CHAPTER 1
Introduction and aims
Global burden of chronic kidney disease

Chronic kidney disease (CKD) is increasingly recognized as an important public health problem.\textsuperscript{1} CKD is not only associated with the risk for progressive renal function loss and, hence, end stage renal disease (ESRD), but also with a substantially increased risk of cardiovascular disease, premature death and loss of quality of life.\textsuperscript{2} The mechanisms underlying this unfavorable risk profile are multiple, and include metabolic derangements induced by renal impairment and proteinuria, such as retention of uremic toxins, lipoprotein disturbances, metabolic acidosis, anemia, hyperuricaemia, hyperkalemia, and coagulation derangements, as well as the consequences of renal sodium retention, with expansion of the extracellular volume and hypertension.\textsuperscript{3}

The prevalence of CKD is increasing all over the world, thereby rendering CKD a serious threat for public health world-wide.\textsuperscript{1} In line with this, an increasing number of patients is reaching ESRD, and requires renal replacement therapy.\textsuperscript{4,5} This trend is observed in The Netherlands as well, where the number of patients on RRT has been steadily rising over the last decades and even has doubled in the last 15 years (Figure 1). This increase in prevalence cannot be attributed to primary renal parenchymal diseases, but results predominantly from an increase in renal disease secondary to comorbid conditions, i.e. cardiovascular disease, diabetes and their combination.\textsuperscript{4} This increase is attributed to the better survival in cardiovascular disease as well as the increase in overweight and obesity, and the ageing of the population.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Number of end stage renal disease (ESRD) patients on chronic renal replacement therapy (RRT) in The Netherlands.}
\end{figure}

Number of end stage renal disease (ESRD) patients being on chronic renal replacement therapy (RRT), as registered on the first of January of the years 1997 to 2013, in The Netherlands. Data derived from the Dutch RENINE registry (data was updated on 26\textsuperscript{th} of June 2013).
Introduction and aims

Lifestyle and chronic kidney disease

Incidence and progression of CKD are associated with hypertension, weight excess and diabetes mellitus, and a history of cardiovascular disease. Lifestyle factors play an important role in the development and progression of these conditions, as demonstrated by an abundant body of evidence. These factors include, but are not limited to, caloric intake, sodium intake, (lack of) physical activity, smoking, and alcohol intake. By inference, lifestyle factors can be anticipated to be important to the development and progression of CKD as well, but in this area, so far, the emphasis on lifestyle factors as relevant targets for intervention is less prominent. An exception to this, however, is the impact of protein and sodium intake on progression of CKD. Animal studies showed substantial benefit of restricted protein and sodium intake, that is supported by short-term studies in renal patients. Long-term human data on nutritional or other lifestyle interventions, however, are extremely sparse, due to issues of feasibility and funding. The MDRD trial, that investigated the effect of dietary protein restriction on progression of CKD clearly showed the difficulties in achieving a persistent change in dietary intake, but also the therapeutic benefit in those who succeeded to restrict their protein intake. It is noteworthy that this study is now roughly 20 years ago and ever since, long-term prospective interventions in CKD exclusively addressed pharmacological intervention. There is, accordingly, reason to assume that the therapeutic potential of lifestyle interventions is not sufficiently addressed and exploited in CKD.

Figure 2. Interaction between kidney disease and its risk factors and treatment.
Lifestyle factors can affect the development and progression of CKD in various ways, as graphically depicted in Figure 2. First, lifestyle factors such as overweight and excessive sodium intake can contribute to the development and severity of diabetes and hypertension, i.e. factors that can exert renal damage. Second, lifestyle factors can exert direct effects on the kidney, as has been demonstrated for weight excess and for high sodium intake, and finally, lifestyle factors can interact with the therapeutic effect of pharmacological intervention, as has been demonstrated for sodium intake, protein intake, and for weight excess. By these multiple actions, the overall effect of lifestyle factors on development and progression of CKD and its complications may be huge, and lifestyle intervention may have the potential to substantially improve cardiovascular and renal outcome in CKD.

Weight excess, obesity and chronic kidney disease
Weight excess is attributed to many factors, among which genetic predisposition, but mainly results from an unhealthy lifestyle – i.e. high caloric intake and lack of physical activity.\textsuperscript{20-22} Weight excess has been implicated in cardiovascular morbidity and mortality, with studies reporting up to 30 to 70\% increased risk of mortality among obese subjects.\textsuperscript{23} It has become increasingly clear that weight excess is associated with progressive renal damage as well. Subjects with morbid obesity have a 5-fold increased risk for ESRD as compared to lean subjects,\textsuperscript{24} but also less extreme weight excess carries distinct renal risk. A BMI over 25 kg/m\textsuperscript{2} was shown to be associated with a 3-fold elevated long-term risk of ESRD.\textsuperscript{25} The prevalence of obesity has been steadily rising over the past decades, not only in the Western world, but in emerging countries as well, and shows no signs of abating yet. In Europe, the prevalence of obesity in men ranges from 10\% in Italy and Latvia, up to 27\% in Greece. The obesity rate in women goes up to 38\% in Greece. A few European countries even exceed the US prevalence of overweight.\textsuperscript{26} In The Netherlands, 40\% and 25\% of the Dutch population are either overweight or obese, respectively.\textsuperscript{27} The obesity epidemic is thus considered responsible, at least in part, for the worldwide increase in prevalence of CKD, and consequently ESRD.\textsuperscript{28,29}

Mechanisms of renal damage in weight excess and obesity: a role for renal hemodynamics?
Weight excess can affect the kidney through several pathways. First, obesity can induce a distinct form of idiopathic focal segmental glomerulosclerosis, a glomerulopathy characterized by mesangial matrix expansion, glomerular sclerosis and hyalinosis – either in presence of absence of glomerulomegaly – and clinically manifested by overt proteinuria.\textsuperscript{30} This entity, however, only occurs in morbid obesity (BMI \textless 40 kg/m\textsuperscript{2}), and is very rare. Second, renal damage can result from comorbid conditions, such as hypertension or insulin resistance/diabetes, leading to hypertensive or diabetic nephropathy, respectively. These nephropathies are characterized by their own distinct histopathological aberrations, although,
both eventually result in nephrosclerosis.\textsuperscript{31,32} Third, renal disease can be accompanied by obesity-associated conditions such as cardiovascular disease, or by dyslipidemia and/or atherosclerosis of the renal arteries and the intrarenal vascular bed, leading to stenosis and subsequent renal parenchymal damage, or atherosclerosis in general.\textsuperscript{33} However, weight excess is associated with renal function decline even independent of the abovementioned conditions.\textsuperscript{7,34} Hence, additional factors are probably involved. These could, among others, include upregulation of adipokines and cytokines by low-grade inflammation and oxidative stress, and/or endothelial dysfunction, as present in weight excess.\textsuperscript{35,36} A role for altered renal hemodynamics should be considered as well.

The renal hemodynamic alterations associated with weigh excess include an increased glomerular filtration rate (GFR), relative to effective renal plasma flow (ERPF), resulting in an increased glomerular filtration pressure and filtration fraction (FF). This renal hemodynamic profile results from a dilated glomerular afferent arteriole, accompanied by a relatively elevated efferent arteriolar vascular tone\textsuperscript{37} (Figure 3). The role of renal hemodynamics in progressive renal damage was first put forward in the 1980's by the work of Brenner and co-workers, who extensively demonstrated that glomerular hyperfiltration, and in particular glomerular capillary hypertension, is an important driving force for progressive renal function loss in remnant kidney models. In this concept, nephron loss leads to an adaptive response in the remnant nephrons that is characterized by glomerular capillary hypertension that serves to preserve glomerular filtration in the short-term. However, this occurs at the expense of glomerular capillary damage in the long-term, resulting in glomerular protein leakage and consequent nephron loss, thus eliciting a vicious circle of progressive renal damage.\textsuperscript{38} Whether this is also the case for obesity-associated renal damage, however, is less well documented. As an unfavorable renal hemodynamic profile is accessible to intervention, by RAAS blockade, it would be of interest to delineate its role in the increased renal risk of weight excess.

Renal disease and type 2 diabetes mellitus
As noted earlier, weight excess is linked with renal disease in part through its association with diabetes mellitus. Type 2 diabetes mellitus is a complex disease with a multifactorial pathophysiology including peripheral insulin resistance, impaired insulin secretion, increased hepatic glucose production, and abnormal regulation of glucagon secretion. Microvascular damage resulting from longstanding hyperglycemia, oxidative stress and low-grade inflammation is thought to eventually result in renal disease.\textsuperscript{31} An unfavorable renal hemodynamic profile, commonly denoted as hyperfiltration, is an early sign of development of diabetic nephropathy which is usually associated with hypertension and microalbuminuria.\textsuperscript{31} Patients with microalbuminuria may progress to macroalbuminuria and eventually overt proteinuria and renal insufficiency.\textsuperscript{31}
Figure 3. Schematic overview of obesity-associated alterations in the renal hemodynamic profile.

Abbreviations: GFR = glomerular filtration rate, ERPF = effective renal plasma flow
Therapy of choice in patients with diabetes and nephropathy is blockade of the RAAS with either angiotensin converting enzyme-inhibition (ACEi) or angiotensin receptor blockade (ARB), which provide renal and cardiovascular protection. \(^\text{39,40}\) Although RAAS blockade is effective in attenuating progression of renal function decline, it can not prevent the development of ESRD in many diabetic patients. This is illustrated in Figure 4, which shows that despite statistically significant improvement of overall outcome, time to occurrence of ESRD or death was only postponed for 5 months by treatment with losartan (i.e. ARB). \(^\text{40}\) Therefore, further enhancement of the renoprotection is of crucial importance and mandatory to improve overall patient outcome, either by development of novel pharmacological strategies or optimizing current treatment. Current research has focused mainly on development of new pharmacological treatments, such as sodium-glucose linked transporter 2 inhibitors, vitamin D analogues/receptor agonists, and endothelin antagonists. However, in the last 20 years no class of drug other than RAAS blockade made it from the

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**Figure 4. Survival curve of the percentage patients with the combined endpoint of ESRD and death.**

![Figure 4: Survival curve](image)

*Figure was adapted from Brenner et al. (N Engl J Med. 2001 20; 345: 861-869). Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy.*
pipeline to evidence-based renoprotection - demonstrating that the development of new
treatment approaches is particularly cumbersome. This provides a strong rationale to put
extra efforts in treatment strategies to optimize current treatment, such as targeting lifestyle
factors.

Sodium restriction as lifestyle intervention in CKD
Dietary sodium restriction is, among the widespread lifestyle recommendations, the most
advocated for prevention and treatment of hypertension and cardiovascular disease. There
is reason to assume that in CKD the benefits of sodium restriction may be even larger than in
hypertension. First, CKD patients usually have some degree of sodium retention. Second,
RAAS blockade is therapy of choice for renal and cardiovascular protection in CKD, and prior
studies of our group have shown that RAAS blockade is less effective, or even ineffective
in patients with volume overload. The other way round, intervention in volume status
by sodium restriction, diuretic treatment or their combination, potentiates the response
to RAAS blockade, as demonstrated in non-diabetic nephropathy. Whether volume
intervention also improves the response to RAAS blockade in diabetes patients, however,
has not been investigated so far. Differences in pathophysiology between nephropathy of
diabetic and non-diabetic origin render straight forward extrapolation of studies in non-
diabetics unwarranted. Traditionally, nephrologists were reluctant to prescribe sodium
restriction in diabetes patients, because experimental data in type 1 diabetes mellitus
suggests presence of a so-called ‘salt paradox’. This is graphically depicted in Figure 4:
it entails an increased proximal tubular reabsorption of anions and cations secondary to
persistent hyperglycemia and proximal tubular hypertrophy, resulting in decreased distal
tubular delivery and consequently activation of the tubuloglomerular feedback response
(TGF). The TGF will in turn increase the GFR by afferent vasodilation to ensure stable
delivery of anions and cations to the distal tubuli. Thus, dietary sodium restriction, by
further promoting proximal sodium reabsorption, may induce glomerular hyperfiltration
and glomerular hypertension, and thereby aggravate renal damage in diabetes. Indeed,
as paradoxal increase in filtration fraction was found during sodium restriction in patients
with uncomplicated type 1 diabetes patients. However, the clinical importance of such a
paradox in human type 2 diabetes mellitus is not well-established as clinical data on sodium
intervention in this population very limited. Even more so, it is unknown whether the salt
paradox is present in patients with diabetic nephropathy, and during treatment with RAAS
blockade. Considering the favorable effects of sodium restriction during RAAS blockade
in non-diabetes patients, it would be highly relevant to study the effects of sodium restriction
in patients with diabetic nephropathy on RAAS blockade.
Pathophysiological effects of sodium restriction in chronic kidney disease.
Dietary sodium restriction increases the effects of RAAS blockade on blood pressure. Moreover, in CKD patients, it increases the antiproteinuric efficacy. The effect on blood pressure may well contribute to the enhanced antiproteinuric efficacy, but on close scrutiny, the increased antiproteinuric effect cannot fully be accounted for by the effect on blood pressure. Thus, sodium restriction during RAAS-blokkade appears to have blood pressure dependent as well as blood pressure independent effects. The mechanisms underlying the latter are not well elucidated. Data from our own group suggest an anti-inflammatory, antifibrotic effect, as supported by the reduced urinary excretion of the fibrotic connective tissue growth factor in response to sodium restriction added to ARB in CKD patients. Moreover, in experimental renal disease glomerular influx of macrophages was decreased in response to sodium restriction and ACEi. Both studies found this effect independent of blood pressure. Second, sodium restriction was found to optimize vascular function by reversing the age- and hypertension-associated endothelial dysfunction, independent of blood pressure. Third, sodium restriction attenuated the dyslipidemia secondary to overt glomerular proteinuria of CKD patients. Apparently, sodium restriction can elicit a wide range of blood pressure independent effects. As these may be relevant to cardiorenal protection, further exploration is warranted.

AIMS OF THE THESIS
The general aim of this thesis is to explore the relevance of selected lifestyle factors in the preventive treatment of CKD, including the relation between lifestyle factors and pharmacological treatment, with focus on the pathophysiological mechanisms. Body composition is an important factor influenced by lifestyle factors, reflecting the influence of nutritional habits and physical activity. In the first part of this thesis we investigate the association between body composition parameters (BMI, body fat distribution, and muscle mass) and outcome in renal patients. As we were particularly interested in the role of renal hemodynamics as a mediating mechanism, we investigate its association with BMI, body fat distribution as well as long-term outcome. In the second part of the thesis, we explore the potential of dietary sodium restriction as a modifiable lifestyle factor, as a tool to modify outcome in renal patients, with a focus on diabetic nephropathy, and finally, in the third part we investigate intermediate mechanisms by which sodium restriction could modify outcome in CKD.

OUTLINE OF THE THESIS
Part I: Body composition parameters as risk factors in renal disease
In chapter 2 we investigate the association between creatinine excretion rate, as a body composition parameter for muscle mass, and thereby physical fitness, and cardiovascular and
all-cause mortality in patients with type 2 diabetes mellitus and renal disease. Subsequently, we focus on body mass index and body fat distribution as body composition parameters for weight excess. We start, in Chapter 3, by reviewing the currently available literature on the impact of weight excess and central body fat distribution on renal hemodynamics and its possible role in progressive renal damage. In Chapter 4, we determine the impact of weight excess on renal hemodynamics in renal transplant recipients, and their (combined) impact on renal and overall outcome. As increasing evidence suggests that the distribution of body fat, rather than weight excess per se is important to identify subjects at risk, we investigate, in Chapter 5, the separate and combined effects of BMI and body fat distribution on renal hemodynamics in healthy subjects. In Chapter 6, we investigate whether direct renin-inhibition (DRI), a new class of RAAS inhibitors, can decrease glomerular pressure in subjects with weight excess and hypertension.

Part II: Effects of sodium intake in diabetic renal patients: clinical
In part II we address the effects of sodium status on the efficacy of RAAS blockade in several settings. First, in Chapter 7, we study the effects of dietary sodium restriction, diuretic, and their combination on the effects of RAAS blockade in patients with diabetic nephropathy. In Chapter 8, we comment on observational long-term data from the literature addressing the role of sodium intake in prognosis in diabetic renal patients.

Part III: Effects of sodium intake in renal patients: mechanisms
In this final part of the thesis we focus on pathophysiological mechanisms affected by sodium restriction in renal patients, with particular focus on blood pressure independent mechanisms. In Chapter 9, we start by demonstrating that the reduction in blood pressure cannot explain the reduction on proteinuria by sodium restriction in renal disease. We subsequently focus on a newly discovered pathway of sodium storage that does not involve changes in extracellular volume. Sodium balance is traditionally regarded as an osmotic process in which the kidneys control total body content of sodium and thereby extracellular volume. Recently, a VEGF-C mediated extrarenal mechanism of sodium and blood pressure regulation was discovered, involving subcutaneous non-osmotic sodium storage. As the effect of altered sodium intake on this pathway was only described in experimental animals, we carried this concept to humans by documenting the effect of sodium intake on VEGF-C in renal patients and healthy subjects (Chapter 10). We subsequently determine, in Chapter 11, the effect of sodium restriction on circulating levels of the anti-inflammatory and anti-fibrotic peptide n-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), as a possible contributor to the enhanced effects of RAAS blockade during sodium restriction. Finally, in Chapter 12, we describe the effects of addition of sodium restriction (and ARB) to ACEi on lipoprotein levels and levels of the pro-protein convertase subtilisin kexin type 9 (PCSK9) pathway in patients.
with renal disease. It is known that PCSK9 plays a key role in lipoprotein metabolism by promoting LDL-receptor degradation. As atherogenic lipoprotein abnormalities are present in proteinuric conditions due to diminished clearance of lipoproteins, we tested whether plasma PCSK9 is elevated in proteinuric states, and determined relationships of PCSK9 with lipoprotein responses to proteinuria reduction by addition of sodium restriction (and ARB) to ACEi.

**Figure 5. Salt paradox in diabetes.**
REFERENCES


PART I

Body composition parameters as risk factors in renal disease