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The Interplay Between Thyroid Dysfunction and Kidney Disease

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Abstract

Hypothyroidism is a highly prevalent endocrine complication in chronic kidney disease (CKD) patients. A large body of evidence has shown that there is a bi-directional relationship between thyroid dysfunction and kidney disease, yet there are many remaining gaps in knowledge in regards to the clinical management of hypothyroidism CKD patients, including those receiving hemodialysis and peritoneal dialysis. Given that hypothyroidism has been associated with many deleterious outcomes including higher risk of 1) mortality, 2) cardiovascular disease, 3) impaired health related quality of life, and 4) altered body composition in both non-CKD and CKD patients, future research is needed to establish the appropriate screening, diagnosis, and treatment approaches in these populations.

Keywords

Thyroid function; thyrotropin; hypothyroidism; hyperthyroidism; chronic kidney disease; dialysis

Introduction

Thyroxine (T4) and triiodothyronine (T3), which account for 85–90% and 10–15% of circulating thyroid hormone, respectively, are produced and secreted by the thyroid gland under tight regulation of the hypothalamus-pituitary-thyroid axis. Although T4 is solely synthesized by the thyroid gland, a large proportion of T3 or reverse T3 (rT3) is produced as metabolically active or inactive forms of thyroid hormone, respectively, in peripheral organs including the kidney. More than 99% of T4 and T3 molecules are tightly bound to the carrier proteins, namely thyroid binding globulin (TBG), transthyretin, and albumin, and only a small fraction circulates as free hormone, which act on target tissues (Figure 1).

Because thyroid hormone has numerous effects on nearly all tissues, thyroid dysfunction may lead to various complications across multiple end-organs including the kidney.
Hypothyroidism is one of the most common endocrine disorders encountered in CKD patients, and it is associated with a higher risk of mortality, impaired health related quality of life (HRQOL), and altered body composition in this population. In the non-CKD population, hypothyroidism is more commonly observed among 1) patients of older age, 2) women vs. men, 3) Caucasians vs. African-Americans, as well as those 4) residing in areas of high iodine intake, 5) with prior exposure to external beam radiation, 6) with a family history of thyroid disease, and/or 7) with ingestion of amiodarone (i.e., an iodine-containing medication). With respect to the latter, given that CKD patients have impaired renal excretion of iodine, they may be at even greater risk for thyroid complications ensuing from excess iodine intake from dietary and/or medication sources as compared with the general population.

In this review, we will discuss the epidemiology, diagnostic considerations, prognostic implications, and management of thyroid dysfunction in CKD patients.

Prevalence of thyroid dysfunction in kidney disease

Hypothyroidism is a relatively common endocrine disorder in the general population, and it is defined by a serum thyrotropin (TSH) concentration above the upper limit of the reference range accompanied by a serum free T4 (FT4) concentration that is low (i.e., overt hypothyroidism) or within reference range (i.e., subclinical hypothyroidism). In the general population, subclinical disease accounts for a large proportion of hypothyroidism, with the prevalence ranging between 4% to 10%. Similar to the non-CKD population, subclinical disease is more common than overt hypothyroidism among CKD patients, while non-dialysis dependent and dialysis-dependent CKD patients demonstrate a substantially higher prevalence of thyroid dysfunction as compared with the general population (Table 1). Moreover, large population-based studies show that there is an increasingly higher prevalence of hypothyroidism with incrementally lower estimated glomerular filtration rates (eGFRs).

Conversely, in the general population, hyperthyroidism is less commonly observed than hypothyroidism, and there has been comparatively less study of this spectrum of thyroid disease in CKD patients. While some but not all studies have shown that hyperthyroidism is associated with higher risk of incident CKD and CKD progression, further research in this area is needed.

Causes of thyroid dysfunction in kidney disease

Although the mechanistic link between thyroid and kidney disease has not been fully elucidated, growing evidence suggests that there is a bi-directional link between these two entities.

Thyroid dysfunction leading to kidney disease

A large body of evidence has shown that thyroid hormone has effects on both kidney structure and function (Figure 2). Hence, if left untreated, hypothyroidism may adversely impact kidney structure in both development and adulthood, which may lead to downstream alterations in kidney function. In experimental models, hypothyroidism has been shown to lead to a decreased kidney-to body weight ratio, truncations in tubular mass, and various alterations in glomerular architecture (i.e., decreased glomerular basement

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membrane [GBM] volume and area, GBM thickening, mesangial matrix expansion, increased glomerular capillary permeability). Notably, an increased prevalence of renal and urinary abnormalities has been observed among children with congenital hypothyroidism.\textsuperscript{53}

Hypothyroidism may also lead to kidney dysfunction via direct and indirect pathways. First, hypothyroidism directly alters 1) renin–angiotensin–aldosterone system (RAAS) production and activity,\textsuperscript{54–57} leading to impaired autoregulation of renal perfusion.\textsuperscript{45} Hypothyroidism also affects the expression and/or activity of a number of renal tubular ion transporters (i.e., Na⁺-K⁺-2Cl⁻,\textsuperscript{58} Na⁺-Pi cotransporter,\textsuperscript{59} Na⁺-H⁺ exchanger,\textsuperscript{60} Na⁺-K⁺-ATPase,\textsuperscript{61,62}), including 2) alterations in renal basolateral chloride channel expression resulting in increased distal chloride delivery and tubulo-glomerular feedback.\textsuperscript{55} In addition, hypothyroidism may lead to 3) decreased cardiac output\textsuperscript{3,54} as a consequence of systolic and diastolic dysfunction and decreased red blood cell production and 4) intrarenal vasoconstriction resulting from reduced synthesis and activity of renal vasodilators (i.e., nitric oxide, adrenomedullin).\textsuperscript{3,55,63} These observations have been corroborated by human case series showing that patients with severe hypothyroidism experienced reductions in RPF and GFR as measured by creatinine-based estimating equations and gold-standard isotopic scans, which were reversed with exogenous thyroid hormone supplementation.\textsuperscript{3,55,66–68} Several large population-based studies have also shown an association between elevated TSH levels and higher risk of incident CKD and CKD progression,\textsuperscript{41,42,69} an in one rigorous study of non-dialysis dependent CKD (NDD-CKD) patients with subclinical hypothyroidism, those treated with exogenous thyroid hormone replacement had an amelioration of eGFR decline over time.\textsuperscript{70}

**Kidney disease leading to thyroid dysfunction**

Kidney disease and the uremic milieu may also lead to perturbations in thyroid status via multiple pathways. First, CKD patients may frequently have metabolic acidosis, which has been shown to result in thyroid status alterations (i.e., elevated TSH and low T4 and/or T3 levels) that may be improved with oral sodium citrate or sodium bicarbonate therapy.\textsuperscript{71,72} Second, given that the vast majority of circulating thyroid hormone is protein-bound, heavy protein losses in nephrotic syndrome or from the dialysate in peritoneal dialysis patients may lead to total body thyroid hormone depletion.\textsuperscript{73,74} Third, various dietary factors commonly observed in CKD such as iodine retention\textsuperscript{32} and selenium deficiency\textsuperscript{75} may also contribute to thyroid dysfunction as further described below. Finally, CKD patients with malnutrition, inflammation, and uremia may manifest thyroid patterns resembling hypothyroidism (i.e., low T3 and/or T4 accompanied by normal TSH levels) which may in fact be due to non-thyroidal illness (i.e., thyroid functional test alterations associated with underlying ill health in the absence of thyroid pathology.\textsuperscript{75,76}
Interpretation of thyroid tests in kidney disease

Thyrotropin (TSH)

In the general population, serum TSH is considered the first-line test for thyroid functional assessment, and since the late 1980’s the most widely used assays are highly sensitive third-generation immunometric tests (i.e., sandwich or non-competitive assays). Given that TSH has a negative inverse logarithmic association with T3 and T4 (i.e., small changes in T3 and T4 induce exponential changes in TSH), it is regarded as the most sensitive and specific single biochemical measure of thyroid function. Serum TSH is also a more robust thyroid function metric in non-thyroidal illness. While low T3 and T4 levels are typically observed with mild to moderate illness, TSH typically remains normal until the onset of severe, critical illness. Consequently, serum TSH is typically used for screening, diagnosis, and treatment monitoring and titration in primary hypothyroidism. In CKD patients, it bears mention that certain TSH alterations may be observed, including impaired clearance, protracted half-life, blunted pulsatility, altered glycosylation leading to impaired bioactivity, and decreased response to thyrotropin-releasing hormone (TRH).

Triiodothyronine (T3)

In CKD patients, one of the most frequently observed alterations in thyroid status include reduced circulating free T3 levels. Notably, the majority of T3 is produced by the peripheral deiodination of T4-to-T3 by type 1 and 2 5’-deiodinase enzymes. Various CKD-related factors may lead to reduced conversion of T4-to-T3 in peripheral organs including the kidneys. For example, chronic metabolic acidosis affects iodothyronine deiodination, reducing the peripheral conversion of T4-to-T3. The presence of inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1 also inhibit the expression of type 1 5’-deiodinase needed for T4-to-T3 conversion. In addition, the peripheral deiodination of T4-to-T3 is also reduced in the setting of non-thyroidal illness and specific medications (i.e., glucocorticoids).

Reverse T3

Reverse T3 is a metabolically inactive form of thyroid hormone that is produced from its precursor, T4, by the type 3 5’-deiodinase enzyme. The type 3 5’-deiodinase enzyme also degrades reverse T3 into inactive diiodothyronine. In hypothyroidism, reduced production of T4 typically results in low reverse T3 concentrations, although levels may be normal or high in mild hypothyroidism. In non-thyroidal illness, reverse T3 levels are typically elevated due to increased production and reduced decomposition. While reverse T3 is oftentimes normal in kidney dysfunction, further research is needed to determine the reliability of this metric in the interpretation of thyroid functional tests CKD.

Thyroxine (T4)

The vast majority of circulating T4 is bound to proteins, which include thyroid hormone-binding globulin (TBG) and, to a lesser extent, prealbumin and albumin. Hence, total T4 assays (i.e., which capture both free and protein-bound T4) may result in spuriously low
total T4 levels in conditions that lead to low binding protein levels, such as malnutrition, nephrotic syndrome, and heavy protein losses in the peritoneal effluent.  

Therefore, measuring free T4 levels (i.e., the minute fraction of biologically active, non-protein bound T4) has superseded total T4 testing in clinical practice.  

However, it bears mention routinely used free T4 assays (i.e., analog method) are dependent upon protein-hormone binding, and may not be accurate in 1) abnormal protein states (i.e., hypoalbuminemia, pregnancy) or 2) in the presence of certain medications (i.e., furosemide, heparin) or substances that impair protein-hormone binding (e.g., uremic toxins such as urea, creatinine, indoles, and phenols). In contrast, direct free T4 assays separate free and protein-bound T4 using equilibrium dialysis or ultrafiltration, and use liquid chromatography tandem mass spectrometry or radioimmunoassay to measure free T4. 

While direct free T4 levels have shown stronger inverse correlations with the log of TSH compared with indirect FT4 in populations with normal and altered protein-hormone binding (e.g., pregnancy), further studies are needed to determine their utility in the classification of thyroid function and prediction of outcomes in CKD.

**Dietary intake and thyroid dysfunction in CKD**

Dietary intake is one of the most potent factors influencing hypothalamus-pituitary-thyroid axis activity. For example, iodine is an essential component of thyroid hormone, which is naturally present in foods that are grown or raised in marine environments (i.e., fish and seaweed), and seaweed and seaweed-based food additives (i.e., alginates, agar-agar, carrageenan, and other seaweed based thickeners) are a source of iodine in a wide variety of foods. In addition, milk and eggs potentially contain iodine due to iodine supplemented animal feeds and their carry-over into animals. However, given that this element is largely renally cleared, iodine retention due to impaired kidney excretion has been hypothesized as a possible mechanism for hypo- and hyperthyroidism in CKD via the Wolff-Chaikoff effect and Jod-Basedow phenomenon, respectively. Several case reports and series have reported iodine-associated hypothyroidism among adult and pediatric dialysis patients consuming high iodine diets (e.g., seaweed) as well as exposure to non-dietary iodine sources (i.e., povidine-iodine cleansing agents, iodinated-contrast media).

Other dietary components also play an important roles in thyroidology, including selenium, l-carnitine, myo-inositol, melatonin, and resveratrol. With respect to the former, selenium is an important trace mineral in the human diet that modulates the peripheral conversion of T4-to-T3 by controlling iodothyronine deiodinase activity. However, in a double-blind randomized controlled trial of hemodialysis patients with selenium deficiency who received oral selenium supplementation vs. placebo, there were no significant differences in TSH, T4, or T3 resin uptake levels after three months. Future studies evaluating the impact of dietary intake upon thyroid status in CKD patients will enhance our understanding of the appropriate nutritional management of this population.
**Thyroid dysfunction and outcomes in kidney disease**

There is a growing body of evidence showing that hypothyroidism and other thyroid functional test derangements are associated with higher mortality risk, cardiovascular disease, and worse patient-centered outcomes in the advanced CKD population (Figure 3).

**Survival**

Multiple studies have shown that hypothyroidism ascertained by higher serum TSH levels is associated with higher all-cause mortality risk in both NDD-CKD and dialysis-dependent CKD patients. Among 227,422 US Veterans with stage 3 CKD, higher baseline and time-dependent TSH levels in the hypothyroid and high-normal range (>5.0 and 3.0–5.0 mIU/L, respectively) were each associated with higher mortality risk even after accounting for differences in socio-demographics and comorbidity status. In another national study of 15,335 NDD-CKD patients transitioning to ESRD, higher TSH levels in pre-ESRD period were associated with higher death risk after dialysis initiation. Across multiple studies of dialysis patients, TSH levels in the high-normal range in hemodialysis patients (i.e., >2.1 mIU/L and >3.0 mIU/L, respectively) and exceeding the reference range in peritoneal dialysis patients (i.e., >5.0 mIU/L) have been associated with worse survival.

**Cardiovascular outcomes**

In the general population, hypothyroidism is a known cardiovascular risk factor. Hence, given the exceedingly high cardiovascular mortality of ESRD patients (i.e., 40% of all deaths), there has been increasing interest in hypothyroidism as a novel, under-recognized cardiovascular risk factor in this population. Supporting this hypothesis includes a cross-sectional study of 51 peritoneal dialysis patients in whom those with subclinical hypothyroidism had a lower left ventricular ejection fraction vs. those who were euthyroid. More recently, in a secondary analysis of 99 hemodialysis patients from the multicenter Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID) trial, patients with TSH levels in the highest three quartiles had worse endothelial function measured by digital thermal monitoring vs. those in the lowest quartile. Several studies have also shown that thyroid dysfunction is associated with coronary artery calcification (CAC) in kidney disease patients, with mixed findings. In a study of 94 ESRD patients eligible for living donor transplantation, lower FT3 and FT4 levels as well as lower TSH levels were associated with higher CAC scores. In contrast, in a subsequent secondary analysis of 104 patients from AIONID trial, incrementally higher TSH levels were associated with higher CAC burden measured by Agatston score.

**Health-related quality of life (HRQOL) and physical function**

Hypothyroidism has also been associated with overall reduction in health-related quality of life (HRQOL), which in turn is an important predictor of survival in NDD-CKD and hemodialysis patients. In a prospective cohort of 450 hemodialysis patients who underwent Short Form 36 assessment, higher TSH levels were associated with impaired HRQOL, particularly in the domains related to physical health (i.e., energy/fatigue, physical function, role limitations due to physical health, pain). Future studies are needed to...
determine if thyroid hormone supplementation improves the HRQOL of CKD patients with thyroid dysfunction.

**Body composition**

Thyroid function plays a critical role in the metabolic status of adults, including regulation of thermogenesis, basal metabolic rate, and body weight. Hypothyroidism is known to result in reduced energy expenditure and modest weight gain, and in the general population, recent studies have suggested that higher TSH are associated with increased fat and fat-free or lean (i.e., skeletal muscle) mass. In a nationally representative cohort of US adults, incremental TSH elevations within the euthyroid range were associated with 1) increased fat and fat-free mass ascertained by Bioelectrical Impedance Analysis (BIA) and 2) increased total fat mass, total and truncal fat percentage, as well as lean mass ascertained by Dual-energy X-ray absorptiometry (DEXA) scan. While less is known about the impact of thyroid status on body composition in ESRD patients, more recent data from a secondary analysis of 103 patients from AIONID trial showed higher TSH levels were associated with increased fat mass and bone mineral content. Further studies are needed to determine whether thyroid-related alterations in body composition impact the health and survival of hemodialysis patients, and whether reduction of TSH with treatment influences muscle and bone parameters in this population.

**Screening and treatment**

Although some of the criteria for thyroid functional test screening in the general population may pertain to CKD patients (i.e., recommended screening in patients with newly diagnosed heart failure by the American College of Cardiology/American Heart Association), existing clinical practice guidelines lack screening recommendations specific to the CKD population. Given that hypothyroidism is frequently latent and undiagnosed in CKD patients due to symptom overlap with uremia (i.e., fatigue, cold intolerance, decreased cognition, depression), further research of the prognostic implications of thyroid dysfunction and the magnitude of the benefits and risks of screening and treatment are needed to guide clinical practice.

Thyroid hormone supplementation is fundamental to the treatment of hypothyroidism, and data from the United States Renal Data System have shown that it is one of the most commonly prescribed medications in NDD-CKD and ESRD patients who are Medicare Part D enrollees. While some rigorous observational data and clinical trials in the general population have shown that treatment reverses adverse cardiovascular outcomes (i.e., diastolic dysfunction, dyslipidemia, endothelial dysfunction, atherosclerosis), to date there has been limited study of exogenous thyroid hormone supplementation in CKD patients. In one study of 2715 dialysis patients whose thyroid function and levothyroxine (L-T4) treatment status were ascertained at baseline, those who were euthyroid on treatment (presumed to be “hypothyroid-treated-to-target”) had similar survival compared to those who were spontaneously euthyroid, whereas patients who were hypothyroid irrespective of treatment status had higher mortality risk. In a more recent study of 227,426 US Veterans with stage 3 CKD in whom thyroid and L-T4 treatment status were ascertained at baseline, a
similar pattern of findings was also observed.\textsuperscript{5} Compared to patients who were spontaneously euthyroid, those who were hypothyroid-treated-to-target had similar to slightly decreased mortality risk, whereas those with untreated hypothyroidism and undertreated hypothyroidism each had higher death risk.

While these observations suggest benefit, given that L-T4 has a narrow toxic-to-therapeutic window, and iatrogenic thyrotoxicosis and/or unwarranted treatment may theoretically lead to complications (i.e., increased protein catabolism, reduced bone mineral density, arrhythmia) rigorous longitudinal studies and randomized controlled trials are needed to provide more definitive information on the safety and effectiveness of exogenous thyroid hormone supplementation in hypothyroid CKD patients.

Conclusion

In summary, CKD patients have a high burden of hypothyroidism, although many cases may remain latent and undiagnosed. While the mechanistic link between thyroid and kidney disease renders further study, growing evidence points to a bi-directional relationship between hypothyroidism and CKD. Given the high prevalence of hypothyroidism in CKD patients, and its associated with worse hard endpoints (i.e., survival, cardiovascular disease), patient-centered outcomes (i.e., HRQOL, physical function), and metabolic status (i.e., body composition parameters) in this population, there is compelling need for further investigation of how to optimally manage thyroid dysfunction in this population.

Acknowledgments

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Thyroid hormone synthesis is tightly regulated by the hypothalamus-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the secretion of thyroid stimulating hormone (TSH) from the anterior pituitary gland. TSH in turn stimulates the production of thyroxine (T4) and triiodothyronine (T3). In peripheral organs including kidney, a large proportion T3 is produced through T4-to-T3 conversion by type 1 5'-deiodinase (D1) and type 2 5'-deiodinase (D2) as a metabolically inactive form of thyroid hormone; some parts of T4 are converted to reverse T3 (rT3) by the type 3 5'-deiodinase.
enzyme (D3) as a metabolically inactive form of thyroid hormone. More than 99% of T4 and T3 molecules are tightly bound to the carrier proteins (e.g., thyroid binding globulin [TBG], transthyretin, albumin) and only a very small percentage circulates as free hormone. These free hormones act on target tissues by binding onto thyroid receptors in the nuclei of target cells. In addition, they provide negative feedback to both the hypothalamus and the pituitary gland, closing the tightly regulated homeostatic thyroid hormone synthesis loop. 

Abbrev.: TRH, thyrotropin releasing hormone; TSH, thyrotropin; T4, thyroxine; T3, triiodothyronine; FT4, free T4; FT3, free T3; rT3, reverse T3; D1, type 1 5'-deiodinase; D2, type 2 5'-deiodinase; D3, type 3 5'-deiodinase.
Figure 2. Effects of hypothyroidism on kidney structure and function.
Abbrev.: GBM, glomerular basement membrane; RAAS, renin angiotensin aldosterone system.
Figure 3. Adverse sequelae of hypothyroidism on clinical outcomes in chronic kidney disease (CKD) patients.
Abbrev.: CV, cardiovascular; HRQOL, health related quality of life; ↑, increased; ↓, decreased.
Table 1.
Prevalence of hypothyroidism in non-dialysis dependent chronic kidney disease (NDD-CKD), hemodialysis (HD), and peritoneal dialysis (PD) patients.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Cohort (N)</th>
<th>Reference TSH level</th>
<th>Prevalence of hypothyroidism according to CKD stage (%)</th>
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<td><strong>2. End-stage kidney disease cohorts</strong></td>
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<td>(1) TSH elevation</td>
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<td>National PD from LDO (1,484)</td>
<td>TSH &gt;5.0–10.0 mIU/L</td>
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(3) Overt hypothyroidism

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<td>Kaptein (1996)³</td>
<td>HD (306)</td>
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</tr>
<tr>
<td>Lin et al. (1998)³³</td>
<td>HD/PD (221)</td>
<td>TSH ≥20 mIU/L + Low TT4 or FT4</td>
<td>-</td>
</tr>
<tr>
<td>Kutlay et al. (2005)³⁴</td>
<td>HD (87)</td>
<td>TSH &gt; 5.5 mIU/L + Low FT4</td>
<td>-</td>
</tr>
<tr>
<td>Meuwese et al. (2012)³⁵</td>
<td>HD (218)</td>
<td>Diagnostic criteria not available</td>
<td>-</td>
</tr>
<tr>
<td>Rhee et al. (2013)⁴</td>
<td>HD/PD (2,715)</td>
<td>TSH &gt; 10 mIU/L</td>
<td>-</td>
</tr>
<tr>
<td>Rhee et al. (2015)⁵</td>
<td>National incident HD from LDO (8,840)</td>
<td>TSH &gt; 10 mIU/L</td>
<td>-</td>
</tr>
<tr>
<td>Rhee et al. (2016)⁶</td>
<td>National PD from LDO (1,484)</td>
<td>TSH &gt; 10 mIU/L</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbrev.: DM, diabetes; eGFR, estimated glomerular filtration rate; HD, hemodialysis; LDO, large dialysis organization; NHANES III, Third National Health and Nutrition Examination Survey; PD, peritoneal dialysis.