

Ideas, Conjectures and Refutations

Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients

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ABSTRACT

Thyroid functional disease, and in particular hypothyroidism, is highly prevalent among chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. In the general population, hypothyroidism is associated with impaired cardiac contractility, endothelial dysfunction, atherosclerosis and possibly higher cardiovascular mortality. It has been hypothesized that hypothyroidism is an under-recognized, modifiable risk factor for the enormous burden of cardiovascular disease and death in CKD and ESRD, but this has been difficult to test due to the challenge of accurate thyroid functional assessment in uremia. Low thyroid hormone levels (i.e. triiodothyronine) have been associated with adverse cardiovascular sequelae in CKD and ESRD patients, but these metrics are confounded by malnutrition, inflammation and comorbid states, and hence may signify nonthyroidal illness (i.e. thyroid functional test derangements associated with underlying ill health in the absence of thyroid pathology). Thyrotropin is considered a sensitive and specific thyroid function measure that may more accurately classify hypothyroidism, but few studies have examined the clinical significance of thyrotropin-defined hypothyroidism in CKD and ESRD. Of even greater uncertainty are the risks and benefits of thyroid hormone replacement, which

bear a narrow therapeutic-to-toxic window and are frequently prescribed to CKD and ESRD patients. In this review, we discuss mechanisms by which hypothyroidism adversely affects cardiovascular health; examine the prognostic implications of hypothyroidism, thyroid hormone alterations and exogenous thyroid hormone replacement in CKD and ESRD; and identify areas of uncertainty related to the interplay between hypothyroidism, cardiovascular disease and kidney disease requiring further investigation.

Keywords: cardiovascular risk, hyperthyrotropinemia, hypothyroidism, renal failure, thyroid functional disease

INTRODUCTION

Epidemiologic studies show that there is a substantially higher prevalence of thyroid functional disease, and in particular hypothyroidism, in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients compared with the general population [1–10]. However, many cases of hypothyroidism may remain latent or undiagnosed in advanced CKD and ESRD due to symptom overlap with uremia and co-existing comorbidities [3]. Despite three decades of research, the mechanistic link and directionality of association between

hypothyroidism and kidney disease remain widely unknown. It has been hypothesized that kidney disease may predispose to thyroid hormone derangements due to nonthyroidal illness, malnutrition, inflammation, iodine retention, metabolic acidosis, medications, mineral deficiencies (e.g. selenium) and exposure to dialytic procedures (i.e. peritoneal effluent losses) [3, 11–17]. Yet other data suggest that hypothyroidism leads to impaired kidney function through alterations in renal hemodynamics and structure [14, 18].

Studies in the general population have shown that hypothyroidism is associated with increased cardiovascular morbidity and possibly mortality, owing to its adverse effects on cardiac contractility, systemic vascular resistance, endothelial function and atherosclerosis [19–21]. In CKD and ESRD patients, cardiovascular disease is the leading cause of mortality, accounting for nearly half of all deaths [22]. Most of these fatalities relate to coronary heart disease (CHD), congestive heart failure (CHF) and sudden cardiac death (SCD), which are incompletely explained by traditional cardiovascular risk factors.

The search for biologically plausible cardiovascular risk factors has prompted increasing interest in hypothyroidism as a predictor of adverse outcomes in the CKD and ESRD populations. Mounting data suggest various thyroid functional test derangements may be associated with greater cardiovascular morbidity and mortality in CKD and ESRD [6, 23–35]. However, disentangling hypothyroidism from nonthyroidal illness and other thyroid hormone alterations observed in kidney disease has been a major hurdle in clarifying its prognostic significance. Given their enormous burden of cardiovascular disease and death, examining whether hypothyroidism is a modifiable cardiovascular risk factor versus an epiphenomenon in the CKD and ESRD populations may be of immediate importance to medicine and public health. In this review, we will provide (i) an overview of the prevalence of hypothyroidism and thyroid hormone alterations frequently observed in CKD and ESRD; (ii) examine mechanisms by which hypothyroidism may increase cardiovascular morbidity and mortality; (iii) summarize existing literature on the prognostic implications of biochemical hypothyroidism, thyroid hormone alterations and thyroid hormone replacement in CKD and ESRD patients and (iv) discuss areas of uncertainty requiring further investigation.

PREVALENCE OF HYPOTHYROIDISM

Hypothyroidism is a relatively common endocrine disorder in the general population, with a prevalence of 5–10% in most US cohort studies [36, 37]. It is characterized by an elevated serum TSH level and a low (i.e. overt hypothyroidism) or normal (i.e. subclinical hypothyroidism) thyroxine (T4) level [38]. Using these biochemical criteria, epidemiologic studies suggest that there is a disproportionately higher prevalence of hypothyroidism in CKD, hemodialysis (HD), and peritoneal dialysis (PD) patients (Table 1) [1–10, 39]. Indeed, data from 14 623 participants in the Third National Health and Nutrition Examination Survey (NHANES III) demonstrate an increasing prevalence of hypothyroidism (defined as TSH

>4.5 mIU/L or treatment with thyroid hormone) with increasingly impaired kidney function [5.4, 10.9, 20.4, 23.0 and 23.1% with estimated glomerular filtration rates (eGFRs) of ≥ 90 , 60–89, 45–59, 30–44 and < 30 mL/min/1.73 m², respectively] [7]. Cross-sectional population-based studies have shown that higher TSH is associated with lower eGFRs and higher prevalence of CKD (defined as eGFR < 60 mL/min/1.73 m²) independent of confounding factors such as age, sex, body mass index, smoking and comorbidities (e.g. hypertension and diabetes) [7, 40, 41]. Limited data also suggest that elevations in TSH are more commonly observed in nephrotic syndrome, presumably due to urinary losses of thyroid hormone bound to carrier proteins [42]. There are fewer studies on hypothyroidism's prevalence in contemporary large-scale dialysis cohorts. However, existing data suggest that 15–25% and 3–5% of dialysis patients have subclinical and overt disease, respectively; wide ranges in the prevalence of hypothyroidism relate to differences in the definition of disease, age distribution and dietary intake of iodine across studies [3, 5, 6, 8, 9].

THYROID HORMONE SYNTHESIS, METABOLISM, AND REGULATION IN KIDNEY DISEASE

The synthesis and secretion of thyroid hormones [e.g. triiodothyronine (T3) and T4] are stimulated by TSH from the pituitary gland, which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. In turn, TRH and TSH are regulated by feedback inhibition from circulating T4, which is converted to T3 in the hypothalamus and pituitary by type 2 5'-deiodinase 2 (D2) [43, 44]. D2 activity increases as T4 levels fall. In peripheral tissues, T4 is converted to T3 via type 1 5'-deiodinase enzymes (D1) and D2 [45, 46]. It is now thought that in humans, D2 is the primary contributor to the peripheral production of T3 [44].

The kidney plays a key role in the metabolism, degradation and excretion of thyroid hormone and its metabolites (Table 2) [3]. Kidney disease may predispose to alterations in regulation of the hypothalamic–pituitary–thyroid axis, as well as changes in thyroid hormone uptake and action. The uremic milieu may also influence the performance of thyroid hormone assays. Consequently, distinguishing between alterations in thyroid hormone measurements resulting from kidney disease versus authentic hypothyroidism is challenging.

Triiodothyronine

Low T3 levels are the most frequently observed biochemical thyroid alteration in CKD [47]. In a cross-sectional cohort of 2284 CKD patients with normal TSH levels, 78.6% of patients with an eGFR < 15 mL/min/1.73 m² had low T3 levels [48]. In contrast to T4 which is largely produced by the thyroid gland, 80% of T3 is produced by peripheral deiodination of T4 to T3 [46]. Low T3 levels were also the most commonly observed thyroid functional test alteration observed in a recent study of 35 patients with acute kidney injury (37.1% of patients) [49]. Deiodination is decreased in uremia, nonthyroidal illness, starvation, inflammation, certain medications (e.g. glucocorticoids),

Table 1. Prevalence of hypothyroidism (overt and subclinical) and elevated TSH levels in end-stage renal disease and chronic kidney disease cohorts

Study (year)	Cohort (n)	Definition of overt or subclinical hypothyroidism or elevated TSH	Prevalence
End-stage renal disease cohorts			
TSH elevation			
Lin [6] (1998)	HD/PD (221)	TSH > 3.1 mIU/L	14.9%
Kutlay [5] (2005)	HD (87)	TSH > 5.5 mIU/L	23.1%
Rhee [39] (2013)	HD/PD (2715)	TSH > assay ULN	12.9%
Subclinical hypothyroidism			
Shantha [9] (2011)	HD (137)	TSH 4.5–10 mIU/L + Normal FT4	24.8%
Ng [8] (2012)	PD (122)	TSH > 4 mIU/L + Normal FT4	15.6%
Meuwese [28] (2012)	HD (218)	Diagnostic criteria not available	1.8%
Rhee [39] (2013)	HD/PD (2715)	TSH: assay ULN to 10 mIU/L	8.9%
Overt hypothyroidism			
Kaptein [4] (1988)	HD* (306)	(1)TSH ≥ 20 mIU/L, or (2) TSH 10–20 mIU/L + exaggerated TRH response + Low TT4 or FT4 index	2.6%
Lin [6] (1998)	HD/PD (221)	TSH ≥ 20 mIU/L + Low TT4 or FT4	5.4%
Kutlay [5] (2005)	HD (87)	TSH > 5.5 mIU/L + Low FT4	3.4%
Meuwese [28] (2012)	HD (218)	Diagnostic criteria not available	5.0%
Rhee [39] (2013)	HD/PD (2715)	TSH > 10 mIU/L	4.3%
Chronic kidney disease cohorts			
TSH elevation			
Bando [1] (2002)	Patients with diabetic and nondiabetic nephropathy (63)	TSH ≥ 10 mIU/L + Normal or low T4	24%
Lo [7] (2005)	NHANES III participants with eGFR across varying ranges (14,523)	TSH > 4.5 mIU/L, OR treatment with thyroid hormone	eGFR ≥ 90: 5.4% eGFR 60–89: 10.9% eGFR 45–59: 20.4% eGFR 30–44: 23.0% eGFR < 30: 23.1%
Subclinical hypothyroidism			
Carrero [23] (2007)	Stage 5 CKD initiating dialysis (210)	TSH > 4.5 mIU/L + T4 < 4.5 µg/dl	8%
Chonchol [2] (2008)	Ambulatory CKD patients (3089)	TSH > 4.5 mIU/L + Normal FT4	9.5%
Targher [10] (2009)	Ambulatory CKD patients (85)	TSH > 4 mIU/L + Normal FT4	10.7%

HD, hemodialysis; PD, peritoneal dialysis; TSH, thyrotropin; ULN, upper limit of normal; TRH, thyrotropin-releasing hormone; TT4, total thyroxine; FT4, free thyroxine; NHANES III, Third National Health and Nutrition Examination Data; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

*19% with ESRD but were pre-HD.

Table 2. Thyroid hormone alterations frequently observed in kidney disease

Thyroid function test	Alterations
Triiodothyronine (T3)	<ul style="list-style-type: none"> • Low T3 levels due to decreased peripheral T4-to-T3 conversion due to uremia, malnutrition, inflammation, mild illness • Impaired binding of T3 to thyroid hormone nuclear receptors • Impaired T3-induced transcriptional activation
Reverse triiodothyronine (rT3)	<ul style="list-style-type: none"> • Normal rT3 levels*
Total thyroxine (TT4)	<ul style="list-style-type: none"> • Decreased TT4 levels due to low protein states (i.e. hypoalbuminemia)
Free thyroxine (FT4)	<ul style="list-style-type: none"> • Altered FT4 levels measured by indirect/estimate methods due to impaired hormone–protein binding associated with uremia, low protein states, medications • Impaired FT4 cellular uptake
Thyrotropin (TSH)	<ul style="list-style-type: none"> • Decreased clearance—but levels typically normal • Blunted response to TRH • Decreased pulsatility • Increased half-life • Impaired glycosylation

*19% with ESRD but were pre-HD.

and in the context of elevated serum cortisol and free nonesterified fatty acids [14, 45, 46, 50–52]. A potent association between low T3 with inflammatory markers has consistently been observed in studies of CKD, HD, PD, CHF and critically ill patients [24, 35, 53, 54]. These collective data suggest that low T3 may be a marker of malnutrition, inflammation and non-thyroidal illness in CKD and ESRD.

Reverse triiodothyronine

In contrast to the D1 and D2 enzymes which produce biologically active T3, type 3 5'-deiodinase enzyme is responsible for: (i) the conversion of T4 to reverse T3 (rT3), a metabolically inactive form of thyroid hormone and (ii) the degradation of T3 to inactive diiodothyronine (T2) [45, 46]. In kidney disease patients, rT3 levels are typically normal. This stands in contrast to: (i) nonthyroidal illness in which rT3 levels are typically high (due to increased generation of rT3 from T4 and decreased clearance of rT3 to T2) and (ii) hypothyroidism in which rT3 levels are typically low [3, 46]. However, it has yet to be determined whether rT3 has a role in distinguishing low T3 observed with hypothyroidism versus uremia versus nonthyroidal illness in CKD and ESRD patients.

Total and free thyroxine

Essentially 99.98% of circulating T4 is bound to carrier proteins (mostly to thyroid-binding globulin, followed by transthyretin, albumin and lipoproteins) [55]. Thus total T4 assays, which measure both free and protein-bound hormone, may result in reduced T4 levels in low-protein states frequently observed in advanced CKD and ESRD patients.

In contrast, the free thyroxine (FT4) analog assay indirectly measures unbound, biologically active hormone. These assays estimate FT4 levels based on antibody sequestration of total T4 proportional to the FT4 concentration (i.e. immunoassays), and are widely used in the clinical setting as they are adapted for an automated platform and are generally accurate [55]. However, the FT4 analog method is protein dependent, and may inaccurately estimate FT4 levels in patients with low or high serum protein levels or pathologic conditions (e.g. uremia, nonthyroidal illness) in which circulating substances and medications (e.g. heparin, furosemide) impair hormone-protein binding [46, 55]. A FT4 index is based on total T4 levels and direct measurement of thyroxine-binding globulin or indirect measurement of serum protein binding, such as the resin uptake ratio. The FT4 index accounts for alterations in serum proteins, but is not adapted for an automated platform, takes longer to perform, and is not widely available.

In contrast to the aforementioned 'indirect' FT4 methods, technological advances in thyroid function testing have led to 'direct' FT4 methods with greater specificity, sensitivity and reproducibility than indirect assays. Direct FT4 assays physically separate free versus protein-bound hormone using ultrafiltration or equilibrium dialysis methods, followed by measurement of free hormone using radioimmunoassay or liquid chromatography tandem mass spectrometry [55–57]. Compared with indirect FT4 levels, direct FT4 levels show a stronger correlation with the inverse log of TSH (i.e. suggesting more accurate thyroid functional assessment) and a weaker

correlation with serum albumin (i.e. suggesting less confounding by protein-energy wasting) in populations with both normal and altered hormone-protein binding (i.e. pregnancy) [58–61]. Although its use is currently limited to reference laboratories, direct FT4 assays may become available for routine clinical use and research given their superior performance characteristics, and may provide heightened opportunity with which to more accurately diagnose and assess prognostic significance of hypothyroidism in CKD and ESRD patients.

Thyrotropin

In the general population, serum TSH is considered the most sensitive and specific single measure of thyroid function owing to its inverse logarithmic association with serum T3/T4, and it is typically used for screening, diagnosis and treatment monitoring in primary hypothyroidism [38]. In kidney disease patients, some TSH alterations may be observed such as altered clearance, blunted response to TRH, decreased pulsatility, increased half-life and impaired glycosylation leading to reduced bioactivity [3, 47]. However, TSH is typically normal in nonthyroidal illness [62], and one clinical study in dialysis patients has suggested that TSH is a more reliable indicator of thyroid function than serum T3 using metabolic testing as a surrogate measure for thyroid status [63]. Furthermore, in dialysis patients, an appropriate rise and fall in TSH has been observed in response to thyroid ablation and exogenous thyroid hormone, respectively, suggesting that the thyroid-pituitary feedback loop remains intact [47]. On the basis of these data, it might be inferred that TSH is a more reliable measure of thyroid function in kidney disease, but further study is needed to identify the optimal metric of thyroid function assessment in order to (i) correctly classify hypothyroidism in CKD and ESRD and to (ii) identify patients in whom thyroid hormone replacement is warranted.

Alterations of thyroid hormone action and uptake

Circulating thyroid hormones enter peripheral cells by thyroid hormone transporters or diffusion across the plasma membrane, and intracellular metabolism of T4-to-T3 accounts for the majority (~80%) of extrathyroidal T3 produced from T4 [64, 65]. T3 then binds to thyroid hormone nuclear receptors, and these T3-nuclear receptor complexes then bind to DNA and modify gene transcription to alter protein synthesis and substrate turnover.

Kidney disease may alter thyroid hormone transport into peripheral tissues, as well as intracellular thyroid hormone nuclear action. Exposure to uremic serum from patients inhibited the cellular uptake of T4 by rat hepatocytes, which may potentially result in low tissue levels of T3 [66]. In another study, serum obtained from uremic patients prior to HD was observed to impair thyroid hormone nuclear receptor-DNA binding and T3-induced transcriptional activation in human cell cultures, which was reversed after HD [67]. Given the variation in local production of T3 and tissue distribution of thyroid hormone nuclear receptors, further studies are needed to determine the impact of uremia on T3 transport and action across different tissues.

HYPOTHYROIDISM AND CARDIOVASCULAR DISEASE

The cardiovascular system is a major target for thyroid hormone action. In the general population, hypothyroidism, even in subclinical forms, is associated with altered cardiac contractility and output, myocardial oxygen consumption, vascular resistance, blood pressure and electrophysiologic conduction [21, 68]. Upon cell entry and binding to nuclear receptors, thyroid hormone transcriptionally regulates a number of cardiac structural and regulatory proteins, membrane ion channels and cell surface receptors, which may explain the diverse effects of thyroid hormone on the heart [69]. Thyroid hormone directly affects gene expression by binding to thyroid hormone nuclear receptors which then affect gene transcription by binding to thyroid hormone response elements of target genes [64]. Thyroid hormone's action on the heart may also be more rapidly mediated via indirect mechanisms [21]. This section will refer to data in the general population in whom there has been substantial research examining mechanistic pathways linking hypothyroidism and cardiovascular disease.

Impaired systolic and diastolic function

Hypothyroidism directly alters cardiac function via alterations in the transcription of gene products which impact myocyte contractility and relaxation (e.g. sarcoplasmic reticulum calcium-ATPase, phospholamban), which may result in decreased systolic function and delayed diastolic relaxation and filling [21, 68]. Independent of gene expression, hypothyroidism also influences intracellular calcium and potassium levels via effects on cardiac ion channels, consequently altering inotropy and chronotropy. Thyroid hormone deficiency may also indirectly affect cardiac function through reductions in peripheral oxygen consumption and metabolic requirements. These functional impairments may be exacerbated by underlying distortions in ventricular architecture related to hypothyroidism (i.e. myocardial fibrosis due to fibroblast stimulation) [70, 71].

Endothelial and vascular function

Hypothyroidism may result in decreased endothelial vasodilator synthesis and availability (e.g. nitric oxide and adrenomedullin), leading to arterial stiffness, impaired vasoreactivity, increased systemic vascular resistance, increased mean arterial pressure and diastolic hypertension [21, 68]. Decreased tissue thermogenesis and metabolic activity may also indirectly decrease systemic vascular resistance.

Altered blood volume and hemodynamics

Hypothyroidism results in decreased blood volume due to (i) decreased erythropoietin and red blood cell synthesis and (ii) decreased renin-angiotensin-aldosterone activity and subsequent increased renal sodium absorption [68, 72]. Decreased cardiac preload, in conjunction with reduced cardiac contractility, peripheral oxygen consumption and metabolic demands and increased systemic vascular resistance, may reduce cardiac

output by as much as 30–50% [73]. Some observational studies and meta-analyses have shown that even subclinical hypothyroidism may be associated with greater CHF risk [74, 75].

Dyslipidemia and atherosclerosis

Hypothyroidism causes dyslipidemia in as many as 90% of patients, most commonly manifested by increased total and LDL cholesterol levels, as well as increased lipoprotein(a) and, in some studies, triglyceride levels [76–78]. This is in part due to decreased fractional clearance of LDL from reductions in hepatic LDL receptor density and activity, as well as decreased catabolism of cholesterol into bile (by the T3-regulated cholesterol 7- α -hydroxylase enzyme) [79, 80]. In untreated hypothyroid patients, dyslipidemia in conjunction with diastolic hypertension may accelerate atherosclerosis. Some [81–83], but not all [84], epidemiologic studies have shown that subclinical hypothyroidism may also be associated with ischemic heart disease. However, in a pooled analysis of 11 cohort studies, subclinically hypothyroid patients with TSH levels ≥ 10 and ≥ 7 mIU/L had increased risk of CHD events and CHD mortality, respectively [85].

Ventricular arrhythmias

Hypothyroid-related changes in cardiac ion channel expression may result in QT interval prolongation, increasing the risk of Torsades de Pointes and SCD particularly when coupled with an arrhythmogenic substrate (e.g. LVH, fibrosis) in CKD patients [21, 86]. Case reports in the general population suggest that these electrophysiologic abnormalities may be reversed with thyroid hormone replacement [87, 88].

Mortality

Given the association of hypothyroidism with cardiac dysfunction, hypertension, atherosclerosis and conduction abnormalities, it might be inferred that hypothyroidism imparts increased mortality risk. However, limited data exist with regards to overt hypothyroidism, and studies of subclinical hypothyroidism and mortality show considerable variation, likely due to heterogeneity in the definition of hypothyroidism, population selection and adjustment for confounding factors [89]. Several meta-analyses have examined the association between subclinical hypothyroidism and mortality, and despite considerable dissimilarities in patient populations, the overall results show a trend towards increased mortality in individuals with subclinical hypothyroidism, particularly among those with higher TSH levels, younger age and higher comorbidity burden [85, 90–92].

Emerging data suggest that the above associations may also depend upon underlying cardiovascular risk. Whereas studies in high cardiovascular risk populations (e.g. recent cardiac events or CHD risk factors) have observed that subclinical hypothyroidism is associated with greater all-cause and cardiovascular mortality [93–95], this has not been consistently observed in average risk groups [84]. A recent study of NHANES III participants demonstrated that subclinical hypothyroidism is associated with greater death risk in those with CHF but not in those without [96]. These data may bear

particular relevance in CKD and ESRD patients given their high prevalence of structural heart abnormalities (i.e. increased left ventricular mass observed in >70% of patients initiating dialysis) [97].

EMERGING CARDIOVASCULAR MECHANISMS

It is plausible that the cardiovascular sequelae of hypothyroidism may be magnified in CKD and ESRD patients given their excessive burden of CHD, CHF and cardiovascular mortality. Furthermore, advanced CKD and ESRD patients may have greater susceptibility to hypothyroid-related cardiovascular perturbations given their impaired capacity for sodium and fluid excretion and increased sympathetic drive [98]. There is emerging data that hypothyroidism may be associated with changes in kidney function, mineral metabolism, hematologic parameters and inflammation, which have been implicated as nontraditional cardiovascular risk factors in CKD and ESRD (Figure 1) [99–101]. However, further studies are needed to confirm the associations between hypothyroidism and the following nontraditional cardiovascular risk factors.

Impaired kidney function and altered structure

In CKD patients, hypothyroidism may directly worsen kidney function, an independent risk factor for cardiovascular disease and death, through alterations in hemodynamics and structure [99]. In terms of the former pathway, hypothyroid-related reductions in cardiac output, rises in peripheral vascular resistance, and intra-renal vasoconstriction may decrease renal blood flow and predispose to prerenal kidney injury [18, 21, 102, 103]. Kidney function may be further impaired due to

hypothyroid-related reductions in renin–angiotensin–aldosterone activity due to both direct (i.e. decreased renin gene expression) and indirect effects (i.e. increased mean arterial pressure [MAP]) resulting in impaired renal autoregulation [14, 18, 104, 105]. In animal studies, hypothyroidism has been shown to reduce single nephron GFR, renal plasma flow and glomerular transcapillary hydrostatic pressure [106, 107]. Case series have observed that severely hypothyroid patients have reduced renal plasma flow and GFR measured by creatinine-based estimating equations and isotopic scans, which were reversed with thyroid hormone replacement [108–111]. Two cohort studies have shown that thyroid hormone replacement in CKD patients with subclinical hypothyroidism was associated with greater kidney function preservation compared with nontreatment [112, 113].

Hypothyroidism may also adversely affect kidney development and structure. In experimental animals, hypothyroidism has been associated with reductions in kidney-to-body weight ratio and truncated tubular mass, as well as adverse changes in glomerular architecture (i.e. decreased glomerular volume and area, glomerular basement membrane thickening, mesangial matrix expansion and increased glomerular capillary permeability to proteins) [72, 114–117]. These findings have yet to be confirmed in clinical studies.

Vascular calcification

Emerging data suggest that hypothyroidism may be associated with vascular calcification, which has been implicated as a predictor—and plausible mediator—of cardiovascular morbidity and mortality in kidney disease patients [118, 119]. Experimental data show that thyroid hormone deficiency downregulates mRNA levels of matrix Gla [120], and decreases Klotho expression, inhibitors of vascular and soft

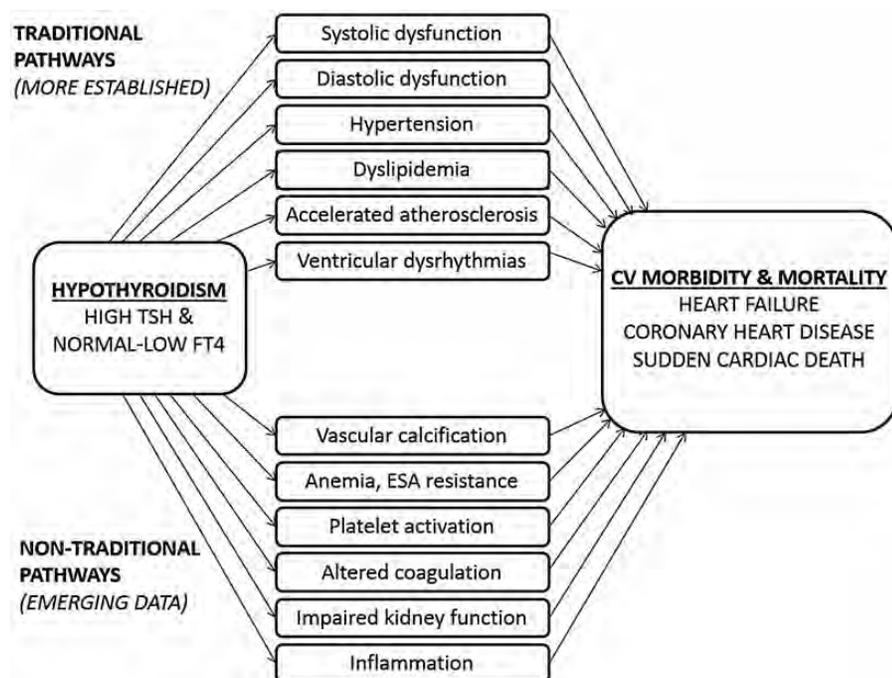


FIGURE 1: Mechanisms of hypothyroidism and cardiovascular disease.

tissue calcification, respectively [121]. In the general population, hypothyroidism is associated with increased serum osteoprotegerin levels, an inhibitor of vascular calcification in experimental studies but a marker of vascular calcification, atherosclerosis and cardiovascular events in clinical studies, which may normalize with exogenous thyroid hormone treatment [122–126]. Elevated TSH and low FT4 have been associated with valvular and coronary artery calcification [127, 128].

Anemia and erythropoietin-stimulating agent resistance

Hypothyroidism may worsen anemia and lead to erythropoietin-stimulating agent (ESA) hyporesponsiveness, each of which are cardiovascular risk factors in kidney disease [100, 129, 130]. Anemia may be observed in up to 43 and 39% of patients with overt and subclinical hypothyroidism, respectively, and may relate to one or more of decreased erythropoietin production, iron deficiency (due to impaired intestinal absorption and incorporation of iron into erythrocytes), vitamin B12 deficiency (in association with autoimmune thyroid disease and pernicious anemia) and blood loss associated with impaired hemostasis (Supplementary data, Figure S1) [131–135]. Hypothyroid HD patients have been observed to require higher monthly ESA doses compared with their euthyroid counterparts, independent of case-mix differences [136]. In a randomized controlled trial of patients with coexisting subclinical hypothyroidism and iron deficiency anemia, those assigned to oral iron and exogenous thyroid hormone experienced a greater rise in hemoglobin, iron and ferritin compared with those receiving oral iron alone [132]. Case reports have described reversible ESA resistance among dialysis patients with overt and subclinical hypothyroidism, but controlled studies are needed to determine whether exogenous thyroid administration reduces intravenous iron and ESA requirements in the CKD and ESRD populations [137–140].

Platelet activation and thromboembolism

Hypothyroidism has been associated with increased platelet reactivity, which plays a central role in thrombosis and thromboembolic events in cardiovascular disease [141, 142]. A study in the general population has shown that platelet aggregation induced by adenosine diphosphate and collagen was increased among hypothyroid patients, and that aggregation normalized following thyroid hormone administration [143]. However, other studies suggest that platelet aggregation may be impaired among hypothyroid patients [144]. Hypothyroidism has also been linked to increased mean platelet volume [145–147], a marker of large platelets which produce greater amounts of vasoactive and prothrombotic factors, and an emerging risk factor for myocardial infarction, stroke and death in the general population and CHD in dialysis patients [148–150].

Coagulation abnormalities

Limited and mixed data suggest that hypothyroidism may be associated with both impaired hemostasis (due to decreased von Willebrand and coagulation factor levels and activity) and hypercoagulability (due to increased coagulation factor activity) [151–155]. Varying patterns of fibrinolysis have been

observed with different severities of hypothyroidism (i.e. decreased versus increased fibrinolysis and risk of bleeding tendency in subclinical versus overt disease, respectively) [131].

Inflammation

Inflammation has been identified as a risk factor for cardiovascular disease and death in both the general and kidney disease populations [156–158]. Inflammation has been shown to result in alterations in peripheral and central (i.e. hypothalamic–pituitary–thyroid axis) thyroid hormone metabolism (nonthyroidal illness) [159, 160]. However, the role of hypothyroidism as a contributor to inflammation remains less certain. Studies examining the association between subclinical hypothyroidism and inflammation have been mixed, and exogenous thyroid hormone administration has not been shown to significantly affect inflammation in this context [161–164]. Although studies examining hypothyroidism and inflammation in CKD patients are limited, TSH appears to show less correlation with inflammatory markers compared with T3 [53].

PROGNOSTIC IMPLICATIONS OF THYROID FUNCTIONAL DISEASE IN KIDNEY DISEASE

Triiodothyronine and thyroxine derangements

There has been increasing interest in hypothyroidism and other thyroid functional disorders as novel determinants of adverse cardiovascular outcomes in CKD and ESRD. Early studies suggested that low thyroid hormone levels may be a physiologic adaptation in ESRD patients who are prone to hypercatabolism, malnutrition and dialytic protein and amino acid losses [165]. However, recent studies in CKD and ESRD patients suggest that low T3 and/or T4 levels are associated with adverse cardiovascular surrogates, including atherosclerosis, vascular calcification, arterial stiffness, impaired flow-mediated vasodilation, intravascular volume deficits, abnormal ventricular conduction and impaired cardiac function (Table 3) [26, 29–31, 33, 121, 166, 167]. Several studies have shown that baseline low T3/T4 levels are associated with greater mortality in ESRD, and in the only study to examine longitudinal thyroid hormone levels (baseline and 3-month follow-up), persistently low T3 was associated with a 2.7- and 4-fold higher all-cause and cardiovascular death risk in ESRD patients (Table 3) [23–25, 28, 32, 35, 166].

The associations between T3 with inflammation, protein-energy wasting, and illness states as well as altered T4 assay performance in these contexts have made the interpretation of these data challenging. In several studies of ESRD patients, associations between low T3 with cardiovascular surrogates and/or mortality were abrogated after adjustment for markers of protein-energy wasting [34, 35, 168, 169]. Two potential interpretations have been suggested based on these observations (Supplementary data, Figure S2): (i) Protein-energy wasting is a confounder of the association between low T3 and cardiovascular morbidity and mortality. (ii) Low T3 is a mechanism by which protein-energy wasting increases cardiovascular morbidity and mortality [35]. The latter is an intriguing

Table 3. Studies of thyroid functional disease and cardiovascular surrogates and mortality in end-stage renal disease and chronic kidney disease patients

Study (year)	Cohort (n)	Definition of thyroid functional disease	Outcome
Cardiovascular surrogates			
Jaroszynski [26] (2005)	HD (52)	Low FT3 syndrome: Low FT3 (ref. range 3.0–7.0 pmol/L) + high rT3 (ref. range 0.15–0.61 nmol/L) FT3 also separately defined as a continuous variable	Delayed ventricular depolarization measured by signal-averaged EKG
Zoccali [34] (2006)	HD and PD (234)	Low FT3: Low FT3 defined as the lowest tertile (ref. range not available)	Decreased left ventricular systolic function and increased left ventricular mass; estimates attenuated to null with adjustment for IL-6 and serum albumin
Kang [27] (2008)	PD (51)	Subclinical hypothyroidism: Baseline TSH > 5 mIU/L + normal FT4 (ref. range 0.6–1.5 ng/dL)	Decreased left ventricular ejection fraction
Tatar [30] (2011)	HD (137)	Low FT3: Low FT3 defined as the lowest tertile FT3 also separately defined as a continuous variable (ref. range 3.10–6.80 pmol/L)	Carotid artery atherosclerosis and increased arterial stiffness (nondiabetics only)
Tatar [31] (2011)	PD (57)	Low FT3: Low FT3 defined as the lowest tertile FT3 also separately defined as a continuous variable (ref. range 2.0–4.4 pg/mL)	Increased arterial stiffness
Yilmaz [33] (2011)	Nondiabetic stage 3–4 CKD (217)	Low FT3: Low FT3 defined as FT3 < median FT3 also separately defined as a continuous variable (ref. range 3.54–6.82 pmol/L)	Impaired flow-mediated vasodilation
Meuwese [166] (2013)	PD (84)	Low FT3: FT3 defined as FT3 < median	Increased vascular calcification
Mortality			
Zoccali [35] (2006)	HD (200)	Low FT3: FT3 defined as a categorical variable (tertiles) FT3 also separately defined as a continuous variable (ref. range not available)	Increased all-cause mortality
Enia [24] (2007)	PD (41)	Low FT3: FT3 defined as a categorical variable (tertiles) FT3 also separately defined as a continuous variable (ref. range not available)	All-cause mortality
Carrero [23] (2007)	Dialysis (187)	Low TT3: Low TT3 defined as TT3 ≤ 78.5 ng/dL	Increased all-cause and cardiovascular mortality with low TT3 but not FT3
Fernandez-Reyes [187] (2010)	HD (89)	Low FT3: FT3 defined as a categorical variable (tertiles) FT3 also separately defined as a continuous variable (ref. range 1.8–4.6 pg/mL)	No association with all-cause mortality
Ozen [169] (2011)	HD (669)	Low FT3 syndrome: Low FT3 defined as FT3 < 1.71 pg/mL + TSH normal (ref. range: 0.35–4.94 μIU/mL) + FT4 level normal or low (ref. range 0.71–1.85 ng/dL) Low FT3: FT3 defined as a categorical variable (tertiles) FT3 also separately defined as a continuous variable (ref. range 1.71–3.71 pg/mL)	Increased all-cause mortality; estimates attenuated to null with concurrent adjustment for serum albumin and CRP

Continued

Table 3. Continued

Study (year)	Cohort (n)	Definition of thyroid functional disease	Outcome
Horacek [25] (2012)	HD (167)	Low TT3: Low TT3 defined as TT3 < 1.0 nmol/L (ref. range 1.0–3.0 nmol/L) Low TT3 also separately defined as TT3 < median	Increased all-cause mortality
Lin [188] (2012)	PD (46)	Abnormal thyroid function defined as: (1) Subclinical hypothyroidism: TSH > 4.0 µIU/mL + normal FT4 (ref. range 4.5–11.0 µg/dL), OR FT4 < 0.59 ng/dL + normal TSH (ref. range 0.25–4.0 µIU/mL) (2) Overt hypothyroidism: FT4 < 0.59 ng/dL + TSH > 4.0 µIU/mL (3) Sick euthyroid syndrome: Low TT4 defined as < 4.5 mg/dL, OR Low TT3 defined as TT3 < 95 ng/dL (ref. range 95–205 ng/dL)	Increased all-cause mortality
Meuwese [28] (2012)	HD (210)	Low TT3: Low TT3 defined as TT3 < 66th percentile Low T4: Low T4 defined as TT4 < 66th percentile	Low TT3 and T4 (basal and persistently low) associated with increased all-cause and cardiovascular mortality
Yang [32] (2012)	CKD with proteinuria (211)	Low T3: Low T3 defined as T3 < 0.60 ng/mL + TSH normal (ref. range 0.35–5.50 µIU/mL)	Increased all-cause and cardiovascular mortality
Rhee [39] (2013)	HD/PD (2715)	Hypothyroidism: Hypothyroidism defined as TSH > assay-specific reference range	Increased all-cause mortality
Meuwese [166] (2013)	PD (84)	Low FT3: FT3 defined as FT3 < median	Increased all-cause mortality

HD, hemodialysis; rT3, reverse triiodothyronine; PD, peritoneal dialysis; FT3, free triiodothyronine; TSH, thyrotropin; FT4, free thyroxine; EKG, electrocardiogram; CKD, chronic kidney disease; TT3, total triiodothyronine; TT4, total thyroxine; CRP, C-reactive protein; CKD, chronic kidney disease.

hypothesis, given that malnutrition and inflammation are among the most potent predictors of cardiovascular mortality in CKD and ESRD, and it remains widely unknown through which mechanisms protein-energy wasting and death are related [170]. On the basis of these data, it remains uncertain whether low T3/T4 levels are a mediator of adverse cardiovascular outcomes or a marker of the malnutrition–inflammation complex in kidney disease patients.

Thyrotropin derangements

To date, only two studies have examined the prognostic significance of hypothyroidism defined by elevated TSH levels in kidney disease patients. In a cross-sectional study of PD patients, subclinical hypothyroidism (defined as elevated TSH with normal FT4 levels) was associated with impaired left ventricular function, and in analyses adjusted for inflammatory markers and CHD, TSH levels were negatively associated with left ventricular ejection fraction [27]. In another study of HD and PD patients, hypothyroidism defined by baseline TSH levels was associated with increased all-cause mortality [39]. At this time, further studies are needed to confirm the validity of TSH as an accurate metric of thyroid function in kidney

disease, and to determine the longitudinal impact of hypothyroidism on the cardiovascular morbidity and mortality of CKD and ESRD patients independent of malnutrition, inflammation and comorbidity status [3, 14, 16, 17].

TREATMENT

Levothyroxine is the 4th and 12th most commonly prescribed medication in CKD and ESRD Medicare Part D enrollees, respectively, but the therapeutic benefits of thyroid hormone replacement in these populations remain unclear [171]. Studies in the general population indicate that restoration of euthyroid status favorably affects cardiovascular risk profiles, and limited data suggest that treatment of subclinical hypothyroidism may reduce cardiovascular events particularly in younger populations [172–176]. To date, there has been limited study of the impact of treatment on surrogate or hard outcomes in hypothyroid CKD and ESRD patients.

In an early study of HD patients with low T3 levels, administration of exogenous T3 resulted in increased protein degradation, suggesting that thyroid hormone repletion in

hypothyroid ESRD patients exacerbates protein malnutrition [165]. However, in a placebo-controlled study of 39 euthyroid HD patients, exogenous T4 administration over 12–16 weeks reduced LDL cholesterol and lipoprotein(a) levels and did not lead to clinical symptoms of thyrotoxicosis [177]. In a recent study of 2715 HD and PD patients, patients with normal baseline TSH levels receiving exogenous thyroid hormone (i.e. presumed to be hypothyroid treated-to-target) had similar all-cause mortality compared to those with normal baseline TSH levels not on treatment (i.e. presumed to be spontaneously euthyroid); in contrast, patients with elevated baseline TSH levels with or without treatment had increased mortality risk [39]. Treatment with exogenous thyroid hormone has been associated with decreased progression or reversal of impaired kidney function in hypothyroid CKD patients (see ‘Impaired kidney function and altered structure’ above) [108–113, 178].

Although these data suggest possible benefit and minimal risk, the narrow therapeutic-to-toxic window and catabolic properties of thyroid hormone treatment warrant more rigorous study in CKD and ESRD patients for two reasons: (i) Markers of protein-energy wasting (e.g. hypoalbuminemia) are stronger mortality predictors than traditional cardiovascular risk factors in CKD and ESRD and (ii) CKD and ESRD patients may be more vulnerable to the risk of unwarranted treatment (i.e. atrial fibrillation, high output heart failure) given their high underlying cardiovascular risk [179, 180]. Some experts suggest that concerns about adverse treatment effects in patients with underlying CHD are largely unfounded [181]. In the largest study examining the impact of exogenous thyroid hormone on CHD exacerbation conducted over five decades ago, patients with atherosclerotic disease were more likely to improve than worsen with treatment [182]. Alternatively, thyromimetics (thyroid hormone synthetic analogues) are an emerging class of drugs with tissue-specific thyroid hormone actions that may selectively improve cardiovascular risk factors (e.g. dyslipidemia) without adverse effects on the heart and other end organs (e.g. tachycardia) [64, 183, 184]. Further studies are needed to determine the longitudinal impact of thyroid hormone treatment and novel pharmacotherapies on hard outcomes in hypothyroid CKD patients.

FUTURE AREAS OF RESEARCH

While there have been advances in our understanding of the interplay between thyroid and kidney disease, including thyroid hormone alterations commonly observed in the uremic milieu, limitations of classic thyroid functional assessment methods in CKD and ESRD, and the prognostic implications of particular thyroid hormone alteration patterns such as the low T3 syndrome in CKD and ESRD patients, many unanswered questions remain: Is hypothyroidism a mere physiologic adaptation in CKD and ESRD, or does it portend pathologic consequences? If pathologic, what are the specific mechanisms underlying the association between hypothyroidism and adverse outcomes in kidney disease (i.e. acceleration of atherosclerosis, impaired cardiac function, metabolic alterations in body composition and temperature [185]) What are

the optimal target ranges for classical biochemical thyroid functional markers (e.g. TSH) in CKD and ESRD? What are the risks and benefits of exogenous thyroid hormone replacement in CKD and ESRD? Can nonpharmacologic interventions such as increasing dialysis dose, frequency and intensity normalize thyroid function in ESRD patients? [186] To determine the prognostic implications of hypothyroidism and its treatment in CKD and ESRD populations, the key challenge and objective of future research studies will be to distinguish authentic hypothyroidism from nonthyroidal illness by (i) using sensitive and specific diagnostic methods to accurately assess and classify thyroid function and (ii) rigorously assessing and accounting for confounders of the association between thyroid functional test abnormalities and clinical endpoints (e.g. inflammation, malnutrition, comorbidities) using sophisticated analytic techniques in well-defined CKD and ESRD study populations.

CONCLUSION

Given the cardiovascular risks associated with hypothyroidism and the excessive burden of cardiovascular disease and death in CKD and ESRD, hypothyroidism may be an under-recognized risk factor and a biologically plausible link to cardiovascular disease and death in this population. Identification of more sensitive and specific thyroid hormone assays will provide greater opportunity to distinguish hypothyroidism from nonthyroidal illness and to define corresponding risk in CKD and ESRD patients. Given the high prevalence of hypothyroidism and exogenous thyroid hormone use in CKD and ESRD patients, further research is needed to determine the prognostic implications of hypothyroidism and to more accurately define the risks and benefits of treatment in these populations.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

None declared.

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