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Original Investigation

Thyroid Function Test Derangements and Mortality in Dialysis Patients: A Systematic Review and Meta-analysis

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Background: We evaluated current evidence associating thyroid function test result derangements with risk for mortality in patients with chronic kidney failure treated by long-term dialysis.

Study Design: Systematic review and meta-analysis of cohort studies.

Setting & Population: Dialysis patients.

Selection Criteria for Studies: We searched PubMed, Web of Science, Science Citation Index, Cochrane Library, and Embase databases from inception through December 2015.

Predictors: Hypothyroidism (thyrotropin level greater than reference range) and low triiodothyronine (T_3) and thyroxine (T_4) levels.

Outcomes: All-cause and cardiovascular mortality.

Results: 12 studies involving 14,766 participants (4,450 deaths) were identified. Of those, 6 studies provided data for cardiovascular mortality (2,772 participants with 327 cardiovascular deaths). Overall, confidence in the available evidence was moderate. Pooled adjusted HRs for all-cause mortality associated with hypothyroidism, low T_3 level, and low T_4 level were 1.24 (95% CI, 1.14-1.34), 1.67 (95% CI, 1.23-2.27), and 2.40 (95% CI, 1.47-3.93), respectively. Pooled adjusted HRs for cardiovascular mortality associated with low T_3 and T_4 levels were 1.84 (95% CI, 1.24-2.74) and 3.06 (95% CI, 1.29-7.24), respectively.

Limitations: Fewer studies reporting on T_4 and thyrotropin outcomes.

Conclusions: In patients treated with long-term dialysis, (cardiovascular) mortality is consistently higher in the presence of thyroid function test result derangements.

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INDEX WORDS: Thyroid disorders; hypothyroidism; triiodothyronine (T_3); thyroxine (T_4); hormones; all-cause mortality; cardiovascular mortality; thyroid function test derangement; haemodialysis; peritoneal dialysis; endocrine; end-stage renal disease (ESRD); meta-analysis.

In patients with chronic kidney disease (CKD), the progressive loss of kidney function has a negative impact on the synthesis, excretion, metabolism, and degradation of thyroid hormones and their metabolites.[1,2] As a consequence, thyroid function test result derangements are common in patients with advanced stages of CKD, particularly in those with end-stage renal disease (ESRD).[1,3-8] The prevalence of clinically overt and subclinical hypothyroidism increases with worsening kidney function.[4-6] In addition, low circulating levels of triiodothyronine (T_3)[1,3,7,8] and thyroxine (T_4) become increasingly common.[9,10] Uremic conditions that are thought to contribute to these alterations are multiple, including retention of iodine and toxins (causing central thyrotropin [thyroid-stimulating hormone] inhibition, triggering thyrotropin clearance, and influencing T_3 levels independently of thyroid function), ineffective protein binding of T_4, reduced T_4 levels in tissues, and primarily, impaired conversion of T_4 into T_3. The latter is attributed to direct effects of systemic inflammation, elevated cortisol levels, malnutrition, mineral deficiency (eg, selenium resulting in reduced deiodinase activity), metabolic acidosis, commonly used medications, and additionally in patients with ESRD, effects of dialytic procedures (eg, peritoneal effluent losses).[1,3,8,11,12]

Observational studies in recent years have attempted to link these thyroid function test result derangements with the cardiovascular complications and elevated mortality risk of patients with CKD and ESRD.[9,10,13-23] If associations are causal, this opens perspectives for thyroid replacement therapy in this high-risk patient population. Here, we evaluate the consistency of reported associations between thyroid function test result derangements and hard end points

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in patients undergoing long-term dialysis by means of a systematic review and meta-analysis.

METHODS

Data Sources and Searches

We systematically searched PubMed and the Web of Science. Complementary searches and backward and forward citation tracking were performed through analyses of reference lists, the Science Citation Index, Cochrane Library, and Embase. The search was from inception through December 2015. We also searched unpublished studies and gray literature in a clinical trial register (www.ClinicalTrials.gov) and conference abstracts for the major nephrology conferences during 2014 to 2015: American Society of Nephrology Kidney Week, European Renal Association/European Dialysis and Transplant Association Congress, and International Society of Nephrology Congress. The search string consisted of 3 parts: (1) the exposure (ie, thyroid disease, hypothyroidism, thyrotropin, T_4, and T_3), (2) study population (ie, CKD, ESRD, kidney failure, uremia, hemodialysis [HD], and peritoneal dialysis [PD]), and (3) outcomes (ie, all-cause mortality, cardiovascular mortality, survival, fatal, and death). Different spellings were accounted for, and Medical Subject Headings (MeSH) were incorporated in the PubMed search (Item S1, available as online supplementary material).

Exposure, Study Population, and Outcome

The exposure was thyroid function test result derangements, defined as the following: (1) low T_3 level (as measured by total or free T_3, either free T_3 level less than the assay-specific reference range or free T_3 level less than the cutoff value), (2) low T_4 level (by total or free T_4, either free T_4 level lower than the reference range or free T_4 level less than the cutoff value), and (3) hypothyroidism (thyrotropin level greater than the reference range). Patient groups with free T_3, free T_4, and thyrotropin levels within the normal range or within the highest level category as reported by each study were used as reference. The study populations consisted of adults with CKD undergoing long-term dialysis, either HD or PD.[24] Study outcomes were all-cause and/or cardiovascular mortality during a minimal follow-up of the study cohort of 3 months.

Inclusion and Exclusion Criteria

Studies were considered for inclusion in the meta-analysis if they: (1) presented data for measured thyroid function test in adult (aged $\geq$ 18 years) patients with CKD undergoing dialysis and (2) provided data for all-cause and/or cardiovascular mortality associated with these measurements. Both cohort studies and case-control studies were eligible, whereas case reports, case series, and review articles were excluded. We did not consider studies addressing a combination of these exposures (eg, hypothyroidism and low free T_3 level and low free T_4 level or thyroid function test result derangements with a concurrent comorbid condition or lifestyle factor). No language restriction was applied. The languages selected a priori as eligible were English, Chinese, Swedish, Spanish, French, Dutch, and German. Studies were eligible only if hazard ratios (HRs) of thyroid function tests for all-cause or cardiovascular mortality were reported.

Study Selection

An a priori established study protocol was applied (Item S2). The search method used to identify all relevant articles was discussed and developed by the authors and the final search string was approved by all. The initial search was performed by 2 reviewers (H.X. and N.B.), who eliminated clearly irrelevant articles based on the title and abstract as defined by the preset selection criteria. The final selection of articles was made by mutual consideration of all authors, based on the reporting of all necessary data and in accordance with the predefined inclusion and exclusion criteria.

Data Extraction and Quality Assessment

For each article identified, we extracted information for study and participant characteristics, thyroid function test description, and analysis strategy (statistical models and adjustment for covariates). For each study, crude HRs were extracted (if reported), as well as HRs based on the most fully adjusted Cox regression models. If different thyroid function test results were reported in one study (eg, low free T_3 or low free T_4 levels or thyrotropin level greater than the reference range), all HRs of the different exposures were extracted. If several level groups (eg, tertiles of free T_3) were reported, the most extreme comparison, that is, lowest versus highest level, was considered for the primary results. We contacted the authors for clarifications of the protocol and provision of HRs in categorical groupings. Data analysis used HRs based on the most adjusted (final) Cox regression model in each study. Risk of bias was assessed using the Newcastle-Ottawa Scale tool.[25] Assessment of quality and generalizability was based on 3 key broad domains considered fundamental for observational studies: selection of study participants, comparability of cohorts on the basis of the design or analysis, and assessment of outcomes. Study-level risk of bias was assessed by 2 authors (H.X. and N.B.), and disagreements in ratings were discussed until consensus. As an overall quality check and in order to ensure transparent reporting of this systematic review and meta-analysis, the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed.

Statistical Analysis

DerSimonian-Laird random-effect meta-analysis and empirical Bayes metaregression models were performed with STATA, version 13.0 (StataCorp LP) and were based on the HRs and standard errors. Values were reported by a forest plot, and uncertainty about the pooled estimates was quantified by 95% confidence intervals (CIs). Statistical heterogeneity was assessed by means of Cochran Q test and I^2 test. I^2 represents the percentage of variation attributable to heterogeneity, which was categorized as low (0%-50%), moderate (51%-75%), or high (>75%).[26]

We could perform additional empirical Bayes metaregression models in studies addressing low free T_3 levels as the exposure. These included type of free T_3 level ascertainment (less than the reference range or cutoff value), type of T_3 measurements (free or total T_3), type of dialysis therapy (HD or PD), mean follow-up (12-36 or >36 months), study sample size (<500 or $\geq$500 participants), confounders in fully adjusted models (with or without adjustment for malnutrition, inflammation, and comorbid conditions), and reported regression models. We also did a sensitivity analysis to further explore the robustness of results and identify any study that may have exerted a disproportionate influence on the summary effect of low free T_3 level on mortality risk. The presence of small study effects and publication bias was evaluated by Begg or Egger regression asymmetry analysis.[27]

RESULTS

Study Selection

We identified a total of 3,962 publications, of which 3,479 remained after removing duplicates (Fig 1). We excluded 3,448 publications based on the title and abstract because they were unrelated to the

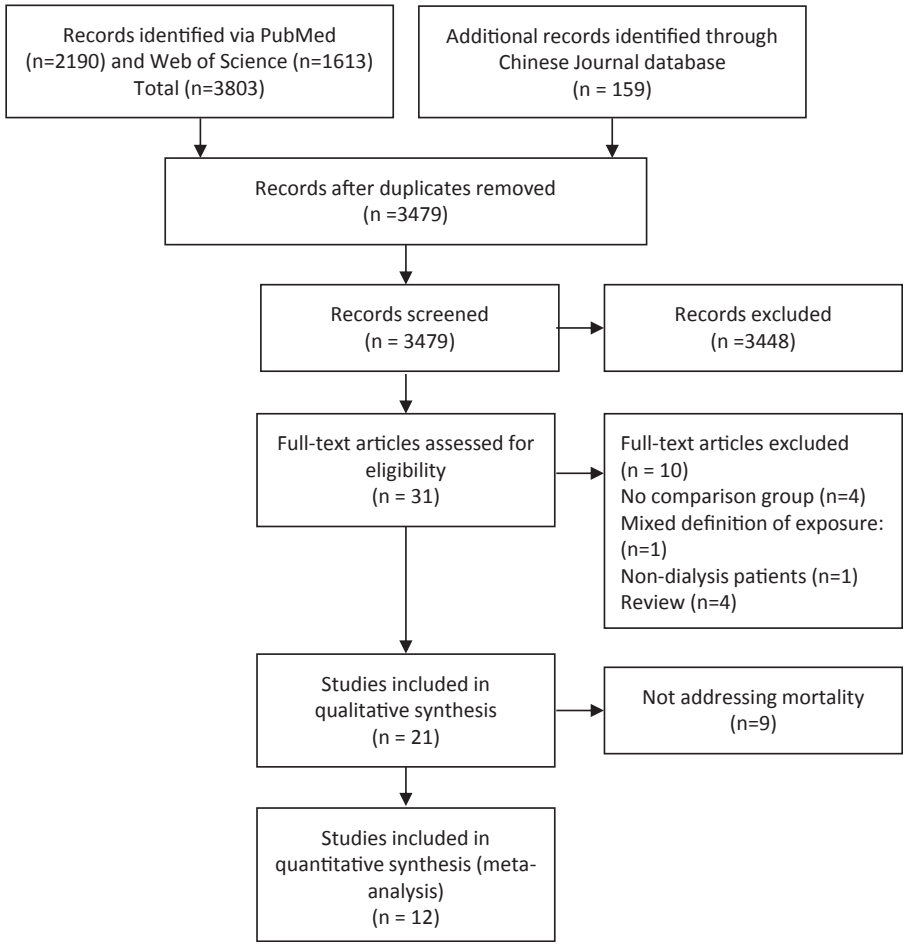

Figure 1. Flow chart for study inclusion; adapted from PRISMA (Preferred Reporting of Systematic Reviews and Meta-analyses).

study of association between thyroid function test result derangements and mortality. Of the remaining 31 articles, we excluded 10 articles that did not meet inclusion criteria after full-text screening (1 study was excluded because of a mixed definition of exposure,[28] 1 study included non–dialysis-dependent patients with CKD,[15] and 4 other studies did not present estimates for a comparison group[29-32]). We further excluded 9 studies because they investigated cardiovascular surrogates[33-41] or cardiovascular disease events,[37] but not mortality risk (detailed in Table S1). Twelve studies met eligibility criteria and were considered for meta-analysis.

Study Characteristics

The 12 studies selected for analysis enrolled a total of 14,766 participants (Table 1), of whom 4,450 died. Six studies provided data for cardiovascular mortality, including 2,772 participants and 327 cardiovascular-related deaths. The studies were from Sweden (n = 3),[9,14,20] South Korea (n = 2),[10,21] Italy (n = 2),[13,18] the United States (n = 2),[16,17] Turkey (n = 1),[19] Germany (n = 1),[22] and Greece (n = 1).[23] None of them showed an overlap in geographical area or time.

Mean age ranged from 51 to 66 years, and the proportion of men ranged from 51% to 74%. Mean duration of follow-up varied between 12 and 55 months. Two studies analyzed several exposures: one addressed both low T_3 and low T_4 levels[9] and the other addressed low T_3 levels and hypothyroidism.[22] Nine studies reported HRs for death associated with low free T_3 levels, 2 in relation to low free T_4 levels, and 3 in relation to hypothyroidism. Among the 9 studies that studied low free T_3 levels, 4 defined it by the reference range,[19,21-23] and 5, by tertiles of distribution,[9,13,18] median,[20] or receiver operating characteristic–derived[14] cutoffs; 6 studies used measurements of free T_3,[13,18-20,22,23] and 3 used measurements of total T_3.[9,14,21] Seven studies included HD patients, 3 studies included PD patients, and 2 studies included both HD and PD patients.[14,16]

Quality Assessment

All studies were population-based cohort studies and had appropriate methods for thyroid function test

Table 1. Description and Characteristics of 12 Observational Studies Reporting on the Association Between Thyroid Function Test Derangements and Risk for Mortality

						Exposure					
Study	Country	Cohort	N	Mean Age, y	Male Sex, %	Low (f) T_3 Level	Low (f) T_4 Level	Hypothyroidism[a]	Mortality	Events	Mean F/U, mo
Zoccali[18] (2006)	IT	HD	200	61	53	<33rd percentile	NA	NA	All-cause	102	42
Enia[13] (2007)	IT	PD	41	66	63	<33rd percentile	NA	NA	All-cause	27	34
Carrero[14] (2007)	SE	HD+PD; euthyroid pts	187	55	63	<Cutoffs derived from receiver operating characteristics	NA	NA	All-cause and CVD	66 (34 CVD)	20
Ozen[19] (2011)	TR	HD; euthyroid pts	669	54	56	<Reference range	NA	NA	All-cause and CVD	165 (94 CVD)	34
Meuwese[9] (2012)	SE	HD	210	62	55	<66th percentile	<66th percentile	NA	All-cause and CVD	103 (40 CVD)	38
Meuwese[20] (2013)	SE	PD	84	64	68	<Median	NA	NA	All-cause	24	32
Koo[21] (2013)	KR	HD	471	57	57	<Reference range	NA	NA	All-cause and CVD	49 (22 CVD)	24
Rhee[16] (2013)	US	HD+PD	2,715	63	60	NA	NA	>Reference range	All-cause	917	20
Drechsler[22] (2014)	DE	HD	1,000	66	53	<Reference range in euthyroid pts	NA	>Reference range, with normal (f) T_3 and (f) T_4	All-cause and CVD	477 (131 CVD)	48
Jung[10] (2014)	KR	PD	235	51	56	NA	<Median	NA	All-cause and CVD	31 (6 CVD)	24
Fragidis[23] (2015)	GR	HD; euthyroid pts	114	62	74	<Reference range	NA	NA	All-cause	69	55
Rhee[17] (2015)	US	HD	8,840	65	51	NA	NA	>Reference range, with normal (f) T_4	All-cause	2,420	12

Note: Euthyroid patients are defined as having both thyrotropin and T_4 levels within the reference ranges.

Abbreviations: CVD, cardiovascular disease; DE, Germany; (f) T_3, (free) triiodothyronine; (f) T_4, (free) thyroxine; F/U, follow-up; GR, Greece; HD, hemodialysis; IT, Italy; KR, Republic of Korea; NA, not applicable; PD, peritoneal dialysis; pts, patients; SE, Sweden; TR, Turkey; TSH, thyrotropin; US, United States.

[a]Thyrotropin level greater than reference value.

measurements. Six studies defined exposure cutoffs with assay reference ranges,[16,17,19,21-23] and the others used cohort-specific cutoffs (eg, tertiles or median). Four studies provided a comparison of baseline patient characteristics according to the analyzed exposures.[9,14,16,20] All studies reported mortality follow-up with cause of death ascertainment from medical records, describing crude and adjusted HRs (Figs S1 and S2). The covariates used in multivariable adjustment are detailed in Table S2. Seven studies considered multivariable adjustment for systemic inflammation biomarkers, which are presumably on the causal pathway of study exposure and outcome[9,10,13,14,18,21,23]; and 2 studies further adjusted for nutritional status and comorbid conditions.[9,21]

Thyroid Function Test Result Derangements and Death

The pooled adjusted HR for all-cause mortality associated with low free T_3 level was 1.67 (95% CI, 1.23-2.27), with moderate heterogeneity ($I^2 = 52.1\%$). The adjusted HR for low free T_4 level was 2.40 (95% CI, 1.47-3.93; $I^2 = 0\%$), and for hypothyroidism, 1.24 (95% CI, 1.14-1.34; $I^2 = 0\%$). These estimates presented low heterogeneity (Fig 2). Pooled adjusted HRs for cardiovascular mortality associated with low free T_3 (HR, 1.84; 95% CI, 1.24-2.74; $I^2 = 28.8\%$) and low free T_4 levels (HR, 3.06; 95% CI, 1.29-7.24; $I^2 = 0\%$) showed similar but stronger HRs, with low heterogeneity (Fig 3). Metaregression models showed similar results but with broader CIs: the HR for all-cause mortality associated with low free T_3 levels was 1.70 (95% CI, 1.16-2.50), and with low free T_4 levels, 2.40 (95% CI, 0.09-59); the HR for cardiovascular mortality associated with low free T_3 levels was 1.84 (95% CI, 1.05-3.21), and with low free T_4 levels, 3.06 (95% CI, 0.01-820). Analysis of publication bias through funnel plots with Begg or Egger tests could not be performed because of statistical heterogeneity.[42]

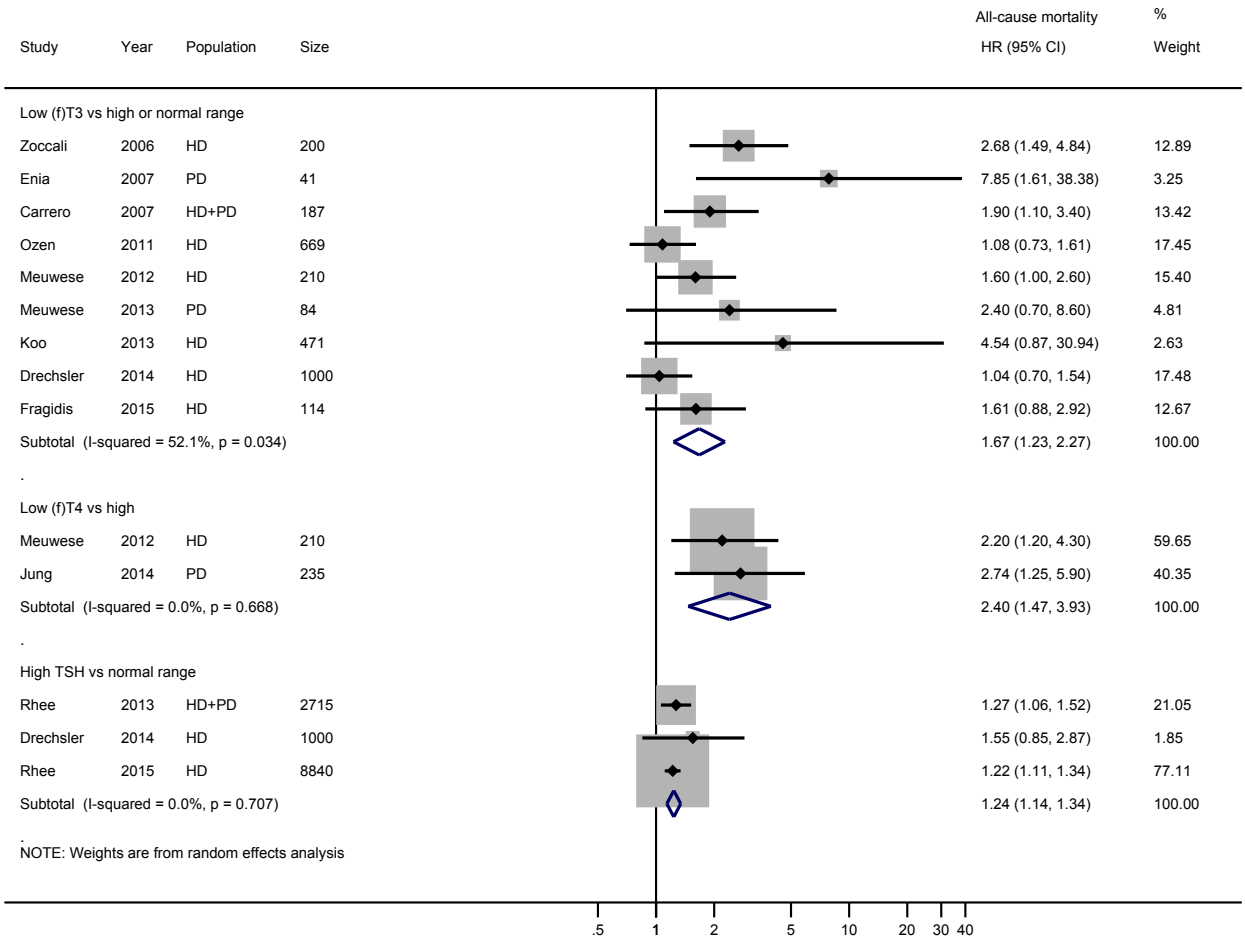

Figure 2. Forest plot depicts the meta-association between various forms of thyroid function test result derangements and risk for all-cause mortality, using the Dersimonian and Laird random-effects model. All hazard ratios (HRs) are based on the most fully adjusted reported model. Abbreviations: CI, confidence interval; (f) T_3, (free) triiodothyronine; (f) T_4, (free) thyroxine; HD, hemodialysis; PD, peritoneal dialysis; TSH, thyrotropin.

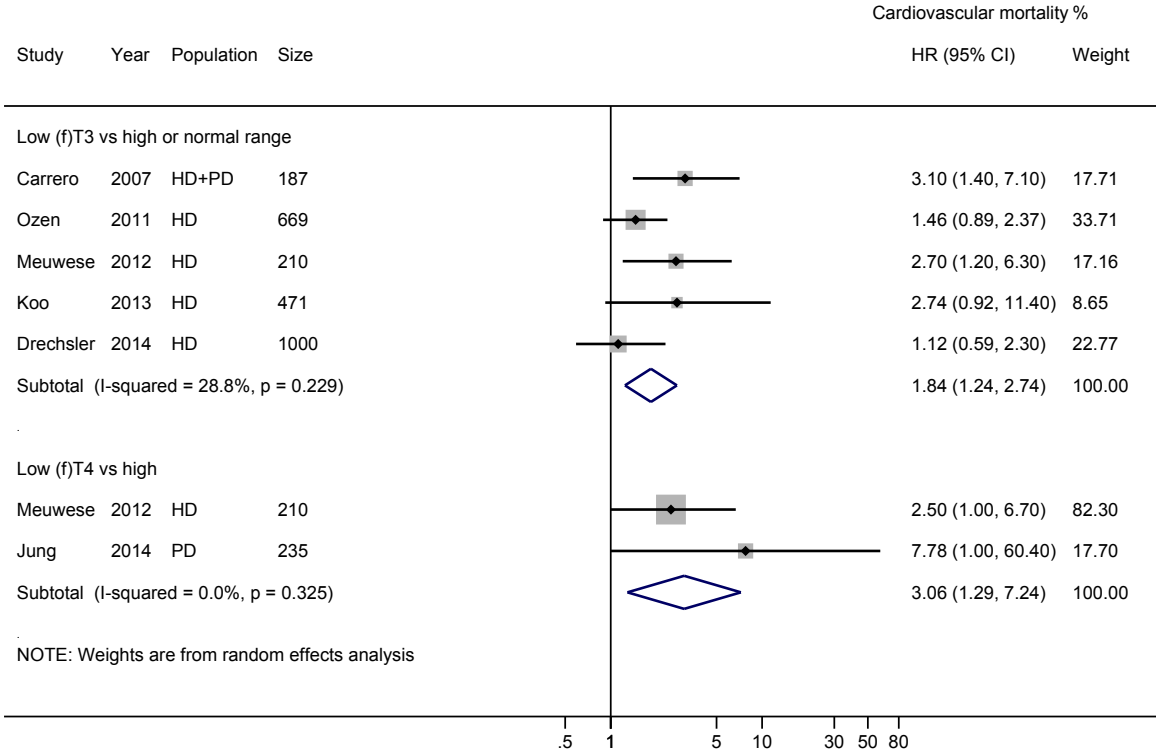

Figure 3. Forest plot depicts the meta-association between various forms of thyroid function test result derangements and risk for cardiovascular mortality, using the Dersimonian and Laird random-effects model. All hazard ratios (HRs) are based on the most fully adjusted reported model. Abbreviations: CI, confidence interval; (f) T_3, (free) triiodothyronine; (f) T_4, (free) thyroxine; HD, hemodialysis; PD, peritoneal dialysis; TSH, thyrotropin.

Metaregression and Sensitivity Analyses of Low T_3

Exclusion of single studies from the analysis did not alter the main findings (Table S3). Metaregression analyses suggested that studies defining low free T_3 level by cohort-specific cutoffs (as compared with studies using reference ranges) and studies using total T_3 measurements (as compared with studies measuring free T_3) tended to have stronger associations with mortality (Table 2). HD patients with longer follow-up and larger sample size had lower HRs as compared with their counterparts. Studies that considered multivariable adjustment for malnutrition, inflammation, and comorbid conditions showed higher HRs (Table 2). Due to an insufficient number of studies, no subgroup analysis for patients by low T_4 levels and hypothyroidism could be performed.

DISCUSSION

In this meta-analysis, risk for all-cause mortality and cardiovascular-related mortality was consistently higher in patients undergoing dialysis with thyroid function test result derangements. This association persisted throughout a number of sensitivity and stratified analyses.

Meta-analysis can be limited by the comprehensiveness of searches, the methodological rigor of included studies, and publication bias, especially when the meta-analysis includes, as in the current study, observational studies rather than randomized controlled trials. We consider the extensive literature evaluation as a strength of the analysis, but acknowledge that the number of retrieved articles was relatively small, reflecting the scarcity of literature on this topic. The pooled HRs are dependent on certain traits of the published studies—availability, quality, and methods—and these might be hampered by statistical heterogeneity and publication bias. We acknowledge a number of limitations that need to be considered when interpreting our findings. First, by excluding studies that did not report death outcomes, we cannot rule out the possibility of selection bias. Second, our analysis plan selected the most adjusted HR presented in the studies, which despite presenting the most conservative risk estimation, may result in outcome reporting bias. Because of statistical heterogeneity, funnel plots for detecting publication bias with the Begg or Egger test were considered not feasible.[42] We attempted to mitigate these biases by in-depth metaregression analyses, observing altogether a general coherence with the main metafindings. Because we based our search on English language−dominated sources, language bias cannot be excluded. Finally, and regarding the study

Table 2. Metaregression Analyses on Association Between Low Free T_3 Level and Mortality Risk

Comparison of Low (f) T_3	No. of Studies	Empirical Bayes Metaregression Pooled HR (95% CI)	*P*	I^2, %[a]
All-cause mortality				
Low (f) T_3, defined as < cohort-specific cutoffs vs < reference range	9	1.75 (0.97-3.14)	0.06	17.8
Total T_3 vs (f) T_3 measurements	9	1.16 (0.46-2.92)	0.7	54.1
In PD vs HD patients	8	2.57 (0.63-10.60)	0.2	49.9
Studies with follow-up > 36 vs 12-36 mo	9	0.83 (0.35-1.95)	0.6	58.0
Sample size ≥ 500 vs <500 patients	9	0.53 (0.33-0.84)	0.02	0
Adjusted for vs not adjusted for malnutrition, inflammation, and comorbid conditions	9	1.15 (0.37-3.51)	0.8	56.9
Cardiovascular mortality				
Low (f) T_3, defined as < cohort-specific cutoffs vs < reference range	5	2.04 (0.66-6.27)	0.1	0
Studies with follow up > 36 vs 12-36 mo	5	0.55 (0.14-2.07)	0.3	13.0
Adjusted for vs not adjusted for malnutrition, inflammation, and comorbid conditions	5	1.69 (0.42-6.86)	0.3	19.6

Abbreviations: CI, confidence interval; (f) T_3, free triiodothyronine; HD, hemodialysis; HR, hazard ratio; PD, peritoneal dialysis.
[a]I^2 represents the percentage of variation attributable to heterogeneity, typically categorized as low (0%-50%), moderate (51%-75%), or high (>75%).

exposure, it has been postulated that commonly used free T_4 assays may be inaccurate in ESRD given the described alterations in T_3 and T_4 levels and the metabolism of thyrotropin.

We found a consistent association between low T_3 level and increased risk for death in long-term dialysis patients. Being based on observational studies, our data cannot prove causality in the associations. However, experimental studies show that low T_3 level impairs cardiac tissue oxygen consumption, increases vascular resistance, and decreases cardiac output.[43,44] Observational studies in patients with CKD and those who progressed to ESRD suggest that low T_3 levels are linked to adverse intermediate surrogates, such as atherosclerosis,[33] vascular calcification,[20,41] arterial stiffness,[33,34] impaired flow-mediated vasodilation,[35,40] intravascular volume deficits and abnormal ventricular conduction,[36,37] and impaired cardiac function,[38] which could also explain the associations reported here. We found overall moderate heterogeneity in our estimates. Heterogeneity may be attributed in part to the use of different T_3 cutoffs and different laboratory methods and measurements of T_3 (free vs total). Other potential explanations related to differences in participant characteristics (eg, study population, varying follow-up time, sample size, and adjustment for confounding factors). However, stratified analyses yielded consistent estimates. Compared with studies that used cohort-based cutoffs (eg, tertiles), those using assay reference range appeared to have lower mortality risk; this may not be surprising if CKD (with or without ESRD) per se renders low T_3 values and thus cutoffs derived from healthy individuals may not correctly identify patients at risk. The mortality risk estimate associated with low T_3 levels was higher in patients with shorter follow-up, with smaller sample size, and undergoing PD treatment. This collectively may indicate a risk of publication bias and the scarcity of literature available. We also report consistency in the associations between low thyrotropin and low T_4 levels, although fewer studies examined these exposures. In our inclusion criteria, we considered only baseline thyroid hormone (T_3 and T_4) assessments. However, 2 additional reports address longitudinal thyroid hormonal states and found that persistently low T_3 and T_4 levels were associated with 2- to 4-fold higher risk for death in patients with ESRD,[9,10] perhaps offering further support to our hypothesis.

Our observations are in line with the evidence from general population studies suggesting that low thyroid hormone levels, even in subclinical forms, may negatively affect cardiovascular health and increase the risk for death.[45,46] This evidence includes various, but not all,[47] meta-analyses reporting an overall increased mortality risk in individuals without CKD with subclinical thyroid functional disorders, particularly among those with younger age,[48] heart failure,[49] high comorbid condition burden,[50] and higher thyrotropin levels.[51] Although the need to treat these subclinical disorders is recommended in some guidelines and consensus papers as a strategy to reduce cardiovascular risk,[52,53] there is a paucity of interventional data in patients with CKD and those who progressed to ESRD. An early interventional study showed that intake of physiologic doses of T_3 (50 mg/d) decreased thyrotropin levels and resulted in a borderline negative nitrogen balance (increased

protein catabolism) in patients with ESRD.[54] This may be the natural consequence of restoring thyroid function and in our opinion may be easily counteracted by increasing protein intake. Outside nephrology, short-term T_3 replacement therapy greatly improved the neuroendocrine profile and ventricular performance in patients with heart failure with low T_3 syndrome.[55] Before trials are conducted, other indirect approaches that may serve as proofs of concept include correcting acidosis,[56,57] oxidative stress,[58] or selenium deficiency.[59] In a placebo-controlled study of 30 euthyroid patients undergoing HD, exogenous T_4 administration over 3 months reduced lipoprotein(a) and total and low-density lipoprotein cholesterol levels, without evidence of thyrotoxicosis.[60] However, in a recent large observational study of patients with ESRD, hypothyroid patients receiving exogenous thyroid hormones were at the same risk for death compared with those without medication.[16]

In summary, all-cause and cardiovascular mortality was found to be consistently higher for long-term dialysis patients with thyroid function test result derangements. These derangements may represent an under-recognized risk factor, with a biologically plausible link to the poor clinical outcomes of this population. The observed associations of this meta-analysis raise the question of whether it would be cost-effective to screen for thyroid function among patients with ESRD and whether patients with subclinical signs of hypothyroidism would benefit from corrections of thyroid hormone deficiencies to the normal range.

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Contributions: Research idea and study design: HX, JJC; data acquisition: HX, NB; data analysis/interpretation: HX, NB, BL, CZ, JJC; statistical analysis: HX, NB; supervision or mentorship: BL, JJC. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. HX and JJC take responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Description and characteristics of excluded observational studies reporting association between thyroid function test derangements and CV surrogates.

Table S2: Description of covariates used in fully adjusted mortality HRs selected for meta-analysis.

Table S3: Sensitivity meta-analysis on association between low free T_3 and mortality risk: omission of single studies.

Figure S1: Quality assessment of included studies.

Figure S2: Individual quality assessment of included studies.

Item S1: Electronic search strategy.

Item S2: Study protocol.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.06.023) is available at www.ajkd.org

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