



HHS Public Access

Author manuscript

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2017 October 01.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2016 October ; 23(5): 407–415. doi:10.1097/MED.0000000000000275.

The Interaction Between Thyroid and Kidney Disease: An Overview of the Evidence

Connie M. Rhee, MD, MSc

Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine School of Medicine, Orange, CA

Abstract

Purpose of Review—Hypothyroidism is highly prevalent in chronic kidney disease (CKD) patients, including those receiving dialysis. This review examines potential mechanistic links between thyroid and kidney disease; current evidence for hypothyroidism as a risk factor for *de novo* CKD and CKD progression; and studies of thyroid functional disorders, cardiovascular disease, and death in the CKD population.

Recent Findings—Epidemiologic data have demonstrated an incrementally higher prevalence of hypothyroidism with increasing severity of kidney dysfunction. Various thyroid functional test abnormalities are also commonly observed in CKD, due to alterations in thyroid hormone synthesis, metabolism, and regulation. While the mechanistic link between thyroid and kidney disease remains unclear, observational studies suggest hypothyroidism is associated with abnormal kidney structure and function. Previously thought to be a physiologic adaptation, recent studies show that hypothyroidism is associated with higher risk of cardiovascular disease and death in CKD.

Summary—A growing body of evidence suggests that hypothyroidism is a risk factor for incident CKD, CKD progression, and higher death risk in kidney disease patients. Rigorous studies are needed to determine impact of thyroid hormone replacement upon kidney disease progression, cardiovascular disease, and mortality, which may shed light into the causal implications of hypothyroidism in CKD.

Keywords

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

Introduction

Thyroid functional disorders are commonly observed in chronic kidney disease (CKD) patients.[1] Primary hypothyroidism, which is typically identified by biochemical tests including an elevated serum thyrotropin (TSH) level in conjunction with a low or normal

Corresponding Author: Connie M. Rhee, MD, MSc, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine School of Medicine, 101 The City Drive South, City Tower, Orange, California 92868-3217, Tel: (714) 456-5142, Fax: (714) 456-6034, crhee1@uci.edu.

Conflicts of Interest
None.

thyroxine (T4) level (defined as overt and subclinical hypothyroidism, respectively),[2] is disproportionately more prevalent in patients with advanced kidney dysfunction compared to those with normal function.[3] In addition, various thyroid functional test abnormalities are frequently seen in CKD patients, resulting from alterations in thyroid hormone synthesis, metabolism, and regulation.[1, 4] While early studies hypothesized that thyroid hormone deficiency may be a physiologic adaptation in kidney disease patients,[5] contemporary data have demonstrated that hypothyroidism is associated with higher risk of cardiovascular disease and death in this population.[1, 6–9] In this review, we will (i) examine potential mechanistic links between thyroid and kidney disease; (ii) describe common patterns of thyroid functional test alterations in CKD; (iii) summarize existing evidence of thyroid hormone deficiency as a risk factor for cardiovascular disease and death in CKD, including underlying pathophysiologic mechanisms; and (iv) discuss the clinical management of hypothyroidism in CKD patients and future areas of research.

Hypothyroidism: A Common Yet Under-Recognized Endocrine Disorder in Kidney Disease

While a greater emphasis has been placed upon other endocrine disorders in CKD (e.g., secondary hyperparathyroidism, diabetes), large observational studies show that hypothyroidism is highly prevalent in kidney disease patients. For example, among 14,623 participants in the Third National Health and Nutritional Examination Survey (NHANES III), there was an incrementally higher prevalence of hypothyroidism (defined as TSH >4.5 mIU/L or receipt of exogenous thyroid hormone supplementation) with increasing severity of kidney dysfunction: 5, 11, 20, 23, and 23% with estimated glomerular filtration rates (eGFRs) of 90, 60–89, 45–59, 30–44, and <30 ml/min/1.73m², respectively.[3] Even after accounting for differences in age, sex, and race/ethnicity, participants with eGFRs <30 ml/min/1.73m² had a 2-fold higher risk of hypothyroidism compared to those with eGFRs >90 ml/min/1.73m². In a more recent study of 461,607 US veterans with Stages 3 to 5 CKD who underwent serum TSH testing from 2004–6 (84% of the cohort), 23% had hypothyroidism (defined as TSH >5.0 mIU/L or receipt of exogenous thyroid hormone replacement).[10] Across these studies, a large proportion of cases have been due to subclinical hypothyroidism. In the aforementioned NHANES III study, 56% of hypothyroid cases were due to subclinical disease.[3] In a study of 3089 ambulatory adults in Italy, it was also found that there was an increasingly higher prevalence of subclinical hypothyroidism with lower levels of kidney function: 7 vs. 18% with eGFRs 90 vs. <60 ml/min/1.73m², respectively.[11]

A high prevalence of hypothyroidism has also been observed in dialysis patients, albeit in comparatively smaller-sized cohorts. In US and Asian hemodialysis and peritoneal dialysis cohorts, the prevalence of hypothyroidism has ranged from 13 to 25%.[9, 12–14] Despite these data, hypothyroidism remains under-recognized in many advanced CKD patients, likely due to symptom overlap with uremia (e.g., fatigue, cold intolerance, decreased cognition).[1, 3]

Mechanistic Links Between Thyroid and Kidney Disease

Thyroid Functional Disease as a Risk Factor for Kidney Disease

While the mechanistic link between thyroid and kidney disease remains unclear, animal studies have demonstrated that hypothyroidism adversely affects *kidney size* and *structure* in both development and adulthood (Figure 1).[15] In neonatal rats, hypothyroidism has resulted in reduced kidney-to-body weight ratio, truncated tubular mass, and various glomerular basement membrane (GBM) changes (e.g., reduced GBM volume and area, GBM thickening, mesangial matrix expansion, and increased glomerular capillary permeability).[15–24] It has also been suggested that hypothyroidism leads to *kidney dysfunction*, vis-à-vis several potential mechanisms, including (1) decreased cardiac output, (2) altered intra-renal hemodynamics (i.e., intra-renal vasoconstriction resulting from decreased vasodilator synthesis and activity), (3) reduced renin-angiotensin-aldosterone production and activity, and (4) increased tubulo-glomerular feedback due to alterations in chloride channel and expression.[15, 23, 25–28] Indeed, in animal studies, induction of hypothyroidism by thyroidectomy has resulted in reduced single nephron glomerular filtration rate, renal plasma flow, and glomerular transcapillary pressure.[29, 30] Multiple case series have also shown that severe hypothyroidism results in creatinine elevations, reduced plasma flow, and decreased GFR as ascertained by indirect estimating equations, and gold standard isotopic scans; in these reports, creatinine elevations and reductions in GFR were reversed with exogenous thyroid hormone replacement.[31–33]

Some, but not all, epidemiologic studies have corroborated an association between hypothyroidism and kidney dysfunction. In a cross-sectional analysis of 461,607 US veterans who underwent repeated measures of serum TSH and creatinine testing at identical time points, each 10 ml/min/1.73m² decrement in eGFR was associated with an 18% higher risk of hypothyroidism, independent of socio-demographics and comorbidities.[10] In a prospective cohort study of 104,633 South Korean patients from the Kangbuk Samsung Health Study who had normal baseline kidney function and serum TSH levels and underwent annual to biennial TSH testing, those in the highest TSH quintile (2.85–5.00 mIU/L) had a 26% higher risk of incident CKD (defined as eGFR <60 ml/min/1.73m² using the CKD Epidemiology Collaboration formula) compared to those in the lowest TSH quintile (0.25–1.18 mIU/L).[34] In analyses that examined TSH across a continuous spectrum using restricted cubic splines, higher TSH levels were associated with a progressively higher risk of CKD up to a TSH level of ~3.20 mIU/L above which risk plateaued, suggesting that even high-normal TSH levels may be a risk factor for kidney dysfunction. However, the thyroid dysfunction—CKD association has not been confirmed in all subpopulations. For example, in an analysis of 558 participants in the Leiden-85 study, a prospective follow-up study of 85-year old inhabitants of Leiden, the Netherlands, cross-sectional analyses showed that those with overt and subclinical hypothyroidism (defined as TSH >4.5mIU/L with free T4 levels in the low or normal range, respectively) had lower mean ± SE eGFR levels than participants with normal kidney function: 53.7 ± 2.0, 55.7 ± 2.1, and 59.5 ± 0.7 ml/min/1.73m²; in contrast, participants with hyperthyroidism had the highest eGFR levels: 61.5 ± 3.1 ml/min/1.73m². [35] In addition, patients with higher TSH levels and lower free T4 levels had lower kidney function at baseline. However, in

longitudinal analyses, there was no association between baseline thyroid functional status nor thyroid hormone concentrations with change in eGFR over a median follow up of five years.

Limited data also suggest that, among patients with “mild” subclinical hypothyroidism and CKD, thyroid hormone replacement may ameliorate kidney disease progression.[36, 37] Among 309 patients with subclinical hypothyroidism and Stages 2 to 4 CKD, compared to untreated patients (42%), those who were treated (58%) had a slower rate of eGFR decline (-2 vs. -6 ml/min/1.73m²/year, respectively) and were less likely to experience a 50% decline in eGFR or end-stage renal disease (adjusted HR [95% CI] 0.28 [0.12–0.68], respectively).[36] In light of the sparse modifiable factors for CKD progression, further rigorous studies examining whether thyroid-hormone replacement therapy modulates kidney function trajectory in hypothyroid CKD patients are needed.

Chronic Kidney Disease as a Risk Factor for Thyroid Dysfunction

Conversely, patients with CKD may be at higher risk for thyroid dysfunction via several suggested pathways (Figure 1). For example, *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.[38] Several case reports and series have reported iodine-associated hypothyroidism among adult and pediatric dialysis patients consuming high iodine diets (e.g., seaweed), exposure to povidine-iodine cleansing agents, and receipt of iodine-contrast media enhanced angiography.[39–42] While several recent observational studies have shown that iodinated contrast media is associated with higher risk of incident hypothyroidism and hyperthyroidism, a more potent association in those with vs. without kidney dysfunction has not been observed.[43–45] Patients with CKD may frequently have *metabolic acidosis*, which has been shown to result in thyroid functional test alterations (elevated TSH and low T4 and triiodothyronine [T3]) levels, partially improved with oral sodium citrate therapy.[46, 47] *Selenium* is an important trace mineral in the human diet that modulates the peripheral conversion of T4-to-T3 by controlling iodothyronine deiodinase activity.[48] However, in a double-blind randomized controlled trial of 64 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.[49] Lastly, given that the vast majority of circulating thyroid hormone is protein-bound, it has been suggested that *heavy protein losses in nephrotic syndrome* or via the *dialysate in peritoneal dialysis* patients may lead to total body thyroid hormone depletion.[50, 51]

Thyroid Functional Test Alterations in Chronic Kidney Disease

Under normal circumstances, thyroid hormone synthesis is under the regulation of the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) produced by the hypothalamus incites the release of TSH from the anterior pituitary, which in turn stimulates the synthesis and secretion of T4, and to a lesser degree T3, by the thyroid gland.[15] While T4 is generated in the thyroid gland, 80% of T3 is produced by the peripheral conversion of

T4-to-T3 by type 1 and 2 5'-deiodinase enzymes. In a multi-loop feedback system, T4 and T3 exert negative feedback inhibition of TRH and TSH.

CKD patients may experience alterations in regulation of the hypothalamic-pituitary-thyroid axis. In addition, as the kidney is involved in the metabolism, degradation, and excretion of certain thyroid hormones and their metabolites, various thyroid functional test alterations may occur in CKD.[1, 4]

Thyrotropin

In the general population, serum TSH is typically used for screening, diagnosis, and treatment monitoring and titration in primary hypothyroidism.[2] In CKD, certain TSH alterations may be observed, such as impaired clearance, protracted half-life, blunted pulsatility, altered glycosylation leading to impaired bioactivity, and decreased response to TRH.[4, 52] Given its inverse logarithmic association with serum T3 and T4 levels (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. Additionally, serum TSH is a more robust thyroid function metric in non-thyroidal illness.[2] Whereas low T3 and T4 levels are typically observed with mild to moderate illness, TSH typically remains normal until the onset of severe, critical illness.[48, 53]

Triiodothyronine and Reverse Triiodothyronine

Limited data indicate that low T3 levels are the most commonly observed thyroid functional test alteration in CKD patients. For example, in a study of 2284 CKD patients who had normal TSH levels, there was an incrementally higher prevalence of low T3 with increasingly impaired kidney function, such that over three-fourths of patients with Stage 5 CKD had low levels: 8, 11, 21, 60, and 79% with eGFRs ≥ 90 , 60–89, 30–59, 15–29, and <15 ml/min/1.73m². [54] As the aforementioned peripheral deiodination of T4-to-T3 is reduced by malnutrition, inflammation, non-thyroidal illness, certain medications, and in the presence of high serum cortisol and free nonesterified fatty acid levels, it has been suggested that low T3 levels are a marker of illness in CKD patients.[10, 48, 53]

Reverse T3 is a metabolically inactive form of thyroid hormone that is produced from its precursor, T4, by the type 3 5'-deiodinase enzyme.[55, 56] This enzyme also degrades reverse T3 into inactive diiodothyronine. In non-thyroidal illness, reverse T3 levels are typically high due to heightened production and reduced decomposition.[4, 56] In hypothyroidism, reduced production of T4 typically results in low reverse T3 concentrations, although levels may be normal or high in mild hypothyroidism. While reverse T3 is oftentimes normal in kidney dysfunction, the clinical significance of these levels in the interpretation of thyroid functional tests in CKD remains undefined.[1]

Total and Free Thyroxine

Given that the vast majority of circulating T4 is bound to proteins, including thyroid-binding globulin, transthyretin, albumin, and lipoproteins, total T4 levels (capturing both free and protein-bound hormone) may be spuriously low in low-protein states.[57] While free T4 levels are used to ascertain the proportion of biologically active, non-protein bound

hormone, routinely used free T4 assays (e.g., analog method) are dependent upon protein-hormone binding, and hence may not be accurate in abnormal protein states (e.g., hypoalbuminemia, pregnancy) or in the presence of certain medications (e.g., furosemide, heparin) or substances that impair protein-hormone binding (e.g., uremic toxins).[56, 57] To overcome this limitation, 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.[57–59] 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).[60–62] further studies are needed to determine their utility in the classification of thyroid function and prognostication of outcomes in CKD.

Thyroid Functional Disease and Outcomes in Chronic Kidney Disease

Cardiovascular Disease

In general population, hypothyroidism has been associated with various adverse cardiovascular outcomes (Table 1).[63] Given that end-stage renal disease patients have a 7 to 10-fold higher mortality risk (40% of deaths due to cardiovascular causes) compared to the general population,[64, 65] there has been increasing interest in hypothyroidism as an under-recognized cardiovascular risk factor in advanced CKD.[1] To date, most studies of thyroid function and cardiovascular endpoints in this population have focused upon low T3 as the thyroid functional test metric, which has been associated with endothelial dysfunction, atherosclerosis, vascular calcification, impaired systolic function, increased left ventricular mass, and abnormal ventricular conduction.[66–72] There have been comparatively fewer studies of thyroid function ascertained by TSH and cardiovascular outcomes in CKD. In a cross-sectional study of 51 ambulatory peritoneal dialysis patients, subclinical hypothyroidism (defined as TSH >5 mIU/L and normal free T4) was associated with impaired left ventricular function.[7] In a recent study of 97 end-stage renal disease patients selected to undergo living donor kidney transplantation, low TSH, free T3, and free T4 levels (interpreted as markers of non-thyroidal illness) were inversely associated with higher coronary artery calcification scores.[68]

Mortality

In the general population, studies of hypothyroidism (largely focused upon subclinical disease) and mortality have been mixed.[73] However, a meta-analysis of 55,287 patients across 11 cohort studies conducted by the Thyroid Studies Collaboration showed that patients with subclinical hypothyroidism and TSH levels >7 mIU/L had a higher risk of coronary heart disease death.[74] It has also been suggested that the hypothyroidism—mortality association may be dependent upon underlying cardiovascular risk. Indeed, in a study of 14,879 NHANES III participants, both hypothyroidism overall and subclinical hypothyroidism were associated with higher mortality in participants with heart failure, but not in those without heart failure.[13] These findings may bear analogy to advanced CKD patients given their high prevalence of structural heart disease.[64]

Early studies of thyroid function in CKD suggested that thyroid hormone deficiency is a physiologic adaptation and a means to conserve metabolism in end-stage renal disease patients who are hypercatabolic and prone to protein-energy wasting and dialytic protein and amino acid losses.[5] However, contemporary studies demonstrating an association between hypothyroidism and higher death risk in dialysis patients have challenged this hypothesis. In the first study to examine thyroid function defined by TSH and mortality, among 2715 incident+prevalent dialysis patients it was found that hypothyroidism ascertained at study entry (defined as TSH > assay reference upper limit of normal) was associated with a 35% higher all-cause mortality risk compared to euthyroidism.[8] Yet in a study of 1000 incident +prevalent diabetic hemodialysis patients from the *Deutsche Diabetes Dialyse Studie* (4D study), baseline subclinical hypothyroidism examined separately or in conjunction with overt hypothyroidism was not associated with sudden cardiac death, cardiovascular events, or all-cause death; notably, only 1.8% of the study cohort had subclinical hypothyroidism (defined as TSH 4.1–15.0 mIU/L with normal free T3 and T4 levels) or overt hypothyroidism (defined as TSH >10.0 IU/L and low free T3 and/or free T4 levels), which may have resulted in limited power to detect significant associations.[6] In a subsequent study of 8840 hemodialysis patients from a large national dialysis organization that examined baseline and repeated measures of TSH over time, it was found that baseline and time-dependent hypothyroidism (defined as TSH >5.0 mIU/L) were associated with a 47% and 62% higher all-cause death risk compared to euthyroidism, respectively.[9] Upon examination of finer gradations of TSH, it was found that higher levels were incrementally associated with higher death risk, such that even high-normal TSH ranges (>3.0–5.0 mIU/L) predicted heightened mortality risk. To explore the hypothesis that hypothyroidism is a physiologic adaptation in advanced CKD patients prone to protein-energy wasting, thyroid function—mortality associations were examined across strata of body mass index. Notably, time-dependent analyses showed stronger associations across higher body mass index categories, while baseline analyses showed that the hypothyroidism—mortality association was abrogated in those with a body mass index ≥ 20 kg/m². In summarizing these collective observational studies, various conclusions may be drawn regarding the association of hypothyroidism with cardiovascular disease and death in CKD (Figure 2).

Management of Hypothyroidism in Chronic Kidney Disease

Future studies examining the impact of exogenous thyroid hormone treatment upon cardiovascular disease and death may yield key insights into the causal implications of hypothyroidism in CKD. Indeed, the United States Renal Data System Annual Data Report has shown that levothyroxine is among the most commonly prescribed medications in non-dialysis dependent CKD and end-stage renal disease who are Medicare Part D enrollees.[65] However, there has been a paucity of data examining exogenous thyroid hormone replacement in hypothyroid CKD patients. As noted above, observational studies have shown that receipt of exogenous thyroid hormone replacement in patients with subclinical hypothyroidism and CKD was associated with decreased CKD progression.[36, 37, 65] Similarly, in a double-blinded randomized controlled trial of 136 patients with subclinical hypothyroidism (defined as TSH of 4.0–7.0 mIU/L and serum thyroid peroxidase antibody positivity) and early type 2 diabetic nephropathy, treatment with levothyroxine for 48 weeks

TSH	thyrotropin
T4	thyroxine
eGFR	estimated glomerular filtration rate
NHANES III	Third National Health and Nutrition Examination Survey
GBM	glomerular basement membrane
T3	triiodothyronine
TRH	thyrotropin-releasing hormone
4D study	<i>Deutsche Diabetes Dialyse Studie</i>

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KEY POINTS

- CKD patients have a disproportionately higher prevalence of hypothyroidism, although many cases may remain latent and undiagnosed.
- The thyroid—kidney mechanistic link has not been fully elucidated, but may be bi-directional.
- Thyroid functional derangements, including hypothyroidism, are linked with cardiovascular disease and death in CKD patients.
- While limited data suggest benefit, future studies are needed to determine the safety and effectiveness of exogenous thyroid hormone replacement in hypothyroid CKD patients.

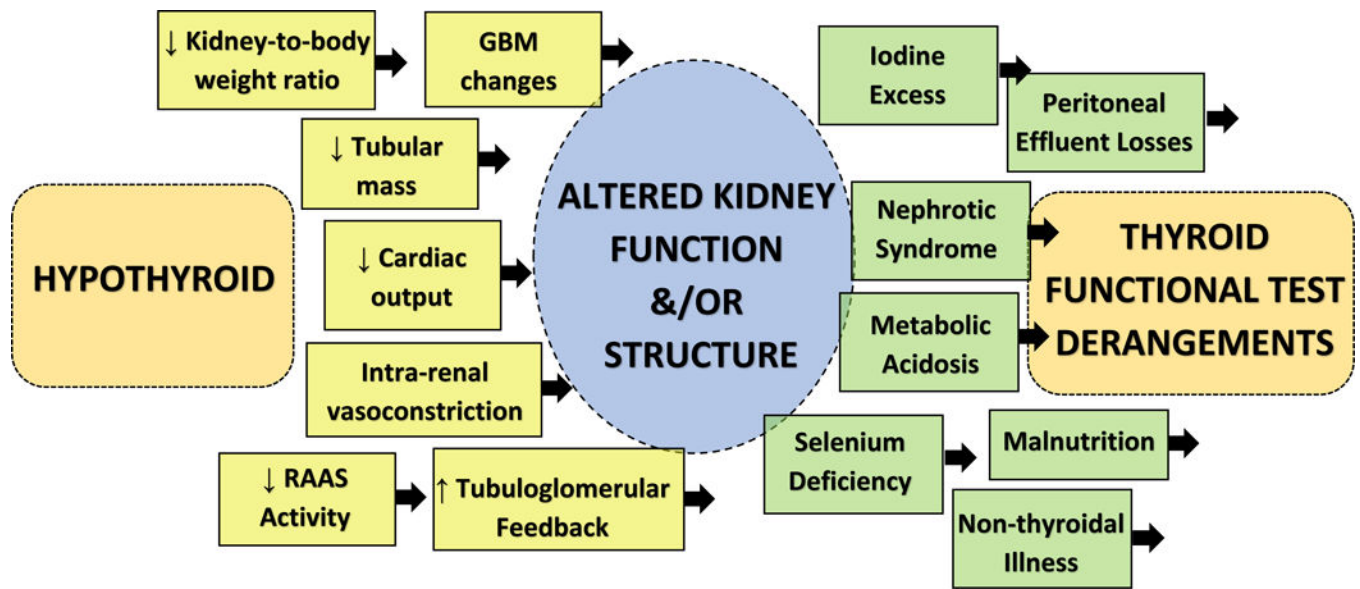


Figure 1. Proposed mechanistic links between thyroid and kidney disease

Abbreviations: GBM, glomerular basement membrane; RAAS, renin angiotensin aldosterone system.

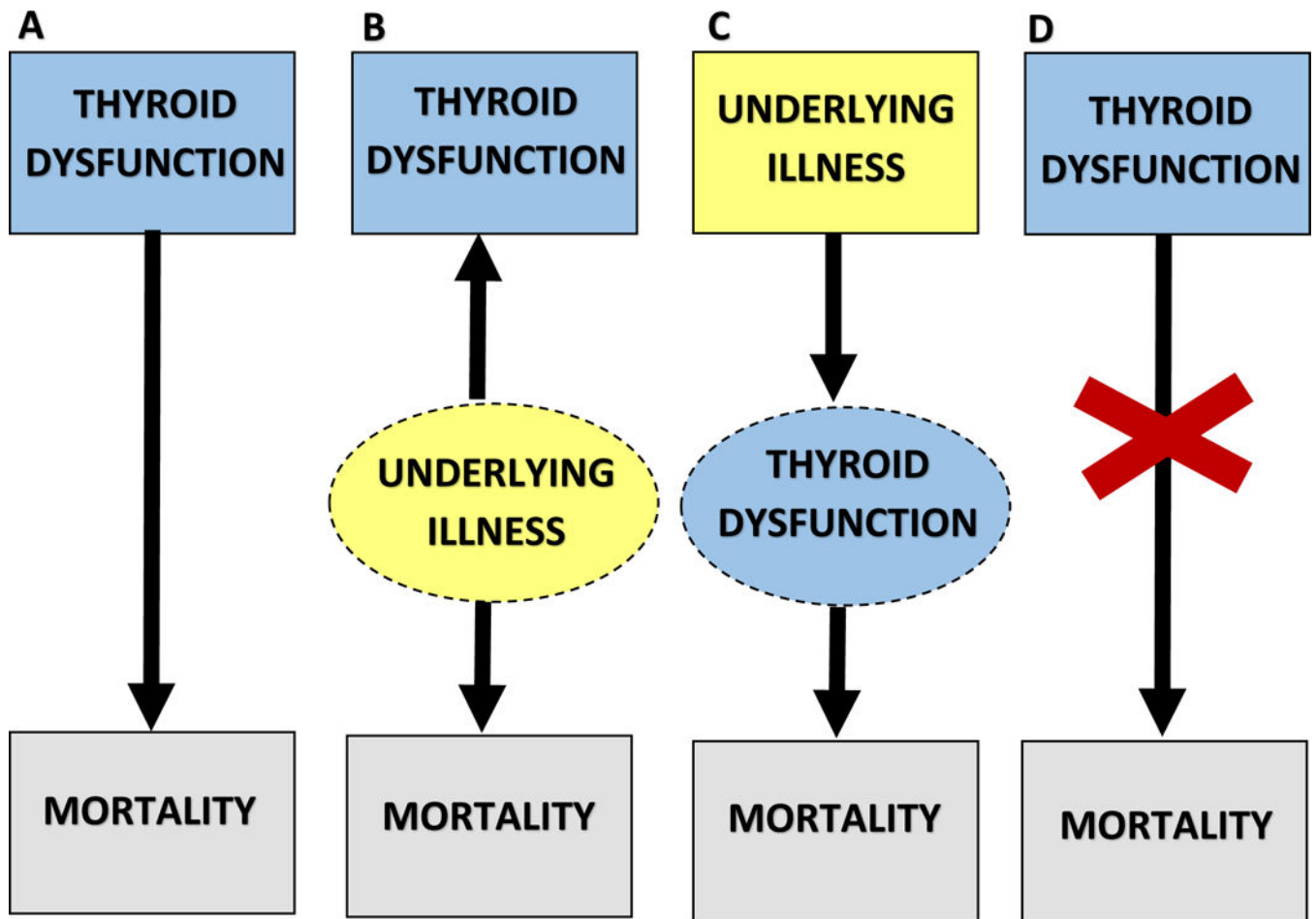


Figure 2. Potential pathways of the association between thyroid dysfunction and mortality in chronic kidney disease patients

Panel A: Thyroid dysfunction is causally associated with mortality. Panel B: Thyroid dysfunction is a marker of illness, which in and of itself is associated with mortality. Panel C: Thyroid dysfunction is an intermediate pathway between illness and mortality. Panel D: Thyroid dysfunction is not associated with mortality in certain populations (i.e., patients with protein-energy wasting).

Table 1

Cardiovascular complications of hypothyroidism.

CARDIOVASCULAR SYSTEM	SEQUELAE OF HYPOTHYROIDISM	PATHOGENESIS
Cardiac function	<ul style="list-style-type: none"> • ↓ Systolic and diastolic function • ↓ Cardiac output 	<ul style="list-style-type: none"> ➤ Altered transcription of myocyte contractility and relaxation genes ➤ Alteration of cardiac ion channels ➤ ↓ Peripheral oxygen consumption and requirements ➤ ↓ Erythropoietin and erythropoiesis → ↓ Blood volume
Endothelial function	<ul style="list-style-type: none"> • Arterial stiffness • Impaired vasoreactivity • ↑ Systemic vascular resistance • Diastolic hypertension 	<ul style="list-style-type: none"> ➤ ↓ Vasodilator synthesis and activity ➤ ↓ Tissue thermogenesis and metabolic activity
Metabolic status	• ↑ Total cholesterol	➤ ↓ Catabolism of cholesterol into bile by cholesterol 7-alpha-hydroxylase enzyme
	• ↑ LDL	➤ ↓ Hepatic LDL receptor density and activity →
	• ↑ Triglycerides	➤ ↓ Fractional clearance of LDL
Vascular disease	• Atherosclerosis	<ul style="list-style-type: none"> ➤ Dyslipidemia ➤ Hyperhomocysteinemia ➤ Hypertension
	• Vascular calcification	➤ ↓ Vascular calcification inhibitors: matrix Gla and klotho
Cardiac conduction	• Ventricular arrhythmia	➤ Changes in cardiac ion channel expression → Prolongation of QT interval