# Metabolic alterations in dialysis patients

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# CHAPTER 1

## Introduction and scope of the thesis

## Background

Chronic kidney disease (CKD) is defined as a reduction of glomerular filtration rate and / or an abnormal urinary excretion of protein. It is frequent, and according to the most recent analysis of the National Health and Nutrition Examination Survey (NHANES) alarmingly increasing. Its prevalence in the United States currently is about 13% [1,2], and in Europe about 10%. The increasing trend observed in the recent decade translates into important problems, both from an individual and a public health perspective. First, more patients develop end-stage renal disease, which is present at an approximately 90% reduction of kidney function. The affected patients require renal replacement therapy, which is provided in the form of dialysis - one of the most expensive chronic therapies - or kidney transplantation. Second, chronic kidney disease and end-stage renal disease per se are strong risk factors for morbidity and mortality [3]. Patients with a moderately impaired kidney function already have a high risk to develop cardiovascular and non-cardiovascular complications[4]. Mortality risk further increases inversely proportionate to the decline in kidney function, and the majority of patients with chronic kidney disease die before reaching end-stage renal disease.

In the patients undergoing maintenance dialysis, the rate of death is excessive and similar to that of cancer. The ERA-EDTA registry reports a 18% first year mortality rate [5]. An even higher annual mortality rate of >20% is reported by the USRDS [6]. Compared to the general population, mortality ranges from a 500 fold increased risk in young patients aged 25-35 years to a 5-fold increased risk in individuals of a high age of 85 years or more [7,8]. Cardiovascular events represent with 43% a major cause of death among dialysis patients [6], and efforts have been undertaken to decrease risk. However, reducing mortality among patients undergoing dialysis has been proven difficult and remains a global challenge. The past 10 years have seen trials of many interventions designed to improve survival and CV outcomes in these patients. Unfortunately, few of these interventions have been shown to be effective, despite beneficial effects in surrogate markers [9-17] (Table 1).

**Table 1.** Randomized trials in hemodialysis (HD) patients

**HD Patients: Randomised Trials with Endpoint Cardiovascular Disease or Death**

| Intervention | Year | N | Event | RR (95% CI) |
|---|---|---|---|---|
| EPO-Hematokrit [9] | 1998 | 1233 | 366 | 1.3 (0.9-1.9) |
| Vitamin E [10] | 2000 | 196 | 48 | 0.46 (0.27-0.78) |
| Acetylcysteine [11] | 2003 | 134 | 51 | 0.60 (0.38-0.95) |
| Carvedilol [12] | 2003 | 114 | 71 | 0.51 (0.32-0.82) |
| Dialyse Dosis x Flux [13] | 2004 | 1846 | 871 | 0.92 (0.81-1.05) |
| Atorvastatin [14] | 2005 | 1255 | 469 | 0.92 (0.77-1.10) |
| ACE-Inhibitor [15] | 2006 | 397 | 130 | 0.93 (0.68-1.26) |
| Folic acid [16] | 2007 | 2056 | 884 | 1.04 (0.91-1.18) |
| Rosuvastatin [17] | 2009 | 2776 | 804 | 0.96 (0.84-1.11) |

[9] Besarab et al, *N Engl J Med* 1998;339:584
[10] Boaz et al, *Lancet* 2000;356:1231
[11] Tepel et al, *Circ* 2003;107:992
[12] Cice et al, *JACC* 2003;41:1438
[13] Cheung et al, *Kidney Int* 2004;65:2380
[14] Wanner et al, *N Engl J Med* 2005;353:238
[15] Zannad et al, *Kidney Int* 2006;70:1318
[16] Jamison et al, *JAMA* 2007;298:1163
[17] Fellström et al, *NEJM* 2009;360:1395

For example, with very promising results from the general population, statins have been tested in dialysis patients in the 4D study [14] and the Aurora study [17]. As a surprise, both studies did not show a significant reduction in their primary endpoint of combined cardiovascular events and of mortality, raising the question of underlying reasons and future options.
Caution is required in translating findings from the general population to patients with chronic kidney disease, and general treatment recommendations can unfortunately not be applied to this patient group. Extrapolation of data from the general population may not meet the special disease pattern of kidney disease patients. One central question is - why?

Metabolic disturbances, which are common and strongly affecting morbidity and mortality in the general population, are also highly prevalent in dialysis patients. In this context, obesity is known to be a risk factor for the development of chronic

kidney disease and progression to end-stage renal disease. Furthermore, up to one half of the dialysis patients suffer from diabetes mellitus type 2, which in most cases is the cause for the failing kidneys and reaching end-stage renal disease (ESRD) [6, 18]. Similarly, Dyslipidemia in dialysis patients is more frequent than in the general population [19] and is characterized by hypertriglyceridemia and low levels of HDL. However, the effects of metabolic disturbances on clinical outcomes, including residual renal function in dialysis, cardiovascular events, and mortality, are not clear. Epidemiological studies in part even show paradoxical associations, which do not necessarily reflect causality however. With the combination of pathphysiological knowledge and epidemiologic reasoning, it is a challenge to reveal and approach true effects. True effects are essential to be identified, separated from clinical and methodological "distorsions", in order to develop new strategies and effectively treat dialysis patients for an improved survival.

Assessing metabolic risk in dialysis patients, three main aspects may be important: 1) the pathophysiologic effects of metabolic disturbances including obesity, diabetes mellitus, adipokine metabolism and lipid abnormalities are unlikely to completely reverse once patients reach dialysis. 2) Specific additional problems related to chronic kidney disease, in particular protein-energy wasting, may act as "competing risk", overshadow other effects and interfere in various hormonal regulations. 3) In advanced chronic kidney disease and end-stage renal disease, the pattern and composition of risk is changing. While myocardial infarction represents the most frequent cause of death in the general population, dialysis patients predominantly die of sudden cardiac death, accounting as a single cause for one quarter of all deaths [6, 14]. Certain disease states may predominantly affect macrovascular events such as myocardial infarction, while others may lead to microvascular complications, contributing differently to overall mortality.

***Aim of this thesis***

The aim of this thesis is to

1) Detect specific effects of metabolic alterations in dialysis patients
2) Provide explanations for conflicting results in the literature
3) Provide a rationale for novel interventions.

In this thesis, the metabolic status of dialysis patients is adressed and its consequences for the decline in residual kidney function, cardiovascular events and survival. The metabolic status includes alterations in nutritional and hormonal status. We will focus on:

1) lipid metabolism
2) diabetes mellitus type 2 and the importance of glycemic control
3) obesity and loss of residual kidney function
4) the role of adipokines and its longitudinal changes for clinical outcomes
5) specific effects of protein-energy wasting, including its impact in hormonal regulations of the bone-mineral axis
6) Vitamin D status and clinical consequences

***Study Populations***

The investigations are performed in two large cohorts of dialysis patients, the 4D and NECOSAD studies:

*4D study*

The 4D study was a prospective randomized controlled trial including 1255 patients with type 2 diabetes mellitus, age 18 – 80 years, and on hemodialysis for less than 2 years. Between March 1998 and October 2002, patients were recruited in 178 dialysis centres in Germany, and randomly assigned to double-blinded treatment with either 20mg atorvastatin (n=619) or placebo (n=636) once daily. Patients were followed up and visited in 6 monthly intervals until the date of death, censoring, or end of the study in March 2004 (median follow-up was 4 years). The primary endpoint of the 4D study was defined as a composite of death from cardiac causes, fatal or nonfatal stroke and nonfatal myocardial

infarction (MI), whichever occurred first (composite cardiovascular endpoint; CVE). Secondary endpoints included death from all causes, cardiac events, and cerebrovascular events.

*Necosad study*

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is an observational, prospective cohort study, in which consecutive patients who were at least 18 years old, had ESRD and started chronic dialysis were included. A total of 2045 patients were enrolled in 38 participating dialysis centres between 1997 and 2006 in the Netherlands (19;21). They were followed up and visited in intervals of 6 months until the date of death, transplantation, withdrawal or end of the study at 01-01-2009. Necosad participants include both patients on hemodialysis and on peritoneal dialysis. Apart from demographic and clinical data, 24 hour urine collections were obtained at all visits. The latter allowed for the unique assessment of residual renal function over time, in addition to cardiovascular and non-cardiovascular mortality.

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