Metabolic alterations in dialysis patients

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CHAPTER 11

Summary and Discussion

In this thesis, metabolic alterations in dialysis patients have been adressed, and their consequences for the decline in residual kidney function, cardiovascular events and survival. Particular attention was thereby given to detect specific effects on –pathophysiologically different- events in dialysis patients, to provide explanations for conflicting results in the literature, and to provide a rationale for novel interventions.

With an annual mortality of about 20%, dialysis patients urgently require novel and effective treatment strategies. Results from the general population, indicating beneficial effects of interventions to control standard and novel risk factors, have been motivating. Although similarly expected to improve survival in the high risk population of dialysis patients, many trials however have been negative, not offering substantial improvements for cardiovascular and overall health by the tested treatments in dialysis patients.

This raises the question of why interventions failed to improve survival in this patient group. Understanding potential reasons is highly important as it may offer the possibility for designing new strategies.

With this aim, the thesis investigated the risk of metabolic alterations on adverse outcomes considering specific pathophysiologies in dialysis patients, and methodological challenges to reveal „true“ effects. One particular aspect thereby was the changing risk pattern in dialysis patients to be taken into account. While myocardial infarction represents the most frequent cause of death in the general population, dialysis patients mainly experience non-ischemic adverse events. With risk factors potentially differently affecting the various outcomes, the thesis investigated specific endpoints to get insight into relevant pathways and effects of metabolic alterations.

The need for such strategy is introduced in **chapter 2**, which outlines lipid disorders in patients with renal disease, clinical effects and current treatments. This review illustrates an abnormal lipid metabolism being common in patients

with the nephrotic syndrome and in patients with chronic kidney disease (CKD) or after kidney transplantation. Main abnormalities of lipid metabolism in the nephrotic syndrome include increases in total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol, apolipoproteins B, C-III and triglycerides, while apo-A1 is reduced. The profound disturbances in lipid metabolism in patients with chronic kidney disease include increased concentrations of triglyceride-rich lipoproteins, small dense and oxidized LDL, and impaired HDL maturation and catabolism. These alterations however are not captured by routine laboratory measurements. The classical guidelines on lipid lowering therapy –such as the national cholsterol education program adult panel III- cannot generally be applied to renal patients, as extrapolation of data from the general population may not meet the special disease pattern of patients with chronic kidney disease. Although post-hoc analyses of statin trials support the administration of statins in patients with early stages of chronic kidney disease (CKD stage 1-3), patients with advanced chronic kidney disease do not benefit to the same extent from lipid-lowering therapy. In particular, there is no rationale to start statin treatment in patients, once they require maintenance hemodialysis. The present guidelines (EBPG and K/DOQI) on the treatment of lipid disorders in patients with chronic kidney disease do not reflect the current evidence.

In **chapter 3**, Obesity was identified as a strong risk factor for the decline in residual renal function (RRF) after patients start dialysis. This finding is important because prior studies have shown that preservation of residual renal function in dialysis patients is associated with better survival. In summary, patients with normal weight had a mean decline of mGFR of 1.2 ml/min per year. Obese patients lost 1.2 ml/min *more* of their mGFR per year, reflecting a 100% higher loss of residual kidney function per year as compared to patients with normal weight. The relative risk to develop anuria was similar among the BMI groups after adjustment for confounders and baseline diuresis. This study provides a rationale for future interventional trials, which must show whether obese patients might benefit from a healthy weight reduction.

Chapter 4 focusses on poor glycemic control and its effects on cardiac and vascular outcomes. Cardiac disease represents the leading cause of death, particularly sudden cardiac death. Evidence suggests that poor glycemic control may impact in the arrhythmogenesis of patients with kidney failure, since it affects the development of comorbidities, the electrolyte balance, the function of potassium and calcium channels, and sympathetic activity. In the present study of 1255 hemodialysis patients with type 2 diabetes mellitus, poor glycemic control as represented by elevated levels of glycated hemoglobin A1c was associated with an increased risk of sudden cardiac death. Patients with a HbA1c above 8% had a twofold higher risk of sudden death compared to those with a HBA1c ≤6%, independently of other known risk factors. While myocardial infarction was not affected, the risks of the combined primary endpoint and mortality significantly increased at higher levels of HbA1c, and were mainly explained by the impact of glycemic control on sudden cardiac death. By pointing out the importance of distinguishing the –pathophysiologically different- causes of death, the present study offers new perspectives for future research on glucose control in populations with high incidences of sudden death. Importantly, these results may suggest novel therapeutic strategies in diabetic hemodialysis patients, in whom sudden cardiac death accounts for a quarter of all deaths. Whether tight glucose control decreases the risk of sudden death without causing side effects, remains to be studied.

In the context of body weight regulation, and related processes of insulin sensitivity, inflammation, and endothelial function, adiponectin represents a hormone of major interest. It is an adipocyte-specific cytokine with a protective role in the development of cardiovascular morbidities in the general population. As chronic kidney disease progresses, adiponectin levels increase and cardiovascular risk profiles change. In **chapter 5** we determined the association of baseline and longitudinal changes in adiponectin with different cardiovascular outcomes in 1255 type 2 diabetic hemodialysis patients in the German Diabetes and Dialysis Study. Within 4 years of follow-up, the hazard ratios to reach pre-specified, adjudicated end points were determined. The increased risk of cardiovascular events observed

with high adiponectin levels at baseline was associated with high risks of sudden death and stroke but not of myocardial infarction. Adiponectin was negatively correlated with C-reactive protein and positively correlated with NT-pro-BNP, the latter significantly attenuating the associations with adverse outcome. Increased longitudinal levels of adiponectin during follow-up were associated with higher risks of adverse cardiovascular outcomes and death; associations weakened by a confounding effect of increased NT-pro-BNP. The study importantly suggests that high basal and increasing adiponectin levels in the dialysis population largely reflect a consequence of disease circumstances. Most likely, this rise is a counter-regulatory response to worsening health in keeping with adiponectin's potential to counteract inflammation.

One very important aspect of „worsening health" in dialysis patients is the wasting syndrome. Wasting increasingly develops, as kidney function declines, and is a complex process of muscle loss, poor food intake, hypercatabolism and inflammation. The wasting syndrome is adressed in **chapter 6**. Known to be associated with a high mortality and cardiovascular events, the processes however are poorly understood and treatments are lacking. In chapter 6, we therefore studied the impact of wasting on specific clinical outcomes, including sudden cardiac death, myocardial infarction, and deaths due to infection in dialysis patients of the 4D study. Compared to the patients without wasting, patients with the wasting syndrome had a 3 fold increased risk of sudden cardiac death, which hardly attenuated after multivariable adjustment. There was a trend for increased risks of stroke and death due to infection, while myocardial infarction was not associated with wasting. The increased risk of combined cardiovascular events by 60 percent was mainly explained by the effect of wasting on sudden cardiac death, since no association was seen for combined cardiovascular events except sudden death. This finding of wasting being strongly associated with sudden cardiac death, but not with myocardial infarction in diabetic hemodialysis patients is important, as it suggests non-atherosclerotic cardiac disease to play a major role for the increased cardiovascular events in patients with wasting. This offers the potential of new treatment strategies, in which patients with the wasting

syndrome should be targeted in the prevention of sudden cardiac death. In this context, they may be considered for further treatments including ß-blocker or implantable cardioverter defibrillator therapy in addition to regular examinations.

Previous studies had identified wasting as a condition strongly affecting metabolic systems and altering conditions associated with outcomes (e.g. the impact of wasting on cholesterol metabolism and the associated mortality). Hints in the literature of a potential influence of wasting in parathyroid hormone metabolism lead to a clinical study presented in **chapter 7**. This study investigated the impact of wasting in the association of parathyroid hormone with cardiovascular events and mortality in dialysis patients. It revealed that the negative effects of a high PTH are observed only in relatively healthy patients without the wasting syndrome, but are nullified in patients suffering from the disease state. The study contributes to explain conflicting results in the literature, showing that the association of parathyroid hormone with adverse outcomes depends on the presence or absence of the wasting syndrome, and more generally speaking on the disease state of the population studied. This finding that wasting was an effect modifier to play a role in the associations of PTH with adverse outcomes is supported by further research presented in **chapter 8**. Here, we performed a study investigating the associations of parathyroid hormone with body mass index, the longitudinal changes, and their effect on mortality in dialysis patients. The results show that PTH importantly varies with BMI, being lowest in underweight and highest in obese patients, and that this association applies to both diabetic and non-diabetic patients. The study points out the impact of nutritional status on PTH levels and associated outcome, as it shows that a decreasing PTH was associated with a high mortality only in the presence, but not in the absence of weight loss. With weight loss being an important part of the wasting syndrome, low and decreasing PTH levels may be symptoms of wasting, and should be considered with caution in dialysis patients.

Vitamin D status is essentially important in the regulation of PTH metabolism, but moreover suggested to play a meaningful role for myocardial and overall health. In **chapter 9**, we investigated the impact of vitamin D status on specific cardiovascular outcomes and fatal infections in haemodialysis patients, who participated in the German Diabetes and Dialysis Study (4D Study). Patients with severe vitamin D deficiency (25[OH]D ≤ 10ng/ml) had a 3fold higher risk of sudden cardiac death compared to those with sufficient 25(OH)D levels >30ng/ml. Furthermore, combined cardiovascular events and all-cause mortality were strongly increased by 80 and 70 percent, respectively. There was a trend for higher risks of stroke and fatal infection, while myocardial infarction and deaths due to heart failure were not considerably affected. The study provides a rationale for future interventions on nutritional Vitamin D supplementation, strongly supported by our further analyses outlined in **chapter 10**. We analyzed the impact of Vitamin D status on adverse outcome including all-cause, cardiovascular, and non-cardiovascular mortality in incident dialysis patients from the NECOSAD study, who included both hemo- and peritoneal dialysis patients, and patients with and without diabetes mellitus. Particular attention was given to potential time-differentiating risks in the short-term (6 months follow-up) and longer term (3 years follow-up). We found an increased risk of mortality in patients with severe vitamin D deficiency. In analyses of specific fatal events we found a strong association of severe vitamin D deficiency with cardiovascular mortality, in particular for short term follow-up analyses. For non-cardiovascular mortality we observed no meaningful association with vitamin D status.
Given that most haemodialysis patients are vitamin D deficient, these findings might have significant clinical implications when considering that natural vitamin D supplementation is considered a relatively safe, easy and cheap therapy. Randomized controlled trials (RCTs) are therefore urgently needed to elucidate whether vitamin D supplementation in dialysis patients reduces cardiovascular risk or mortality.

In summary, the clinical research performed in this thesis detected specific effects of metabolic alterations in dialysis patients. Since mortality comprises various causes of death, the composition of which is meaningfully different as

compared to the general population, this implies that particular interventions may not generally decrease deaths but only the specific outcomes being mediated by the targeted risk factors. One consequence should be that in interventional trials in dialysis patients, the endpoints ought to be chosen very critically and carefully. Another consequence is that dialysis patients potentially require a combination of treatments rather than single interventions, in order to decrease the –pathophysiologically different- problems resulting in overall deaths.

Secondly, the thesis contributes to explain conflicting results in the literature, as thorough methodological concepts were applied to dissect true effects from confounding, and considering effect modification as appropriate. As mentioned within the various chapters of this thesis, many observational studies in dialysis patients did not yield unequivocal results. With our major methodological challenge to provide risk estimates as accurate as possible based on current knowledge, we used an etiologic approach as recommended by clinical epidemiologists, and thereby considered the recommendations to distinguish between confounding and intermediate variables. Furthermore, the analyses were not based on forward or backward selection procedures, by which important confounders may be missed, or spurious factors (e.g. by chance large hazard ratio in the data) included. In line with the scientific epidemiological suggestions, we primarily approached pathophysiological effect sizes, using (apart from a crude model) multivariate adjustments with carefully selected variables based on clinical suspicion and literature knowledge to ascertain independent effects.

Third, the present work outlined in this thesis provides a strong rationale for novel interventions in dialysis patients. Considering the excess mortality and paucity of data for effective treatments in dialysis patients, randomized controlled trials are urgently needed. With new information on specific endpoints, methodological advances to approach true effects, and furthermore emerging new risk factors being addressed in this thesis, challenges to design and conduct promising interventional studies are ready to meet. By proving the hypotheses being generated in this work, dialysis patients may face novel treatments to substantially improve cardiovascular and overall health.