General introduction, aims and outline of the thesis
Chapter 1

Introduction

End-stage renal disease

A kidney is a filtering system made up of about a million filtering units called nephrons. Healthy kidneys are essential for the maintenance of the constant extracellular environment that is required for adequate functioning of the cells. This is achieved by excretion of waste products of metabolism, such as urea, creatinine, and uric acid, and by specifically adjusting the urinary excretion of water and electrolytes to match net intake and endogenous production. In addition, the kidneys produce hormones that participate in the regulation of blood pressure, red blood cell production, and bone- and mineral metabolism.

The most common causes of kidney failure are diabetic nephropathy, vascular disease and glomerulonephritis. In all of these cases, there is a progressive loss of nephrons. If the kidneys are damaged, they become less efficient at removing waste products. When the amount of functioning kidney tissue is greatly diminished chronic kidney disease (CKD) will develop. End-stage renal disease (ESRD) is reached as soon as the renal function drops below 10 to 15 percent of the normal function.

ESRD is worldwide an emerging health problem. In the Netherlands there has been a gradual rise in the prevalence of ESRD in the past decennia. The last 15 years the number of ESRD patients in the Netherlands has increased from 5731 in 1990 to 12038 in 2006.1

Renal replacement therapy

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. Because there is a shortage of available donor kidneys the kidney transplant waiting lists are extensive, and transplantation is not possible in some patients. Most ESRD patients therefore need dialysis treatment to replace their kidney function. The most common type is haemodialysis (HD), in which waste products are removed from the blood by diffusion across a non-biological membrane in an artificial kidney. HD is usually performed at a dialysis centre three times per week for three to four hours.2 The second type of dialysis is peritoneal dialysis (PD). In this modality waste products in the blood of peritoneal micro vessels diffuse into the peritoneal cavity which is filled with dialysis fluid. By withdrawing the dialysis fluid from the peritoneal cavity, waste products can be removed from the blood. Usually, between one and a half and three litres of fluid is run in and out four times a day.3

At 1 January 2006, there were 5437 patients receiving dialysis treatment in the Netherlands, an equivalent of 333 per million inhabitants. Of these patients, 4132 (76%) were on HD and 1305 (24%) on PD.1
Mineral metabolism

Together with the gastro-intestinal tract and bone tissue, the kidneys regulate the calcium and phosphorus homeostasis. The regulation of mineral metabolism in healthy individuals is summarised in Figure 1. Calcium and phosphorus are minerals that are of great importance for the composition of bones and the regulation of several processes in the body. When kidney function deteriorates, it significantly affects the regulation of calcium and phosphorus concentrations.

Healthy kidneys convert inactive vitamin D into active vitamin D (calcitriol) by means of 1,25 dihydroxycholecalciferol, which is produced by the kidney. If renal functioning is affected, the production of 1,25 dihydroxycholecalciferol reduces quickly. This reduced vitamin D production leads directly to hypocalcaemia because less calcium is absorbed from the intestine. In addition, the renal clearance of phosphorus decreases with a deteriorating kidney function and phosphorus concentrations increase. The phosphorus retention leads to hypocalcaemia as well, because phosphorus forms a complex with calcium, which is called calcium-phosphorus (Ca x P) product. Hypocalcaemia in its turn leads to an increased production of parathyroid hormone (PTH) by the parathyroid glands, which is called secondary hyperparathyroidism. Disturbances in mineral and bone metabolism, i.e. hyperphosphataemia, hypocalcaemia, and hyperparathyroidism are all commonly observed in patients with CKD.

Figure 1. Mineral metabolism in healthy individuals.

Abbreviations: Ca, calcium; P, phosphorus; PTH, parathyroid hormone
Medication

To correct and prevent hyperphosphataemia a phosphate restricted diet and different types of phosphate binding agents can be prescribed. The disadvantage of the very effective aluminium-based phosphate binders is that accumulation of aluminium can lead to bone disease and encephalopathy. Calcium-based phosphate binders are also effective, but they increase the calcium intake substantially, which can lead to an undesirable hypercalcaemia. Finally, there is a rather new category of phosphate binders that are free of aluminium and calcium, consisting of sevelamer hydrochloride and lanthanum carbonate. Next to phosphate binders, vitamin D is often prescribed, which causes a suppression of PTH. A disadvantage of vitamin D is that it causes an increase of the plasma calcium and phosphorus concentration, which can lead to hypercalcaemia and more deposition of calcium-phosphorus.

Effects of disordered mineral metabolism

Despite major advances in dialysis knowledge, mortality rates have not improved and are still substantially increased in dialysis patients. Annual mortality was 17% in 2005; while this was 18% in 1990. Cardiovascular disease is the most common cause of death in ESRD patients. About 50% of patients die of cardiovascular causes, and the prevalence of cardiovascular disease is markedly higher in ESRD patients than in the general population. Traditional risk factors for cardiovascular disease such as older age, hypertension, and smoking can not completely explain the high prevalence. Amongst new risk factors like (chronic) inflammation and hyperhomocysteinaemia, disorders of mineral metabolism could play a role in this phenomenon.

In 1998, Block et al. published the first study that showed that elevated phosphorus, Ca x P product and PTH levels are associated with increased mortality risk in HD patients. In the following years some other observational studies demonstrated associations between disordered mineral metabolism and (cardiovascular) morbidity and mortality. Based on these studies and on expert-opinion, the American Kidney Diseases Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation published their guideline for bone metabolism and disease in CKD in 2003. In this guideline K/DOQI recommends tight control of serum calcium, phosphorus, Ca x P product and intact PTH (iPTH) concentrations.

Although the few observational studies that formed the basis for the K/DOQI guideline were well-performed and had large sample sizes, more studies were needed. This was underlined by the fact that all studies published before 2003 consisted of patients who were treated with HD and were insured via Medicare, a United States social health insurance program. The characteristics of this specific patient group are considerably different from those of dialysis patients in the Netherlands. There were, for example, no data available concerning PD patients while the proportion of PD patients in the Netherlands is substantial. Therefore, it was
uncertain whether the K/DOQI targets were appropriate for dialysis patients in the Netherlands as well. Moreover, only (cardiovascular) mortality and morbidity were considered as clinical outcomes while the influence of disordered mineral metabolism on other outcomes, such as quality of life, complaints and preservation of residual renal function, 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.

NECOSAD

The poor survival of dialysis patients was the reason in 1997 to start the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a multicentre prospective follow-up study among ESRD patients new on dialysis. The aims of NECOSAD were to monitor the quality and adequacy of dialysis treatment in the Netherlands, to provide evidence for the development and testing of guidelines, and to study the effect of cardiovascular risk factors. In NECOSAD patients were followed from the initiation of dialysis until transplantation or death. In a vast majority (80%) of dialysis units in the Netherlands all new ESRD patients were consecutively invited to participate in the study. In the years between 1997 and 2007, about 2000 patients were included. From all patients, demographical, medical, biochemical, and quality of life data were collected at dialysis initiation, three and six months after the start of dialysis and thereafter every six months. NECOSAD stopped, after 10 years of follow-up, at 31 December 2007. Patient data from NECOSAD comprised the basis for the majority of the studies in this thesis, which focussed on mineral and bone metabolism in dialysis patients in the Netherlands.

Aim

The aim of the research reported in this thesis was to evaluate the K/DOQI guideline by assessing the effects of disordered mineral metabolism on important clinical outcomes in incident dialysis patients in the Netherlands.

Outline

In Chapter 2 the proportions of HD and PD patients from NECOSAD that achieve the targets as recommended by K/DOQI are described. Moreover, the associations between disordered mineral metabolism and all-cause mortality are reported. Because cardiovascular disease is the leading cause of death in patients suffering from ESRD, we focus in Chapter 3 on cardiovascular morbidity and mortality in relation to mineral metabolism. In addition to morbidity and mortality, physical well-being is an important outcome measure of dialysis treatment. In Chapter 4 we therefore report an evaluation of the associations between plasma calcium, phosphorus, Ca x P product and iPTH concentrations, and physical complaints, i.e. muscle and skin problems that patients experienced during their treatment. The decline of
residual renal function during dialysis treatment and its relationship with mineral metabolism is subsequently presented in Chapter 5. In Chapter 6 we focus on mineral metabolism in pre-dialysis patients. Plasma concentrations of patients from the Pre-dialysis Patients Records (PREPARE) study were evaluated and associations with mortality and with decline of residual renal functions are described.

Because of the important differences between dialysis patients in the United States and those in the Netherlands, we examined the recommendations in the current K/DOQI guideline in more detail in Chapter 7. We determined the exact shape of the relationship between plasma concentrations and all-cause mortality risk. It has been hypothesised that the association of disordered mineral metabolism with (cardiovascular) mortality can be explained by the development of vascular calcification. In Chapter 8 we describe associations between parameters of mineral metabolism and (progression of) aortic calcification based on plain annual chest X-rays. We also studied associations between (progression of) aortic calcification and mortality and report the results in this chapter. The general discussion in Chapter 9 elaborates on the observed results and discusses a number of methodological issues. In addition, we provide recommendations for clinical practice and offer directions for future research.

References

1. RENINE. Registratie Nierfunctievervanging Nederland. Statistisch Verslag 2006