Hypothyroidism and chronic kidney disease: An undervalued two-way relationship

Joana Coutinho, Catarina Reis Santos, Ernesto Rocha
Nephrology department, ULS Castelo Branco

ABSTRACT

There is long-standing evidence that thyroid disease and kidney disease have a two-way relationship, as they can aggravate and lead to each other. The exact nature of this association and its clinical implications have been a matter of debate, as co-sharing of risk factors and appropriate prospective studies that allow for causal relationships to be inferred are lacking.

Hypothyroidism is currently regarded by the American Heart Association as a modifiable cardiovascular risk factor and a reversible cause of heart failure. Among the nephrology community, while hypothyroidism has been an increasingly prevalent issue, formal guidelines on how to proceed when such association occurs are lacking and its clinical implications are often underappreciated among practitioners. Whether renal disease caused the thyroid disturbance or vice-versa, there is evidence pointing to thyroid dysfunction being a risk factor for incident chronic kidney disease and its progression and it is linked to increased overall mortality in CKD patients. The authors provide a review of current scientific evidence on this complex relationship.

Keywords: Cardiovascular risk, Chronic Kidney Disease, Hypothyroidism, Mortality

INTRODUCTION

Thyroid hormones are critical regulators of cell biology processes such as growth, differentiation and energy production. The kidney, on the other hand, is responsible for the body’s internal homeostasis, regulating extracellular water and electrolytes. Though their target of action is different, one at the cellular level and the other at the extracellular level, these two organs have long been recognized as working in tandem during pathophysiological processes to maintain cellular, tissue and bodily homeostasis.

The nature of this thyroid-kidney relationship is not yet completely clarified. A significant number of studies into the association between these two diseases have reached conflicting results. One of the difficulties in establishing a causal relationship is the co-sharing of risk factors that may pose as confounders (old age, obesity, smoking, coronary artery disease, hypertension, hyperuricemia). Hypothyroidism is currently regarded by the American Heart Association (AHA) as a modifiable cardiovascular risk factor and an increasingly recognized risk factor for CKD progression. Hypothyroidism is linked to worse outcomes in CKD patients, which are possibly explained by additional mechanisms other than the traditional cardiovascular system. The authors provide a review of current scientific evidence on this topic.

METHODS

Literature search was performed using Pubmed and Cochrane Library databases and the search terms “hypothyroidism and chronic kidney disease” and with a combination of “cardiovascular disease”, “vascular calcification”, “thyroid hormonal replacement”, “dyslipidemia”, “anemia”, “cognitive dysfunction” with “thyroid disorders” and “kidney disease”. We identified further references from the original articles and studied only English language articles. Priority was given to articles reporting prospective studies and randomized controlled studies.

DISCUSSION

Mechanisms by which thyroid disturbances influence renal disease

Thyroid hormones exert effects on the kidney both at the structural and functional level, influencing its glomerular, tubular and endocrine functions. Such effects are very much dependent on age and human development stage. T3 and T4 are biological activators of kidney growth and development, critical to the fetal and early infancy period. In fact, an increased prevalence of renal and urinary tract anomalies has been observed in children with congenital hypothyroidism. After the early infancy period, thyroid hormones exert direct effects on physico-chemical functions of the kidney, affecting its tubular and endocrine functions, and affect the kidney indirectly through their influence on cardiac and endothelial function.

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Cardiac function is directly affected by thyroid hormones through genomic and non-genomic mechanisms. T3, the biologically active form, is responsible for the regulation of gene expression of structural proteins crucial for myocardial contractility/relaxation system, cardiac conduction system, and through non genomic pathways, T3 modulates myocardial oxygen consumption11. Overt hypothyroidis-m is clearly linked to left ventricular diastolic dysfunction and T3 levels have been shown to correlate well with heart failure functional class as classified by the New York Heart Association (NYHA) [16–
Cardiac dysfunction in hypothyroidism is indirectly aggravated by reduced peripheral oxygen consumption which reduces the release of vasoactive agents by the endothelium and promotes impaired vasoactivity and arterial stiffness19. The metabolic dis-
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Thyroid hormones can influence RAS system directly or by increasing the response of tissues to the action of the sympathetic system; however the intricate mechanistic pathways remain to be elucidat-
ed26-27. Thyroid hormones’ effects on RAS components are complex and dependent on age25-27. Thyroid hormones modulate renin gene expression and angiotensin converting enzyme (ACE) activity at both circulating and tissue levels29. The reduction of ACE activity in the kidney of rat models with overt hypothyroidism was reversible by hormonal replacement29 as was plasma renin activity reduction. How-
ever, only one study analyzed RAS activity in subclinical thyroid dis-
orders, finding no differences in plasma renin activity or plasma aldos-
terone between patients with subclinical hypothyroidism and normal individuals30.

Thyroid hormones’ influence on tubular functions of the kidney occurs mainly through modulation of ATPase pump gene transcription, reducing its activity and interfering with tubular reabsorption of sodium and calcium. Hyponatremia is a common complication of overt hypothyroidism and is mostly attributed to impaired water excretion by thyroid hormones influence on the NHE3 transporter and NaPi2 transporter. Increased distal delivery of sodium is the leading cause of hypothyroidism urinary concentrating deficit, as expression and activity of other transporters such as NKCC2 and AQP2 have proven to be unchanged in hypothyroidism31. Urinary calcium excretion parallels to sodium excretion in thyroid deficiency; however it is rarely clinically significant32.

Aging, thyroid hormones and vascular calcification: a very complex system

Over the last decade, efforts have been made to investigate thyroid hormone influence in medial vascular calcification, a nontraditional cardiovascular risk factor of CKD patients. In prevalent peritoneal dialysis patients, while T3 levels correlate inversely to coronary artery scores and arterial stiffness33, the intervening factors on the molecular level and their part in such a complex system is intriguing. Klotho and matrix GLA protein (MGP), known participants in the CKD-vascular-bone system, are so far the main culprits in thyroid-related vascular calcification34. At present, evidence points to the fact that CKD and hypothyroidism could synergistically promote vascular calcification.

Klotho is a hormone produced by the distal nephron that can be circulating/soluble or membrane-bound, with different clinical implications at each level. Klotho deficiency is known to occur early in CKD35. Membrane-bound Klotho functions as co-receptor for Fibroblast Growth Factor-23 (FGF23) and Klotho deficiency in CKD could cause resistance to FGF23 action on the kidney as a phosphaturic agent35,36. The hyperphosphatemia would then promote vascular smooth muscle cells’ osteogenic differentiation37. Matrix Gla Protein gene expression, a natural inhibitor of such osteogenic differentiation, seems regulated by thyroid hormones, and is decreased in vitro in hypothyroidism34.

Soluble Klotho is the only known mammalian anti-aging hormone and its deficiency is associated to organ atrophy, infertility, vascular calcification, atherosclerosis, osteomalacia, osteoporosis, peripheral insulin sensitivity, metabolic disturbances, and cerebral changes, all of which occur in “normal” aging38. Klotho synthesis occurs in the distal nephron under control of thyroid hormone, and Klotho deficiency should lead to accelerated aging; however, thyroid influence at the tissue level is dependent on the developmental stage. In fact, evidence from observational studies suggest there is an age-dependent susceptibility to mild hypothyroidism and in the extreme elderly (>85 years of age) this may actually confer a protective mechanism for protein catabolism and energy saving, reducing their cardiovascular risk39,40. In younger end stage renal disease patients, however, free T3 levels were positively associated with circulating levels of MGP and Klotho and correlated to vascular calcification scores, suggesting there might be a synergism34.

Other complications of CKD in which hypothyroidism may play a role

Thyroid hormones are involved in the regulation of erythroid dif-
ferentiation and modulate erythropoietin (EPO) gene expression. It has been suggested that in hypothyroid conditions, reduced EPO levels might account for anemia41. However, thyroid hormones also influence peripheral tissue oxygen consumption and seem to influence other participants in erythropoiesis, such as hypoxia inducible factor 1, which is known to induce various forms of anemia. Overt hypothyroidism was proposed as a cause of EPO resistance in dialysis patients, assuming euthyroid status is needed for a normal response to recom-
binant EPO42; however only one observational study has established the relationship between hypothyroidism and EPO dosages43. Further studies are warranted to evaluate whether thyroid hormone
replacement reduces EPO and iron needs in CKD patients. Meanwhile, hypothyroidism should be regarded as a contributing factor to anemia in CKD patients.

Mild cognitive dysfunction is a recently recognized complication of CKD. According to the U.S. Renal Data System, it more than doubles the mortality risk of CKD patients and increases days spent in hospital. Hypothyroidism could both contribute to the vascular calcification that is thought to underlie the white matter degeneration that is seen in CKD, or could act synergistically, further compromising specific cognitive domains of memory and executive function, as is reported in hypothyroid disorders. Though classically these two conditions cause a different spectrum of neurologic disorders, symptoms may overlap and hypothyroidism is a condition that must be excluded when considering the mild cognitive impairment in CKD patients.

Mechanisms by which kidney disease influences thyroid function

The kidney is responsible for degradation and excretion of thyroid hormones and iodine clearance, so understandably kidney dysfunction will interfere with thyroid hormone levels. As thyroid hormones are protein-bound, kidney diseases associated to proteinuria and/or increased protein catabolism will also indirectly influence thyroid hormone bioavailability. Theoretically speaking, one could divide thyroid hormone abnormalities into those induced by the uremic milieu of renal disease and those related to renal substitution therapy.

Thyroid stimulating hormone (TSH) is cleared by the kidneys and increased half-life of TSH is the norm in CKD; however even at lower glomerular filtration rates, TSH levels seem to remain normal in the majority of patients. The increased half-life of TSH seems to blunt TSH response to Thyroid releasing hormone (TRH). Reduction in glomerular filtration rate leads to reduced iodine clearance, contributing to enlargement and colloid degeneration of the thyroid gland. Thyroid gland colloid degeneration is generally insidious, with very subtle clinical changes and not clinically relevant for most patients. Nevertheless, dialysis has been associated to an increased risk of thyroid nodules and thyroid cancer.

On the other hand, the uremic milieu can blunt thyroid hormones’ bioavailability to peripheral tissues, leading to a state of thyroid resistance. T3 and T4 level abnormalities are the most common in CKD and low T3 levels is by far the most common abnormality observed in advanced CKD stages; however this may just reflect reduced availability to peripheral tissues due to low protein status or reduced peripheral conversion of T4 to its active form, T3. Factors that contribute to this low activity of iodothyronine deiodinase are malnutrition, inflammation and metabolic acidosis, all of which are fairly prevalent in CKD.

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![Figure 1](image_url)

Pathophysiological changes of thyroid hormones in chronic kidney disease. TSH – thyroid stimulating hormone. TRH – thyroid releasing hormone.
In the third National Health and Nutrition Examination Survey (NHANES III), hypothyroidism was reported to be increasingly prevalent as glomerular filtration rate declines, affecting 23% in patients CKD stage 5, with more than half of the patients having subclinical hypothyroidism51,52. In the few studies conducted in the dialysis population, the prevalence of subclinical hypothyroidism has been the greatest in peritoneal dialysis patients, presumably due to higher protein losses53. In the hemodialysis population, additional factors contributing to thyroid hormones disturbances are the use of heparin, which reduces T4 bioavailability to peripheral tissues, and greater losses of selenium, a trace metal that modulates peripheral conversion of T4 to T354. Despite the initial enthusiasm regarding selenium supplementation to correct for thyroid hormones disturbances, this has not been proven useful in clinical practice55,56.

A summary of the pathophysiological changes in thyroid hormones observed in CKD is provided schematically in Figure 1.

Clinical implications of thyroid disease for CKD patients

The American Heart Association guidelines in 2016 included overt hypothyroidism as a reversible cause of heart failure, making formal recommendations for treatment with hormonal replacement therapy, which can improve cardiac function3. In subclinical hypothyroidism, while some of the same biological disturbances have been observed, namely increased systemic vascular resistance, arterial stiffness, and altered endothelial function22, there is no consensus on whether hormonal replacement can be of benefit to stabilize heart function and reduce cardiovascular mortality57,58.

In CKD patients, hypothyroidism, even subclinical, is linked to accelerated GFR decline and increased mortality59-62. Hormonal replacement therapy can potentially reduce GFR decline63,64. A study by Shin et al into patients with CKD stage 2 to 4 with subclinical hypothyroidism demonstrated that the rate of decline in eGFR was significantly attenuated by levothyroxine therapy to TSH within normal range target (~4.31±0.51 vs. ~1.08±0.36 [mL/min]/[year·1.73 m²], p<0.001), even after adjustment for age, sex, diabetes, mean arterial pressure, and serum albumin, cholesterol, and triglyceride concentrations (p<0.001)65.

Lastly and most importantly, thyroid disease in CKD patients has been clearly linked to an increase in overall mortality, not just in end-stage renal failure, but also in earlier stages of CKD, as recently recognized in a study by Rhee et al18. In Rhee’s cohort of patients with CKD stage 3, there was an increased risk of death from 17% to 27% for hypothyroid patients, over a median follow-up period of 5.5 years.

FINAL REMARKS AND TAKE HOME MESSAGES

In the light of current evidence, thyroid functional disease must be considered as much a modifiable cardiovascular risk factor for CKD patients, as it is for heart failure patients, if not a risk factor for CKD progression itself. Apart from contributing to cardiovascular risk, there is growing evidence that hypothyroidism may impact other CKD complications, such as vascular calcification, anemia or mild cognitive impairment. Hypothyroidism is certainly associated to mortality across different CKD stages. As such, hypothyroid CKD patients, regardless of CKD stage, should be treated to target normal TSH levels, as it is probably the most reliable surrogate measure of thyroid function. Exception should probably be made for asymptomatic extreme elderly patients (>85 years of age) in whom hypothyroidism has been hypothesized to be a protective mechanism for protein catabolism and energy saving.

Subclinical hypothyroidism is the most conflicting issue, as studies suggest it may have prognostic value in a specific population, namely CKD patients. Shin et al. published very interesting data on how CKD patients with subclinical hypothyroidism should be treated with hormonal replacement, as an improvement of cardiovascular function could stabilize progression of CKD. Most studies into the treatment of subclinical hypothyroidism have excluded patients aged <18 years or >75 years, pregnant, with terminal malignancy or nephrotic range proteinuria. Taking these considerations into account, the authors suggest that CKD patients who should be considered for treatment are those with CKD stages 2 to 5, including CKD5D, aged 18 to 75 years, not pregnant, not nephrotic and without malignancy, who have unspecific symptoms of hypothyroidism (such as depression, fatigue or constipation), high titer of anti-TPO and dyslipidemia. Treatment should be initiated with the lowest dose of levothyroxine available, 0.25μg, as the toxic-to-therapeutic window of levothyroxine treatment is narrow. After treatment initiation, TSH levels should be monitored after 6 weeks and adjustments made to target TSH within normal reference range levels. After achieving target TSH, levels should be monitored every 3 months.

Clearly, the thyroid-kidney interaction cannot be disregarded and nephrologists need to be increasingly aware of hypothyroidism as a risk factor for cardiovascular disease. However, further studies are needed to understand the exact mechanistic pathways of this interaction and who is likely to benefit from hormonal replacement therapy. A well-designed prospective double-blind randomized trial (THYROID-HD) has just started recruitment to investigate whether levothyroxine therapy improves outcomes in hemodialysis patients with subclinical hypothyroidism66, which is a first step to providing advancements in this field.

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Correspondence to: Joana Coutinho, MD

Nephrology department, ULS Castelo Branco
Avenida Pedro Alvares 6000-084 Castelo Branco Portugal

E-mail: jcoutinho@ulscb.min-saude.pt