Mineral metabolism and clinical outcomes in dialysis patients
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General discussion
Disorders of mineral metabolism, such as hypercalcaemia, hyperphosphataemia, and hyperparathyroidism, are common in patients suffering from end-stage renal disease (ESRD). Moreover, some studies showed that these potentially modifiable disorders play a role in the high mortality rates that are observed in 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 (CKD) in 2003. In this guideline K/DOQI recommends tight control of serum calcium, phosphorus, calcium-phosphorus (Ca × P) product and intact parathyroid hormone (iPTH) concentrations. The aim of the research reported in this thesis was to evaluate this K/DOQI guideline by assessing the effects of disordered mineral metabolism on important clinical outcomes in incident haemodialysis (HD) and peritoneal dialysis (PD) patients in the Netherlands. In this chapter we summarise our findings and comment on them. We also provide recommendations for clinical practice and offer directions for future research.

Results

In their guideline, K/DOQI recommends serum concentrations of albumin-corrected calcium between 8.4 and 9.5 mg/dl (2.10 and 2.37 mmol/l), and serum concentrations of phosphorus between 3.5 and 5.5 mg/dl (1.13 and 1.78 mmol/l). Ca × P product concentrations should be maintained at less than 55 mg²/dl² (<4.4 mmol²/l²) and iPTH concentrations should be in the range of 150 to 300 pg/ml (ng/l). We studied achievement of these targets by dialysis patients in the Netherlands (Chapter 2) and found that three months after the start of dialysis therapy the majority of patients had plasma calcium and phosphorus concentrations higher than the range advised by K/DOQI. The target for Ca × P product was met by about 55% of the patients, while more than half the patients had plasma iPTH concentrations less 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.

In the subsequent chapters of this thesis we described how disorders of mineral metabolism according to the K/DOQI guideline are associated with poor clinical outcomes. We showed that hyperphosphataemia and an elevated Ca × P product are associated with an increased risk of all-cause (Chapter 2) and cardiovascular mortality (Chapter 3) in both HD and PD patients. In addition, elevated plasma concentrations of calcium, phosphorus, and Ca × P product appear to be risk factors for muscle- and skin complaints (Chapter 4). Finally, elevated plasma calcium and iPTH concentrations were found to be associated with an increased risk of progression of vascular calcification in the aortic arch. The effects of disordered plasma calcium, phosphorus, Ca × P product and iPTH concentrations on clinical outcomes in dialysis patients are summarised in Table 1.
In conclusion, we showed in this thesis that disorders of mineral metabolism are common in both HD and PD patients in the Netherlands, and that only a small proportion adheres to the targets as advised in the K/DOQI guideline for bone metabolism and disease in CKD. We demonstrated that these disorders are associated with important negative clinical outcomes, such as increased all-cause mortality and an increased cardiovascular mortality, more cardiovascular hospital admissions, and more muscle and skin problems. Our findings therefore support a strict control of mineral metabolism in dialysis patients. However, keeping mineral metabolism under control might not be as simple as it seems. The studies presented in this thesis, as well as other studies from the United States and from Europe, clearly indicate that it is very difficult for dialysis patients and their attending nephrologists to regulate mineral metabolism.\textsuperscript{2-4}

Control of mineral metabolism: a “mission impossible”?\textsuperscript{5,6}

Several factors could play a role in the low achievement of the currently advised targets. First of all, it is possible that nephrologists were not fully aware of the importance of keeping mineral metabolism under control and were not aiming for these targets. To examine the influence of the introduction of the K/DOQI guideline in October 2003, we evaluated the achievement of the targets proposed in this guideline before and after 2004. We found that achievement had only slightly improved after 1 January 2004 and we can speculate that the publication of the guideline for bone metabolism and disease in CKD only marginally improved regulation of mineral metabolism.

Secondly, it is extremely difficult to determine the optimal treatment strategy in disorders of bone and mineral metabolism, because the interactions between plasma concentrations mutually and with different types of medications are complicated. For example, the use of calcium-based phosphate-binding agents lowers plasma phosphorus concentration but it also causes an elevation of the plasma calcium concentration, which can lead to an undesired hypercalcaemia. The prescription of vitamin D to suppress PTH levels also causes an increase in calcium and phosphorus levels through the absorption from food in the intestine and an increased release from the bone. So, despite the broad range of available medication and the efforts of dedicated nephrologists to create treatment algorithms for application in daily clinical practice, an instant solution is still not available. The currently available types or dosages of medication may not be sufficient to treat these persistent disorders, indicating that the development of new or improved drugs should be encouraged.

Central to achievement of the treatment targets is the adherence of patients to dietary advice and prescribed medication. Adherence refers to “the extent to which a person’s behaviour, i.e. taking medication, following a diet and executing lifestyle changes, corresponds to the agreed recommendations from a health care provider”.\textsuperscript{5} Dialysis patients are told what to eat, how much to drink and what medication regimen, consisting of an average of 12 different drugs,\textsuperscript{6} to
follow in often complex schedules. It is therefore not surprising that patients do not adhere all the time to what they have been prescribed. Previous studies have pointed out that adherence of dialysis patients to their therapy is often poor. There are currently no standards for measuring adherence in dialysis patients. High plasma phosphorus concentrations are often seen as a marker for both dietary and medication incompatibility since diets high in phosphorus and not taking phosphate binders are clearly associated with elevated phosphorus levels. Within our study we observed that despite the fact that at least 90% of the patients had been administered phosphate-binding agents, mean phosphorus concentrations were still too high. This could point to poor adherence of the patients. However, there are patients with hyperphosphataemia with good adherence who simply do not respond well to some types of phosphate binders. In addition, high plasma phosphorus level may be due to dietary incompatibility or to inadequate dialysis therapy and is therefore not the best choice as an adherence measure. To improve adherence, we need more attention to adequate measurement of compliance, to simpler dosage regimens, and to the education and stimulation of patients.

For all of the above mentioned reasons, keeping mineral metabolism under control in dialysis patients often seems a “mission impossible” to many nephrologists.

Differences between HD and PD patients

An important strength of the NECOSAD cohort is that it includes both HD and PD patients. This gave us the opportunity to evaluate the current K/DOQI guideline, which was primarily directed at HD patients, in both patient groups.

Although it has been shown that a somewhat better control of serum phosphorus is possible in patients on continuous ambulatory peritoneal dialysis (CAPD) compared to those on HD, phosphorus control is problematic in PD patients as well. The majority of the PD patients in NECOSAD were treated with CAPD (87%) and had a significantly lower mean plasma phosphorus concentration than HD patients three months after the start of dialysis (5.37 versus 5.79 mg/dl, \( P <0.0001 \)). We found that a large proportion of both HD (53%) and PD (41%) patients had plasma phosphorus concentrations exceeding the target-range advised in the K/DOQI guideline, indicating that phosphorus retention is, like in HD, a major problem in PD patients.

Considering phosphorus balance there are some differences between HD and PD treatment. Due to obligatory protein losses via the peritoneal fluid, CAPD patients are often prescribed a high-protein diet containing 1.2-1.3 g/kg/day, which provides a phosphate intake of up to 1200 mg/day. Effective phosphorus removal with dialysis is therefore essential. With PD treatment on average 315 mg/day (2200 mg/week) of phosphorus is removed from the body, which is less than with different types of HD treatment. The elimination of phosphorus in PD patients depends on the dwell volume and the glucose concentration of the dialysate.
Additional gastrointestinal elimination of phosphorus by oral phosphate-binding agents is necessary in almost all patients to achieve a neutral phosphorus balance.

There were no marked differences between the two patient groups in the effects of disturbed mineral metabolism on treatment outcome. The findings from our studies were comparable for HD and PD patients and the few differences in outcomes that we found appeared to be non-significant after adjustment for patient characteristics, such as age and general state of health.

Differences between dialysis and pre-dialysis patients

Disorders of mineral metabolism develop early in the course of CKD. A decrease in 1,25-dihydroxy vitamin D and an increase in PTH are the first mineral metabolism alterations in CKD which occur from the moment that the residual renal function drops below 60 ml/min/1.73 m² (CKD stage III). The increase in PTH is generally associated with calcium and phosphorus levels within the normal range. Once secondary hyperparathyroidism progresses to an uncontrolled stage it is associated with elevated calcium, phosphorus, and Ca x P product. So, disorders of mineral metabolism are already present before the initiation of dialysis treatment.

To investigate problems of mineral metabolism in the pre-dialysis phase, we focussed in Chapter 6 on CKD patients who had a glomerular filtration rate (GFR) <20 ml/min/1.73m² but who were not yet on dialysis. We found that hyperphosphataemia and an elevated Ca x P product in these patients were, as in dialysis patients, associated with an increased mortality risk. Moreover, hyperphosphataemia was related to a higher rate of decline of residual renal function (RRF). This latter finding is in accordance with other studies performed in pre-dialysis patients, but is in contrast with our findings in dialysis patients, which indicated that there were no associations between disordered mineral metabolism and the decline of RRF during dialysis treatment. The discrepancies between studies in pre-dialysis and dialysis patients suggest that the associations between mineral metabolism and RRF differ depending on the stage of CKD. Whereas disorders of mineral metabolism are important determinants of renal function in the pre-dialysis phase, we can speculate that other factors dominate once dialysis treatment has been started. Possible factors with a stronger influence on renal function than parameters of mineral metabolism might include fluctuations in blood pressure or hypovolemic episodes. Keeping mineral metabolism in control, especially plasma phosphorus concentrations, can delay the deterioration of RRF during the pre-dialysis phase, but not anymore during dialysis treatment.
Chapter 9

Methodological issues

The majority of the studies in this thesis were based on patient data from NECOSAD; a large multicentre prospective cohort study in which consecutive ESRD patients are followed from the initiation of dialysis until transplantation or death. A strong point of NECOSAD is the comprehensive data collection, which took place at dialysis initiation, three and six months after the start of dialysis and every six months thereafter. This repeated data collection made it possible to analyse trends over time during dialysis treatment. Although the sample size of NECOSAD may seem small in comparison with the enormous cohorts of HD patients in the United States, the more than 2000 included patients can be seen as a large, representative sample of all dialysis patients in a small country like the Netherlands.

There are also some methodological limitations. First, NECOSAD is an observational cohort study. Such observational studies are known to have some disadvantages when compared to randomised clinical trials. The main limitation of an observational study design is that it is by nature hypothesis generating and cannot prove causation. Because treatment allocation is not randomly assigned, adjustment for prognostic factors is necessary to remove confounding as much as possible. Confounding, sometimes referred to as confounding bias, is regarded as undesirable as it obscures the actual effect of an exposure on outcome. Confounding can be controlled by adjusting for it after completion of a study using stratification or multivariable analysis. Obviously, adjusting for confounding in multivariate analysis can only take place accurately when information is collected during the study. Although we performed a comprehensive literature search to identify potential confounders, we cannot completely exclude the possibility that the adjustment for confounders was incomplete. There were some variables that might have had a confounding effect in the associations between parameters of mineral metabolism and outcomes, such as the administration of phosphate-binding agents or vitamin D and measures of bone mineral density. These variables were, however, not measured in NECOSAD and could therefore not be included in our statistical analyses. An incomplete adjustment for confounding in multivariable analysis could lead to an under- or over-estimation of the actual effect. It is, however, impossible to predict the impact of incomplete adjustment since the effects of these missing confounders are unknown.

In NECOSAD, biochemical measurements were not determined in a central lab, but in the different participating centres, which used different assays. For most variables this is not a problem as different methods yield very similar results. However, there has been a profound debate about the application of different PTH measuring methods. Recent studies have shown that first generation immunometric iPTH assays, as were mainly used in NECOSAD, not only detect full-length (1-84) PTH but also other PTH fragments, including the PTH-(7-84) fragment. These fragments may have inhibitory effects on bone cell metabolism and contribute to adynamic renal bone disease. iPTH levels are therefore poorly predictive of bone turnover state. An ideal PTH assay should discriminate between the bioactive whole PTH-(1-
84) molecule and PTH fragments, including the PTH-(7-84) fragment. These new assays have been developed in the last decade and are currently more and more applied in dialysis centres worldwide. However, during the major part of the NECOSAD study period, these new assays were not available in the dialysis centres that participated in the study and iPTH assays were used instead. iPTH values also varied to a large extent in our study because assays from different manufacturers were applied in the participating centres, yielding different results. It is likely that the broad range of iPTH concentrations observed in our study led to an underestimation of the true effects of iPTH concentration on outcomes.

Recommendations for clinical practice

The findings that are presented in this thesis underscore the importance of a tight control of mineral metabolism in haemodialysis and peritoneal patients. To achieve optimal treatment, the following recommendations could be applied in daily clinical practice:

- Because of the early development of mineral metabolism disorders, monitoring and controlling mineral metabolism is inevitable already during the pre-dialysis phase.

- Monitoring plasma or serum concentrations carefully is a necessary first step for diagnosing and treating disorders of mineral metabolism. In all stages of CKD plasma or serum calcium, phosphorus and PTH concentrations should therefore be measured on a regular basis. The measuring frequencies recommended in the K/DOQI guideline for bone metabolism and disease in CKD, seem appropriate and feasible in clinical practice. K/DOQI advises to measure calcium and phosphorus at least once a month and PTH at least once per three months in the final stage of CKD (stage V). Measurements should be made more frequently when a patient receives concomitant therapy for abnormalities in plasma calcium, phosphorus and PTH.

- Although the present K/DOQI guideline was primarily directed at HD patients, we can conclude from this thesis that the recommendations in the guideline are suitable for application in both HD and PD patients in the Netherlands. The currently advised targets for calcium, Ca x P product and iPTH are appropriate for application in daily clinical practice. The present upper cut-off value for phosphorus of 5.5 mg/dl (1.78 mmol/l) seems to be still too high to avoid an excess risk of mortality. Using a lower threshold, preferably <4.5 mg/dl (1.45 mmol/l), is recommendable but the feasibility of this lower target can be questioned.

- To obtain such low phosphorus levels an optimal treatment regimen is necessary, which can only be achieved by intensive dietary counselling and administration of a balanced mix of medications. We would like to underscore the importance of educating and stimulating dialysis patients in order to achieve optimal adherence. Patient education by the dietician
or dialysis nurse, explaining the necessity and practical application of dietary phosphate restriction and the correct use of phosphate binding agents, is inevitable. Simpler dosage regimens might contribute to a better adherence as well.

Directions for future research

There is still a lot to be learned regarding mineral metabolism in patients with different stages of CKD. Future research is needed to answer the several remaining questions.

First of all, the precise mechanisms underlying the associations between disordered mineral metabolism and poor outcome, i.e. vascular calcification and (cardiovascular) morbidity and mortality, should be unravelled. Long term animal studies are of vital importance before these mechanisms can be studied in patients. Understanding the exact mechanisms is an essential step for the future development of new drugs or nutritional solutions that can help to optimise treatment options. More research is needed to establish the role of novel types of medication, such as calcimimetics and new vitamin D analogues, in the treatment of disorders of bone and mineral metabolism.

Further research is also needed to clarify the role of (non-)adherence to treatment regimens considering mineral metabolism. Measurement methods should be validated and clear definitions should be established. Possibly, linking adherence levels to clinical outcomes could result in clinically relevant definitions of non-adherence. These definitions should indicate which level and type of adherence are associated with adverse outcomes, such as morbidity and mortality.

Finally, the role of disorders of mineral metabolism during the pre-dialysis phase deserves more attention. Especially study initiatives that combine patients from different stages of CKD to form a complete picture should be encouraged.

Conclusion

The K/DOQI guideline for bone metabolism and disease in CKD was published in 2003 and advised regulation of mineral metabolism in dialysis patients based on studies in HD patients that focussed on long-term effects of disordered mineral metabolism. With the work reported in this thesis we have demonstrated that disorders of mineral metabolism are also associated with short-term effects, such as hospital admissions and muscle- and skin complaints. Moreover, we have demonstrated that keeping mineral metabolism under control is of vital importance in PD patients as well as in HD patients.
The studies described in this thesis provide evidence for a strict control of bone and mineral metabolism in chronic HD and PD patients. Despite of the large amount of pre-clinical and clinical studies in the field of bone and mineral metabolism in relation to renal failure, there is at present no consensus about which treatment regimen is optimal for patients with disorders of mineral metabolism. As long as there are no alternative treatment options, such as more effective forms of medication, nutritional solutions, or possibly just the creation of an efficient treatment algorithm, striving for the currently recommended targets seems the best choice.

References

16. Goodman WG. New assays for parathyroid hormone (PTH) and the relevance of PTH fragments in renal failure. Kidney Int 2003; Suppl 87: S120-S124
<table>
<thead>
<tr>
<th>Table 1. Overview of the associations between mineral metabolism and clinical outcomes in dialysis patients</th>
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<tr>
<td>Calcium</td>
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<tr>
<td>&lt; 8.4 mg/dl</td>
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<tr>
<td>8.4-9.5 mg/dl</td>
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<td>&gt; 9.5 mg/dl</td>
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<tr>
<td>Phosphorus</td>
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<td>&lt; 3.5 mg/dl</td>
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<td>3.5-5.5 mg/dl</td>
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<td>&gt; 5.5 mg/dl</td>
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<td>Ca x P product</td>
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<td>&lt; 55 mg/dl</td>
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<tr>
<td>≥ 55 mg/dl</td>
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<tr>
<td>iPTH</td>
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<tr>
<td>&lt; 150 pg/ml</td>
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<tr>
<td>150-300 pg/ml</td>
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<td>&gt; 300 pg/ml</td>
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Grey column is the reference category (Hazard Ratio or Odds Ratio of 1.0).
+ Significantly increased risk of outcome compared to the reference category
0 No different effect compared to reference category
- Significantly decreased risk of outcome compared to the reference category

Results are presented for haemodialysis (HD) and peritoneal dialysis (PD) patients separately when the effects were different. In all other cases results are combined for HD and PD patients.