Mineral metabolism and clinical outcomes in dialysis patients
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Summary
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End-stage renal disease (ESRD) is a condition in which the amount of functioning kidney tissue is greatly diminished and the kidneys fail to excrete waste products and excess fluid from the blood. When ESRD occurs, it rapidly leads to death unless renal replacement therapy is started. There are two major types of renal replacement therapy: kidney transplantation and dialysis. Due to a shortage of available donor kidneys, most ESRD patients are committed to long term haemodialysis (HD) or peritoneal dialysis (PD) to replace their kidney function.

Despite increasing knowledge and technical improvements, mortality rates are still substantially increased in dialysis patients. Annual mortality was 17% in 2005, while this was 18% in 1990. These high mortality rates were the reason in 1997 to start the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicentre prospective cohort study in which ESRD patients are followed from the initiation of dialysis therapy until transplantation or death.

From 1998 some studies indicated that disorders of mineral metabolism such as hyperphosphataemia and hypercalcaemia could play a role in the high mortality among ESRD patients. Therefore the American Kidney Diseases Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation published their guideline for bone metabolism and disease in chronic kidney disease in 2003. In this guideline K/DOQI recommends tight control of serum albumin-corrected calcium, phosphorus, calcium-phosphorus (Ca x P) product and intact parathyroid hormone (iPTH) concentrations.

The K/DOQI guideline was based on a limited number of observational studies, performed in a specific group of patients. The characteristics of this patient group are considerably different from those of dialysis patients in the Netherlands. It was therefore uncertain whether these K/DOQI targets were appropriate for dialysis patients in the Netherlands as well. Only (cardiovascular) mortality and morbidity were considered as clinical outcomes while the influence of disordered mineral metabolism on other outcomes remained unknown. These remaining questions, and the fact that disorders of mineral metabolism are potentially treatable risk factors, were the starting point for the studies described in this thesis.

The aim of this thesis, which is based on data from NECOSAD, was to evaluate the effects of disordered mineral metabolism on important clinical outcomes in incident dialysis patients in the Netherlands. Chapter 1 provides an introduction to the studies presented in this thesis.

In Chapter 2 we describe the achievement of the K/DOQI targets in dialysis patients in the Netherlands. Three months after the start of dialysis therapy, the majority of patients had plasma calcium and phosphorus concentrations higher than the advised range. The target for Ca x P product was exceeded by almost half of the patients and about 55% of the patients had plasma iPTH concentrations lower than the proposed target range. Joint achievement of all targets was low: only about 5% of the patients achieved all four targets. This low achievement
was not only observed shortly after the start of dialysis, but remained rather stable during the following five years on dialysis treatment. Subsequently we assessed associations of disorders of mineral metabolism with all-cause mortality (Chapter 2). We observed that plasma phosphorus concentrations greater than the K/DOQI targets were significantly associated with an around one and a half times increased mortality risk in both HD and PD patients. Mortality risk was also increased with about 50\% in HD and PD patients with an elevated Ca x P product.

In Chapter 3 we report a study to evaluate the relationship between mineral metabolism and cardiovascular disease (CVD), focusing particularly on the comparison between HD and PD patients. Although the K/DOQI guideline was predominantly based on studies in HD patients, in clinical practice it is also applied to PD patients. To validate implementation of the K/DOQI guideline in PD patients, we studied associations between mineral metabolism and the risk of cardiovascular morbidity and mortality in PD patients compared to HD patients. Around 40\% of all hospitalisations were caused by CVD and in HD patients with hypercalcaemia the risk of CVD-related hospitalisation was increased with 40\%. In addition, HD patients with elevated plasma phosphorus concentrations and Ca x P product had a one and a half fold higher cardiovascular mortality risk than patients who met the targets. For PD patients with plasma phosphorus and a Ca x P product above the K/DOQI-threshold, cardiovascular mortality risk was more than two-fold higher. Because effects of elevated plasma phosphorus and Ca x P product concentrations on cardiovascular mortality risk were similar in both patient groups, it seems appropriate to adopt the current guideline in PD patients.

Next to mortality and hospitalisation, the physical discomfort that a patient experiences is an important outcome of dialysis treatment. In Chapter 4 we therefore explored the effects of disordered plasma calcium, phosphorus, Ca x P product, and iPTH concentrations on the risk of muscle and skin complaints. Muscle pain, cramps, and itching (pruritus) and dry (xerosis) skin were common symptoms; more than 65\% of the patients reported muscle and skin complaints at baseline. Our findings demonstrate that disturbed mineral metabolism is not only associated with increased morbidity and mortality, but also with more muscle and skin complaints. Effects of disorders of mineral metabolism were especially strongly associated with having pruritus. The risk of pruritus was significantly increased in patients with severely elevated plasma calcium, phosphorus and Ca x P product levels. Compared to patients who met the target, patients with elevated plasma calcium concentrations had a significantly increased risk of xerosis. Hyperphosphataemia was also significantly associated with an increased risk of muscle pain while iPTH concentrations below the target range were associated with a lower risk of cramps.

Preserving residual renal function (RRF) is one of the primary goals for nephrologists managing patients with CKD. After the initiation of dialysis treatment, preservation of RRF
remains equally important, because it contributes significantly to the overall health and well-being of dialysis patients and a loss of RRF in these patients is associated with increased mortality. In Chapter 5 we therefore examined associations of mineral metabolism with loss of residual renal function (RRF) in HD and PD patients. We included patients who were not anuric at dialysis initiation and calculated relative risks of total loss of RRF. We found that both HD and PD patients with the highest phosphorus and Ca x P product concentrations had the lowest baseline glomerular filtration rate (GFR) values. During follow-up, 15% of HD and 12% of PD patients became anuric. No significant associations of mineral metabolism with the risk of becoming anuric were observed.

To determine whether disorders of mineral metabolism and their effects were already present before dialysis treatment had been started, we studied the effects of disordered mineral metabolism in pre-dialysis patients. This analysis is described in Chapter 6. With this study, based on patient data from the Pre-dialysis Patients Records (PREPARE) study, we aimed to determine the association of plasma phosphorus with mortality and renal function loss in pre-dialysis patients. We observed that for each mg/dl higher phosphorus concentration, the adjusted mean decline in renal function significantly increased. In addition, an increase in phosphorus concentration was associated with a higher all-cause mortality risk. These findings indicate that the effects of hyperphosphataemia on mortality are similar in dialysis and pre-dialysis patients, whereas the effects of phosphorus on RRF differ, depending on the stage of CKD.

In Chapter 7 we examined the recommendations in the current K/DOQI guideline in more detail. Several studies found associations between higher plasma calcium and phosphorus and mortality in dialysis patients. However, different predefined categories and reference-values were applied in these studies and the precise shape of these relationships remains unclear. We therefore reassessed the current K/DOQI guideline for bone metabolism and disease in CKD. Multivariable Cox regression and restricted cubic splines regression were applied to study effects of time-updated plasma concentrations on mortality in a flexible manner. Elevated phosphorus concentration was significantly associated with higher mortality whereas the association of high calcium with mortality was borderline significant. Within the ranges that we studied, we could not identify a threshold where an appreciable change in mortality risk occurred. Mortality risk started to increase at a relatively low phosphorus concentration (4.5 mg/dl; 1.45 mmol/l). We concluded that a low-normal plasma calcium concentration combined with a low-normal plasma phosphorus concentration was associated with the lowest mortality and that a plasma phosphorus concentration lower than upper threshold advised in the K/DOQI guideline, deserves recommendation.

It has been hypothesised that the association of disordered mineral metabolism with (cardiovascular) mortality can be explained by the development of vascular calcification. Previous studies showed that simple imaging methods can be useful for detection of vascular
calcifications in dialysis patients. In **Chapter 8** we describe associations between mineral metabolism and progression of aortic calcification based on plain annual chest X-rays. In a subsample of 384 dialysis patients from NECOSAD, X-rays were screened for calcification of the aortic arch. Aortic vascular calcification showed to be common; at baseline 96 (25%) patients had severe calcification and 205 (53%) patients had moderate calcification. For 237 of the 288 patients with no or moderate calcifications at baseline, X-rays were available for follow-up. During follow-up on dialysis, aortic calcification progressed in 30% of the patients and hypercalcaemia and hyperparathyroidism at baseline were associated with an increased risk of progression. Moreover, progression of aortic calcification was significantly associated with increased risk of both all-cause and cardiovascular mortality.

In **Chapter 9** we elaborate on the most important findings of this thesis and discuss a number of methodological issues. To achieve optimal treatment, the recommendations provided in this chapter could be applied in daily clinical practice. First, it is important to start monitoring and controlling mineral metabolism during the pre-dialysis phase. Furthermore, we advise to apply the currently advised targets for calcium, Ca × P product and iPTH in daily clinical practice. The present upper cut-off value for phosphorus of 5.5 mg/dl (1.78 mmol/l) still seems to be too high to avoid an excess risk of mortality. Using a lower threshold, preferably <4.5 mg/dl (1.45 mmol/l), is recommendable. To obtain such low phosphorus levels, an optimal treatment regimen combined with appropriate education and stimulation to improve adherence of dialysis patients is necessary. Although we gained new information with the studies described in this thesis, further research is needed to answer the several remaining questions. In **Chapter 9** we therefore offer directions for future research.

The K/DOQI guideline for bone metabolism and disease in CKD, which was published in 2003, recommends controlling mineral metabolism in dialysis patients based on studies that focussed on long-term effects of disordered mineral metabolism in HD patients. In this thesis we demonstrate that disorders of mineral metabolism are associated with short-term effects, like hospitalisations and muscle and skin complaints, as well. Moreover, we provide evidence that keeping mineral metabolism under control is of vital importance in PD patients.

In conclusion, the work in this thesis shows that disorders of mineral metabolism are common in HD and PD patients in the Netherlands, and that only a small proportion of them meet the targets as advised in the K/DOQI guideline. We have demonstrated that these disorders are associated with negative clinical outcomes. Our findings therefore support a strict control of mineral metabolism in dialysis patients.