1 Introduction and aims of thesis

General introduction

Aging of the population along with the rising prevalence of obesity, type 2 diabetes, and hypertension have led to a worldwide increase in prevalence of chronic kidney disease (Figure 1) (CKD) (1). In the United States, the prevalence of patients with CKD was estimated at 14 percent in the period from 2005 until 2010 (1). CKD may ultimately result in end stage renal disease (ESRD), necessitating dialysis or renal transplantation (2). In line with the rise in prevalence of CKD, the costs of ESRD are also rising in the United States, already costing approximately $34 billion in the year 2011, which is 6.3 percent of total Medicare costs (1). In the Netherlands, the number of patients with CKD has been estimated to be 1 million, of which 16 000 patients with ESRD (3).

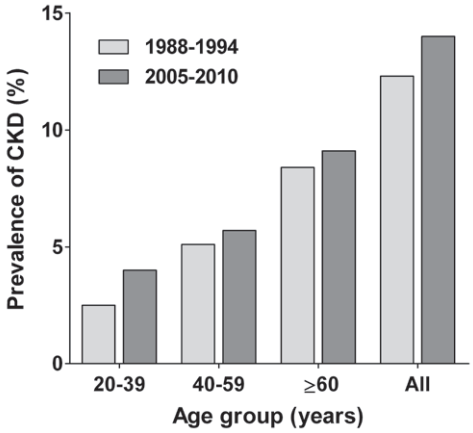

Figure 1. Prevalence of CKD, by age group based on the 2012 USRDS Annual data report. Adapted from JAMA 2007;298(17):2038–2047

CKD is defined by a state of kidney damage or decreased kidney function for three or more months (4). Kidney damage is identified by the presence of pathological abnormalities or a rise in markers of kidney damage. Decreased kidney function is defined by a glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2 (4). Once diagnosed with CKD, patients are classified into one of the five stages of CKD, which are determined by the level of GFR, albuminuria, or both (5). The highest stage of CKD (i.e. CKD stage 5) is defined by a GFR of less than 15 mL/min per 1.73m^2 and is also known as ESRD.

The stages of CKD have been defined based on the associated risk of future CKD-related morbidity and mortality (4). This is especially important because patients with CKD are at a considerable increased risk of morbidity and mortality, and this risk increases with decreasing kidney function (6). The risk of mortality decreases after renal transplantation, but remains high compared to the general population (7). It is impor-

tant to realize that the high mortality rates among patients with CKD more often result from CKD-related comorbidities, than from kidney failure itself. A longitudinal study that investigated 27,998 patients with CKD stages 2 to 4 at baseline has reported that death was far more common as adverse outcome than dialysis at all stages of CKD (8,9). CKD patients are at a 5-fold increased risk of cardiovascular disease compared to the general population (10,11). Furthermore, in young patients receiving dialysis therapy, the risk of cardiovascular mortality has been estimated to be 1,000-fold higher compared to age-matched patients (12). The increased risk of cardiovascular disease in patients with CKD has been found to be independent of the classical cardiovascular risk factors (13). Specific, CKD-related, metabolic abnormalities, vascular calcification, and oxidative stress have been suggested to potentially contribute to this vascular injury (13,14).

Crosstalk

An integrative pathophysiological approach may open important new perspectives, as organ crosstalk can exert major effects on disease onset and progression. This has already been shown for cardiorenal interaction (15,16). There are data to suggest that interaction between the kidney and the liver, as the two major metabolic organs of the body, may be relevant to CKD as well. The hepatorenal axis, however, has mainly received attention in the context of acute liver failure. Acute liver failure is thought to result in an imbalance between vasoconstrictor factors and vasodilator factors that adversely affect the renal circulation, which may subsequently lead to renal dysfunction (17). The combination of renal dysfunction and liver dysfunction has been defined as the hepatorenal syndrome. The probability of developing the hepatorenal syndrome is approximately 20 percent in the first year and increases to 40 percent in the fifth year after a diagnosis of severe liver dysfunction (17,18). There are two types of the hepatorenal syndrome. Type 1 is characterized by a rapid progression in renal function, whereas type 2 is characterized by a relatively slow progression in renal function (17). The average prognosis of patients with the hepatorenal syndrome varies from 8 to 10 weeks to up to 6 months, depending on the type of hepatorenal syndrome (17).

The condition of hepatorenal syndrome demonstrates that the kidney can be profoundly affected by liver disease, but the possible role of the liver in chronic kidney disease has hardly been subject of investigation. In this thesis we will investigate several aspects of liver function, in the nonfailing liver, with respect to relevance for kidney disease and its complications.

Bilirubin

A commonly used marker of liver function is bilirubin. Bilirubin is the end product of heme catabolism. Heme is split into carbon monoxide, ferrous iron, and biliverdin by the enzyme heme oxygenase-1 (HO-1) (Figure 2) (19,20). Biliverdin is subsequently reduced to unconjugated bilirubin by biliverdin reductase (19,20). In healthy subjects, unconjugated bilirubin by far makes up the largest proportion of circulating bilirubin (21). Bilirubin is then conjugated by the liver and subsequently excreted in the bile (Figure 2). For decades, bilirubin has been thought to be a toxic waste product. Recent studies have, however, indicated that bilirubin has cytoprotective and antioxidant properties (22–24). In animal studies, exogenous administration of bilirubin protected against kidney ischemia reperfusion injury and renal mesangial expansion, the latter being a typical feature of diabetic nephropathy (25). In addition, patients with both type 2 diabetes and diabetic nephropathy exhibited lower total bilirubin levels compared to patients without diabetic nephropathy (26). Therefore, we postulated that bilirubin is not merely a marker of liver function, but also a potential renoprotective agent if the bilirubin concentration is within the normal range. However, little is known about the association of bilirubin with renal function in humans. Therefore, in **chapter 2,** we prospectively investigated whether bilirubin was associated with progression of diabetic nephropathy in patients with type 2 diabetes. In **chapter 3** we prospectively investigated whether bilirubin was associated with development of late graft failure and mortality after renal transplantation.

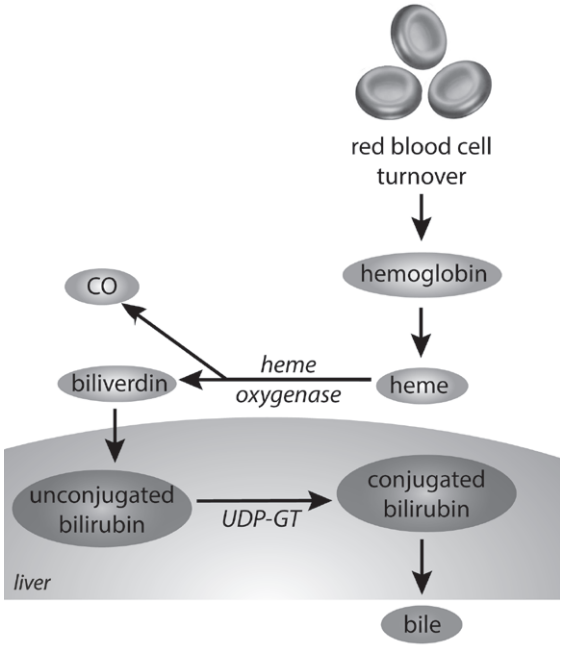

Figure 2. Schematic overview of bilirubin production.
CO, carbon monoxide; UDP-GT, uridine diphosphate glucuronyltransferase

The suggested protective effects of bilirubin raise questions about why its concentrations vary between healthy individuals and how bilirubin concentrations can be elevated. Since HO-1 is the enzyme that catalyzes the rate limiting step in heme degradation (27,28), induction of HO-1 could result in higher levels of end products of heme degradation, including bilirubin. It has been suggested that bilirubin levels are largely utilized in the presence of increased oxidative stress (29). Several studies have demonstrated that smoking, a major contributor to oxidative stress (29–31), is inversely associated with bilirubin concentrations. Furthermore, a healthy dietary pattern like the Mediterranean diet was found to be associated with decreased plasma markers of oxidative stress (32–34). However, little is known about the effects of diet and lifestyle on bilirubin concentrations. In **chapter 4** we aimed to investigate the associations of the Mediterranean diet, individual food groups, and lifestyle factors such as smoking with bilirubin concentrations in elderly men without major chronic diseases.

Urea production

Another kidney-related marker generated by the liver is urea. Urea is a waste product of protein metabolism, that is excreted by the kidneys. As such, urea can be used as a marker of protein intake (35). Lowering dietary protein intake is an important component of management of CKD patients (36–38). In these patients, moderate to high protein intake is supposed to aggravate proteinuria, a risk factor for progression of CKD (36,39–41). However, dietary protein restriction increases the risk of malnutrition (42–44). This may particularly be the case in patients with advanced CKD, because they often experience a loss of appetite with advancing kidney disease (42–44). Furthermore, patients with ESRD (CKD stage 5) experience increased catabolism of protein during treatment with dialysis. Studies in dialysis patients have consistently shown that low protein intake is associated with higher rates of morbidity and mortality (45,46). Accordingly, upon the start of dialysis, patients are recommended to consume relatively high amounts of protein rather than maintaining a low protein diet (38,47,48). However, dietary guidelines are lacking once patients have undergone transplantation. Therefore, in **chapter 5,** we investigated the association of urinary urea excretion with graft failure and mortality in RTR.

Obesity, the liver, and the kidney

The liver may not only have distant effects on kidney function, the kidney and the liver may also be parallel victims of adverse factors to which they are both exposed. Obesity may be one of such factors, because it has been shown to increase both the risk of kidney

dysfunction and of liver dysfunction (49,50). The increased risk of kidney dysfunction associated with obesity is partly attributed to comorbidities such as hypertension and lipid disorders. However, obesity may also directly lead to CKD. Pathologic histological findings such as podocyte hypertrophy, mesangial cell expansion, and focal segmental glomerular sclerosis are more commonly present among obese individuals compared to healthy individuals, independent of blood pressure and serum glucose (51,52). In the liver, the major obesity-related abnormality is hepatic fat accumulation. In the absence of alcohol abuse (which is a different cause of fat accumulation in the liver that is independent of obesity), the presence of hepatic fat accumulation is defined as nonalcoholic fatty liver disease (NAFLD) (53). NAFLD is common among patients with obesity. Compared to individuals without obesity, the prevalence of NAFLD is almost five times higher among obese individuals (54,55). At present, hepatic fat accumulation is one of the most common causes of liver injury (53), with NAFLD now becoming one of the most important indications for liver transplantation (53).

The definition of obesity is a controversial issue. A high BMI is often used to define obesity, but it is important to emphasize that a high BMI is not only determined by high fat mass, but also by other potentially beneficial constituents, like muscle mass. It may be because of this notion that several studies have reported absent or even inverse associations of BMI with renal outcomes. A prospective study of 499 patients with CKD has reported that BMI was not associated with an increased rate of progression of existing CKD (56). Another study of 3,334 participants aged 65 years and older showed a surprising inverse association of BMI with CKD in older diabetic patients (57). In that study, BMI was not associated with CKD in patients without diabetes (57). Furthermore, the lack of an association of BMI with outcomes has been repeatedly observed in patients with chronic diseases (58–61). Because the presence of NAFLD is an indicator of high fat mass, we hypothesized that NAFLD might be a better predictor of progression of renal dysfunction than BMI. To this end, we investigated whether ALT, as a marker of NAFLD, was associated with progression of renal function and mortality in patients with type 2 diabetes in **chapter 6** (Figure 3).

Like mentioned, muscle mass is another constituent of BMI. A high muscle mass is an established marker of better outcomes, both in RTR (62) and in other populations, including the general population (63,64). It has been hypothesized that protein energy malnutrition and physical activity underlie the association of muscle mass with outcome (62). We hypothesized that BMI is a better marker of a high fat mass, if muscle mass is also taken into account. Accordingly, we investigated whether a high muscle mass, as determined by 24h urinary creatinine excretion, confounded associations of BMI with outcomes in **chapter 7**.

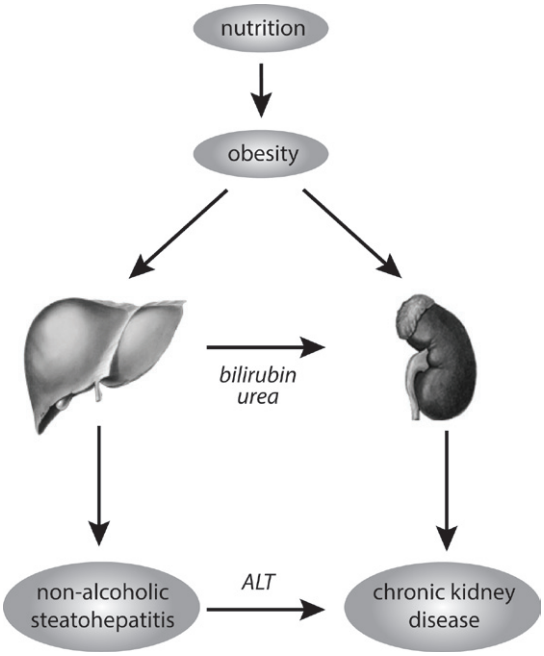

Figure 3. Simplified hypothetical associations of the hepatorenal axis. ALT, alanine aminotransferase

General overview of thesis

The aim of this thesis is to investigate the possible role of the nonfailing liver in chronic kidney disease and its complications. In **chapter 2,** we will prospectively investigate whether bilirubin is associated with decline in renal function in patients with diabetic nephropathy. In **chapter 3,** we will prospectively investigate the associations of bilirubin with graft failure and mortality in RTR. In **chapter 4**, we will focus on possible ways to naturally elevate bilirubin concentrations, by investigating associations of a healthy dietary pattern, individual food groups, and lifestyle components such as smoking with bilirubin concentrations in elderly men without major chronic diseases. In **chapter 5,** we will investigate another kidney-related product that is generated by the liver; urea. In this chapter, the association of urinary urea excretion with graft failure and mortality is studied in RTR. In **chapter 6**, we will investigate whether ALT, as a marker of hepatic fat accumulation, may be a predictor of progression of renal function and mortality in patients with type 2 diabetes. In **chapter 7**, we zoom in on the association of BMI with outcomes, by investigating whether BMI is a better marker of a high fat mass, and therefore a better predictor of mortality in RTR, if muscle mass is also taken into account.

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