Metabolic aspects of dietary sodium restriction as a therapeutic Intervention
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Summary and general discussion

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Introduction

The studies described in this thesis aimed to explore the interaction between sodium intake and metabolic factors. We were interested in this interaction, as both factors are involved in renal and cardiovascular risk profile in the general population and in renal patients. Usually however, they are considered separately. Prior evidence of interaction between sodium status and metabolic factors prompted us to explore this in a more systematic way, as the combined effects of sodium status and metabolic factors, including their interaction, might well be more relevant to clinical risk profile and patient outcome than the isolated effects of a single factor. Thus, this thesis pursues to offer a more integrated perspective on the combined effects of sodium intake and metabolic factors and their interaction, to contribute to further improvement of preventive measures in healthy subjects as well as renal patients.

In this final section of the thesis the main findings of our studies will be presented and put into the perspective of dietary sodium restriction as a tool for the management of chronic kidney disease. Special attention will be given to interaction of the metabolic status of a subject on the one hand and sodium intake on the other.

Dietary sodium: a blind spot in science and in clinical care

In chronic kidney disease (CKD) prevention of progressive renal function loss and its cardiovascular (CV) complications are main treatment aims. Reduction of elevated blood pressure and proteinuria are the cornerstones of intervention. Animal data, short-term studies in CKD patients, and hard endpoint studies in the general population and in CV patients support the role of excess sodium intake as a potent risk factor, mainly by its effects on blood pressure and proteinuria. As sodium intake is a modifiable risk factor one might anticipate reduction of sodium intake to be a main target in intervention in CKD. Unfortunately, despite the recommendation in current guidelines to reduce dietary sodium intake to 3-5 g NaCl/ day (1), this is not the case. Hard end point studies on the impact of sodium intake on renal and CV events in CKD patients are strikingly absent. Moreover, most of the large hard end point intervention studies in diabetic and non-diabetic CKD (i.e Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), Irbesartan Diabetic Nephropathy Trial (IDNT), Irbesartan in Patients with Diabetes and Microalbuminuria (IRMA), Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID), African American Study of Kidney Disease and Hypertension (AASK), modification of diet in renal disease (MDRD)) fail to report 24h sodium excretion (UNaV), even when 24h urine was available for assessment of proteinuria (2-9), with exception of the (Ramipril Efficacy In Nephropathy) REIN study. In the REIN I (10) and II (11)
cohort baseline UNaV was approximately 200 and 170 mmol/24h, respectively. Somewhat lower values were reported in Italian CKD patients from routine nephrology care (±150 mmol/24h) (12) and in the Dutch Masterplan cohort (155 mmol/24h) (13) with values close to those in general population cohorts where the mean UNaV is 170 mmol/day (14-16). This should be a matter of substantial concern, as it suggests that measures to restrict dietary sodium are absent or ineffective. In fact, in the Masterplan cohort, only 17 % of CKD patients reached the target for sodium excretion. Of all other stated treatment goals, sodium target was lived up to by the lowest amount of patients. The rise in sodium intake in children that has been documented over the last years suggests that excess sodium intake may become an even larger problem in the future (17;18).

Impact of sodium intake on cardiovascular and renal outcome: hard end points

Large cohort studies have demonstrated an association between excess sodium intake and long term CV and overall mortality in the general population and in patients with CV disease. The effect is partly attributed to an association between sodium intake and blood pressure, but blood-pressure-independent effects are present as well (14;19). It has been argued that low sodium intake is associated with an increased risk for CV disease, attributed to excess stimulation of the renin-angiotensin-aldosterone-system (RAAS) (20). However, this was based on data obtained by dietary recall which is notoriously unreliable (21). Cook et al. recently

**Figure 1: proposed relationships between high sodium intake and renal damage**
reported landmark data on the long term effects of a dietary sodium restriction program (22). Strikingly, dietary counseling for 18 months only, leading to reduction of around 30% to 100 mmol/day in subjects at risk for hypertension during the counseling period, but without further follow-up, led to a 25% reduction in CV events documented 13 years after the original study, supporting the feasibility of sodium intervention programs to modify long term outcome.

Impact of sodium intake on intermediate renal end-points

Renal outcome is invariably worse during high sodium intake in animal models of renal disease (23;24). In human, however there is no information on the effect of high sodium intake on hard renal end points. Nonetheless, there is substantial information available regarding the effect of sodium intake on intermediate renal end-points.

Blood pressure

The response of blood pressure to reduction in sodium intake, the so-called sodium-sensitivity of blood pressure, varies between individuals. Whereas in healthy subjects only a minority is sodium-sensitive (25), blood pressure generally responds to low sodium intake in CKD patients (26;27) in proteinuric patients (28) in overweight and diabetic subjects (29), and in old age (30). Sodium sensitivity is related to the extent of structural renal damage in experimental models (31) and in renal patients (32;33), which underlines the intricate association between renal disease, sodium handling and sodium sensitivity of blood pressure.

Proteinuria/albuminuria

Proteinuria consistently predicts the long term protective effects on renal and CV damage and thus is the main prognostic marker in CKD.

Restriction of dietary sodium consistently reduces urinary excretion of protein or albumin (27;28;34;35). In white salt sensitive hypertensive subjects, high sodium intake (250 mmol/day) was associated with an almost 35% increase in albumin excretion as compared to low sodium intake (20 mmol/day)(34). The antiproteinuric effect in black (mostly salt sensitive) hypertensives was 19% when reducing dietary sodium intake (35). In IgA nephropathy reduction of dietary sodium from 12 to ± 5 g/day reduced urinary protein by ~30 to 50% (32), and in patients with non-diabetic proteinuria dietary sodium restriction (UNaV from 200 to 90 mmol/24h) reduced proteinuria from 3.9 to 2.7 g/24h (-31%)(28). In these studies in hypertension and CKD the reduction in proteinuria during low sodium intake was generally
but not invariably associated with a lower blood pressure. On the other hand, as we addressed in chapter 1, in healthy subjects, reduction of dietary sodium from 200 to 50 mmol/24h significantly reduced urinary albumin excretion within the normal range, independent of blood pressure, indicating specific renoprotective effects of dietary sodium restriction (figure 3, panel d) (36;37). This is in line with the blood-pressure independent association between UNaV and albuminuria in the general population (15).

The study by Vogt et al allowed head-to-head comparison of the effect of sodium restriction with pharmacological intervention (fig 2c). Remarkably, the effect of sodium restriction to ~90 mmol/24h on proteinuria was similar to the effect of losartan 100 mg in the same patients. Of note, this is the same range as the effects of RAAS-blockade in large hard end point studies such as the RENAAL study (-35%), the IRMA study (-24 and -38% with 150 and 300 mg irbesartan, respectively) and the AVOID study (20% reduction in alb/creat ratio) (6-8) where no specific attempt to reduce sodium intake was made.

Glomerular hyperfiltration

Abundant evidence in animal studies (38) as well as sparsely available human data (39-41) support a pathogenic role of glomerular hyperfiltration in progressive renal damage. High sodium intake induces glomerular hyperfiltration in essential hypertension (27) and, as described in chapter 1, this phenotype is also apparent in normotensive, young, but overweight men. The pathogenic relevance of sodium-induced hyperfiltration is supported by the parallel rise in urinary protein in hypertensive subjects (27;32). In hypertensive subjects sodium-induced hyperfiltration was associated with a rise in blood pressure. In the overweight subjects blood pressure remained normal during high sodium intake, but an exaggerated rise in extracellular volume was observed (described in chapter 2). Patients with overt diabetes might be an exception to this rule, showing a paradoxical increase in filtration fraction during low sodium intake (42) possibly due to dysregulation of tubuloglomerular feedback (43).

The early renal phenotype: when does physiology pass into pathophysiology?

Weight excess, an emerging risk factor for renal damage (44-47), potentiates the effect of excess sodium intake in many clinical settings. First, weight excess and sodium excess both contribute to hypertension. Obesity is associated with sodium sensitivity of blood pressure which can be ameliorated by weight loss (48). Even more importantly, the long term impact of high sodium intake on cardiovascular prognosis and on kidney damage is particularly present in overweight or obese subjects (15;49;50), which can only partly be attributed to blood
pressure. Recent data support an adverse effect of high sodium intake on obesity-associated renal risk (41;51). Glomerular hyperfiltration is likely to be involved in the long term adverse effects of weight excess on the kidney (40).

In line with this observation, studies in this thesis demonstrated subtle, though distinct deviations in renal physiology in young overweight subjects, which were unmasked by a high sodium intake. In chapter 1 we described, in a group of 95 healthy, normotensive young men, the renal hemodynamic effects of switching dietary sodium intake from low (50 mmol Na⁺/24 hr) to a high sodium intake (200 mmol Na⁺/24 hr). These levels were chosen to reflect a level of sodium intake corresponding to a well-kept dietary sodium restriction, and a level somewhat above the average population level, so, liberal but not extreme. We stratified our analysis for the presence of overweight. It shows that, in the overweight group, with an average body mass index (BMI) of only 27 kg/m² a high sodium intake induced a hyperfiltration-like renal hemodynamic profile, with a high glomerular filtration rate (GFR) and filtration fraction, whereas this effect was absent in their lean counterparts (figure 2). In chapter 2 we demonstrated, in a subset of the subjects described in chapter 1, that the higher GFR and FF in response to high sodium in subjects with a higher BMI was associated with an exaggerated rise in extra cellular fluid volume (ECFV). What could be the relevance of this finding? It is important to realize here that BMI increases gradually with age and displays so-called tracking, and accordingly a higher BMI in young adults predicts overweight and obesity in later life (52). Subjects at risk for complications of weight excess can thus with a reasonable reliability be identified long before the end-organ damage is established, providing a window of opportunity for prevention in younger overweight subjects. So, weight excess will progress with ageing and the susceptible individuals will develop hypertension and diabetes at middle age. By that time, the kidney has been exposed to BMI-dependent glomerular hypertension for many years, which may (partly) explain the substantial proportion of subjects with renal damage at diagnosis of type 2 diabetes (53). Thus, in the sequence of events of the complications of weight excess, the renal abnormalities can occur before hypertension and diabetes, as also supported by the predictive effect of micro-albuminuria for subsequent hypertension and diabetes (54;55). Of note, a higher FF is associated with blunted sodium excretion by its effects on peri-tubular starling forces (56), which may explain the elevated ECFV in our overweight subjects, and which can well be involved in the development of (obesity-) hypertension over time.

The renal hemodynamic response to a high sodium intake in overweight subjects, i.e. hyperfiltration, reported in chapter 1 is remarkably similar to studies in sodium sensitive hypertensive subjects (27;34;57). This unfavorable renal hemodynamic profile in situations of a high sodium intake is associated with inappropriately high activity of the renal RAS (58). This phenomenon has been studied extensively in the past and, like in salt sensitive
hypertensives, has been observed in obesity and type II diabetes (59;60), conditions which often go along with salt sensitive hypertension. Even in salt-sensitive normotensive young men, increased activity of the renal RAAS has been observed (25). Inappropriate high activity of the renal RAAS during sodium loading is associated with an insufficient renal vasodilator response, probably hampering sufficient excretion of sodium and expansion of ECFV. This led us to the hypothesis that the body can compensate for this by increasing activity of natriuretic peptide axis, which acts reciprocally to RAAS by its effect on natriuresis. In chapter 7 we tested this hypothesis, by relating the level of N-terminal pro brain natriuretic peptide (NT-proBNP) to activity of the renal RAAS. The results confirmed our hypothesis: young healthy subjects with the highest levels of NT-proBNP (within the normal range), showed evidence of an increased activity of the intrarenal RAAS, namely, blunted response of the effective renal plasma flow to a high sodium intake corrected by inhibition of angiotensin converting enzyme (ACE) and a blunted renal response to exogenous angiotensin II (61). These findings suggest that already at a early state, long before kidney damage occurs, subtle deviations in normal physiology can be identified. It furthermore may indicate that in the early stages of inappropriate high renal RAAS activity, the body can compensate for this by increasing natriuretic activity in order to stay euvolemic.

Figure 2: Filtration Fraction (FF) for lean versus overweight subjects during low sodium (LS) and high sodium (HS) intakes. During LS FF is similar in lean (BMI < 25 kg/m2) and overweight (BMI > 25 kg/m2) subjects. During HS, a rise in FF occurs in overweight subjects only, resulting in a significantly higher FF than in lean subjects. * p < 0.05 versus LS and versus LS and HS in lean subjects. Adapted from the results in chapter 1.
Impact of sodium intake on the response to renoprotective intervention, in particular RAAS-blockade

It has long been known that dietary sodium restriction is needed to optimize the effect of several classes of antihypertensives (62;63), and in fact, the classical vasodilators were ineffective without sodium restriction. Blockade of the RAAS by either angiotensin converting enzyme inhibition (ACEi) inhibition, or angiotensin II receptor blockade (ARB) is evidence-based first-line therapy in diabetic and non-diabetic CKD (4;6;7;10). The efficacy of ACEi and ARB on blood pressure and urinary protein leakage is consistently potentiated by restriction of dietary sodium to 3-5 g/day, in essential hypertension (35;64) and in diabetic and non-diabetic CKD (28;37;65;66). It is important to note that low sodium intake increases the maximum dose-response for proteinuria and blood pressure (67), rather than shifting it to the right. Thus, sodium restriction increases the maximum therapeutic gain of RAAS-blockade. It is of clinical interest that during RAAS-blockade, due to blunting of RAAS-dependent homeostatic responses, blood pressure becomes responsive to dietary sodium restriction also in patients that did not respond to low sodium intake in the untreated condition (64). Better awareness of this effect of RAAS-blockade among clinicians and patients might be helpful to optimize patient motivation for dietary compliance. The other way around, high sodium intake is a determinant of resistance to RAAS-blockade (28;36;37;65;66). No data are available so far on the impact of sodium intake on improvement of hard renal end points during RAAS-blockade in CKD, but data on RAAS-blockade in isolated micro-albuminuria in the general population support the presence of such an effect (68).

Large interindividual differences in the responses of blood pressure and proteinuria to RAAS blockade have been reported, with a poor antiproteinuric response predicting poor long term outcome (69). Interestingly, restriction of dietary sodium (28), or addition of a diuretic (36) improves the individual therapy response particularly in patients with a poor response to monotherapy RAAS-blockade. These observations were made despite standardization of sodium intake, suggesting that for a given sodium intake some patients have inappropriate volume expansion. Of note, volume expansion is common in renal patients, even in the absence of edema. (70). The effect of dietary sodium restriction with or without RAAS-blockade is illustrated in figure 3 that summarizes different studies including the effects of sodium intake on albuminuria in healthy subjects as described in chapter 1 (28;36;37). During RAAS-blockade, low sodium diet induced an additional fall in proteinuria from ~30 % to ~50-60 % from baseline, with a further fall to ~80 % from baseline during low sodium diet combined with diuretic (figure 3, panel a, c). The effect of adding low sodium diet or a diuretic to RAAS-blockade was more or less equivalent (panel b and c). However, combination of the two is required to obtain the optimal effect (28). Thus, diuretic treatment cannot replace lack of dietary
measures to reduce dietary sodium!

Figure 3: Urinary protein (UP) or albumin (UAE) excretion (bars, right y-axes) and mean arterial pressure (MAP, lines, left y-axes) in four clinical studies in proteinuric patients (panel a-c) and healthy volunteers (panel d) during high sodium diet (HS, open bars) and low sodium diet (LS, grey bars). Dashed bars are as add-on therapy to RAAS-blockade. HCT=hydrochlorothiazide. # p<0.05 as compared to HS for both MAP and UP. * p<0.05 vs HS for UAE, no effect of sodium intake on MAP. Adapted from (37) panel a, (36) panel b, (28) panel c and (chapter 1) panel d.

Thus, excess sodium intake leads to resistance to RAAS-blockade. However, it is not the only determinant of therapy-responsiveness. The extent of pre-existent structural renal damage at onset of therapy limits the antiproteinuric effects of RAAS-blockade, as shown retrospectively in human (71), and prospectively in rats (72) – with less antiproteinuric effect in individuals with more interstitial (pre-) fibrotic lesions. Sodium restriction, however, can overcome this blunting of the antiproteinuric response by interstitial changes (73). Thus, presence of renal lesions is not a reason to withhold RAAS-blockade but rather to intensify RAAS-blockade-
based treatment (74). In experimental animals, adverse renal effects of a very low sodium intake during ACEi have been observed, namely renal interstitial fibrosis, probably due to clinically significant hypotension (75). Such extreme hypotension however not usually occurs in renal patients, even during maximal RAAS-blockade with low sodium diet, unless volume depletion by intercurrent pathology ensues. It is reasonable to assume that absence of symptomatic hypotension in patients indicates a sufficient renal perfusion pressure.

Mechanisms of resistance to RAAS blockade during high sodium intake

High sodium intake suppresses renin release, and hence activity of the RAAS. It would seem self-evident that blockade of a non-active system does not result in clear-cut therapeutic effects. However, this fails to explain why high sodium intake as a suppressor of the RAAS is devoid of therapeutic effects.

Effects of high sodium intake on tissue ACE activity might explain this seeming discrepancy. High sodium intake increases renal ACE activity in healthy and proteinuric rats (76), untreated or during ACEi, along with a rise in proteinuria. The lack of effect on plasma ACE activity (76), also in human (77), may be reason that this has not caught attention so far. However, it is well-established that tissue ACE activity is more relevant to the pathogenesis of end-organ damage than plasma ACE activity (78). Higher renal ACE activity predicts renal damage in rat models of renal disease (79;80), and blunts renal efficacy of ACEi and ARB (81). Experimental data support the functional impact of the sodium-induced rise in tissue ACE. In rats maintenance treatment ACEi only inhibited vascular conversion of angiotensin I when low sodium diet was given concomitantly. (82) (figure 4).

The sparsely available human data suggest that high sodium intake increases vascular ACE activity in human as well. High sodium intake increased the peripheral vascular conversion of exogenously infused angI to angII (83). This is in line with similar data by van der Kleij (77), that additionally showed that the sodium-induced rise in tissue ACE is modified by the ACE (I/D) genotype, being particularly present in subjects with one or two D-alleles (77). This suggests that the benefits of sodium restriction might be particularly present in the ACE (DD) genotype, as supported by retrospective data in proteinuric patients (84). Of note, renal ACE activity is also modified by ACE (I/D) genotype (85) and upregulated in human kidney disease (86).
Direct mechanisms of sodium induced organ damage

In addition to effects on hemodynamics, high sodium intake exerts direct tissue effects of possible relevance to progressive renal damage and its complications, as summarized in two excellent reviews (87;88). Briefly, high sodium intake can affect endothelial function by effects on transforming growth factor-β1 (TGF-β1) via nitric oxide (NO) (87), as well as by NO independent endothelial effects (89). Also high sodium intake increases renal TGF-β1 (90). Recent data showed that high sodium intake stimulates cardiotonic steroids, in particular marinobufagenin that facilitates sodium excretion, but also exerts profibrotic effects (91).

Moreover, high sodium intake can induce paradoxical activation of the aldosterone receptor and accordingly induce renal and cardiac damage via the profibrotic properties of aldosterone (92;93). The common denominator of these sodium-induced pathways appears to be their long term pro-fibrotic effects.

In chapter 8 of this thesis we presented a novel interesting view describing the link between hemopexin (Hx), an acute phase protein, sodium intake and angiotensin II related organ damage. We demonstrated that the level of Hx-activity is negatively correlated to the response of blood pressure to exogenous angiotensin II. Furthermore during a high sodium diet, Hx-activity was decreased, enhancing the blood pressure response to angiotensin II. These data are in line with in vitro data, indicating that active Hx inactivates the angiotensin II type I (AT1)
receptor (94). Angiotensin II is thought to play a key role in cardiovascular and kidney damage, mainly by affecting the AT1-receptor (95). Together, these data provide a possible mechanism in which a high sodium intake can, by means of a lower Hx-activity, lead to cardiovascular and kidney damage by increasing the bio-availability of the AT1-receptor.

Metabolic effects of sodium restriction

The beneficial effects of dietary sodium restriction range from its effect on systemic blood pressure and renal hemodynamics to a lower urinary excretion of protein. Even bone metabolism can be positively affected by lowering the intake of dietary sodium (96). In contrast, sodium intake has been demonstrated to have adverse metabolic effects too, which can potentially hamper its beneficial effects. Next to its unfavorable influence on the ratio between pro- and anti-atherogenic lipids, sodium restriction has also been linked to increased insulin resistance (97-99). An extensive meta-analysis by the Cochrane Collaboration revealed that in general, a low sodium intake is associated with an increase in total cholesterol and low density lipoprotein cholesterol (LDL-C)(100). However, interpretation of this analysis is hampered by considerable differences in the populations studied, varying from healthy subjects to patients with severe hypertension and type 2 diabetes mellitus. Furthermore, the duration of sodium restriction was variable, ranging from one to 12 weeks. Moreover, the achieved difference in sodium intake between the high and low sodium intake differed between over 250 mmol Na⁺/24 hr to less than 100 mmol Na⁺/24 hr. In order to get a better understanding of the physiologic effects of sodium restriction on plasma lipid profile we studied the effects of dietary sodium restriction (50 mmol Na⁺/24 hr) in a homogenous group of young, healthy, non-obese and normotensive men. The results of this study were presented in chapter 3 of this thesis. It demonstrates that in these subjects a low sodium intake goes along with a decrease in high density lipoprotein cholesterol (HDL-C) and its main apolipoprotein constituent Apo A-1. There was no effect on total cholesterol, LDL-C and triglycerides.

In terms of glucose and lipid metabolism, among others determining the artherogenic profile of a subject, recently the fat cell itself has been recognized as an important regulatory organ, secreting active adipokines as leptin and adiponectin. Adiponectin is believed to have direct effects on glucose and lipid metabolism and has anti-inflammatory and cardioprotective properties. Hypoadiponectemia is linked to development of diabetes (101;102), essential hypertension (103) and myocardial infarction (104). Chapter 4 of this thesis sheds new light on how the level of adiponectin is regulated. We observed that a high sodium intake, i.e. physiologic suppression of the RAAS, increased the level of circulating adiponectin. Infusion
of exogenous angiotensin II suppressed the level of adiponectin, supporting a link between RAAS activity and metabolic status. Animal as well as human data increasingly points to adiponectin as a key player in the metabolism of HDL-C and Apo A-1 (105;106). This suggests that the decrease in HDL-C and Apo A-1 as induced by low sodium as described in chapter 3 might be attributed to a decrease in adiponectin. Therefore in this chapter we correlated the change in HDL-C and Apo A-1 to the change in adiponectin. Because most of the actions of adiponectin are performed by the high molecular weight fraction of the molecule (107), in this study we choose to measure HMW-adiponectin instead of total adiponectin. Apparently, pathways other than that linked to adiponectin are involved in the sodium induced decrease in HDL-C and Apo A-1, as these changes were unrelated to the change in HMW-adiponectin.

As described earlier, restriction of dietary sodium, alone or in combination with RAAS inhibition, is a potent measure to reduce urinary protein excretion in renal patients. Antiproteinuric therapy is optimal when RAAS blockade is combined with maximal volume depletion which can be reached by a combining sodium restriction and a diuretic in addition to RAAS-blockade (28). As part of the nephrotic syndrome, severe proteinuria often goes along with disturbance in the plasma lipid profile including an elevated total cholesterol, LDL-C and triglycerides and inconsistent effects on HDL-C with levels lower, unchanged or even higher compared to controls (108-110). In chapter 5 of this thesis we describe the effects of maximal antiproteinuric therapy on the lipid profile of 32 patients with proteinuria of non diabetic origin. Therapy consisted of a combination of ACE inhibition, hydrochlorothiazide and a low sodium diet. We demonstrated that in addition to a decrease in total and LDL-C, HDL-C was decrease by 11% upon therapy. A lower HDL-C is prognostically unfavorable in many conditions (111), but whether this also applies to the reduction in HDL-C observed here, is not established. The extent of HDL-C decrease was correlated to the extent of proteinuria reduction, suggesting that it might be due to the reduction of proteinuria as such, and not the specific intervention by which it was obtained. However, the effect of antiproteinuric therapy on HDL-C in this study correlated to a decrease in adiponectin. Our findings in chapter 4, demonstrating the regulation of circulating adiponectin by RAAS activity, suggest that the decrease in HDL-C during reduction of proteinuria may in part be ascribed to changes in adiponectin as induced by intervention in RAAS activity. Remarkably, upon antiproteinuric therapy there was also a decrease in cholesteryl ester transfer protein (CETP) mass. CETP which has the ability to transfer cholesteryl ester from HDL-C towards apo B containing lipoproteins, plays a key role in lipoprotein metabolism (112-114). The decrease in CETP was strongly correlated to the decrease in LDL-C, suggesting that effects in the reverse cholesterol transport are involved in the decrease of atherogenic lipoproteins upon anti-proteinuric intervention.

The findings we presented in chapter 3-5 of this thesis suggest an interaction between
metabolic status and activity of the RAAS. In chapter 6 of this thesis we investigated the possible link between CETP-mass and the responsiveness of the RAAS to dietary sodium restriction. The ratio for this originated from the observation that when CETP is inhibited with torcetrapib, a marked improvement of the lipid profile is observed. Torcetrapib as combined with atorvastatin indeed resulted in a 70% increase in HDL-C compared to atorvastatin alone, but unfortunately was also associated with increased cardiovascular mortality (115) in high risk patients. Furthermore, CETP inhibition was associated with increased blood pressure and higher aldosterone levels, suggesting an interaction between CETP and regulation of RAAS activity. We therefore hypothesized that the individual level of CETP might be predictive of the regulation of the RAAS by sodium restriction. However, we could not detect such an effect. In healthy subjects, individual levels of CETP were unrelated to the response of the circulating RAAS parameters (plasma renin activity and aldosterone) to sodium restriction. Therefore, the adverse effects of torcetrapib, are likely to be related to an unexpected off-target effect specific to torcetrapib, rather than to in CETP-inhibition per se.

Conclusive remarks and future directions

Ample evidence supports the beneficial effects of sodium restriction in CKD, as recognized by its recommendation in current guidelines. So far, however, in clinical practice the management of dietary sodium intake in the renal patient is largely ineffective. This is partly due to the practical difficulties of implementing sodium restriction because most of the dietary salt is not added, but present in pre-manufactured food products (116). This relic from the times that salt was needed as a preservative is no longer needed in our era of refrigerators. This issue should be taken up by health authorities and the food industry, as strongly promoted by the World Action on Salt and Health (WASH)-initiative (117), which deserves firm support from the nephrology community.

Importantly, over the last decennia the kidney is increasingly threatened by obesity, an emerging epidemic, now and in the future. Obesity is an important independent risk factor for kidney damage (44) and is highly prevalent in renal patients. Furthermore, once kidney damage has ensued, excess of weight is related to further deterioration of renal function and eventually progression to ESRD (51;118;119).

As illustrated throughout the different chapters in this thesis, there is a mutual interaction between sodium intake and metabolic factors in determining renal and cardiovascular damage. First, as demonstrated in the first part of the thesis, the effects of a high sodium intake on the glomerular filtration rate and the ECFV are increased by overweight. Second, as illustrated in
the second part of the thesis, sodium restriction in itself can have a considerable impact on different metabolic processes, which are not always right away beneficial. It would be important therefore, to establish whether such short term metabolic adverse effects might limit the favorable effects of lower sodium intake on long term morbidity and mortality. Accordingly, there is evidence for an intriguing interaction between sodium intake and RAAS activity on the one hand and overweight and lipid metabolism on the other hand in the overall renal and cardiovascular risk profile. This is of great importance as both sides of this alliance are potentially modifiable and can serve as a target for intervention. Therefore, closer monitoring of body weight and dietary intake of sodium in the general population as well as in patients is warranted to improve prevention of renal and cardiovascular disease. In line with the second part of the thesis, there is need for a thorough further investigation on how the complex metabolism of lipids and apolipoproteins is affected by sodium intake and RAAS activity.

At the practical level, it is a matter of concern that the prevalence of obesity in the general population as well as in renal patients is high and is still increasing (120). Furthermore, monitoring of dietary sodium by 24h urine collection seems to get into disregard, and has in fact been incriminated as burdensome and unreliable (121). In the pursuit of renal awareness, simple screening for CKD is recommended by the combination of eGFR and spot urine for albuminuria. However, spot urine cannot provide information on dietary sodium (or protein) intake, depriving patient and health professionals from dietary awareness and from proper feedback on efforts to implement dietary advices. It is important to realize that the trade-off between burden and benefits of collecting 24h urine depends on the severity of the renal condition, and thus is different for screening purposes in low risk populations and for individual management of patients with a grim prognosis. For patients with proteinuric CKD, all possible efforts should be made to reduce blood pressure and proteinuria, and the benefits of sodium restriction simply cannot be missed in the therapeutic arsenal. Sodium restriction to the recommended level of 50-85 mmol/24h lowers proteinuria by ~30% on top of RAAS-blockade, and even on top of RAAS-blockade combined with a diuretic. Based on the association between proteinuria reduction and long term outcome (6), it is reasonable to expect of ~25% in renal and cardiovascular endpoints from better dietary sodium management. In addition to a consistent reduction of proteinuria and albuminuria in response to dietary sodium restriction, a recent meta-analysis showed that weight loss, by any means, is also a potent measure to reduce proteinuria and albuminuria (122). Therefore, whereas hard endpoint data are still urgently needed on both points, nephrologists should not wait to put much more effort into reducing dietary sodium intake and reduce overweight.
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