Susceptibility to hyponatremia in the elderly: causes and consequences
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Chapter 7

General summary and discussion
GENERAL SUMMARY AND DISCUSSION

The aim of this thesis was to link the increased susceptibility to disturbances in water- and sodium balance in elderly patients and increased mortality risk.

In the first part of my thesis, I have focused on the possibility to predictors of adverse outcome (death or dependency) in elderly patients by examining the predictive value of commonly used estimates of the renal function and disturbances in water- and sodium balance. In addition, the predictive value of the Charlson Comorbidity Index in this population was examined.

In the second part, I have focused on the effects of different types of thiazide diuretics on adverse outcomes (death or cardiovascular events) in elderly hypertensive patients and on the pathogenesis of disturbances in water- and sodium balance associated with the use of thiazide diuretics in this group.

Identification of “high risk” elderly patients

Elderly patients have an increased risk of hospitalization and re-admission, institutionalization and progressive functional decline compared to younger patients. This not only affects quality of life, but also has a great impact on health resources and health cost expenditure. Therefore adequate assessment of high risk subjects in this rapidly growing, but also heterogeneous, group is useful for optimizing treatment and individual decision-making.

Hypo- and hypernatremia are frequently observed in hospitalized elderly patients, both at presentation and during admission. An increased risk of adverse outcome, including a higher risk of osteoporosis, fractures and all-cause mortality, is already present at low-normal plasma sodium concentrations ( < 137 mmol/L). In chapter 4, we assessed the prevalence of hypo- and hypernatremia in acutely admitted elderly patients and determined whether deviations in plasma sodium levels were associated with short-term mortality and functional decline. We showed that hyponatremia, defined as a plasma sodium < 135 mmol/L, is highly prevalent in acutely admitted elderly patients and that deviations in plasma sodium are associated with a 50% greater risk of mortality within 3 months after presentation and a longer length of hospital stay. However, we could not demonstrate that plasma sodium had an independent effect on mortality risk or functional status as the significance of our finding disappeared after correction for co-morbid conditions known to be associated with hypotremia including liver cirrhosis, heart failure and kidney disease. In other words, the cause rather than the presence of hyponatremia contributed to the increased mortality risk in this group. This finding is also supported by another study showing that hyponatremia was not independently associated with increased mortality risk after the underlying disease state was taken into account. Recently, a large cross-sectional study showed that in the general US population hyponatremia was associated with a more than a 3 fold risk of all-cause mortality. After correction for age, gender and for co-morbid conditions known...
to be associated with hyponatremia mortality risk remained more than two times higher compared to subjects without hyponatremia. These findings suggest an inherent negative impact associated with a chronic hyponatremic state beyond that of the underlying disease state. One explanation for the discrepancy with our results may relate to the fact that in acute illness plasma sodium levels are more prone to effects of water intake, whereas measurement of plasma sodium in steady state conditions better reflects the severity of the underlying disease state. This notion is further supported by the finding that the independent association with mortality was strongest in predefined co-morbidities known to be associated with hyponatremia such as liver disease, kidney disease, congestive heart failure and coronary artery disease.

Besides the contribution of acute disturbances in water and salt homeostasis, as reflected by altered plasma sodium levels, we also examined the contribution of the kidneys as principal regulator of water and salt homeostasis, in predicting outcome in acutely ill elderly patients. In Chapter 3 we compared the predictive value of two commonly used equations for kidney function, the Cockcroft-Gault equation and the Modification of Diet in Renal Disease (MDRD) as a prognostic marker for all-cause mortality in acutely admitted elderly patients. We demonstrated that the Cockcroft-Gault equation had superior prognostic value for mortality within the first year after discharge compared to the MDRD equation. These differences in predictive value may be explained by the denominator body weight that is included in the Cockcroft-Gault, but not the MDRD, formula. Body weight reflects nutritional reserves in patients and may be indicative of underlying disease. In order to be able to use an equation for kidney function in predicting the outcome in the elderly body weight appears to be an important component. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was shown to be a more accurate predictor of adverse outcome compared to the MDRD. Since body weight is not included in the CKD-EPI equation and this study was performed in middle-aged individuals it remains to be determined whether this equation is also superior in identifying high-risk elderly patients.

In Chapter 2, we assessed the validity of the Charlson Comorbidity Index. The Charlson Comorbidity Index is an estimate of the individual disease burden, based on history of co-morbid conditions including cardiovascular disease, diabetes mellitus, renal failure, acquired immunodeficiency syndrome (AIDS), and malignancy. Although its ability to predict mortality has been validated in many different populations, including patients with cancer, renal disease, stroke, liver disease and patients admitted to an intensive care unit, the Charlson Comorbidity Index has not been validated for acutely hospitalized elderly patients. We showed that the Charlson Comorbidity Index is an adequate method to predict both long-term and short-term mortality in acutely admitted patients aged above 65 years with a discriminatory ability consistent with other prognostic models that commonly drive clinical decisions, such as the Framingham risk score and the CHADS2 index. The main advantage of the Charlson Comorbidity Index over other recently developed predictive models in the elderly is that it can be easily calculated without the need for collection of
additional variables because it is exclusively based on medical history. Although we did not study the use of the Charlson Comorbidity Index in acutely admitted elderly patients, information concerning individual prognostication seems to become increasingly important in clinical decision making. Therefore, future studies may focus on the potential use of the Charlson Comorbidity Index as a prognostic tool in decision making processes in acutely ill elderly patients, in hospital as well as in primary care.

**Benefits and risks related to the use of thiazide diuretics in elderly patients.**

Cardiovascular disease (CVD) remains the major risk for mortality in elderly patients. The relationship between increased blood pressure and cardiovascular events has been described in a large number of observational studies. A logical intervention to prevent CVD in the elderly is the treatment of hypertension, particularly when considering that the overall prevalence of hypertension displays a steep increase with aging, rising to a prevalence >50% in persons above 50 years of age. There is ample evidence that treatment of hypertension – both combined systolic diastolic hypertension and isolated systolic hypertension – in the elderly is beneficial in reducing cardiovascular events and all-cause mortality. Treatment of hypertension causes an immediate reduction in the number of cardiovascular events, particularly stroke, thereby increasing disability free years and quality of life. Since the introduction of the first hypertension guidelines in 1967, thiazide-diuretics are the cornerstone of antihypertensive treatment. Many studies have shown that thiazide diuretics decrease cardiovascular morbidity and mortality in middle-aged and elderly hypertensive patients, including those aged 80 years and older. Based on their pharmacological properties thiazide diuretic can be divided in “thiazide-like” diuretics and “thiazide-type” diuretics. Thiazide-like diuretics, like chlorthalidone, have a longer half-life and are more effective in lowering 24-hour BP than thiazide-type diuretics. However, the greater BP lowering efficacy with thiazide-like diuretics has been associated with an increased number of adverse events, in particular hyponatremia and hypokalemia. Because of their different pharmacological properties, it is conceivable that thiazide-type and thiazide-like diuretics differ with regard to their capacity to lower the risk of CVD. In Chapter 6, we performed a meta-analysis to compare the effects of thiazide-type and thiazide-like diuretics, given alone or in combination, on cardiovascular events and all-cause mortality. As direct comparisons are lacking, we used an indirect approach to compare data from randomized controlled trials that examined thiazide-type or thiazide-like diuretics with either placebo or other BP lowering therapy. In general, thiazide-like and thiazide-type diuretics did not differ with regard to the incidence of coronary events, cerebrovascular events and all-cause mortality. However, when comparable antihypertensive effects were achieved, thiazide-like diuretics were more effective in reducing cardiovascular events and heart failure compared to thiazide-type diuretics. This is consistent with a recent meta-analysis which showed that chlorthalidone, a thiazide-like diuretic, is associated with less cardiovascular events compared to hydrochlorothiazide, a thiazide-type diuretics.
In a sensitivity analysis of studies stratified for age, the beneficial effect of thiazide-like diuretics compared to thiazide-type diuretics on cardiovascular events and heart failure remained present. In addition, we noted a similar incidence of adverse events, defined as discontinuation because of side effects or occurrence of serious adverse events, between the two thiazide diuretics contrasting the results of two retrospective studies showing a greater incidence of electrolyte abnormalities and lower persistence rates for chlorthalidone compared to hydrochlorothiazide\textsuperscript{24, 25}. Despite the well-known beneficial effects of thiazide-like and thiazide-type in reducing cardiovascular endpoints in patients with hypertension, the use of thiazide diuretics can be complicated by hyponatremia. Hyponatremia related to thiazide diuretics is the most common cause of hospital admission for electrolyte abnormalities in elderly patients\textsuperscript{27-31}. Vice versa, the use of thiazide diuretics is associated with an almost 5 times higher risk of hyponatremia in elderly populations\textsuperscript{32}. This is likely due to the extensive use of thiazide-like and thiazide-type diuretics in the population at large\textsuperscript{30,32}. Besides age, several factors have been associated with an increased risk of developing thiazide-induced hyponatremia (TIH); however its pathogenesis is still incompletely understood. We therefore examined the effects of a single re-challenge on water and sodium balance in chapter 5. A previous study already showed that, after a single re-challenge, patients previously admitted with TIH have lower plasma sodium levels after single re-exposure to a thiazide diuretic compared to matched controls and associated with weight gain as a result of reduced water excretion at low ADH levels\textsuperscript{33}. Based on these findings and recent in vitro experiments, we hypothesized that TIH is caused by direct effect of thiazide diuretics on the expression of the aquaporin (AQP)2 water channel that is responsible for the reabsorption of water in the kidney\textsuperscript{34-37}. After a single re-challenge of the thiazide-type diuretic hydrochlorothiazide, plasma sodium levels decreased in all patients, but more so in patients with previous TIH. In line with previous experiments the decrease in plasma sodium occurred at maximal suppression of ADH. In contrast to recent in vitro experiments, we could not find evidence for a direct effect of thiazide on AQP2 expression. Despite lower plasma osmolality patients with a history of TIH had a higher water intake and lower urea excretion compared to controls. Whether the increase in water intake related to TIH is caused by altered osmosensing or to differences in habitual water intake alone remains to be established. In this respect it is interesting that at least 60% of the normal variations in plasma sodium can be explained by genetic factors\textsuperscript{38}. In addition, a recent study showed that a nonsynonymous polymorphisms in the transient receptor potential channel-4 (TRPV4), involved in osmosensing, is associated with an increased risk of hyponatremia in an elderly population\textsuperscript{39}. These data suggest that osmosensing and thirst sensation may be more genetically determined and less ‘habitual’ than currently anticipated.

**Perspectives**

When treating older patients, it is desirable to have an expedient tool to predict outcome, especially for making decisions in case of acute illness or around major surgery.
The best tool is simple, accurate, reproducible and applicable for different populations. Because the prognostic value depends on the risk and circumstances that determine adverse outcome they should be validated in different populations. The Charlson Comorbidity Index, representing individual disease burden, has most of these features as it is easy to use, widely applicable and has been validated in various populations and in different clinical settings, including our own cohort of acutely admitted elderly patients. However, the Charlson Comorbidity Index relies on an accurate and complete past assessment of co-morbid conditions. In this regard, risk stratification by estimation of kidney function, for instance by using the Cockcroft-Gault formula, might be less prone to bias because it only relies on simple objective biometric values. However it remains to be established whether, next to the Charlson Comorbidity Index, the Cockcroft-Gault formula improves risk prediction. Further, we showed that plasma sodium concentration is a powerful predictor of mortality in acutely admitted elderly patients. However, the predictive value of plasma sodium disappeared after correction for variables commonly associated with changes in plasma sodium, suggesting that plasma sodium is not an independent predictor of adverse clinical outcome in these patients. As the predictive value of plasma sodium levels is strongly influenced by comorbidity it, may be suggested that plasma sodium is a reflection of a patients’ underlying disease burden rather than an independent predictor of adverse outcome. Therefore, the presence of hyponatremia may still serve as a useful risk marker for increased mortality risk in acutely ill elderly patients for example in acute situations where the status of a patients’ comorbid condition is still unknown or has not yet been established.

Finally, it remains intriguing why elderly patients have an increased risk to develop hyponatremia. Previous studies have attributed this to an age related decrease in both renal water excretion capacity and diminished extra-renal water loss. Our study in patients with a past history of TIH shows that liberal water intake likely contributes to the increased susceptibility for hyponatremia related to the use of thiazide diuretics. Future studies should address whether TIH can simply be related to an increase in habitual water intake or to altered osmosensing. Regardless of the exact cause, our findings suggest that it may be prudent to advice patients who receive thiazide diuretics on the possible hazards of an increased water intake, in contrast to the general tendency to advice elderly patients to drink ample amounts of water.
REFERENCES