that is routinely used in clinical laboratories in automated machines. The enzyme is found throughout the body in the form of isoenzymes that are unique to the tissue of origin. Highest concentrations are found in the liver and bone, but the enzyme is also present in the intestines, placenta, kidneys, and leukocytes (Iba K et al. 2004). Specific ALP isoenzymes to identify the tissue source can be determined after fractionation and heat inactivation, but these procedures are not widely available in clinical laboratories. Bone-specific ALP (b-ALP) is measured with an immunoradiometric assay. Elevated levels of t-ALP are generally due to an abnormal liver function, an increased bone activity, or bone metastases. Levels are normally higher in children with growing bones than in adults, and often are increased after fracture. In addition, t-ALP and b-ALP can be elevated in both primary and secondary HPT, osteomalacia, and in the presence of bone metastasis and Paget's disease. In patients with CKD–MBD alkaline phosphatise may be used as an adjunct test, but if values are high, then liver function tests should be checked. t-ALP could reasonably be used as a routine test to follow response to therapy. The more expensive testing for b-ALP can be used when the clinical situation is more ambiguous. Testing for t-ALP is inexpensive and therefore may be helpful for following patients' response to therapy or determining bone turnover status when the interpretation of PTH is unclear. The use of b-ALP, an indicator of bone source, may provide additional and more specific information, although it is not readily available (Iba K et al. 2004).

3. CKD – MBD and bone abnormalities

Disorders of mineral metabolism are also associated with abnormal bone structure. It has been shown that the gold standard test for bone quality is its ability to resist fracture under strain. In animal models, this resistance can be directly tested with three-point bending mechanical tests. Bone quality is impaired in CKD, as the prevalence of hip fracture is increased in dialysis patients compared with the general population in all age groups. Dialysis patients in their forties have a relative risk of hip fracture that is 80-fold higher than that of age-matched and sex-matched control subjects. Furthermore, hip fracture in dialysis patients is associated with a doubling of the mortality observed in hip fractures in nondialysis patients (Coco M and Rush H., 2000; Alem et al., 2000). It has been shown that risk factors for hip fracture in CKD patients include age, gender, duration of dialysis, and presence of peripheral vascular disease. There are also analyses that found race, gender, duration of dialysis, and low or very high PTH levels as risk factors for hip fracture. It has been reported that both hip and lumbar-spine fractures occur independent of gender and race in CKD patients. Other risk factors for abnormal bone identified in studies from the general population are also common in CKD, including smoking, sedentary lifestyle, and hypogonadism (Alem et al., 2000). These factors are likely to increase the risk of bone fragility and fractures in CKD but have not been well evaluated. Extremes of bone turnover found in patients with CKD have significant impact on fragility and are likely additive to bone abnormalities commonly found in the aging and sedentary general population (Vassalotti et al., 2008; Melamed et al., 2008).

3.1 Classification of renal osteodystrophy by bone biopsy

Bone biopsy is performed to understand the pathophysiology and course of bone disease, to relate histological findings to clinical symptoms of pain and fracture, and to determine

whether treatments are effective. The traditional types of renal osteodystrophy have been defined on the basis of turnover and mineralization as follows: mild, slight increase in turnover and normal mineralization; osteitis fibrosa, increased turnover and normal mineralization; osteomalacia, decreased turnover and abnormal mineralization; adynamic, decreased turnover and acellularity; mixed, increased turnover with abnormal mineralization. It has been suggested recently that by performing bone biopsies in patients with CKD the most important parameters which should be determined are bone turnover, bone mineralization, and bone volume (TMV) (Moe et al., 2009).

3.1.1 Bone turnover

In CKD patients a spectrum of bone formation rates varies from abnormally low to very high. Other measurements that help to define a low or high turnover (such as eroded surfaces, number of osteoclasts, fibrosis, or woven bone) tend to be associated with the bone-formation rate as measured by tetracycline labeling. This is the most definite dynamic measurement, hence it was chosen to represent bone turnover. It should be noted that an improvement of a bone biopsy cannot be determined on the basis of a simple change in the bone-formation rate, because the restoration of normal bone may require either an increase or a decrease in bone turnover, depending on the starting point (Melsen and Moselkilde, 1978).

3.1.2 Bone mineralization

It is a parameter which reflects the amount of unmineralized osteoid. Mineralization is measured by the osteoid maturation time or by mineralization lag time, both of which depend heavily on the osteoid width as well as on the distance between tetracycline labels. The classic disease with an abnormality of mineralization is osteomalacia, in which the bone-formation rate is low and the osteoid volume is high. Some patients have a modest increase in osteoid, which is a result of high bone formation rates. They do not have osteomalacia because the mineralization lag time remains normal. The overall mineralization, however, is not normal because unmineralized osteoid is increased.

3.1.3 Bone volume

Bone volume contributes to bone fragility and is separate from the other parameters. The bone volume is the end result of changes in bone-formation and resorption rates: if the overall bone formation rate is higher than the overall bone resorption rate, the bone is in positive balance and the bone volume will increase. If mineralization remains constant, an increase in bone volume would also result in an increase in BMD and should be detectable by dual-energy X-ray absorptiometry (DXA). Although both cortical and cancellous bone volumes decrease in typical idiopathic osteoporosis, these compartments are frequently different in patients with CKD. In dialysis patients with high PTH levels, the cortical bone volume is decreased but the cancellous volume is increased. (Lindergard et al., 1985).

3.2 Bone markers

Generally, two different types of bone markers are used to determine the bone patophysiology:

3.2.1 Collagen based bone markers

Active osteoblasts secrete pro-collagen type I, and the pro-peptides at both C-terminal and N-terminal ends are immediately cleaved and can be measured in the circulation. The collagen molecules are then covalently bonded through pyridinoline cross-linking. The fragments containing these pyridinoline links (at both the C-terminal and N-terminal ends of the peptides) are released during bone resorption: carboxyterminal (CTX) and aminoterminal (NTX) cross-linking telopeptide of bone collagen, respectively. These collagen-based markers have been studied in normal populations, where there are significant but moderate correlations with bone-formation/resorption rates. These markers are usually increased after bone fracture (Ureña and De Vernejoul, 1999; Ivaska et al., 2007).

3.2.2 Non collagen type of bone markers

Osteoblasts secrete other proteins that have been used to assess their function, including b-ALP, osteocalcin, osteoprotegerin, and receptor activator for nuclear factor kB ligand. Osteoclasts secrete tartrate-resistant acid phosphatase. Osteocytes secrete FGF-23 in response to phosphate and calcitriol. High levels of FGF-23 are seen in patients with CKD, but this is a new measurement, and clinical significance remains to be determined. Some of these markers are excreted by the kidneys, so in CKD, the serum concentrations may merely represent accumulation instead of bone turnover (Rogers and Eastell, 2005).

Renal phosphate excretion is physiologically regulated mainly by proximal tubular cells, which express Na/Pi Type II cotransporters at their apical membrane that control phosphate reclamation. Renal phosphate reabsorption is mediated primarily through the Na/Pi IIa co-transporter, whereas approximately one-third of phosphate ions are reabsorbed through the Na/Pi IIc cotransporter. FGF-23 mediates its phosphaturic effect by reducing the abundance of the Na/Pi IIa cotransporter in proximal tubular cells (Baum et al., 2005). In animal studies, transgenic mice over-expressing human or mouse FGF-23 have severe renal phosphate wasting because of suppression of renal Na/Pi cotransporter activity, whereas FGF-23 inactivation leads to hyperphosphatemia (Liu et al., 2006). In addition, FGF-23 may inhibit gastrointestinal phosphate absorption by reducing intestinal Na/Pi IIb cotransporter activity in a vitamin D dependent manner (Liu et al., 2006). In CKD patients, circulating FGF-23 levels gradually increase with renal function declining. Although the increase in FGF-23 is most pronounced in patients with advanced CKD, it may begin at a very early stage. Apparently, FGF-23 and PTH stimulate phosphaturia in a similar manner by reducing phosphate reclamation through Na/Pi IIa cotransporters. Nonetheless, PTH is not indispensable for FGF-23 activity, as the phosphaturic effects of FGF-23 are maintained in animals after parathyroidectomy (Liu et al., 2006). In CKD patients, the increase in FGF-23 starts with modestly impaired estimated glomerular filtration rate, when serum phosphate levels are still within the normal range CKD (KDOQI stages 2–3), whereas FGF-23 levels increase by more than 100-fold in advanced CKD (KDOQI stage 5) compared with healthy controls (Imanishi et al., 2004). However, this is inconsistent with the observation that there is no increase in the accumulation of degraded FGF-23 in advanced CKD. These data instead favor a mechanism involving increased FGF-23 secretion as the cause of elevated FGF-23 levels. Instead of decreased renal clearance, an end organ resistance to the phosphaturic stimulus of FGF-23 may exist because of a deficiency of the necessary Klotho cofactor (Kurosu et al., 2006). Moreover, higher FGF-23 levels in CKD may reflect a physiological

compensation to stabilize serum phosphate levels as the number of intact nephrons declines. As a result, FGF-23 increases urinary phosphate excretion and decreases gastrointestinal phosphate absorption directly and through inhibition of 1a-hydroxylase and reduction of circulating calcitriol levels indirectly. Oversecretion of FGF-23 allows the body to maintain phosphate levels within a 'physiological' range until very advanced CKD stages (Miyamoto K et al. 2004).

4. CKD – MBD – and vascular calcification

Tissue calcification is a complex and highly regulated process in bone and teeth, and also at extraosseous sites. The most threatening localization of unwanted calcification is at vascular sites, where it may manifest as both medial and intimal calcification of arteries. Studies in the general population have identified calcification in most of atherosclerotic plaques. Calcification seems to be a part of the natural development of atherosclerotic plaques, with extensive calcification associated with late-stage atherosclerosis. In the general population, atherosclerotic plaque calcification is associated with cardiovascular events such as myocardial infarction, symptomatic angina pectoris, and stroke. Medial calcification causes arterial stiffness, resulting in an elevated pulse pressure and increased pulse wave velocity, thereby contributing to left ventricular hypertrophy, dysfunction, and heart failure. Furthermore, an advanced calcification of the heart valves may lead to dysfunction contributing to heart failure and a risk of endocarditis development (Vliegenthart et al. 2002; Vliegenthart et al. 2002).

4.1 Different types of vascular calcification

It is generally well recognized that the prevalence of calcification increases with progressively decreasing kidney function and is greater than that in the general population. Cardiovascular calcification is associated with increased frequency of major cardiovascular diseases, and could be of predictive importance for adverse clinical outcomes, including cardiovascular events and death (Foley RN et al., 1998). There is an increased prevalence of cardiovascular calcification in patients even at early stages of CKD. Thus, an important percentage of CKD patients are at high risk of cardiovascular events from vascular calcification. Two patterns of vascular calcification have been described: namely intimal and medial calcification. In the general population, an elevated coronary artery calcium (CAC) score almost exclusively reflects the atherosclerotic disease burden. In two small autopsy studies, it became apparent that, in dialysis patients, CAC is also predominantly localized in the coronary intima, whereas the medial calcifications observed in a minority of such patients seemed to be adjacent to plaque areas just beneath the internal elastic lamina. Although the coronary vascular bed may differ considerably from other arteries with regard to the calcification process and its manifestations, the same group observed a 'pure' medial calcification in the coronary arteries during the early stages of CKD (Schwarz et al., 2000). A 'pure' medial calcification, in the absence of intimal disease, was also observed in epigastric arteries obtained from dialysis patients at the time of renal transplantation (Amann K., 2008;).

4.2 Promoters and inhibitors of calcification

Vascular calcification is the result of passive and active processes, as is bone mineralization. It has been shown that that normal extracellular phosphate concentration is required for

bone mineralization, while lowering this concentration prevents mineralization of any extracellular matrix. However, simply raising extracellular phosphate concentration is not sufficient to induce pathological mineralization, because of the presence in all extracellular matrices of pyrophosphate, an inhibitor of mineralization (Riser et al., 2011). They further showed that extracellular matrix mineralization normally occurs only in bone because of the exclusive coexpression in osteoblasts of Type I collagen and of tissue non-specific alkaline phosphatase (Tnap), an enzyme that cleaves pyrophosphate. Pyrophosphate probably is the most important non-protein inhibitor of vascular calcification. Its extracellular concentration is strictly regulated by several enzymes. It is generated by PC-1 nucleotide triphosphate pyrophosphohydrolase and metabolized to inorganic phosphate by nucleotide pyrophosphatase/phosphodiesterase (NPP1), in addition to Tnap. Its hydrolysis to inorganic phosphate actually transforms it from a calcification inhibitor to a promoter. In addition to pyrophosphate other inhibitors are also present locally in VSMCs, including matrix-gla protein (MGP) and Smad6 proteine (Lomashvili et al., 2008; Rutsch et al., 2001; Johnson et al., 2005).

4.3 Contribution of experimental models in vascular calcification

Arterial calcification assessed by all the available imaging studies cannot accurately differentiate calcification that is localized to the intima from calcification in the media adjacent to the internal elastic lamina, or in the medial layer (Figure 1 and 2). Thus, there is neither definitive evidence to suggest that isolated medial calcification is distinct from the calcification that occurs in the natural history of atherosclerosis nor is there definite proof against it. Experimental and ex vivo studies suggest that the vascular smooth muscle cell may be critical in the development of calcification by transforming into an osteoblast-like phenotype (Giachelli CM, 2004). Elevated phosphorus, elevated calcium, oxidized low-density lipoprotein cholesterol, cytokines, and elevated glucose, among others, stimulate this transformation of vascular smooth muscle cells into osteoblast-like cells in vitro using cell-culture techniques. These factors likely interact at the patient level to increase and/or accelerate calcification in CKD. Given the potential complexity of the pathogenesis and the inability of radiological techniques to differentiate the location of calcification, the approach to all patients with calcification should be to minimize atherosclerotic risk factors and control biochemical parameters of CKD–MBD. In addition, the pericyte in the media and adventitia may have a role in the secretion of vascular calcification-inducing factors (Giachelli et al., 2004). The stimulus for such a transformation may depend on the location of calcification within the artery wall (Figure 2A and 2B). For example, in intimal lesions, atherosclerosis may be the most important stimulus. However, in patients with CKD and medial calcification, there may be additional, or additive, factors potentially explaining why medial calcification of the peripheral arteries can be seen without intimal changes and is more common in CKD than in the non-CKD population (Moe et al., 2003).

Over the past decade, several animal studies have provided evidence for an accelerated progression of atherosclerosis in association with the uremic state. We and others have used the apolipoprotein e knockout (*Apoe*–/–) mouse with superimposed CKD and observed that in this experimental model of severe hypercholesterolemia the development of atheromatous lesions was greatly enhanced compared with the rate of lesion development in nonuremic *Apoe*–/– mice (Massy et al., 2005; Ivanovski et al., 2005). Additionally, in our

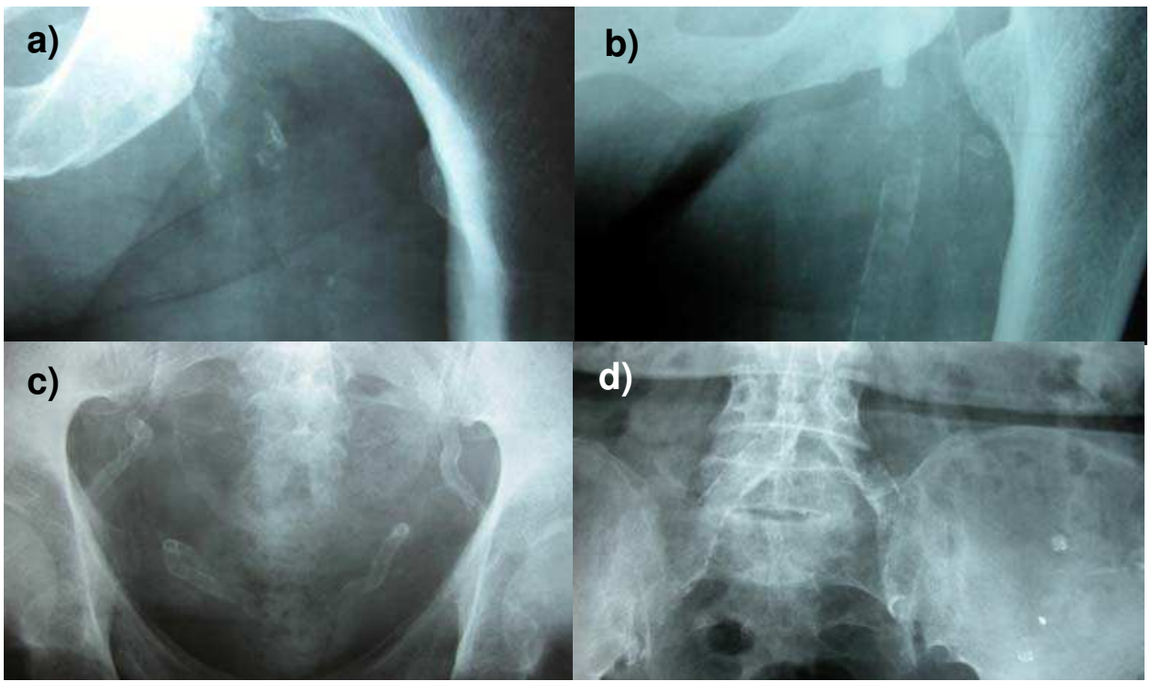


Fig. 1A. Intima and media calcification by radiography. a) Femoral artery intimal calcification; b) Femoral artery medial calcification; c) Pelvic artery medial calcification; d) Iliac arteries mixed calcification. (London et al. 2003).

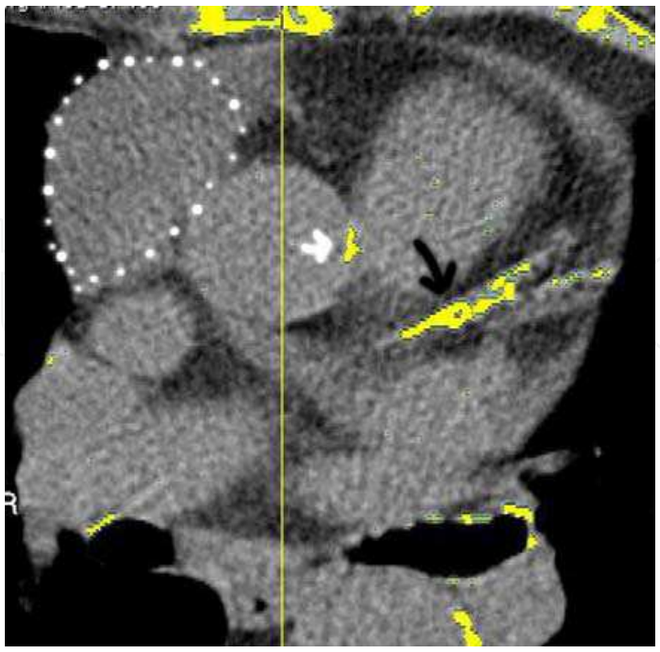
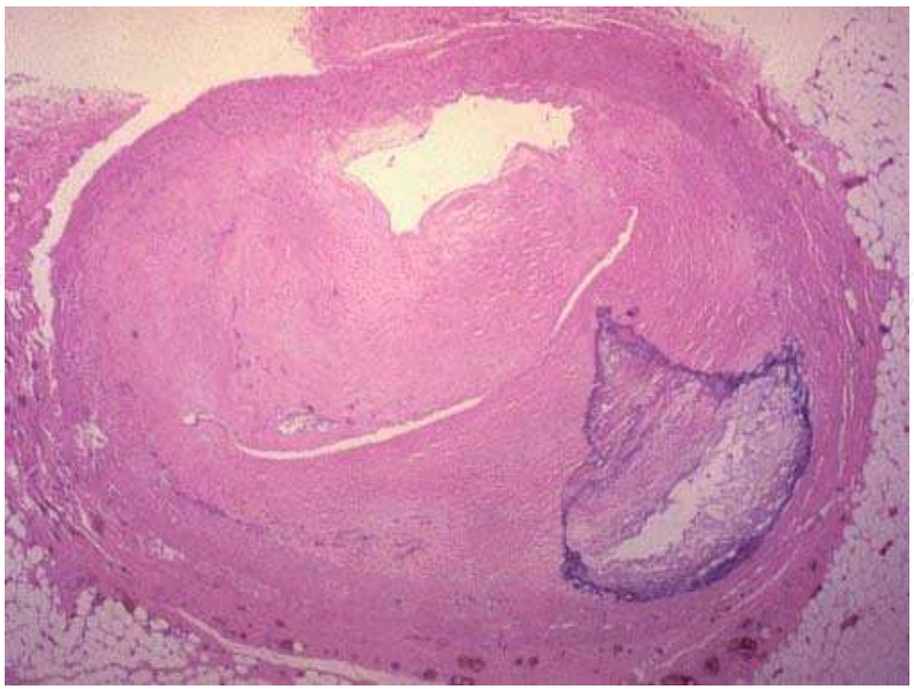


Fig. 1B. Coronary artery calcification by Electron beam computed tomography (EBCT), (scan courtesy of Pr P. Raggi).



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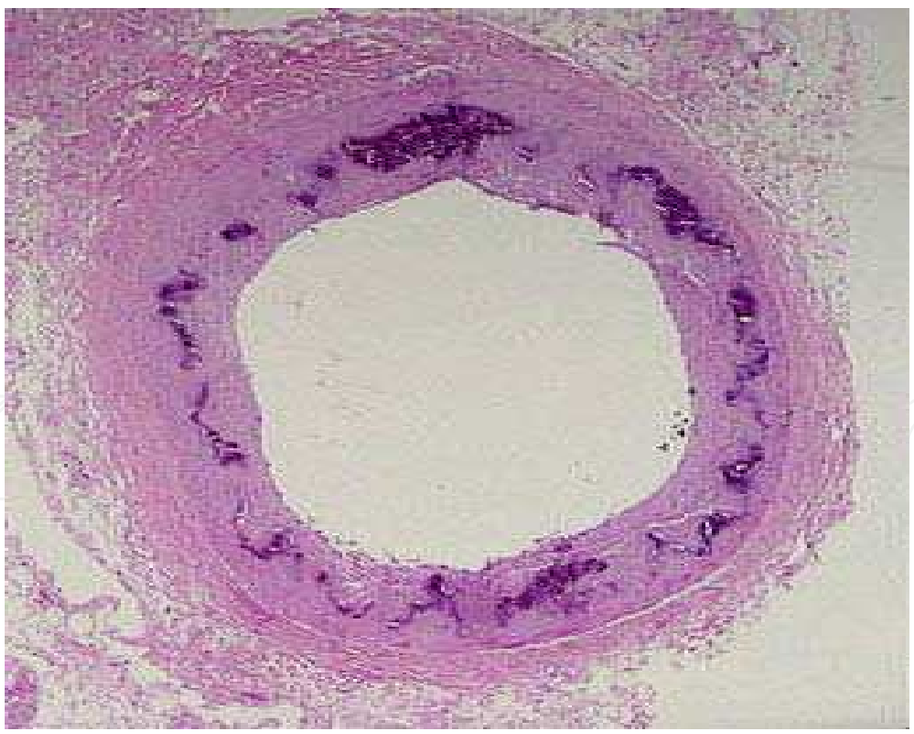


B

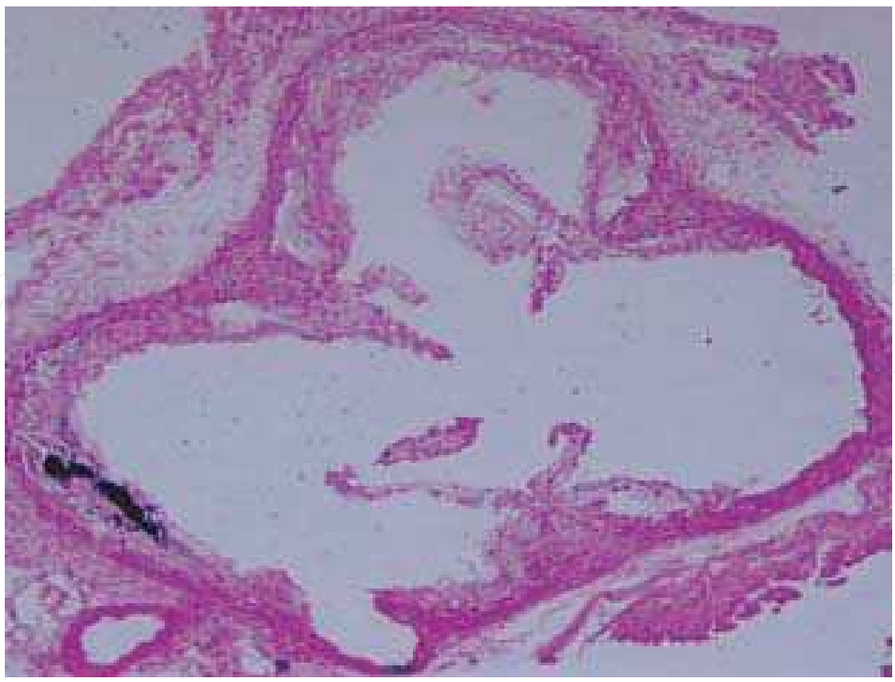
Fig. 2. Localization of different types of vascular calcification in humans. A) Intimal; B) Medial; (London et al. 2003).

model, accelerated calcification of the aortic wall both in the intima and the media, (Figure 3A and 3B, respectively) occurred in the absence of hypertension, and fetuin a deficiency greatly enhanced intimal calcification. Similar observations have been made using another hyper cholesterolemic animal model of severe atherosclerosis with superimposed CKD, namely the LDL receptor knockout mouse model (Mathew et al. 2007; Davies et al. 2005). Of note, the first cardiovascular changes observed in early stages of CKD in *Apoe–/–* mice as well as in wild type mice were left ventricular hypertrophy, altered left ventricular relaxation and increased aortic stiffness in the absence of identifiable morphological changes of the vessel wall. The observed cardiac and aortic abnormalities were not associated with the degree of aortic calcification or the level of serum total cholesterol, but with the extent of subendothelial dysfunction and the severity of CKD. Our findings have revealed that the cardio vascular lesions observed in early stage of acute kidney injury are likely functional. Although the above experimental findings need to be confirmed by additional studies in the clinical setting, they open up the possibility of attenuation of atherosclerosis and even reversal by adequate therapeutic strategies. Findings from experimental observations favor the existence of two different types of vascular disease linked to CKD, namely early arteriosclerosis, in the absence of atherosclerosis, and the acceleration of already existing or subsequently developing atherosclerosis by the uremic state (Drueke and Massy, 2010).

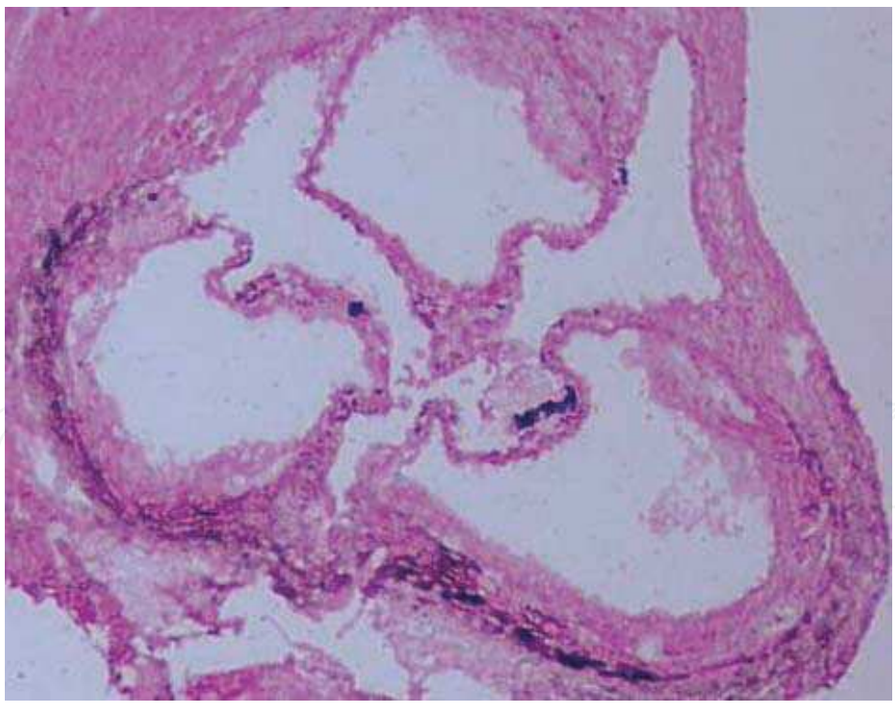
Finally, a rare but very severe form of medial calcification of small (cutaneous) arteries is calciphylaxis, also called calcific uremic arteriolopathy. This complication is strongly associated with CKD-related disturbances of mineral metabolism, including secondary HPT, in approximately one-third of cases. It is characterized by ischemic, painful skin ulcerations followed by superinfections, and is associated with high mortality. Relationships with dysregulated calcification inhibitors (fetuin-A and matrix Gla protein) have been implicated in the pathogenesis of calciphylaxis (Schoppet et al., 2008; Suliman et al., 2008), but because of the relatively low incidence of the disease, no conclusive data are available to firmly comment on the nature of the disease process or to allow generalizable treatment options to be recommended.

4.4 Management of patients with vascular/valvular calcification

Recently it has been confirmed that cardiovascular calcification development and progression can be influenced by treatment. Given that vascular calcification is associated with increased cardiovascular risk, and that the pathogenesis seems to be related to CKD–MBD abnormalities and atherosclerosis, it is appropriate to evaluate and modify both. CKD–MBD longitudinal studies have also shown that the progression of vascular calcification to be modifiable by the choice of phosphate binders. Aluminum-containing phosphate binders have been widely abandoned because of serious adverse effects including adynamic bone disease, microcytic anemia, dementia, and death (Alfrey et al., 1976). They were initially replaced by calcium-containing, aluminum-free phosphate binders. Subsequently, several studies showed that the high amounts of calcium ingested with these binders were associated with vascular calcification whose progression could be slowed by the calcium-free, aluminum-free binder sevelamer (Block et al., 2005; Chertow et al., 2002; London et al., 2008). The Treat-to-Goal study compared sevelamer-HCl to calcium-containing phosphate binders, analyzing the progression of coronary artery and aortic calcification (by EBCT) in prevalent HD patients over 1 year. Although calcification scores progressed with calcium-



(a)



(b)

Fig. 3. Extent and localization of different types of atherosclerotic lesion calcification in apoE−/− mice with CRF. von Kossa staining. a) solid type of plaque calcification, magnification ×25; b) non-plaque calcification, magnification×25. (Phan et al. 2008).

containing phosphate binders, treatment with sevelamer-HCl was associated with a lack of calcification progression (Chertow et al., 2002). A similar design was used, and the results showed more calcification progression in patients treated with calcium based binders compared with sevelamer-HCl in the Renagel in New Dialysis Patients study, which studied incident HD patients who were randomized within 90 days after starting dialysis treatment (Block et al., 2005). The Calcium Acetate Renagel Evaluation-2 study showed that the use of sevelamer-HCl and calcium acetate was associated with equal progression of CAC when statins were used to achieve a similar control of the serum low-density lipoprotein cholesterol in the two study arms (Qunibi et al., 2008). Interestingly, in Calcium Acetate Renagel Evaluation-2, the combination of sevelamer- HCl and atorvastatin was actually associated with a higher progression rate of CAC than that in Treat-to-Goal, instead of showing an amelioration of CAC progression with the combination of calcium acetate and statin. It is difficult to reconcile these differences, although one potential explanation is that the Calcium Acetate Renagel Evaluation- 2 study patient population had a higher number of cardiovascular risk factors than did that of the Treat-to-Goal study (Floege J., 2008).

Although abnormalities of calcium phosphate homeostasis have long been linked with dysfunction of large arteries in these patients, more recent studies have suggested a role in the pathogenesis of atherosclerosis in smaller, critical arteries, most notably the coronary arteries (London et al., 2003). Coronary artery calcification (CAC) is a strong predictor of atherosclerotic disease in the general population. It has been recognized that most population studies measuring CAC did not necessarily exclude individuals on the basis of kidney function and thus include variable numbers of CKD patients. In general, this literature evaluating the general population supports the view that CAC is part of the development of atherosclerosis and occurs almost exclusively together with atherosclerosis in human arteries. It seems that calcification occurs early in the atherosclerotic process; however, the amount of calcification per lesion has a variable relationship with the associated severity of luminal stenosis. The relationship between the degree of calcification in an individual lesion and the probability of plaque rupture is unknown. In the general population, the overall coronary calcium score can be considered as a measure of the overall burden of coronary atherosclerosis. The American College of Cardiology/American Heart Association document indicates that the relationship between CAC and cardiovascular events in the CKD population is less clear than that in the non-CKD population because of a relative lack of informative studies and the possibility that medial calcification may not be indicative of atherosclerotic disease severity. The almost exclusive relationship between magnitude of calcification and atherosclerosis burden is controversial in CKD patients (Amann, 2008), in contrast to the situation in the general population. Antiatherosclerotic strategies using statin treatment have been shown to have a beneficial impact on the atherogenic profile, atheroma progression, and cardiovascular events in patients with no known CKD (Nissen et al. 2004). In our experimental model, we have shown that statins had a beneficial effect on uremia enhanced vascular calcification in apoE knock out mice with chronic kidney disease. This effect was observed despite the absence of changes in uremia accelerated atherosclerosis progression, serum total cholesterol levels or osteopontin and alkaline phosphatase expression. This observation opened the possibility of a cholesterol independent action of statins on vascular calcification via a decrease in oxidative stress (Ivanovski et al., 2008). In CKD patients, there are no data on the effects of statins on arterial

calcification, as compared with those of placebo. Even worse, the 4D study failed to show a benefit of atorvastatin treatment on the outcome of diabetic dialysis patients. Studies in progress like SHARP (Study of Heart and Renal Protection) and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) failed to show a better understanding of the benefits of correcting atherosclerotic risk factors on cardiovascular events and mortality in patients with CKD stages 3–5 and 5D (Baigent et al., 2003).

An association of vascular calcification with high phosphate intake has so far not been directly demonstrated in uremic patients, probably owing to the fact that it is difficult, if not impossible, to assess phosphate (protein) intake in a quantitative manner over prolonged time periods. Indirect evidence for a role of oral phosphate, however, has recently been provided by Russo et al (Russo et al., 2007). They showed that in patients with CKD stage 3-5, coronary artery calcification score progressed significantly over a time period of 2 years, in association with a significant increase in phosphaturia. Many pharmaco-epidemiologic studies have shown a survival benefit in CKD patients receiving active vitamin D derivatives, as compared to those who did not receive such treatments. Finally, let us not forget that association does not imply causation. We clearly need randomized prospective trials showing that active reduction of serum phosphorus, PTH, or alkaline phosphatases and normalization of serum calcium leads to an improvement in patient outcomes, and that specific treatments given to the patients improve outcome, as compared to either placebo or other treatments (Drueke and McCarron, 2003).

To date, there are no published prospective studies in humans that have evaluated the impact of calcimimetics or calcitriol and vitamin D analogs on arterial calcification. However, a recent observational study showed a U-curve type of relationship between serum 1,25(OH)2D3 and arterial calcification in children and adolescents with CKD stage 5D. No such association existed between serum 25(OH)D and arterial calcification. In one study in adult patients with CKD stage 5, no independent association of serum 25(OH)D or 1,25(OH)2D3 levels with arterial calcification was observed, (London et al., 2007). Although the authors of another report identified an association between 25(OH)D deficiency and the magnitude of vascular calcification (Matias et al., 2009). The experimental data supporting less toxicity of vitamin D analogs compared with calcitriol are not completely consistent across studies, but, in general, support the claim that there is reduced calcification with equivalent PTH lowering with different vitamin D analogs (Lopez et al., 2008**).** Experimental studies showed differential effects of calcimimetics and calcitriol on extraosseous calcification, the former being neutral or protective, the latter being a dose-dependent risk factor for calcification. In our studies, we have analysed the role of chronic renal failure (CRF) on the arterial wall changes including atherosclerosis and vascular calcifications in CRF apoE-/- mice experimental model (Massy, Ivanovski et al. 2005). Furthermore, we have studied the effect of different non-calcium (Phan et al., 2005) and calcium phosphate binders (Phan et al., 2008) and role of control of phosphatemia on vascular calcification and atherosclerosis (Ivanovski et al. 2009). We have also showed for the first time that the phosphate binder La carbonate is capable of preventing both uremia-enhanced vascular calcification and atherosclerosis in experimental model of CKD (Nikolov et al., 2011). These effects were comparable to those of sevelamer on vascular calcification and atherosclerosis, as previously reported by us for sevelamer-HCl in this model (Phan et al., 2008).

5. CKD – MBD summary

Mineral and bone disorders are complex abnormalities that cause morbidity and decreased quality of life in patients with CKD. To enhance communication and facilitate research, a new term has been established, CKD–Mineral and Bone Disorder (CKD-MBD), to describe the syndrome of biochemical, bone, and extraskeletal calcification abnormalities that occur in patients with CKD. Also, it has been recommended that the term renal osteodystrophy be used exclusively to define alterations in bone morphology associated with CKD. The latter can be further assessed by histomorphometry, with results reported on the basis of a classification system that includes parameters of turnover, mineralization, and volume. The international adoption of the proposed uniform terminology, definition, and classification to describe these two disorders caused by CKD enhanced communication, facilitated clinical decision making, and can promote the evolution of evidence based clinical-practice guidelines worldwide. This issue of Advances in CKD further describes the clinical manifestations and pathophysiology of CKD-MBD. The optimal management of CKD-MBD (Chronic Kidney Disease – Mineral and Bone Disorder) should be achieved without increasing the risk of metastatic calcification, including that of blood vessels.

6. References

Andress DL. (2006). "Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation". Kidney Int.; 69(1): 33-43.

Alem AM, Sherrard DJ, et al., (2000). "Increased risk of hip fracture among patients with end-stage renal disease". Kidney Int.; 58(1): 396-9.

Alfrey AC, LeGendre GR, et al. (1976). "The dialysis encephalopathy syndrome. Possible aluminum intoxication. " N Engl J Med. 22;294(4):184-8.

Amann K. (2008). "Media calcification and intima calcification are distinct entities in chronic kidney disease". Clin J Am Soc Nephrol.: 3: 1599-605.

Baigent C, Landry M. (2003). "Study of Heart and Renal Protection (SHARP)." Kidney Int Suppl.; (84): S207-10.

Baum M, Schiavi S, et al. (2005). "Effect of fibroblast growth factor-23 on phosphate transport in proximal tubules. " Kidney Int; 68: 1148–1153.

Block GA, Hulbert-Shearon TE et al. (1998). "Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study." Am J Kidney Dis.; 31(4): 607-17.

Block GA, Spiegel DM et al. (2005). "Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis.", Kidney Int. 2005 Oct;68(4):1815-24.

Bucay N, Sarosi I et al. (1998). "Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification." *Genes Dev;* 12:1260-1268

Chertow GM, Burke SK,. (2002). "Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients." Kidney Int.; 62(1): 245-52.

Coco M, Rush H. (2000). Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. Am J Kidney Dis.; 36(6): 1115-21.

Davies, M. R., Lund, R. J., et al. (2005). Low turnover osteodystrophy and vascular calcification are amenable to skeletal anabolism in an animal model of chronic kidney disease and the metabolic syndrome. *JASN*. 16, 917–928.

Drüeke TB, McCarron DA. (2003). "Paricalcitol as compared with calcitriol in patients undergoing hemodialysis." N Engl J Med. 31; 349(5): 496-9.

Drüeke, TB., (2008) "Arterial intima and media calcification: distinct entities with different pathogenesis or all the same?" Clin J Am Soc Nephrol. 3(6):1583-4.

Drüeke TB, Massy ZA. (2010). "Atherosclerosis in CKD: differences from the general population". Nat Rev Nephrol.; 6: 723-35.

Eknoyan G, Lameire N, et al., (2004). The burden of kidney disease: improving global outcomes. Kidney Int.; 66(4): 1310-4.

Felsenfeld AJ, Rodríguez M et al. (2007). "Dynamics of parathyroid hormone secretion in health and secondary hyperparathyroidism." CJASN; 2(6):1283-305.

Floege J. (2008). "Calcium-containing phosphate binders in dialysis patients with cardiovascular calcifications: should we CARE-2 avoid them?" NDT.; 23(10):3050-2.

Foley RN, Parfrey PS et al. (1998). "Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis; 32 (5 Suppl 3):S112-9.

Fukagawa, M., Y. Hamada, et al. (2006). "The kidney and bone metabolism: Nephrologists' point of view". J Bone Miner Metab. 24(6): 434-8.

Ganesh SK, Stack AG et al. (2001). "Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients." J Am Soc Nephrol.;12(10): 2131-8.

Gao P, and D'Amour P (2005). "Evolution of the parathyroid hormone (PTH) assay--importance of circulating PTH immunoheterogeneity and of its regulation.", Clin Lab.; 51(1-2): 21-9.

Giachelli CM. (2004). "Vascular calcification mechanisms." J Am Soc Nephrol.;15(12): 2959-64.

Hollis BW and Napoli JL. (1985). "Improved radioimmunoassay for vitamin D and its use in assessing vitamin D status." Clin Chem.; 31(11): 1815-9.

Huan J, Olgaard K, et al. (2006). "Parathyroid hormone 7-84 induces hypocalcemia and inhibits the parathyroid hormone 1-84 secretory response to hypocalcemia in rats with intact parathyroid glands." JASN;17(7):1923-30.

Iba K, Takada J et al. (2004). "The serum level of bone-specific alkaline phosphatase activity is associated with aortic calcification in osteoporosis patients." J Bone Miner Metab.; 22(6): 594-6.

Ivaska KK, Gerdhem P et al. (2007). "Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women." J Bone Miner Res.; 22(8):1155-64.

Ivanovski, O., I.G. Nikolov, et al. (2009). "The calcimimetic R-568 retards uremia-enhanced vascular calcification and atherosclerosis in apolipoprotein E deficient (apoE-/-) mice." Atherosclerosis. 205(1):55-62.

Ivanovski O, Szumilak D, et al., (2005). "The antioxidant N-acetylcysteine prevents accelerated atherosclerosis in uremic apolipoprotein E knockout mice. " Kidney Int. 2005 Jun;67(6):2288-94.

Ivanovski O, Szumilak D, et al. (2008). "Effect of simvastatin in apolipoprotein E deficient mice with surgically induced chronic renal failure. " J Urol.; 179(4):1631-6.

Imanishi Y, Inaba M, et al., (2004). "FGF-23 in patients with end-stage renal disease on hemodialysis." Kidney Int.; 65(5): 1943-6.

Johnson K, Polewski M et al. (2005). "Chondrogenesis mediated by PPi depletion promotes spontaneous aortic calcification in NPP1-/- mice." Arterioscler Thromb Vasc Biol.;25(4):686-91.

Kurosu H, Ogawa Y, et al. (2006). "Regulation of fibroblast growth factor-23 signaling by klotho." J Biol Chem; 281: 6120–6123.

Lindergård B, Johnell O et al. (1985). "Studies of bone morphology, bone densitometry and laboratory data in patients on maintenance hemodialysis treatment. ", Nephron. 1985; 39(2): 122-9.

Liu S, Tang W, et al. (2006) "Fibroblast growth factor 23 is a counter-regulatory phosphaturic hormone for vitamin D. " J Am Soc Nephrol.;17(5):1305-15.

Lomashvili KA, Garg P et al. (2008). "Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification." Kidney Int.; 73(9): 1024-30.

London GM and Drueke TB (1997). "Atherosclerosis and arteriosclerosis in chronic renal failure." *Kidney Int;* 51:1678-1695

London GM, Guerin AP *et al. (2003).* "Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality." *Nephrol Dial Transplant;* 18:1731-1740

London GM, Marchais SJ, et al., (2008). "Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD."; JASN; 19(9): 1827-35.

London GM, Guérin AP et al. (2007). "Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency."; JASN.; 18(2):613-20.

Lopez I, Mendoza FJ et al. (2008). "The effect of calcitriol, paricalcitol, and a calcimimetic on extraosseous calcifications in uremic rats.", Kidney Int.; 73(3):300-7.

Massy, Z.A., O. Ivanovski, et al. (2005). "Uremia accelerates both atherosclerosis and arterial calcification in apolipoprotein E knockout mice". J Am Soc Nephrol. 16(1):109-16.

Malluche HH, Mawad H, et al. (2003). "Parathyroid hormone assays--evolution and revolutions in the care of dialysis patients." Clin Nephrol.; 59(5):313-8.

Mathew, S., Lund R.J., et al. (2007). "Reversal of the adynamic bone disorder and decreased vascular calcification in chronic kidney disease by sevelamer carbonate therapy." JASN. 18, 122–130.

Matias PJ, Ferreira C et al. (2009). "25-Hydroxyvitamin D3, arterial calcifications and cardiovascular risk markers in haemodialysis patients."; 24(2): 611-8.

Melamed ML, Eustace JA et al. (2008). "Third-generation parathyroid hormone assays and all-cause mortality in incident dialysis patients: the CHOICE study. ", NDT; 23(5): 1650-8.

Melsen F and Moselkilde L. (1978). Tetracycline double labeling of iliac trabecular bone in 41 normal adults. Calcif Tiss Res; 26: 99–102.

Moe, S., T. Drüeke, et al. (2006). "Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO)". Kidney Int. 69(11): 1945-53.

Moe SM, Drüeke TB, et al. (2009). "KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD).". Kidney Int Suppl.; (113): S1-130.

Moe SM, Duan D et al. (2003). "Uremia induces the osteoblast differentiation factor Cbfa1 in human blood vessels."; Kidney Int.; 63(3):1003-11.

Miyamoto K, Segawa H et al. (2004). "Physiological regulation of renal sodium-dependent phosphate cotransporters." Jpn J Physiol.; 54(2): 93-102.

Neves KR, Graciolli FG et al. (2007). "Vascular calcification: contribution of parathyroid hormone in renal failure." *Kidney Int;* 71:1262-1270

Nikolov, I.G., N. Joki, et al. (2010). "Chronic kidney disease bone and mineral disorder (CKD-MBD) in apolipoprotein E-deficient mice with chronic renal failure". Bone. 47(1):156-63.

Nikolov I.G, N. Joki et al., (2011). Lanthanum carbonate, like sevelamer-HCl, retards the progression of vascular calcification and atherosclerosis in uremic apolipoprotein E-deficient mice. Nephrol Dial Transplant. In press.

Nissen SE, Tuzcu EM et al. (2004). "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial." JAMA. 3; 291(9): 1071-80.

Palmer SC, Strippoli GF et al. (2005). "Interventions for preventing bone disease in kidney transplant recipients: a systematic review of randomized controlled trials." Am J Kidney Dis.;45(4): 638-49.

Parfitt AM, Drezner MK et al. (1987). "Bone histomorphometry: standardization of nomenclature, symbols, and units". Report of the ASBMR Histomorphometry Nomenclature Committee. J Bone Miner Res.;2 (6): 595-610.

Phan, O., O. Ivanovski, et al. (2005). "Sevelamer prevents uremia-enhanced atherosclerosis progression in apolipoprotein E-deficient mice". Circulation. 1;112(18):2875-82.

Phan, O., O. Ivanovski, et al. (2008). "Effect of oral calcium carbonate on aortic calcification in apolipoprotein E-deficient (apoE-/-) mice with chronic renal failure." Nephrol Dial Transplant. 23(1):82-90.

Portale AA, Halloran BP et al. (1987). "Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D." J Clin Invest.; 80(4): 1147-54.

Qunibi W, Moustafa M, et al. (2008). "A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study." AJKD.; 51(6): 952-65.

Riser BL, Barreto FC, et al., (2011). Daily peritoneal administration of sodium pyrophosphate in a dialysis solution prevents the development of vascular calcification in a mouse model of uraemia. Nephrol Dial Transplant. 2011, in press.

Rogers A and Eastell R. (2005). "Circulating osteoprotegerin and receptor activator for nuclear factor kappaB ligand: clinical utility in metabolic bone disease assessment." J Clin Endocrinol Metab.; 90(11):6323-31.

Rutsch F, Vaingankar S et al. (2001). "PC-1 nucleoside triphosphate pyrophosphohydrolase deficiency in idiopathic infantile arterial calcification." Am J Pathol.; 158(2): 543-54.

Russo D, Miranda I et al. (2007). "The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer." KI; 72(10): 1255-61.

Saenger AK, Laha TJ, et al. (2006). "Quantification of serum 25-hydroxyvitamin D(2) and D(3) using HPLC-tandem mass spectrometry and examination of reference intervals for diagnosis of vitamin D deficiency."Am J Clin Pathol.; 125(6): 914-20.

Schwarz U, Buzello M et al. (2000). "Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure."Nephrol Dial Transplant.; 15(2): 218-23.

Schoppet M, Shroff RC, et al. (2008). "Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? " Kidney Int.; 73(4): 384-90.

Slatopolsky E and Delmez JA. (1994). "Pathogenesis of secondary hyperparathyroidism." Am J Kidney Dis.; 23(2):229-36.

Slatopolsky E, Finch J et al. (2000). "A novel mechanism for skeletal resistance in uremia." Kidney Int; 58(2): 753-61

Slinin Y, Foley RN et al. (2005). "Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study." J Am Soc Nephrol.;16(6): 1788-93.

Stevens LA, Djurdjev O, et al. (2004). "Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: vidence for the complexity of the association between mineral metabolism and outcomes." JASN; 15(3):770-9.

Suliman ME, García-López E, et al., (2008). Vascular calcification inhibitors in relation to cardiovascular disease with special emphasis on fetuin-A in chronic kidney disease. Adv Clin Chem. 2008;46:217-62.

Tentori F, Blayney MJ et al. (2008). "Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS)." Am J Kidney Dis.;52(3): 519-30.

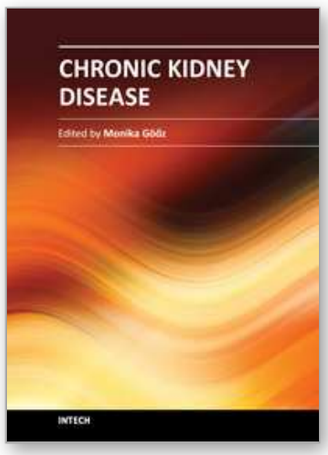
Tsugawa N, Suhara Y, et al. (2005). "Determination of 25-hydroxyvitamin D in human plasma using high-performance liquid chromatography--tandem mass spectrometry." Anal Chem.; 77(9): 3001-7.

Ureña P and De Vernejoul MC. (1999). "Circulating biochemical markers of bone remodeling in uremic patients." Kidney Int.; 55(6): 2141-56.

Vassalotti JA, Uribarri J, et al. (2008). "Trends in mineral metabolism: Kidney Early Evaluation Program (KEEP) and the National Health and Nutrition Examination Survey (NHANES) 1999-2004." Am J Kidney Dis.; 51(4 Suppl 2): S56-68.

Vliegenthart R, Hollander M et al. (2002). "Stroke is associated with coronary calcification as detected by electron-beam CT: the Rotterdam Coronary Calcification Study." Stroke.;33(2):462-5.

Vliegenthart R, Oudkerk M et al. (2002). Coronary calcification detected by electron-beam computed tomography and myocardial infarction. The Rotterdam Coronary Calcification Study. Eur Heart J.; 23(20): 1596-1603.



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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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