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## **Nutritional status in chronic dialysis patients : associations with development of disease and survival**

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## **General discussion and summary**





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The main objective of this thesis was to study the association between nutritional status and survival in end-stage renal disease patients who are maintained on a chronic dialysis treatment. The majority of the studies presented in this thesis have been performed in the Netherlands Cooperative Study on the Adequacy of Dialysis-2 Study (NECOSAD-II), a prospective, longitudinal, observational multi-center cohort study that has been performed since 1997 in The Netherlands. The first part of this general discussion will reflect on the strengths and limitations of the nutritional status information and other data in NECOSAD-II. The second part will translate our findings into implications and recommendations for future research.

### **STRENGTHS AND LIMITATIONS**

Strengths of NECOSAD-II include its large sample size, the 6-monthly measurements and the long follow-up. Another important strength of the NECOSAD-II study design is that only incident dialysis patients were included. Most large cohort studies in the dialysis population have been performed in prevalent populations.<sup>1,2</sup> Studies in prevalent patient populations can be very valuable for public health planning, but outcome studies in prevalent patient populations may lead to inconsistent results. The reason for this is that dialysis patients who have a better health status may live longer and may represent a relatively large proportion in a prevalent dialysis cohort. A cohort of incident dialysis patients who are included and followed from the start of their dialysis treatment, like NECOSAD-II, provides valid information about the prognosis of a patient with end-stage renal disease starting hemodialysis or peritoneal dialysis treatment.

#### **Assessment of nutritional status**

Several nutritional parameters have been measured at the start of dialysis and every six months of follow-up in NECOSAD-II. In principle, nutritional status may be best measured with reference standards such as magnetic resonance imaging, total body potassium, or total body nitrogen. However, since epidemiological studies investigating survival need to have large sample sizes, these methods are too expensive and time-consuming and surrogate measures are needed. The following paragraphs will discuss the strengths and limitations of each nutritional parameter

that has been studied in this thesis. In addition, the parameters that have been used to study comorbidity and inflammation will be discussed.

#### *Body mass index*

In **chapter 2, 3, and 4** body mass index (BMI) was used as a measure of body fatness independent of height. In the general population this is an internationally accepted measure, used by the World Health Organization to define cut-off points for normal weight (18.5 to 25 kg/m<sup>2</sup>), underweight ( $\leq 18.5$  kg/m<sup>2</sup>), overweight (25 to 30 kg/m<sup>2</sup>) and obesity ( $\geq 30$  kg/m<sup>2</sup>).<sup>3</sup> A drawback of weight and BMI is that these measures cannot distinguish between body fat, muscle mass, and water.<sup>4</sup> Whereas a high BMI is an indicator of body fat, a low BMI may be especially indicative of a low lean body mass, which is related to health impairment. Therefore, BMI may not be an optimal measure of fat mass in chronically diseased populations as chronic dialysis patients.

In **chapter 4**, serial (6-month) measurements of BMI during time on dialysis were used to calculate weight changes. A problem with studying weight changes in observational studies is that it is unknown whether the observed weight loss was intentional or unintentional. Whereas benefits might be expected from healthy weight reduction, unintentional weight loss may be secondary to underlying illnesses that are related to outcome (reverse causation).<sup>5</sup> The weight loss observed in a chronically diseased population as the hemodialysis population is most likely unintentional, representing protein-energy wasting. In addition, in dialysis patients an increase in extracellular fluid may mask losses of body mass.<sup>6,7</sup> Even when hemodialysis patients are being dialyzed until the patients' estimated dry weight, true weight loss during time on dialysis may be obscured by an insidious increase in body water content.<sup>8</sup> Despite the fact that in NECOSAD-II much attention was paid to accurately establishing 'dry weight' of the hemodialysis patients, these considerations should be taken into account in the interpretation of our results.

#### *Skinfolds*

In **chapter 4** skinfold measurement was used in the aim to distinguish between fat mass and muscle mass. Skinfold measurement is based on a two-compartment

model which divides the composition of the body into fat and fat-free mass and is limited by assumptions regarding fat distribution, hydration status and because of inter-observer error.<sup>9:10</sup> Several studies that compared skinfold thickness with bioelectrical impedance analysis, dual-energy X-ray absorptiometry and near-infrared interactance techniques for the determination of body fat in hemodialysis patients concluded that skinfold thickness was the most simple, long-established, and inexpensive method and useful in daily practice for assessing body fat in patients on long-term hemodialysis therapy.<sup>11:12</sup> In **chapter 4** it was shown that the skinfold measurement was not sufficiently sensitive to detect changes in body composition during 6-month intervals, possibly because the changes were too small. Thus, although skinfold measurement can be used to evaluate body composition by classifying the patients having adequate muscle mass or muscle mass depletion, it may not be suitable to evaluate small changes in body composition of chronic hemodialysis patients.

#### *Serum albumin*

Although it is known for many years that serum albumin is a negative acute phase reactant,<sup>13:14</sup> it is considered as a useful indicator of protein-energy nutritional status in dialysis patients and mentioned in current guidelines,<sup>15</sup> mainly because of its strong association with outcome.<sup>8</sup> **Chapter 5** showed that one g/dL decrease in serum albumin was associated with an increased mortality risk of 47% in hemodialysis patients and 38% in peritoneal dialysis patients. These mortality risks were in part explained by the inflammatory pathway and were not a consequence of protein-energy wasting. In contrast to what was reported in other studies,<sup>16-18</sup> serum albumin was not an independent predictor of mortality risk in our study after adjustment for markers of nutritional status, protein intake and inflammation. One explanation for this may be that the sample sizes of the hemodialysis and peritoneal dialysis groups were small. Other factors affecting serum albumin levels as metabolic acidosis, insulin resistance, hydration status and protein losses in the urine and dialysate may also play a role in explaining the mortality risk associated with serum albumin. Although one of the limitations of **chapter 5** may be that we were not able to study this in further detail, our findings imply that serum albumin is not a precise measure of nutritional status in chronic dialysis patients.



*The normalized protein equivalent of nitrogen appearance (nPNA)*

The normalized protein equivalent of nitrogen appearance (nPNA) has been used in **chapter 5** to estimate dietary protein intake. nPNA, estimated from interdialytic changes in urea nitrogen concentrations in serum and urine, is a valid estimate of protein intake and simple to use in the clinical setting.<sup>15</sup> Because of the strong influence of body weight on both net protein breakdown under fasting conditions and dietary protein requirements, the measure is normalized to the standard body weight of the patient. A limitation of nPNA is that patients should be stable and neither anabolic nor catabolic,<sup>19,20</sup> which may limit its use in dialysis patients.

*The subjective global assessment of nutritional status (SGA)*

The SGA classification is based on the clinical judgment of four subscales representing the patients' recent weight change, dietary intake and presence of gastro-intestinal symptoms, and a physical examination of loss of subcutaneous fat mass and muscle wasting (Appendix),<sup>21-23</sup> and may therefore provide a comprehensive evaluation of the nutritional status. Despite its subjective nature, the SGA has been found reliable and valid.<sup>23-25</sup> Only one study compared the SGA with a reference method of nutritional status in dialysis patients.<sup>26</sup> In this comparison with total body nitrogen the SGA was only able to detect the presence of severe malnutrition rather than the degree of malnutrition.<sup>26</sup> However, only 76 dialysis patients were included in this study, which may not have been sufficient to detect differences between the different SGA categories. Although we could not study the concurrent validity of the SGA in comparison with a reference method of nutritional status in **chapter 6**, patients with moderate or severe protein-energy wasting at baseline according to the SGA had a lower BMI, and lower nPNA, serum cholesterol and serum albumin concentrations compared to patients with a normal nutritional status. Furthermore, the strength of the association of the SGA with future adverse health outcome may be considered highly clinically relevant. **Chapter 6** showed a dose-response trend of the 7 points of the SGA classification in relation to mortality, implying that the 7-point SGA can be used in clinical practice to distinguish different degrees of protein-energy wasting associated with increasing risks of mortality.

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*The presence of comorbidity and inflammation*

In NECOSAD-II comorbidity was defined as the presence of clinical diagnoses of non-renal diseases as reported by the patients' nephrologists at the time of inclusion of the patients. For the adjustment of our analyses in **chapters 4, 5 and 6** for pre-existing comorbid conditions, the comorbidity index of Khan was calculated in which age and comorbid conditions are combined into three risk groups classifying patients to have a low, medium or high mortality risk.<sup>27</sup> Adjustment for comorbidity by using such a summarization of comorbidity may be associated with more residual confounding compared with adjusting for the separate comorbid conditions.<sup>28</sup> However, the latter may not always be necessary because the influence of comorbidity showed less important after adjustment for age, sex, primary kidney disease, treatment modality and country, in a study that compared outcomes between patient groups of five European countries.<sup>29</sup> The analyses in **chapter 7** that studied the nutritional status, inflammation and cardiovascular diseases as exposure were adjusted for diabetes en malignancy.

In **chapter 5 and 7** the patients were classified according to their serum concentrations of C-reactive protein (CRP), a pro-inflammatory cytokine. In these analyses we defined the presence of inflammation as a serum concentration of CRP of  $\geq 10$  mg/L. This arbitrary cutoff point to define systemic inflammation has been used previously<sup>30:31</sup> and corresponds well to findings that 90% of all adults in a large population-based study displayed CRP levels below that threshold.<sup>32</sup> Furthermore, by using a receiver operating characteristics curve for CRP as a predictor of death, a European study showed that the cut-off point at which sensitivity and specificity were equally high (65%) was at a CRP level of 9 mg/L. By using a cut-off point of 10 mg/L acceptable values for sensitivity (about 60%) and specificity (70%) were achieved.<sup>33</sup>

More recently, the cytokine IL-6 has been suggested as the best predictor of outcome in dialysis patients since it may play a key role in the pathogenesis of both protein-energy wasting and atherosclerosis in the dialysis population.<sup>34:35</sup> However, in clinical practice CRP concentration is most commonly used as marker of inflammation.<sup>36</sup> Furthermore, the balance between pro- and anti-inflammatory

cytokines rather than the absolute amount might be crucial for the progression of atherosclerosis.<sup>36;37</sup> Hence, a single CRP concentration may not be the most appropriate method to define the presence of chronic inflammation. Nevertheless, in case of non-differential misclassification associations may be biased towards the null and true effects may have been larger.

### **Assessment of outcome**

For the assessment of outcome in NECOSAD-II, information on mortality (date and cause of death) has been obtained similarly in the whole dialysis population, independent of the nutritional status parameters at baseline or during follow-up. In 7 years after the start of dialysis, 660 deaths were recorded in the study population described in **chapter 6** (n=1601), resulting in a strikingly high mortality rate (15/100 person-year). In the first year after the start of dialysis the cumulative mortality as computed by the Kaplan-Meier method was 15% in hemodialysis patients and 7% in peritoneal dialysis patients; in 7 years of dialysis treatment this was 74% in hemodialysis patients and 55% in peritoneal dialysis patients. Besides the event of death, there were several other reasons why participants were lost to follow-up, including kidney transplantation (30%), refusal of further participation (10%), transfer to a non-participating dialysis center (4%), recovery of renal function (1%), or other (1%) (**chapter 6**). In the survival analyses, these patients were censored at the date of loss to follow-up for other reasons than death and thus contributed survival time until this date. However, we cannot completely rule out any influence of competing events over time on dialysis. For example, since undergoing a kidney transplantation may be related to body mass index at baseline<sup>38</sup> and the prognosis of the patients, selection bias may occur. Furthermore, since the Kaplan-Meier method assumes the same probability of survival in patients who are lost to follow-up as in patients who remain in the study, the cumulative mortality may be overestimated in the dialysis population due to the large proportion of patients that left the study because of a kidney transplantation. A competing risk analysis, which calculates the cumulative incidences for all possible reasons of loss to follow-up<sup>39;40</sup> may be the method of choice in future analyses of the cumulative mortality in dialysis populations.

**Causal interpretations: how valid are the observational comparisons?**

There has been much debate about whether observational epidemiology can serve causal inference. In the ideal situation, association can be interpreted as causation when the exposed and unexposed are exchangeable, i.e. when the exposure groups only differ in their exposure status and the findings would be the same if the exposed group were unexposed and vice-versa. In investigations of intended beneficial effects of treatments, randomization is the favorite method which attempts to obtain exchangeable groups.<sup>41,42</sup> Observational studies of unintended adverse events may provide data as valid as randomized trials as long as the (self) assignment to exposure groups can be considered unrelated to the prognosis of the subjects.<sup>41,43</sup> When exposure groups can not be considered exchangeable at baseline, confounding may occur.

When contrasting obese dialysis patients with dialysis patients with a low BMI, or when contrasting dialysis patients with a normal nutritional status with patients with protein-energy wasting, these patients are considered completely alike, except for their BMI or their nutritional status. However, it can be argued whether these patient groups can be considered exchangeable.

*General confounding*

In principle, each analysis in this thesis has been adjusted for known confounding variables. A variable that may confound the association of interest has been defined as a variable that is both related to the exposure and known to determine prognosis, but is not an intermediate variable within the causal pathway of the association of interest.<sup>44</sup> All analyses of associations of nutritional parameters with mortality have been adjusted for age, sex, primary kidney disease and comorbidity. In addition, since patients who start with a hemodialysis treatment and patients who start with a peritoneal dialysis treatment may differ in both nutritional status and outcome, the analyses in **chapter 5** and **7** were adjusted for initial treatment modality as well. It can be argued that initial treatment modality may also lie within the causal pathway between nutritional status and mortality; adjustment would then be inappropriate. Adjustment for primary kidney disease may also involve uncertainty, since some patients may have signs of two kidney diseases.

Nevertheless, both adjustment for primary kidney disease and adjustment for treatment modality only marginally changed the risk estimates. Because of the observational study design residual confounding by imperfectly measured or unknown confounders may still be present.

*Are the groups comparable?*

The usual control for potential confounders may not suffice in observational studies of nutritional status and mortality in dialysis populations. The hypothesis that a higher level of adiposity, i.e. increased fat mass, may provide a survival advantage for patients with end-stage renal disease was based on the observed obesity-survival paradox.<sup>45</sup> This hypothesis may be an example of how causal inference can go wrong in observational epidemiology. It can be argued to what extent dialysis patients exposed to a high BMI can be considered exchangeable with dialysis patients exposed to a low BMI. In chronic dialysis patients, the underlying reasons and causal pathway for having a low BMI may be fundamentally different from the underlying reasons for having a high BMI. For instance, patients with a low BMI may have lost weight due to protein-energy wasting that is associated with mortality. This implies that a low BMI itself does not increase mortality risk, but that factors associated with protein-energy wasting reduce body weight, thereby increasing the mortality that is attributed to low BMI (reverse causation). Likewise, the underlying reason for being an obese dialysis patient may differ from the reasons of being a lean dialysis patient. For example, the main primary kidney disease in overweight and obese dialysis patients was diabetic nephropathy (20% and 42%, respectively), whereas patients in the lower BMI categories more often had glomerulonephritis or renal vascular disease as primary kidney diseases (**chapter 4**). Since obesity is a risk factor for chronic kidney disease, either directly or through the development of diabetes, a proportion of obese dialysis patients may have developed chronic kidney disease because of their obesity.<sup>46,47</sup> Differences in disease history are likely to be related with a different health status and a different probability of mortality, irrespective of BMI. As a consequence, dialysis patients with a high BMI may not be exchangeable with dialysis patients with a low BMI and a direct comparison between these two groups may remain to suffer from confounding. This confounding bias is similar to confounding by indication in observational studies of intended treatment

effects and can not be controlled away statistically. Hence, causal interpretations of the effects of both low and high BMI on the basis of the observed associations of 'reverse epidemiology' in dialysis patients remain uncertain.

#### *Causal interaction*

**Chapter 8** explains the concept of causal interaction of risk factors and presents measures to evaluate the presence of interaction in applied data analysis. Causal interaction between two risk factors occurs when they act together in causing disease and is explicitly defined as a departure of additivity on a risk difference scale over strata of exposure combinations.<sup>44;48;49</sup> Assuming additivity of effects, **chapter 2** showed that men who are obese, physically inactive, or who smoke, were not more susceptible to develop chronic kidney disease than women. Having all three of these habits resulted in higher risk of chronic kidney disease than expected, implying an interaction effect between obesity, smoking, and physical inactivity in the general population. **Chapter 7** showed excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular diseases in the chronic dialysis population. Departure of additivity of effects was examined using logistic regression analysis in **chapter 2** and with Cox regression analysis in **chapter 7**. It may seem counterintuitive that a model is fitted on the multiplicative scale and that two risk factors are selected to be examined on an additive scale. In contrast to multiplicative models, additive models are difficult to apply. With the data in **chapter 7** an additive model was fitted as well and departure from additivity confirmed our analyses (data not shown).

The contribution of causal interaction to an understanding of biological mechanisms has been debated.<sup>50</sup> For example, from the observed interaction effect in **chapter 2** it cannot be inferred whether obesity, physical inactivity and smoking interact in the development of chronic kidney disease via a hemodynamic or nonhemodynamic mechanism, which are both possible.<sup>51;52</sup> Similarly, no biological processes can be inferred between protein-energy wasting, inflammation and cardiovascular diseases on the basis of the excess mortality shown in **chapter 7**. The exact pathways through which these three risk factors interact therefore remain to be further studied.

## External validity

### *Representativeness of the patient population*

The majority of the dialysis centers in the Netherlands (38 out of 50 in 1997) participated to include eligible patients in NECOSAD-II. There were few inclusion criteria: end-stage renal disease patients needed to be 18 years of age or older; they had to start with their first renal replacement therapy (including no prior kidney transplantation); they had to be in clinically stable condition; and the patients had to have sufficient knowledge of the Dutch language to be interviewed. Compared with the Dutch Renal Replacement Registry,<sup>46;53</sup> the NECOSAD-II population was similar to the Dutch end-stage renal disease population with regard to age, sex, dialysis therapy, primary kidney disease and mortality. Because of the large proportion of 93% of white patients in NECOSAD-II our analyses might have limited implications for non-white dialysis patients. Similar to the Dutch general population, less than 1% of the hemodialysis population had a BMI $\geq$ 40 kg/m<sup>2</sup> in NECOSAD-II (**chapter 3**). Therefore, it was not possible to explore mortality risks for BMI categories greater than 40 kg/m<sup>2</sup>. The analyses in **chapter 3** and **4** were restricted to hemodialysis patients and may not be extrapolated to patients starting with peritoneal dialysis treatment.

### *Missing data*

As is common in medical research, there were missing data in NECOSAD-II. For each research question in this thesis, a complete case analysis was performed, excluding patients with missing values in the exposure variable at baseline. Figure 1 shows a flow chart of the included patients in NECOSAD-II, the reasons of lost to follow-up within 3 months after the start of dialysis, the number of consecutive exclusions and sample sizes in chapters 3, 4, 5, 6 and 7. In case of selective missing values (for example, patients' skinfolds may have not been measured because they felt too weak) the selected sample sizes may not be representative for the total dialysis population. The extent of possible selection due to missing data in our studies is unknown, except for the analyses described in **chapter 5** and **7** in which patients were selected with a measured serum C-reactive protein concentration at three months after the start of dialysis. For these laboratory analyses, a sub sample of

patients had been selected from whom blood samples were available both at three and six months after the start of dialysis. Consequently, patients had been selected on the basis of having survived at least the first six months after the start of dialysis. Although this may not have interfered with the research questions regarding inflammation, the results may not be representative for patients with a shorter survival time on dialysis. In case of missing values during time of follow-up in the time-dependent analyses (**chapter 4** and **chapter 6**), the last known observation of each patient was carried forward.

## IMPLICATIONS AND CONCLUSIONS

### Main findings

In the context of these strengths and limitations, and in light of the current literature, we will summarize our main findings and translate them into implications.

#### *Obesity and development of chronic kidney disease*

Obesity is one of the established risk factors of cardiovascular disease and is associated with increased mortality in the general population.<sup>54-57</sup> In **chapter 2**, we showed that overweight and obesity were associated with increased risks of the development of chronic kidney disease. These findings are supported by a recent meta-analysis that showed relative risks of chronic kidney disease of 1.40 (95% CI 1.30-1.50) in overweight individuals, and 1.83 (1.57-2.13) in obese individuals, compared with normal-weight individuals.<sup>51</sup> It was furthermore estimated that in industrialized countries 16.5% of chronic kidney disease cases in men and 26.3% women could be related to overweight and obesity.<sup>51</sup> However, causal interaction between sex and obesity was not examined in this meta-analysis. **Chapter 2** showed that men were not more susceptible than women to the effect obesity on the development of chronic kidney disease. Possibly, BMI is not the optimal measure to estimate sex differences, rather than measures of body fat distribution. At this moment a sex difference in the association between obesity and chronic kidney disease seems unlikely.



Recently, much research has been performed to study the etiology of obesity and chronic kidney disease, suggesting that obesity increases the risk of chronic kidney disease as well as its progression. In **chapter 2** we showed that obesity was an independent risk factor for chronic kidney disease, also beyond pathways via diabetes, hypertension and cardiovascular disease, the most common causes of chronic kidney disease. Indeed, obesity may exert direct effects on renal damage as well via renal hemodynamic alterations, such as insulin resistance, the renin-angiotensin system and the tubulo-glomerular responses to increased proximal sodium reabsorption, and possibly an inappropriate activity of the sympathetic nervous system and increased leptin levels.<sup>58-62</sup> It also has been shown that weight loss may improve glomerular hemodynamics and may delay progression of chronic kidney disease in obese persons.<sup>63</sup> Thus, in the general population obesity is a common, strong and modifiable risk factor for chronic kidney disease. Healthy weight reduction and control programs increasing physical activity in obese people may prevent chronic kidney disease and its progression to end-stage renal disease.<sup>64;65</sup>

#### *Obesity and mortality in chronic dialysis patients*

In the past decade, the prevalence of obesity at the start of dialysis strongly increased with a rate of increase in BMI among incident dialysis patients that was twice the rate of increase in the total US population.<sup>66</sup> This may be due to an increase in diabetic nephropathy.<sup>47</sup> Currently in the US, diabetes mellitus accounts for 44% of new cases of treated ESRD,<sup>67;68</sup> compared to 24% in Europe.<sup>46</sup> In many transplantation centers obesity is considered as a relative contra-indication for renal transplantation due to a higher mortality, a reduced allograft survival and a higher incidence of peri- and postoperative complications compared to normal weight.<sup>69-72</sup> As a consequence, obese patients have a decreased probability of wait-listing for transplantation.<sup>38;73</sup> Since survival studies in dialysis patients have indicated that the association of obesity with mortality is opposite to that observed in the general population,<sup>1;74;75</sup> the phenomenon of 'reverse epidemiology' has resulted in confusion and uncertainty about whether weight loss should be advised in morbidly obese dialysis patients who are awaiting kidney transplantation.<sup>72;76</sup>

**Chapter 3** showed that the association of BMI and mortality was similar, and not reversed, in the hemodialysis population and the general population of equal baseline age and duration of follow-up, implying that effects of duration of follow-up and age should be taken into account for a valid interpretation of the association between BMI and mortality in the hemodialysis population. Compared with dialysis patients in the normal BMI range no protective effect of a high BMI at the start of dialysis was found on subsequent mortality in 7 years of follow-up in the hemodialysis population (**chapter 3**). A possible explanation for this discrepancy with the survival advantage reported in the literature<sup>1:75;77</sup> may be that our reference group with a normal BMI on average had a better clinical condition and a better prognosis than reference groups in other dialysis populations, possibly because the majority of the patients received pre-dialysis care.<sup>78</sup> On the other hand, the fact that most other studies have been performed in prevalent dialysis populations, in which only the healthiest obese patients might have survived, may also play a role.

It is conceivable that greater energy reserves in obesity may protect dialysis patients against the effects of protein-energy wasting.<sup>45;79;80</sup> However, results in **chapter 4** suggest that weight loss of more than 1% within 6 months was associated with increased mortality risks in the hemodialysis population, independent of BMI. It is therefore unclear whether obesity may protect against the effects of protein-energy wasting.

With regard to pathophysiologic mechanisms underlying the effects of obesity, current research suggests that fat, or adipose tissue has both beneficial and adverse consequences in chronic kidney disease.<sup>81</sup> Recent studies show that adipose tissue is both a storage depot for energy and a source of circulating signaling molecules. Adipose tissue secretes a number of adipokines including leptin and adiponectin, as well as cytokines, such as resistin, visfatin, tumor-necrosis factor- $\alpha$  and interleukin-6. Adipokine serum levels are markedly elevated in chronic kidney disease, likely due to a decreased renal excretion.<sup>82</sup> It has been described that elevated circulating adipocytokine levels in chronic kidney disease may have detrimental effects on the vascular, central nervous system and musculature, which

via multiple mechanisms may contribute to increased systemic inflammation, premature atherosclerosis and even protein-energy wasting.<sup>82</sup>

An epidemiological analysis that may provide insight in the long-term effects of obesity, studied 320 252 middle-aged adults in the general population and showed a strong relation between BMI and increased risk of end-stage renal disease and mortality in both subjects with and without chronic kidney disease.<sup>83</sup> Compared with normal weight individuals, the adjusted relative risks for overweight, class I, II, and III obesity were 1.87 (1.64-2.14), 3.57 (3.05-4.18), 6.12 (4.97-7.54), 7.07 (5.37-9.31) for end-stage renal disease and 1.04 (1.02-1.06), 1.20 (1.17-1.24), 1.42 (1.35-1.50), 1.71 (1.58-1.86) for mortality, respectively.<sup>83;84</sup> These results suggest that, compared to non-obese subjects, obesity is a risk factor of both end-stage renal disease and mortality.<sup>84</sup>

#### *Protein-energy wasting and mortality in chronic dialysis patients*

Both **chapter 3** and **chapter 4** showed that underweight was associated with a two-fold increased mortality risk in hemodialysis patients. It was hypothesized that pre-existing comorbidity and loss of weight during hemodialysis may explain the high mortality risk associated with low BMI. In **chapter 4** it was shown that pre-existing comorbidity and weight loss during the previous 6 months only explained a minor part of the increased mortality risk of a low BMI. In the same analysis, time-dependent weight loss of 1-5% (HR: 1.52, 95%-CI: 1.06-2.16) and >5% (2.18, 1.44-3.29) was associated with increased mortality, independent of comorbidity and the level of BMI. The few other studies that examined weight change in relation to mortality in the dialysis population also found that weight loss during dialysis was associated with poor survival.<sup>1;2;72;85</sup> It must be noted that it is unknown whether the weight loss was intentional or unintentional in these observational studies. However, it is most likely that the observed weight loss was unintentional, as a consequence of underlying illnesses instead of healthy intentions to lose weight prior to a kidney transplantation, which may have resulted in the observed increased mortality (reverse causation). These results imply that weight loss during time on dialysis may be a warning signal, independent of the BMI of the patient.

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Factors associated with a low BMI and weight loss during time on dialysis need to be explored further.

In **chapter 4** skinfold measurements were used as surrogate measures of fat mass and muscle mass. Muscle mass depletion at baseline as assessed with the arm muscle area was associated with an increased mortality risk (HR:1.52, 95%-CI: 1.04-2.21, time-dependent HR:1.64, 95%-CI: 1.12-2.39), whereas fat mass as assessed with the sum of four skinfolds was not associated with mortality. These results suggest that in relation to the survival of hemodialysis patients, preservation of muscle mass may be more important than preservation of fat mass, independent of BMI. This is supported by a recent study that showed that the increased mortality in overweight end-stage renal disease patients was due to low lean body mass and not to the increased fat body mass.<sup>86</sup>

At the start of dialysis, 28% of the dialysis patients suffered from protein-energy wasting, of whom 5% suffered from severe protein-energy wasting (**chapter 6**). Compared with a normal nutritional status, moderate to severe protein-energy wasting, as assessed with the subjective global assessment of nutritional status (7-point SGA), was independently associated with a twofold increased mortality risk in 7 years of follow-up. In time-dependent analyses, the mortality risk of severe protein-energy wasting was even stronger, fivefold, implying that the short-term impact of nutritional status is more important than the long-term effect (**chapter 6**). Therefore, our results imply that the nutritional status of dialysis patients should be assessed regularly, in accordance with the recent European Best Practice Guideline on nutrition,<sup>15</sup> at least every 6 months. Routine monitoring of the nutritional status in dialysis patients is important since protein-energy wasting is more difficult to treat when severe.<sup>87</sup> Our results imply that the 7-point SGA can be used in clinical practice to distinguish different degrees of protein-energy wasting associated with increasing risks of mortality.

During the past decade, many studies hypothesized that protein-energy wasting, inflammation and cardiovascular diseases may be pathophysiologically linked in patients with chronic renal failure.<sup>88-96</sup> **Chapter 7** is the first study to show an

interaction effect between protein-energy wasting, inflammation and cardiovascular diseases in chronic dialysis patients, resulting in an excess mortality of 16/100 person-years. The moderate interaction effects (2 to 3/100 person-years) between each two risk factors imply that indeed all three risk factors are necessary to result in the large overall interaction effect. Although these epidemiological data support the presence of an interaction effect between protein-energy wasting, inflammation and cardiovascular disease, underlying pathophysiological mechanisms cannot be inferred from this interaction effect. The exact role of inflammation in the association of nutritional status, cardiovascular disease and mortality therefore remains unclear<sup>75;78-79</sup> and further studies investigating the role of inflammation are necessary.

In contrast to the effects of obesity, the effects of protein-energy wasting on mortality in dialysis patients may at least in part be causally interpreted. Current clinical practice to treat protein-energy wasting consists of dietary counseling, oral nutritional supplements, and intradialytic parenteral nutrition in order to increase the nutritional intake of the patients. Only few studies investigated the effect of nutritional therapy on survival.<sup>97-99</sup> A recent randomized trial showed no effect on morbidity and mortality of oral nutrition in addition to intradialytic parenteral nutrition, but suggested that an improvement in prealbumin during nutritional therapy was associated with a decrease in mortality in malnourished hemodialysis patients.<sup>99</sup> Studies of novel preventive and therapeutic strategies to improve nutritional status in dialysis patients, such as appetite stimulants, growth hormone, androgenic anabolic steroids, and anti-inflammatory drugs, have shown contradictory and inconclusive results.<sup>100</sup> However, a recent randomized trial showed that treatment with human growth hormone increased lean body mass in hemodialysis patients.<sup>101</sup> Another randomized controlled trial showed that anabolic steroids and resistance exercise increased muscle mass.<sup>102</sup> Resistance exercise may also enhance the anabolic effects of nutritional supplementation.<sup>103</sup> Although the results of these recent randomized trials are very promising, survival studies of interventions targeted at causes of protein-energy wasting that decrease nutritional intake or increase nutritional requirements are needed.

### **Conclusions: randomized controlled trials are needed**

The main conclusions of this thesis are:

- Obesity, smoking and physical inactivity were associated with the development of chronic kidney disease, and men were not more susceptible than women to these risk factors.
- The association between BMI and mortality in the hemodialysis population was similar, and not reversed compared with the general population of equal baseline age and duration of follow-up.
- The twofold increased mortality risk of a low BMI at baseline may in part be explained by low muscle mass and pre-existing comorbidity.
- Weight loss and muscle mass depletion, as assessed with the arm muscle area, were both associated with an increased mortality risk in hemodialysis patients, independent of BMI. Fat mass as assessed with the sum of four skinfolds was not associated with mortality.
- Serum albumin is not a precise measure of nutritional status in chronic dialysis patients.
- Protein-energy wasting interacted with inflammation and cardiovascular disease, resulting in excess mortality in chronic dialysis patients.
- Compared with a normal nutritional status, protein-energy wasting was associated with a twofold increased mortality risk in 7 years of follow-up. In time-dependent analyses, this mortality risk was even stronger (fivefold), implying that the short-term impact of nutritional status is more important than the long-term effect.
- The 7-point SGA can be used in clinical practice to distinguish different degrees of protein-energy wasting associated with increasing risks of mortality.

Taken all these findings together, there is no sufficient evidence to conclude that fat mass or obesity may improve survival in dialysis patients. It remains to be studied whether intentional weight reduction by healthy lifestyle and diet and exercise programs may improve outcomes in obese dialysis patients and after transplantation. Most importantly, the results of this thesis emphasize the importance of maintaining a good nutritional status in chronic dialysis patients. In order to improve survival in the dialysis population more attention should be paid

to patients with a declining nutritional status instead of overweight. Therefore, routine monitoring of the nutritional status in dialysis patients (at least every 6 months) is indicated; the 7-point SGA (Appendix) can be used for this.

As mentioned in the discussion about causal interpretations earlier in this chapter, usual adjustment for confounding in a statistical model may not suffice to translate epidemiological observations into evidence that is causally sufficiently strong to directly lead to interventions. In order to provide answers on the questions raised by these observed associations of nutritional status and mortality the following randomized controlled trials are proposed:

- 1) In order to provide evidence that a higher level of adiposity may improve survival in chronic dialysis patients a randomized controlled trial in dialysis patients with a normal weight would be needed to study the effect of increased fat mass on survival.
  - Although energy-dense foods might be used as means to increase body mass index, the method of increasing fat mass (by increasing calories by increasing fat, carbohydrate, or protein intake, or by decreasing physical activity?) may be importantly related to outcome and true randomization of increased fat mass will remain highly unfeasible. Similar to a randomized trial of stopping with smoking, it may be more feasible to randomize and study the effect of decreased fat mass:
  
- 2) A randomized controlled trial in obese dialysis patients to study the effect of intentional weight reduction on survival on dialysis and after a kidney transplantation.
  - Because interventions with healthy lifestyle and diet and exercise programs may not be effective and because it will remain difficult to determine whether the observed weight loss was truly intentional, interventions with bariatric surgery may provide a solution.<sup>104;105</sup> Although an ethical concern may be that bariatric surgery is accompanied with high risks of complications, it may be feasible to randomize eligible patients for surgery to estimate the effect of decreased fat mass on survival and

simultaneously provide an answer on the question whether increased fat mass improves survival.

- 3) Most importantly, randomized clinical trials in chronic dialysis patients with protein-energy wasting are needed to study whether nutritional therapy alone or in combination with resistance exercise and/or other anabolic stimuli is effective in the treatment of protein-energy wasting by increasing muscle mass and prevention of weight loss and whether this would lead to improved survival.



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