MAYO CLINIC

ORIGINAL ARTICLE

Thyroid Status and Death Risk in US Veterans With Chronic Kidney Disease

Connie M. Rhee, MD, MSc; Kamyar Kalantar-Zadeh, MD, MPH, PhD; Vanessa Ravel, MPH; Elani Streja, MPH, PhD; Amy S. You, MS; Steven M. Brunelli, MD, MSCE; Danh V. Nguyen, MS, PhD; Gregory A. Brent, MD; and Csaba P. Kovesdy, MD

Abstract

Objective: Given that patients with non–dialysis-dependent chronic kidney disease (NDD-CKD) have a disproportionately higher prevalence of hypothyroidism compared with their non-CKD counterparts, we sought to determine the association between thyroid status, defined by serum thyrotropin (TSH) levels, and mortality among a national cohort of patients with NDD-CKD.

Patients and Methods: Among 227,422 US veterans with stage 3 NDD-CKD with 1 or more TSH measurements during the period October 1, 2004, to September 30, 2012, we first examined the association of thyroid status, defined by TSH categories of less than 0.5, 0.5 to 5.0 (euthyroidism), and more than 5.0 mIU/L, with all-cause mortality. We then evaluated 6 granular TSH categories: less than 0.1, 0.1 to less than 0.5, 0.5 to less than 3.0, 3.0 to 5.0, more than 5.0 to 10.0, and more than 10.0 mIU/L. We concurrently examined thyroid status, thyroid-modulating therapy, and mortality in sensitivity analyses.

Results: In expanded case-mix adjusted Cox analyses, compared with euthyroidism, baseline and time-dependent TSH levels of more than 5.0 mIU/L were associated with higher mortality (adjusted hazard ratios [aHRs] [95% CI], 1.19 [1.15-1.24] and 1.23 [1.19-1.28], respectively), as were baseline and time-dependent TSH levels of less than 0.5 mIU/L (aHRs [95% CI], 1.18 [1.15-1.22] and 1.41 [1.37-1.45], respectively). Granular examination of thyroid status showed that incrementally higher TSH levels of 3.0 mIU/L or more were associated with increasingly higher mortality in baseline and time-dependent analyses, and TSH categories of less than 0.5 mIU/L were associated with higher mortality (reference, 0.5-<3.0 mIU/L) in baseline analyses. In time-dependent analyses, untreated and undertreated hypothyroidism and untreated hyperthyroidism were associated with higher mortality (reference, spontaneous euthyroidism), whereas hypothyroidism treated-to-target showed lower mortality.

Conclusion: Among US veterans with NDD-CKD, high-normal TSH (≥3.0 mIU/L) and lower TSH (<0.5 mIU/L) levels were associated with higher death risk. Interventional studies identifying the target TSH range associated with the greatest survival in patients with NDD-CKD are warranted.

 ■ Mayo Clin Proc. 2018;93(5):573-585

Thyroid dysfunction is a highly prevalent yet underrecognized endocrine complication affecting a large proportion of patients with chronic kidney disease (CKD).[1,2] Several large population-based studies found that hypothyroidism is increasingly more common with incrementally impaired kidney function.[3-7] Data from 14,623 participants in the Third National Health and Nutrition Examination Survey have shown that the prevalence of hypothyroidism was 5.4%, 10.9%, 20.4%, 23.0%, and 23.1% among those with estimated glomerular filtration rates (eGFRs) of 90 or more, 60 to 89, 45 to 59, 30 to 44, and less than 30 mL/min/1.73 m^2, respectively.[5] More recently, among a large national cohort of 461,607 US veterans with stage 3 to 5 CKD, for every 10 mL/min/1.73 m^2 decrement in eGFR, there was an 18% higher likelihood of hypothyroidism.[6] Although there are comparatively fewer reports in patients with end-stage renal disease (ESRD), a similarly high prevalence (~22%) of hypothyroidism has been observed in large dialysis cohorts.[8,9]

In the general population, adverse cardiovascular sequelae may result from untreated

For editorial comment, see page 555

From Harold Simmons Center for Chronic Disease Research and Epidemiology, University of California Irvine School of Medicine, Orange, CA (C.M.R., K.K.-Z., V.R., E.S.,

Affiliations continued at the end of this article.

hypothyroidism (eg, altered cardiac structure and function, endothelial dysfunction, dyslipidemia, accelerated atherosclerosis, and electrophysiologic changes[10-13]) as well as with hyperthyroidism (eg, atrial fibrillation, heart failure, and coronary ischemia[12,14]). Hence, this high burden of thyroid dysfunction may have an important bearing on the survival of patients with kidney disease, who suffer from disproportionately high cardiovascular death risk (~40% of deaths[15,16]). Indeed, a growing body of evidence reports that hypothyroidism, defined by elevated serum thyrotropin (TSH) levels as the most sensitive and specific clinical goal standard of thyroid function assessment,[17-19] is associated with higher mortality in some,[8,9,20,21] but not all,[22] studies of the dialysis population. Recent data have also corroborated a link between hyperthyroidism and sudden cardiac death among hemodialysis patients from the *Die Deutsche Diabetes Dialyse Studie* (also known as the 4D Trial),[22] and with all-cause mortality in a national peritoneal dialysis cohort.[9] However, little is known about the association between thyroid status and mortality risk in patients with CKD who are non–dialysis-dependent (NDD).

To address this knowledge gap, we conducted a study examining the relationship between thyroid status and mortality risk among a large longitudinal cohort of US veterans with stage 3 CKD and repeated measures of serum TSH over time. We hypothesized that both higher and lower TSH levels were independently associated with higher mortality risk in this nationally representative NDD-CKD cohort. On the basis of previous studies of thyroid status and mortality in the dialysis population,[8,20] we were also specifically interested in examining the TSH threshold of 3.0 mIU/L or more as the level above which higher mortality is observed in patients with NDD-CKD.

PATIENTS AND METHODS

Source Cohort

We conducted a historical cohort study using data from the "Racial and Cardiovascular Risk Anomalies in Chronic Kidney Disease" study, constructed to examine US veterans with incident CKD who underwent care within the Veterans Affairs (VA) health care system over the period of October 1, 2004, to September 30, 2012.[23-26] Patients were included provided that they underwent at least 1 TSH measure anytime during the study period; had the requisite covariates needed to calculate eGFR (eg, age, race, and serum creatinine) within 1 year of study entry (ie, date of the baseline TSH); and had stage 3 CKD (eGFR, 30-<60 mL/min/1.73 m^2) at study entry. Patients were excluded if they were receiving dialysis at the time of study entry; had an improbable TSH level (ie, 0 mIU/L); or had an implausible follow-up time value. The study was approved by the institutional review committees of the Memphis and Tibor Rubin VA Medical Centers.

Exposure Ascertainment

The exposure of interest was thyroid status defined by serum TSH concentration (irrespective of treatment status). In primary analyses, we examined thyroid status categorized as TSH levels of more than 5.0, 0.5 to 5.0, and less than 0.5 mIU/L (based on thresholds used in the general population for ascertainment of hypothyroidism, euthyroidism, and hyperthyroidism, respectively).[8,9,17] In secondary analyses, we examined thyroid status using more granular categorizations of TSH, defined according to the usual TSH ranges for these designations: overt-hypothyroid (>10.0 mIU/L), subclinical-hypothyroid (>5.0-10.0 mIU/L), high-normal (3.0-5.0 mIU/L), low-normal (0.5-<3.0 mIU/L), subclinical-hyperthyroid (0.1-<0.5 mIU/L), and overt-hyperthyroid (<0.1 mIU/L) ranges.[8,9,20] We were specifically interested in the TSH threshold of 3.0 mIU/L or more as the level above which higher mortality may be observed.[8,20] We also examined TSH as a continuous predictor of mortality using restricted cubic spline analyses with knots defined at the 33rd and 66th percentiles of observed TSH values.

We first examined the association between *baseline thyroid status* and all-cause mortality to ascertain *long-term* associations of thyroid status with death risk.[27] Given that underlying illness may influence serum TSH levels in the absence of true thyroid functional disease while also increasing patients' risk of death, we conducted 2 types of sensitivity analyses of baseline thyroid status and mortality risk: (1) analyses that included a 30-day lag period between the date of baseline TSH measurement and start

Mayo Clin Proc. ■ May 2018;93(5):573-585 ■ https://doi.org/10.1016/j.mayocp.2018.01.024
www.mayoclinicproceedings.org