

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/29973> holds various files of this Leiden University dissertation.

Author: Meuwese, Christiaan Lucas

Title: Nontraditional cardiovascular risk factors in end-stage renal disease : studies on inflammatory markers and thyroid hormones

Issue Date: 2014-12-03

Chapter 1

General Introduction

1



Chronic kidney disease and end-stage renal disease

In human physiology, the kidneys serve an important task as illustrated by their capacity to regulate volume status, plasma osmolality, blood purification, vitamin D metabolism, and hematopoiesis. Thus, when the kidneys fail, a cascade of pathological consequences is initiated. Kidney failure can occur in an acute setting, being then referred to as acute kidney injury, or in a more lingering, chronic form, which is known as chronic kidney disease.¹ Chronic kidney disease encompasses a broad spectrum of renal dysfunction syndromes in which 5 severity stages are recognized. On one side of the spectrum is stage 1, which corresponds to the presence of renal disease without any loss in renal function. On the other extreme end is stage 5 chronic kidney disease and end-stage renal disease (*ESRD*), in which the estimated glomerular filtration rate (eGFR) has fallen below 15 mL/min/1.73m².¹

Throughout the different stages of chronic kidney disease, increasingly intensive treatment is necessitated to prevent decompensation of the various physiological systems. In end-stage renal disease, and despite optimal pharmacological treatment, the kidneys are no longer able to maintain homeostasis and renal replacement therapy is necessary. This can be done by either renal transplantation or dialysis, the latter option crudely coming in two forms: 1) hemodialysis and 2) peritoneal dialysis. In hemodialysis, blood is flushed through an extracorporeal device and purified by a semipermeable membrane. In peritoneal dialysis, the endogenous peritoneal membrane assists in the removal of uremic toxins and fluids. Both forms of dialysis generally yield an improvement in prognosis and reduction in symptoms.

Cardiovascular risk in end-stage renal disease

Despite dialysis treatment, mortality rates are approximately eight times higher in patients with end-stage renal disease than in age- and sex- matched individuals without renal disease.² Approximately 50 and 10 percent of all patients with end-stage renal disease survive 5 and 10 years after initiation of dialysis, respectively.² Although mortality hazard for both cardiovascular and non-cardiovascular causes are an eight fold higher than in age and sex matched individuals,² the majority of deaths in ESRD is attributable to cardiovascular causes.³ Congruently, the incidence of coronary artery disease, left ventricular hypertrophy, and congestive heart failure is also substantially elevated in end-stage renal disease.^{4,5} This increased cardiovascular risk cannot be explained by an increased occurrence of so called traditional risk factors (e.g. smoking, hypertension and obesity).⁶

During the last decade, we have come to realize that when renal function declines, a wave of so called nontraditional cardiovascular risk factors overshadows the importance of traditional ones.⁷ So far, several non-traditional cardiovascular risk factors have been described including an increased sympathetic nerve activity, hemodynamic overload, endothelial dysfunction, oxidative stress, an increased grade of inflammation, and hormonal alterations, all of which having profound effects on the cardiovascular system.⁷ For many of these disturbances, however, uncertainty remains on whether they represent causal risk factors or merely epiphenomena of other processes. This thesis aimed at studying the states of sustained inflammation and low thyroid hormones as plausible candidates for cardiovascular risk factors in patients with end-stage renal disease.

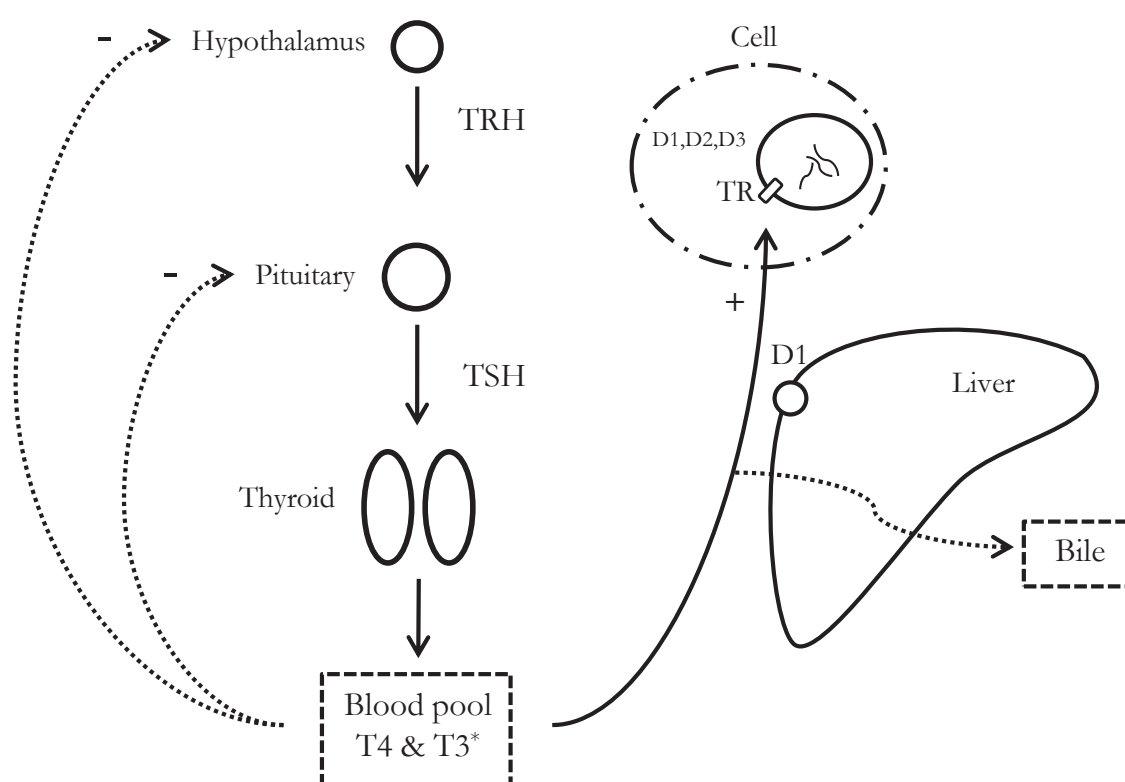


Figure 1. The hypothalamic-pituitary-thyroidal (HPT)-axis. TRH: Thyroid Releasing Hormone, TSH: Thyroid stimulating hormone, T4: thyroxine, T3, triiodothyronine, TR: thyroid hormone receptor. D1: Deiodinase type 1 (D2: type 2, D3: type 3), TR: thyroid hormone receptor. * The largest part of the blood pool is bound to thyroxine binding globuline (TBG), transthyretin and albumin.

Inflammation and non-thyroidal illness in end-stage renal disease

1. *An elevated inflammatory state in end-stage renal disease*

In end-stage renal disease, an increased inflammatory state, as expressed by elevations in serum inflammatory markers, is encountered in the majority of patients.⁸ As will be reviewed in **Chapter 2**, a variety of stimuli, such as infections, comorbidities, accumulation of toxins and fluid overload, contribute to its genesis. Partly dependent on the type of stimulus, the inflammatory cascade is initiated with the recruitment of polymorphonuclear cells and monocytes and activation of the acute phase response. Whereas some parts of this inflammatory cascade are different, depending on the type of stimulus, a rather non-specific and common feature is that of the acute phase response belonging to the innate immune system.⁹

The acute phase response is hallmarked by elevations in serum positive acute phase reactants (e.g. C-reactive protein (CRP)), and decreases in negative acute phase reactants (e.g. albumin and transferrin). The function of the acute phase response has not been fully elucidated but is believed to serve several purposes including; 1) the opsonization and entrapment of pathogens, 2) activation of complement pathways, 3) modulating immune response differentiation, and 4) assistance in tissue repair.¹⁰ Apart from these immune modulatory functions, the acute phase response seems responsible for other provisionary adaptations, meant to prevail in the face of illness. These adaptations include adjustments in the central thermostat causing an increase in body temperature (fever), stimulating protein degradation, and the initiation of a hibernating modus by a central and peripheral downregulation of the Hypothyroidal-Pituitaric-Thyroidal (HPT)-axis.¹¹ Although functional to certain pathogens, this response seems dysfunctional in the face of chronic kidney disease and end-stage renal disease.

2. *Nonthyroidal illness in end-stage renal disease*

The regulation of serum thyroid hormone levels is a complex process in which multiple endocrine organs are involved. As illustrated in **Figure 1**, under direct influence of pituitaric Thyroid Stimulating Hormone (TSH), which is again produced in response to hypothalamic Thyroid Releasing Hormone (TRH), the thyroid gland synthesizes free Thyroxine (fT4) and, to a lesser extent, the biologically more active free triiodothyronine (fT3). After being released into the blood stream, a great portion of fT4 and fT3 binds to binding proteins such as Thyroxine-Binding Globulin (TBG), transthyretin (TTR), and albumin. The complex of protein bound thyroid hormones is measured as total levels (TT3 and TT4 for total triiodothyronine and total thyroxine, correspondingly) in the blood. At a tissue level, different subtypes of deiodinase enzymes regulate local fT3 levels by activating and inactivating fT4 and fT3, respectively. Serum fT4 and fT3 levels provide a direct feedback to hypothalamic TRH production, and pituitaric TSH production thereby yielding a tight control of serum levels.

Alterations in thyroid hormone levels are found in a large proportion of all patients with ESRD.¹²⁻¹⁵ These alterations constitute part of a so called “Nonthyroidal illness syndrome”. This syndrome is defined as the presence of thyroid hormone alterations in the absence of primary disease in the HPT-axis.¹¹ Throughout its spectrum, a wide variety of thyroid hormone derangements occur. The origin of these alterations is thought to be offset by successive changes at all levels of the HPT-axis. Factors responsible for these changes specifically associated to end-stage renal disease pertain to an increased inflammatory state, protein-energy wasting, comorbidities, accumulation of iodine and medication usage (as will be extensively reviewed in **Chapter 5**). Although nonthyroidal illness can be viewed upon as an adaptive state serving to survive in times of scarcity and disease, several adverse cardiovascular consequences could make it inappropriate in the setting of end-stage renal disease.

Fluctuations of serum inflammatory markers and thyroid hormones over time

Because the majority of triggers for the genesis of an inflammatory response and nonthyroidal illness fluctuate over time, also the presence and severity of these both risk factors show a large temporal oscillation. When interpreting the impact of the inflammatory response and nonthyroidal illness on cardiovascular outcome, it seems essential to take into account this temporal variation for a number of reasons. Firstly, a dose response association between different variability patterns and outcome would strengthen the belief in causality. Secondly, it could provide insight in underlying triggers for both risk factors. Thirdly, it could assist in discovering pathways intermediating both risk factors and cardiovascular death which could in turn contribute to the identification of potential treatment targets. Finally, from a predictive point of view, knowledge of factors’ temporal variability may improve identification of patients at highest risk and those who may benefit from treatment.

Main study questions

This thesis aimed at increasing our understanding on two plausible risk factors for cardiovascular disease in patients with end-stage renal disease. The following two main questions were addressed:

1. Is there an association between an increased inflammatory state and (cardiovascular) mortality in patients in end-stage renal disease and which mechanisms could contribute to such link?
2. Is there an association between thyroid hormone alterations and (cardiovascular) morbidity and mortality in patients with end-stage renal disease and which mechanisms could contribute to such link?

Patient populations

The studies included in this thesis were performed in cohorts from the Netherlands and Sweden. Below follows a short description of the patient populations included:

Dutch cohorts:

- For the *Netherlands Cooperative Study on the Adequacy of Dialysis* (NECOSAD) study, incident dialysis patients from 38 dialysis centers in the Netherlands were recruited and collected between 1997 and 2002. Out of the total cohort, serum C-reactive protein levels were assessed at 3 and 6 months after start of HD therapy in 472 patients. After inclusion, patients were followed over time during which events of death and censoring due to other reasons were recorded.
- The *Leiden 85 Plus Study* is a population-based cohort of 85-year old individuals. Between 1997 and 1999, all residents of Leiden, the Netherlands, celebrating their 85th birthday (belonging to the 1912-1914 birth cohort) were asked to participate. Out of the 705 individuals who were found eligible, 14 died before the recruitment phase, 92 refused participation and 37 participants refused blood sampling, leaving 562 participants to be included in the current study. During follow-up, participants were visited annually until reaching the age of 90 years or death.

Swedish cohorts:

- The *Mapping of Inflammatory Markers in Chronic Kidney Disease I* (MIMICK-I) cohort comprises prevalent patients with end-stage renal disease undergoing maintenance hemodialysis therapy at the Karolinska University Hospital and its satellite dialysis units throughout the city of Stockholm. From October 2003 through September 2004, 254 patients were invited to participate. Six declined and one subject was not included because of an active HIV infection. 247 patients were followed for 12 weeks during which clinical characteristics were gathered and blood was withdrawn on a weekly basis. After 12 weeks, 23 patients had insufficient data and were excluded. Eventually, a total of 224 patients were included for the current analyses.
- The *Mapping of Inflammatory Markers in Chronic Kidney Disease II* (MIMICK-II) cohort was designed to study inflammatory marker variability in patients on peritoneal dialysis (PD) and follows the same design as MIMICK-I. In this case, included patients were individuals undergoing maintenance PD in the city of Stockholm. Recruitment lasted from March 2008 to April 2011. All patients on maintenance PD therapy in the region of Stockholm (n=164) were invited to participate. Out of these 164 individuals, 80 were excluded because of unwillingness to participate (n=55), imminent transplantation (n=6), death (n=2), a switch to hemodialysis (n=8), or because of medical or mental disorders that precluded their entry into the study (n=9). Eventually, the cohort comprised 84 patients.

Reference list

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am. J. Kidney Dis.* 39, S1-266 (2002).
2. de Jager D. J. et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA.* 302, 1782-1789 (2009).
3. Foley R. N. et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J. Am. Soc. Nephrol.* 16, 489-495 (2005).
4. Foley R. N., Parfrey P. S., Sarnak M. J. Epidemiology of cardiovascular disease in chronic renal disease. *J. Am. Soc. Nephrol.* 9, S16-S23 (1998).
5. Herzog C. A., Ma J. Z., Collins A. J. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N. Engl. J. Med.* 339, 799-805 (1998).
6. Stenvinkel P. et al. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? *Clin. J. Am. Soc. Nephrol.* 3, 505-521 (2008).
7. Bongartz L. G. et al. The severe cardiorenal syndrome: 'Guyton revisited'. *Eur. Heart J.* 26, 11-17 (2005).
8. Stenvinkel P. Inflammation in end-stage renal disease: the hidden enemy. *Nephrology. (Carlton.)*. 11, 36-41 (2006).
9. Koj A. Initiation of acute phase response and synthesis of cytokines. *Biochim. Biophys. Acta.* 1317, 84-94 (1996).
10. Young B., Gleeson M., Cripps A. W. C-reactive protein: a critical review. *Pathology.* 23, 118-124 (1991).
11. Warner M. H., Beckett G. J. Mechanisms behind the non-thyroidal illness syndrome: an update. *J. Endocrinol.* 205, 1-13 (2010).
12. Kaptein E. M. et al. The thyroid in end-stage renal disease. *Medicine (Baltimore).* 67, 187-197 (1988).
13. Lim V. S., Fang V. S., Katz A. I., Refetoff S. Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. *J. Clin. Invest.* 60, 522-534 (1977).
14. Song S. H. et al. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. *Nephrol. Dial. Transplant.* 24, 1534-1538 (2009).
15. Ozen K. P. et al. Nutritional State Alters the Association between Free Triiodothyronine Levels and Mortality in Hemodialysis Patients. *Am. J. Nephrol.* 33, 305-312 (2011).

