Insulin resistance, renal dysfunction and cardiovascular disease, studies in a high and a low risk population
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CHAPTER I

Introduction and aims of this thesis
Introduction

Chronic kidney disease is a worldwide health problem, affecting millions of people.1-6 The magnitude of the problem is poorly described by the number of people that will initiate renal replacement therapy, as the incidence of 1-3 per 10,000 per year in the general population may seem small.7-15 However, chronic dialysis treatment and transplantation have an enormous impact on the life of individual patients and their families, and renal replacement therapy is very costly.7, 8 The annual worldwide costs are estimated at 70 to 75 billion US dollars to maintain the renal replacement therapy of the roughly 1.1 million world wide dialysis patients in 2001. A staggering 1,000 billion US dollars are estimated to be spent on dialysis treatment between 2001-2010.7 Moreover, the number of patients requiring renal replacement therapy is increasing, by up to 7% annually according to some reports.7-15

Importantly, the health problems associated with chronic kidney disease are not restricted to the relatively few people with end-stage renal disease (ESRD). Recent studies indicated that in the general population, chronic kidney disease considered as “mild renal insufficiency” is associated with an increased risk for cardiovascular disease and mortality. Thus, millions are affected by chronic kidney disease, making it a world wide health problem.1-6

The reason why the numbers of patients initiating renal replacement therapy is growing has puzzled many.7-17 The underlying cause of end-stage renal disease has shifted from classic causes, such as glomerulonephritis and interstitial nephritis, to atherosclerosis and diabetic nephropathy. Nowadays the latter two account for 40-50% of cases as primary diagnosis in many countries.12-17 Yet, diabetic nephropathy does not seem to be the whole explanation because over the past twenty years in the US, the number of diabetic patients initiating dialysis has increased roughly 10-fold more than the number of patients with diabetes.15 The increase in the number of diabetic patients with ESRD was observed in two studies despite (1) improved and more widespread use of renoprotective medication (ACE inhibitors), (2) more effective detection of even incipient diabetic nephropathy and (3) the findings were regardless of sex, age or race (Caucasian/African American).15 Another study indicated that the increase in diabetic ESRD was not due to (1) increased diabetes prevalence, (2) US population growth and (3) improved survival of patients with myocardial infarctions and strokes.14 An increase in background obesity and/or other lifestyle-related factors could be an alternative explanation for
the increase of diabetic ESRD.\textsuperscript{14,15} Fortunately, recent publications suggest that the epidemic of diabetic nephropathy is perhaps slowing, but none the less, in the vast majority of patients diabetes is the cause of ESRD.\textsuperscript{16,17}

The epidemic of obesity seems to contribute to development of type 2 diabetes and subsequent renal disease.\textsuperscript{13-17} In recent years, studies indicated that obesity per se is also a risk factor for ESRD in the general population.\textsuperscript{18,19} This was first shown in Japan by Iseki et al\textsuperscript{18} in 100,753 persons and subsequently by Hsu et al\textsuperscript{19} in 320,252 persons in California. In the Californian study there was a graded, strong relationship between a higher BMI starting at a BMI of 25.0 kg/m\textsuperscript{2}, and the risk for ESRD, which was independent of sex, age, race, hypertension and diabetes. Not only is obesity associated with ESRD, there is sufficient evidence that obesity plays a role in renal function decline.\textsuperscript{20-26} Praga et al\textsuperscript{20} showed that obesity in conjunction with a reduced renal mass due to unilateral nephrectomy was associated with accelerated renal function decline and increasing presence of proteinuria. Among 14 obese patients (BMI >30 kg/m\textsuperscript{2}) at the time of nephrectomy, 13 (92\%) developed proteinuria and renal insufficiency. In contrast, among the 59 patients with BMI <30 kg/m\textsuperscript{2}, only 7 (12\%) developed these complications (difference P <0.001).\textsuperscript{20} Furthermore, obesity is also related to accelerated renal function decline in renal transplant recipients and in patients with IgA nephritis.\textsuperscript{21,22} More importantly, studies show that reducing obesity ameliorates proteinuria and glomerular hyperfiltration, which are both putative mechanisms of renal function decline.\textsuperscript{23,24} Thus, obesity appears to accelerate renal function decline in those with a reduced renal mass, in patients with kidney disease and in the general population.\textsuperscript{18-24} Putative mechanisms how obesity can cause a decline in renal function was not addressed by the above studies. Our primary hypothesis investigated in this thesis was that fasting hyperinsulinaemia as compensatory response to insulin resistance is involved in accelerated renal function decline.

**Renal function decline**

Renal function decline is often not disease specific. Studies in the 1970's showed in various renal diseases that the rate of renal function decline in a given patient is more or less constant over time, even after the initial renal disease activity had passed.\textsuperscript{27-31} This suggests that renal function decline is driven by a single common mechanism. Brenner and colleagues formulated a unifying hypothesis for such a common mechanism.\textsuperscript{31,32} This hypothesis was coined “intact nephron-hypothesis” or “glomerular hyperfiltration theory”. The theory states that the adaptive response
of the remaining nephrons to maintain renal function is detrimental for the kidney on the long-term.\textsuperscript{32} The initial adaptation of the kidney after nephron loss was already recognized in the 1940’s,\textsuperscript{33} with a rapid increase in glomerular filtration rate (GFR) within 3 days after uninephrectomy, reaching a maximum after 2-3 week.\textsuperscript{31, 34} The increase in GFR can only result from increased filtration of the remaining nephrons because the number of nephrons is limited to what is endowed at birth (or after renal transplantation).\textsuperscript{35, 36} Animal studies with single nephron GFR (sNGFR) measurements disclosed that sNGFR increased as a consequence of an increase in plasma flow by afferent, and less so by efferent vasodilatation, resulting in what is called “glomerular hyperfiltration”.\textsuperscript{28, 37} Glomerular hyperfiltration is accompanied by increases in glomerular hydraulic pressure (or glomerular hypertension), initially without an increase in systemic blood pressure, but this often ensues late.\textsuperscript{28, 37}

This renal adaptation to nephron loss can initiate development of glomerulosclerosis and filtration of increasing amounts of macromolecules including proteins into the tubular fluid.\textsuperscript{28, 31, 38} Proteinuria is associated with induction of tubulointerstitial inflammation and fibrosis, which can result in tubular atrophy and involution of whole nephrons.\textsuperscript{31, 39-43} The adaptation of increased sNGFR to maintain sufficient GFR results in further damage of remaining nephrons, which again increases sNGFR and a vicious circle ensues, with ensuing glomerulosclerosis.\textsuperscript{28, 31}

**Hyperinsulinaemia as possible accelerator of renal function decline**

Insulin is a hormone secreted by β-cells of the pancreas. Insulin has various effects, but insulin is best known for its glucose lowering effects.\textsuperscript{44} The glucose lowering effects are induced through the activation of the insulin receptor (by insulin) which makes \textasciitilde80% cellular membranes of the body permeable to glucose.\textsuperscript{44, 45} Insulin-resistant states, such as obesity, are characterised by resistance against this effect. The gold-standard to assess insulin resistance is by measuring systemic glucose disposal during insulin infusion (hyperinsulinaemic euglycaemic ‘clamp’).\textsuperscript{46} Insulin-sensitive subjects require more infusion of glucose to maintain euglycaemia during such a ‘clamp’, compared to insulin-resistant subjects during infusion of a similar amount of insulin.\textsuperscript{47, 48} Obese subjects in general require higher circulating insulin concentrations to achieve the same effect on glucose metabolism as lean subjects.\textsuperscript{47} Insulin concentrations are thus elevated in insulin-resistant subjects to maintain euglycaemia and overcome insulin resistance.\textsuperscript{47, 48} A properly functioning pancreas is a premise for insulin con-
centrations to be elevated in insulin resistant states. Hyperglycaemia and eventually diabetes can ensue when this compensation of the pancreas fails.

Insulin has more functions and effects than stimulation of uptake of glucose. Insulin is one of the most potent anabolic hormones known, and insulin promotes synthesis and storage of lipids and proteins, while inhibiting their degradation and release into the circulation. Insulin also has vasodilatory effects, which was first suggested by Baron and colleagues. Importantly, the metabolic and vascular effects of insulin are not directly related to each other. Perry et al decreased insulin sensitivity with dexamethasone over 6 days in a double blind, placebo-controlled, cross-over randomized trial and noted 30% less insulin stimulated glucose uptake, but an unchanged insulin-mediated vasodilatation. Vice versa, pharmacological reduction of endothelial function impaired insulin-mediated vasodilatation, but did not reduce insulin stimulated glucose uptake in muscle or adipose tissue.

Besides systemic vascular effects, insulin also has renal and hemodynamic effects. High insulin concentrations are known to induce glomerular hyperfiltration. Hyperinsulinaemia resulted in time- and dose-dependent increases in renal plasma flow in healthy subjects. Likewise, effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) increased during insulin infusion. This increased glomular hyperfiltration could be caused by insulin induced vasodilatation in the kidney. Also the increase in GFR due to infusion of insulin was positively associated with glucose uptake during the hyperinsulinaemic euglycaemic clamp. In another study, Ter Maaten et al showed that insulin’s stimulatory effect on blood flow differs between skeletal muscle and renal vasculature and between insulin resistant and insulin sensitive subjects. Thus, not only is there a difference between insulin’s metabolic and vascular effects, but insulin’s effects also differ within the human vasculature. Increases in ERPF were also impaired in insulin resistant compared to insulin sensitive healthy persons during acute exogenous hyperinsulinaemia. Another well known effect of insulin is that it promotes renal tubular sodium and water absorption, which could increase blood pressure, thereby contributing to a possible increased renal function decline.

Insulin resistance also has non-hemodynamic effects which could cause renal function decline. For example, insulin resistance increases endothelial dysfunction and up-regulates numerous cytokines. Fasting hyperinsulinaemia compensating for insulin resistance is hypothesized to increase renal function decline in kidney disease patients such as renal transplant recipients and in the general population. Compensatory
hyperinsulinaemia could thus be one of the factors linking obesity and lifestyle factors to the increased incidence of ESRD through renal/hemodynamic or systemic/non-hemodynamic effects.\textsuperscript{68,69}

**Renal transplantation and insulin resistance**

Renal transplantation is the therapy of choice for most ESRD patients. Transplantation ends the need for dialysis and the need for a stringent protein, volume, and potassium restricted diet. These factors contribute amongst other to an improved quality of life after transplantation.\textsuperscript{70-72} A lower complication and mortality rate is another important reason why renal transplantation is preferable over dialysis.\textsuperscript{73-77} However renal transplant patients still suffer from a 3-5 times higher risk for cardiovascular mortality compared to the general population, as can be seen in figure 1.\textsuperscript{77-80} There inherently is a selection bias between dialysis patients and transplant recipients, because healthier ESRD patients are placed on the waiting list for transplantation. Never the less, long-term survival is better among those on the waiting list who eventually undergo transplantation than those that remain on the waiting list.\textsuperscript{75,76}

Another threat facing renal transplant recipients is failure of the renal allograft. Fortunately, one-year graft survival has steadily improved after

**Figure 1**

**Annual cardiovascular mortality in dialysis, renal transplant recipients (RTR), and the general population**

Cardiovascular mortality defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary oedema in the dialysis, RTR, and the general population. Cardiovascular mortality is underestimated in RTR due to incomplete ascertainment of cause of death in these patients. Figure adapted from Foley RN, Parfrey PS, Sarnak MI. Cardiovascular Disease in Chronic Renal Disease, Clinical Epidemiology of Cardiovascular Disease in Chronic Renal Disease. American Journal of Kidney Diseases, Volume 32, Number 5 Supplement 3 S112-S119
renal transplantation from approximately 40% in the 1970's, to over 95% in 2001.\textsuperscript{80-82} The impressive improvement early after transplantation can be appreciated in figure 2. However, the lines run nearly parallel after roughly 1 year, indicating that long-term graft survival has mostly improved due to short term success.\textsuperscript{81, 83, 84} Increased mortality (often due to cardiovascular disease) and chronic transplant dysfunction are two main reasons why long term renal allograft survival has not improved over the past decades.\textsuperscript{83, 84} Renal transplant recipients receive one kidney at transplantation and are thus endowed with a relative lower nephron mass compared to the general population. Therefore, renal transplant recipients would be expected to suffer more from hyperfiltration compared to the general population and could offer a more ‘extreme model’ to investigate whether hyperinsulinaemia and/or insulin resistance are associated with faster renal function decline.\textsuperscript{85} On the other hand, renal transplant recipients are subject to many other risk factors for renal function decline such as nephrotoxic immunosuppressive medication, increased inflammation, and proteinuria. Therefore the ‘model’ could be ‘too extreme’, leaving hyperinsulinaemia as a relative bystander in determining the rate of renal function decline.

**Figure 2**

**Graft survival of first cadaver kidney transplants according to different years of transplantation.**

![Graft survival graph]

*Figure with kind permission of Professor G. Opelz of the Collaborative Transplant Study. Figure is available online at: http://www.ctstransplant.org (Figure: K-14101-0208)*
Insulin resistance, cardiovascular disease and skeletal muscle

Insulin resistance is better known as a cardiovascular risk factor than as a renal risk factor. Renal transplant recipients constitute a high risk population for cardiovascular disease, which needs no further introduction after the previous paragraphs. For the general population, cardiovascular disease is one of the most prevalent life-threatening diseases and persons with cardiovascular disease are likely to die from their disease. Insulin resistance is also thought to underlie cardiovascular disease, in a large part through what is now known as the ‘metabolic syndrome’. This syndrome has been proposed by Reaven in 1988 who named it ‘syndrome X’ in his famous Banting lecture (a lecture named after the Nobel Prize Laureate Sir F.G. Banting who administered pancreas extracts to diabetic dogs and observed lowering of blood glucose in 1921). Reaven hypothesized that insulin resistance was an important reason underlying hypertension, dyslipidemia, hyperglycaemia, and diabetes. Components have been ‘added’ to the metabolic syndrome during the past decades including central body fat distribution, hyperuricemia, coagulation abnormalities, increased oxidative stress, chronic low-grade inflammation, and endothelial dysfunction. The amount of skeletal muscle could be a factor involved in the pathophysiology of the metabolic syndrome that has yet received little attention.

Skeletal muscle is an important body compartment, comprising approximately 40% of total body weight in non-obese men and 30% in non-obese women. Skeletal muscles are metabolically very active due their role in movement and physical activity. In humans muscles only consume 20% of resting energy expenditure, but high-intensity aerobic exercise can increase energy consumption more than a 50-fold in working muscles, causing a 15-fold increase in total energy expenditure. Furthermore, skeletal muscles are responsible for approximately 75% of glucose uptake. It was already recognized in 1887 by Chauveau and Kaufman that when a horse chews on hay the concentration of glucose in the blood draining its masseter muscle substantially decreased. Skeletal muscles are also the major site of peripheral insulin resistance, and muscle mass is positively correlated with insulin stimulated glucose uptake (i.e. insulin sensitivity), even in obese subjects. The quantity of skeletal muscle is thus an important determinant of insulin resistance. Therefore, low muscle mass, for what ever underlying reason, could possibly increase progression of cardiovascular disease through its relation to insulin resistance.
**Populations investigated in this thesis**

**High risk population for renal dysfunction and cardiovascular disease**
The first half of the thesis concerns the renal transplant population, a population at high risk for renal dysfunction and cardiovascular disease. **Chapters 3 and 4** concern a prospective cohort study for which all renal transplant patients visiting the outpatient clinic at University Medical Center in Groningen (UMCG) between August 2001 and July 2003 were asked to participate if they had a functioning graft for at least one year (figure 3). A total of 606 renal transplant patients signed written informed consent, from an eligible 847 (72% consent rate).

**Figure 3**
Outline of renal transplantation study

![Diagram](attachment:image)

**Low risk population for renal dysfunction and cardiovascular disease**
The second half of the thesis (Chapters 5-7) concerns the general population, a population at low risk for renal dysfunction and cardiovascular disease. The research was performed within the framework of the PREVEND study (Prevention of Renal and Vascular ENdstage Disease). The PREVEND is a prospective, community based cohort study started in 1997. All 85,421 inhabitants of the city of Groningen, the Netherlands, aged between 28-75 years were asked to answer a short questionnaire and to send a morning spot urine in the city of Groningen, the Netherlands (figure 4). The cohort that formed the PREVEND study (n=8,592) visited
an outpatient clinic twice and were invited to participate in a second screening between 2001 and 2003, and a third screening between 2003 and 2006.

The initial cohort of n=8,592 was constructed with an oversampling of those with high levels of albuminuria, since this was the main research topic of the PREVEND study. To investigate the ‘true’ general population, a random sample of n=3,432 persons was taken to correct for the oversampling of those with high levels of albuminuria.

**Aim of this thesis**

This thesis addresses the relation between the one hand hyperinsulinemia and on the other hand insulin resistance and renal function decline and progression of cardiovascular disease in population at
high (renal transplant population) and low risk (general population).

The first part of this thesis concerns the renal transplant population. In such patients it was unknown whether surrogate measures of insulin resistance are valid measures of insulin resistance, as measured by the gold standard with the euglycaemic hyperinsulinaemic clamp. This was investigated in chapter 2. The validated measures were used to investigate determinants of insulin resistance in a large number of renal transplant patients because it was unknown to which extent both traditional, non-transplant related factors (such as obesity) and transplant-related factors contribute to insulin resistance long-term after transplantation (chapter 3). In chapter 4 we studied the relation between muscle mass (assessed by 24h creatinine excretion), mortality and graft loss. We also questioned whether that relation was dependent on insulin resistance.

In the general population in chapter 5 we investigated the relation between fasting insulin and the age accelerated decline in renal function. The association between insulin resistance and cardiovascular disease is well known. However, few studies investigated this in women and there could be a marked gender difference because it has been described that diabetes increases cardiovascular disease risk more in women than men. Therefore, in chapter 6, we investigated the association between fasting insulin and cardiovascular disease with a putative gender difference. In the general population we also investigated the association between muscle mass (assessed with creatinine excretion), mortality and cardiovascular disease. We again questioned whether the association was dependent on insulin resistance (chapter 7). Finally, in chapter 8, the results of the thesis are discussed and summarized.

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