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ORIGINAL ARTICLE

The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease

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ABSTRACT

Background. Recent studies have shown an increasing risk of hypothyroidism with incrementally lower estimated glomerular filtration rate (eGFR) in cohorts comprised of patients with normal to mildly impaired kidney function. We sought to confirm these findings in a nationally representative cohort of Veterans Affairs patients with moderate-to-severe chronic kidney disease (CKD).

Methods. This study examined the association between kidney function and hypothyroidism among 461 607 veterans with Stage 3 to 5 CKD who underwent repeated measurements of serum creatinine and thyrotropin (TSH) at identical time points between October 2004 and September 2006. Kidney function was defined by eGFR using the Chronic Kidney Disease Epidemiology Collaboration formula. In primary analyses, the association between eGFR and hypothyroidism (defined as serum TSH > 5 mIU/L and/or receipt of thyroid

hormone supplementation) was estimated using multivariable random effects logistic regression. In secondary analyses, the association between eGFR and serum TSH level was estimated using multivariable random effects linear regression.

Results. At baseline, 68.9, 25.5, 5.3 and 0.3% of patients had Stage 3A, 3B, 4 and 5 CKD, respectively. For every 10 mL/min/1.73 m^2 lower eGFR, there was an 18% higher risk of hypothyroidism: adjusted odds ratio 1.18 [95% confidence interval (CI) 1.17–1.20, $P < 0.001$]. In secondary analyses, we observed that a 10 mL/min/1.73 m^2 lower eGFR was associated with a 0.11 mIU/L higher serum TSH (95% CI 0.10–0.11 mIU/L higher serum TSH, $P < 0.001$).

Conclusions. In a nationally representative cohort of patients with moderate-to-severe CKD, there is an inverse association between eGFR and risk of hypothyroidism.

Keywords: chronic kidney disease, estimated glomerular filtration rate, hypothyroid, thyroid

INTRODUCTION

Chronic kidney disease (CKD) is a highly prevalent condition in the US population that is associated with a wide range of adverse sequelae [1]. Various endocrine disorders (e.g. secondary hyperparathyroidism, insulin resistance) have been recognized as extra-renal complications of CKD, and as potential predictors of morbidity and mortality in this population [2, 3]. These endocrine derangements include thyroid functional disease, and in particular hypothyroidism, typically ascertained using biochemical tests [i.e. elevated serum thyrotropin (TSH) with a low or normal thyroxine (T4) level] [4]. Case series have observed that hypothyroid patients have reduced renal plasma flow and glomerular filtration rate (GFR) measured by creatinine-based estimating equations and isotopic scans, which were reversed with thyroid hormone supplementation [5, 6]. Corroborating these data are several cross-sectional population-based studies showing that there is an increasing prevalence of hypothyroidism with incrementally impaired kidney function [7–10].

However, interpretation of these data are limited by residual confounding (i.e. serum TSH levels may be influenced by illness states associated with CKD in the absence of thyroid pathology) [11], and utilization of creatinine-based estimating equations that may misclassify kidney function particularly at estimated glomerular filtration rate (eGFR) levels >60 mL/min/1.73 m^2 [i.e. Modification of Diet in Renal Disease (MDRD) formula in lieu of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [12,13]]. Furthermore, the degree to which these findings apply to populations with moderate-to-severely impaired kidney function remains widely uncertain, as previous studies were largely comprised of participants with normal–to-mildly impaired kidney function with a lower comorbidity burden than that observed in US CKD patients [7, 9, 10]. To address these limitations, we sought to validate findings in a more broadly representative population with moderate-to-severe CKD. This study therefore was designed to estimate the association between eGFR, and hypothyroidism among a contemporary cohort of CKD patients receiving care within the national Veterans Affairs (VA) Health Care System.

MATERIALS AND METHODS

Study cohort

We conducted analyses using administrative data from the national VA Health Care System, the largest integrated healthcare system in the USA. The national VA database aggregates longitudinal information on veterans' sociodemographics, diagnostic and procedural codes, laboratory results, medications, ambulatory and inpatient encounters and vital status, and has been employed in numerous epidemiologic studies [14]. The study protocol was approved by the Memphis VA Medical Center Institutional Review Board.

The source cohort was previously described in detail [14]. Briefly, it consisted of all patients with an eGFR of <60 mL/min/1.73 m^2 measured between 1 October 2004 and 30 September 2006. Patients were included if they had at least one or more serum creatinine value(s) and at least one or more serum TSH value(s) measured during or after this period. Patients were excluded if they received thyroid suppressive medications (e.g. anti-thyroid drugs, iodine therapy). Given that the population of interest was non-dialysis-dependent CKD patients, we excluded patients receiving dialysis between the period of 1 October 2004 and 30 September 2006, as ascertained from VA Centers of Medicaid and Medicare files.

Assessment of kidney function, thyroid functional status and comorbidities

The exposure of interest was kidney function, which was defined by eGFR calculated from serum creatinine measurements and sociodemographic data using the CKD-EPI formula [13]. The outcome of interest was thyroid functional status, which was ascribed in three ways. In primary analyses, we defined thyroid functional status using laboratory and prescription dispensation data: patients with an elevated serum TSH (defined as TSH > 5 mIU/L) [15] and/or receipt of exogenous thyroid hormone supplementation [exogenous T4, exogenous triiodothyronine (T3) or combination T3/T4 therapy] were considered to be hypothyroid, whereas patients who neither had an elevated TSH nor received thyroid hormone supplementation were ascribed as being non-hypothyroid. To make distinction between previously hypothyroid patients whose thyroid functional status was restored by exogenous thyroid hormone supplementation versus those who remained hypothyroid, we also separately considered patients with untreated/partially treated hypothyroidism (defined as TSH > 5 mIU/L, irrespective of treatment status) in sensitivity analyses. In secondary analyses, we then examined thyroid functional status using serum TSH. Data on comorbidities including the presence of coronary heart disease (CHD; defined as the presence of diagnostic codes for coronary artery disease, angina or myocardial infarction or procedure codes for percutaneous coronary interventions or coronary artery bypass grafting), congestive heart failure (CHF), liver disease, malignancy, chronic lung disease, rheumatologic disease and peptic ulcer disease were collected

from the VA Inpatient and Outpatient Medical SAS Datasets with the use of International Classification of Diseases, Ninth Revision diagnostic and procedure codes and Current Procedural Terminology codes recorded between 1 October 2004 and 30 September 2006. The Charlson Comorbidity Index was calculated using the Deyo modification for administrative datasets, without including CKD [16].

Statistical analyses

Using repeated measures of kidney function and thyroid functional status assessed at identical points in time, we examined the association between eGFR as a time-varying exposure and thyroid functional status as a longitudinal outcome. In primary analyses, we first examined the association between eGFR and thyroid functional status defined as a binary outcome using multivariable-adjusted random effects logistic regression models. Given that serum TSH levels may be influenced by sociodemographics (e.g. age, race/ethnicity) and comorbidity status (i.e. nonthyroidal illness), all multivariable regression models were adjusted for age (in 10-year increments); sex; race/ethnicity (non-Hispanic White, non-Hispanic Black and Hispanic, referred to as Caucasian, African-American and Hispanic for the remainder of this report; and missing or other race/ethnicity); presence of baseline CHD, CHF, liver disease, malignancy, chronic lung disease, rheumatologic disease, peptic ulcer disease and Charlson comorbidity index. In sensitivity analyses, we (i) incrementally adjusted for baseline statin use and baseline cholesterol level, and (ii) excluded patients with a suppressed TSH (<0.5 mIU/L) level. In secondary analyses, we examined the association between eGFR and serum TSH as a continuous outcome using multivariable-adjusted random effects linear regression models. Given that thyroid hormone treatment was not included in this secondary exposure definition, we also conducted sensitivity analyses in which we excluded patients receiving exogenous thyroid hormone supplementation. Analyses were performed using Stata MP version 11 (StataCorp, College Station, Texas).

RESULTS

Study population description

Among 559 962 veterans with Stage 3 to 5 CKD, 83.7% had at least one serum TSH measured during the study period. The distribution of baseline characteristics among patients with versus without TSH measurement(s) was overall similar (data not shown). After applying the inclusion/exclusion criteria, among 467 112 eligible patients the mean ± SD age was 74.3 ± 9.2, and 97.0% of patients were male, 88.0% were Caucasian and 39.3% had diabetes. Using the CKD-EPI formula, we observed that 68.9, 25.5, 5.3 and 0.3% of patients had Stage 3A, 3B, 4 and 5 CKD (eGFR: 45 to 59, 30 to <45, 15 to <30 and <15 mL/min/1.73 m^2), respectively. Among patients with TSH measurement(s), 8.0% had an elevated TSH, 21.0% were receiving thyroid hormone supplementation and 23.3% had either an elevated TSH or receipt of thyroid hormone supplementation at baseline. In comparison to patients who neither had an elevated TSH nor received thyroid hormone supplementation (i.e. non-hypothyroid), hypothyroid patients tended to be older; had a lower mean eGFR; were more likely to be Caucasian, had a more advanced stage of CKD (e.g. Stage 3B or 4 CKD), CHD or CHF; and were less likely to be African-American (Table 1).

Table 1. Baseline characteristics among all national VA patients with CKD who underwent ≥1 TSH measurement, according to thyroid functional status

	Thyroid functional status*	
	Non-hypothyroid (n = 358 233)	Hypothyroid (n = 108 879)
% of patients with ≥1 TSH measurement	76.7	23.3
Age (years)	73.8 ± 9.2	75.9 ± 8.9
Female (%)	2.5	4.9
Race/ethnicity		
Non-Hispanic White (%)	87.7	92.9
Non-Hispanic Black (%)	9.6	4.4
Hispanic (%)	1.2	1.5
Other/Missing (%)	1.5	1.1
Baseline eGFR (mL/min/1.73 m^2)	50.6 ± 12.9	48.4 ± 12.7
CKD stage		
Stage 3A (%)	70.5	63.3
Stage 3B (%)	24.4	29.4
Stage 4 (%)	4.8	6.9
Stage 5 (%)	0.3	0.4
Charlson comorbidity index	3.7 ± 1.8	3.9 ± 1.9
CHD (%)	41.9	46.9
Diabetes mellitus (%)	39.2	39.5
CHF (%)	13.2	17.7
Liver disease (%)	0.6	0.8
Malignancy (%)	17.1	18.0
Chronic lung disease (%)	22.9	24.3
Dementia (%)	2.0	2.3
Rheumatologic disease (%)	2.0	2.4
Peptic ulcer disease (%)	2.8	2.7
Statin use (%)	69.0	69.9
Cholesterol level (mg/dL)	170 ± 35	168 ± 36

*All P-values < 0.001 except for diabetes mellitus in which the P-value was 0.05.

Association between eGFR and thyroid functional status

We first conducted analyses examining the association between kidney function and risk of hypothyroidism among all patients with complete covariate data (n = 461 607). In multivariable-adjusted analyses, we observed that for every 10 mL/min/1.73 m^2 lower eGFR, there was an 18% higher risk of hypothyroidism: adjusted odds ratio (aOR) 1.18 [95% confidence interval (CI) 1.17–1.20, P < 0.001]. When we incrementally adjusted for baseline statin use and baseline statin use + baseline cholesterol level, the associations remained statistically significant: aOR 1.18 (95% CI 1.16–1.20, P < 0.001) and aOR 1.13 (95% CI 1.11–1.15, P < 0.001), respectively (Table 2). In sensitivity analyses that excluded patients with low serum TSH levels < 0.5 mIU/L (n = 6069), the association also remained significant: aOR 1.18 (95% CI 1.16–1.20, P < 0.001).

In sensitivity analyses, we then examined the association between kidney function and risk of untreated/partially treated hypothyroidism among all patients with complete covariate

Table 2. Association between eGFR and thyroid function in national VA patients with CKD

	Multivariable adjusted[a]		Multivariable + statin adjusted[b]		Multivariable + statin + cholesterol adjusted[c]	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Risk of hypothyroidism[d]						
↓ eGFR 10 mL/min/1.73 m^2	1.18 (1.17–1.20)	<0.001	1.18 (1.16–1.20)	<0.001	1.13 (1.11–1.15)	<0.001
Risk of untreated or partially treated hypothyroidism[e]						
↓ eGFR 10 mL/min/1.73 m^2	1.09 (1.08–1.10)	<0.001	1.09 (1.08–1.10)	<0.001	1.09 (1.08–1.10)	<0.001

[a]Adjusted for age, sex, race/ethnicity, Charlson comorbidity index, CHD, CHF, chronic lung disease, liver disease, malignancy, rheumatologic disease and peptic ulcer disease (n = 461 607).
[b]Adjusted for covariates in multivariable-adjusted model, plus baseline statin use (n = 461 607).
[c]Adjusted for covariates in multivariable-adjusted model, plus baseline statin use and baseline cholesterol level (n = 317 847).
[d]Hypothyroidism defined as serum TSH > 5 mIU/L or receipt of thyroid hormone supplementation. Risk of hypothyroidism estimated using random effects logistic regression.
[e]Untreated or partially treated hypothyroidism defined as serum TSH > 5 mIU/L, with or without receipt of thyroid hormone supplementation. Risk of untreated or partially treated hypothyroidism estimated using random effects logistic regression.

Table 3. Association between eGFR and serum TSH level in national VA patients with CKD

	Δ in serum TSH level[a]			
	Multivariable adjusted[b]		Multivariable adjusted + exclusion of thyroid hormone supplementation users[c]	
	↑ TSH (95% CI)	P-value	↑ TSH (95% CI)	P-value
↓ eGFR 10 mL/min/1.73 m^2	0.11 (0.10–0.11)	<0.001	0.03 (0.02–0.03)	<0.001

[a]Units in mIU/L. Change in serum TSH estimated using random effects linear regression.
[b]Analyses are adjusted for age, sex, race/ethnicity, Charlson comorbidity index, CHD, CHF, chronic lung disease, liver disease, malignancy, rheumatologic disease and peptic ulcer disease (n = 461 607).
[c]Analyses are adjusted for age, sex, race/ethnicity, Charlson comorbidity index, CHD, CHF, chronic lung disease, liver disease, malignancy, rheumatologic disease and peptic ulcer disease; patients receiving thyroid hormone supplementation excluded (n = 364 454).

data. In multivariable-adjusted analyses, we observed that for every 10 mL/min/1.73 m^2 lower eGFR, there was a 9% higher risk of untreated/partially treated hypothyroidism: aOR 1.09 (95% CI 1.08–1.10, P < 0.001). In analyses incrementally adjusted for baseline statin use and baseline statin use + baseline cholesterol level, the estimates were unchanged and remained statistically significant (Table 2).

Association between eGFR and serum TSH level

In analyses examining the association between kidney function and change in serum TSH among all patients with complete covariate data (n = 461 607), we observed that a 10 mL/min/1.73 m^2 lower eGFR was associated with a 0.11-mIU/L higher serum TSH (95% CI 0.10–0.11 mIU/L higher serum TSH, P < 0.001). In sensitivity analyses that excluded patients receiving thyroid hormone supplementation, a 10 mL/min/1.73 m^2 lower eGFR was significantly associated with a higher serum TSH, albeit of a smaller magnitude: 0.03-mIU/L higher serum TSH (95% CI 0.02–0.03 mIU/L higher serum TSH, P < 0.001) (Table 3).

DISCUSSION

Among a large, nationally representative cohort of veterans with CKD, we observed that nearly one-quarter of patients had hypothyroidism ascertained by laboratory tests or receipt of thyroid hormone supplementation. Moreover, we demonstrated that there was a significant association between lower eGFR and risk of hypothyroidism independent of age, sex, race and comorbidity status, and these associations were robust across a number of sensitivity analyses that incrementally adjusted for statin use and cholesterol level; that separately considered hypothyroid patients who were untreated/partially treated versus those whose thyroid functional status was restored with treatment; and that excluded patients with suppressed TSH levels.

Our findings add to a growing body of literature demonstrating a relationship between impaired kidney function and hypothyroidism. Several epidemiologic studies that have largely been conducted within European-based cohorts have demonstrated an inverse association between eGFR and serum TSH levels and/or risk of hypothyroidism [7, 8, 10]. These include a recent study conducted among 558 elderly patients ≥85 years of age from the Leiden-85-Plus cohort showing that hypothyroid patients (including those with subclinical hypothyroidism) had lower eGFR compared with their euthyroid counterparts in cross-sectional analyses; however, an association between lower baseline thyroid function and a decline in kidney function over time was not observed in longitudinal analyses [10]. In the largest US-based study that has examined the association between hypothyroidism and kidney function to date, Lo *et al.* [9] demonstrated that there is a higher prevalence of hypothyroidism

with incrementally lower categories of eGFR among Third National Health and Nutrition Examination Survey participants: 5.4, 10.9, 20.4, 23.0 and 23.1% with eGFRs of ≥90, 60–89, 45–59, 30–44 and <30 mL/min/1.73 m^2, respectively. However, across these collective studies there was a low representation of patients with moderate-to-severe kidney dysfunction (i.e. disproportionate prevalence of patients with normal-to-mildly impaired kidney function) and associated comorbidities (e.g. diabetes) that limits the generalizability of these findings to patients with advanced CKD. In addition, interpretation of these data is limited by (i) the utilization of the MDRD equation in lieu of the CKD-EPI formula for eGFR estimation, which may have resulted in misclassification of kidney function [12, 13], as well as (ii) the inability to account for illness states resulting in TSH fluctuations in the absence of thyroid pathology (i.e. nonthyroidal illness) [11].

To our knowledge, our study is the largest examination of the relationship between eGFR and thyroid functional status conducted to date. Using the national VA data with exceptional capture of sociodemographic, comorbidity, laboratory and prescription dispensation data and the CKD-EPI equation to more accurately estimate eGFR, we confirmed that the association between impaired kidney function and hypothyroidism is robust even after accounting for severity of illness using the Charlson comorbidity index, as well as individual comorbid states.

The observational nature of our study cannot establish a causal relationship between decreased eGFR and hypothyroidism. While the mechanistic link and directionality of association between these two entities remain uncertain, it has been hypothesized that hypothyroidism may directly worsen kidney function via reductions in cardiac output, increases in peripheral vascular resistance, intra-renal vasoconstriction and alterations in glomerular structure (e.g. decreased glomerular volume and area) [17, 18]. A recent cohort study has shown that thyroid hormone replacement in subclinically hypothyroid patients with CKD is associated with greater kidney function preservation versus nontreatment, suggesting that hypothyroid-related perturbations in kidney function may be modifiable [19]. Conversely, it has also been suggested that kidney disease may predispose to thyroid hormone derangements due to iodine retention, metabolic acidosis, medications, mineral deficiencies (e.g. selenium), exposure to dialytic procedures (i.e. peritoneal effluent losses) and metabolic adaptation to malnutrition [18, 20–22].

The strengths of our study include its examination of a large sample size of nationally representative CKD patients with comprehensive capture of sociodemographics, serum TSH and creatinine and prescription data; utilization of a more accurate metric for eGFR estimation and classification (i.e. CKD-EPI equation [12,13]); and comprehensive adjustment for comorbidity factors as potential confounders of the kidney–thyroid function association. However, several limitations bear mention. First, the indications for which TSH was measured are not known, and it is possible that the requirement for TSH measurement may have resulted in a cohort with a higher-than-average perceived risk of thyroid functional disease. However, TSH levels were measured in the vast majority (83.7%) of national veterans with Stage 3 to 5 CKD, and we observed a balanced distribution of baseline covariates among patients with versus without TSH measurement(s). Second, our study population was largely comprised of males versus females (97.0 versus 3.0%, respectively), which may limit generalizability to female patients. However, the overall large sample size of our study population allowed us to examine large absolute number of female veterans (n = 14 188), enabling us to conduct the largest study of kidney function and hypothyroidism in female CKD patients than has heretofore been possible. Third, while serum TSH is considered the most sensitive and specific single measure of thyroid function [4], we were unable to more granularly define thyroid functional status using concomitant serum TSH and free T4 levels due to sparse free T4 data. Fourth, serum TSH and creatinine levels were measured at the discretion of medical providers, and as a result the frequencies of longitudinal TSH and eGFR measurements that patients contributed to the analyses were heterogeneous. Lastly, hypothyroidism may influence serum creatinine levels due to changes in muscle metabolism and volume status independent of its effects on GFR [18], and we cannot exclude the possibility of residual confounding by these factors and other unmeasured covariates.

In conclusion, our study supports an inverse association between eGFR and risk of hypothyroidism across the spectrum of CKD. Given the disproportionately high prevalence of hypothyroidism in kidney disease compared with the general population [9]; the exceedingly high morbidity and mortality of CKD patients and the paucity of modifiable factors for impaired kidney function, further study is needed to (i) delineate the mechanistic pathways linking hypothyroidism and CKD and (ii) determine the impact of exogenous thyroid hormone treatment on incident CKD and CKD progression.

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CONFLICT OF INTEREST STATEMENT

None declared.

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