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Thyroid Status, Quality of Life, and Mental Health in Patients on Hemodialysis

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Abstract

Background and objectives In the general population, there is increasing recognition of the effect of thyroid function on patient-centered outcomes, including health-related quality of life and depression. Although hypothyroidism is highly prevalent in patients on hemodialysis, it is unknown whether thyroid status is a risk factor for impaired health-related quality of life or mental health in this population.

Design, setting, participants, & measurements We examined the association of thyroid status, defined by serum thyrotropin, with health-related quality of life and depressive symptoms over time in a prospective cohort of 450 patients on hemodialysis from 17 outpatient dialysis facilities from May of 2013 to May of 2015 who underwent protocolized thyrotropin testing, Short-Form 36 surveys, and Beck Depression Inventory-II questionnaires every 6 months. We examined the association of baseline and time-dependent thyrotropin categorized as tertiles and continuous variables with eight Short-Form 36 domains and Beck Depression Inventory-II scores using expanded case mix plus laboratory linear mixed effects models.

Results In categorical analyses, the highest baseline thyrotropin tertile was associated with a five-point lower Short-Form 36 domain score for energy/fatigue (P=0.04); the highest time-dependent tertile was associated with a five-point lower physical function score (P=0.03; reference: lowest tertile). In continuous analyses, higher baseline serum thyrotropin levels (+Δ1 mIU/L) were associated with lower role limitations due to physical health (β=−1.3; P=0.04), energy/fatigue (β=−0.8; P=0.03), and pain scores (β=−1.4; P=0.002), equivalent to five-, three-, and five-point lower scores, respectively, for every 1-SD higher thyrotropin. Higher time-dependent thyrotropin levels were associated with lower role limitations due to physical health scores (β=−1.0; P=0.03), equivalent to a three-point decline for every 1-SD higher thyrotropin. Baseline and time-dependent thyrotropin were not associated with Beck Depression Inventory-II scores.

Conclusions In patients on hemodialysis, higher serum thyrotropin levels are associated with impaired health-related quality of life across energy/fatigue, physical function, and pain domains. Studies are needed to determine if thyroid-modulating therapy improves health-related quality of life of patients on hemodialysis with thyroid dysfunction.

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Introduction

Epidemiologic data show that patients with advanced CKD, including those receiving dialysis, have a substantially higher prevalence of thyroid disease, including hypothyroidism, compared with their non-CKD counterparts (1–7). Furthermore, large cross-sectional studies have shown an increasingly higher burden of hypothyroidism with incrementally impaired kidney function (1,4). Although increasing evidence shows that hypothyroidism, defined by an elevated serum thyrotropin (TSH) level, is associated with higher mortality in patients on dialysis (3,5), the underlying mechanisms for heightened death risk (*e.g.*, cardiovascular, metabolic, and hematologic pathways) remain undefined (8).

In the general population, hypothyroidism has pervasive effects on multiple end organs, among which the neuropsychiatric system is a major target of thyroid hormone action (9,10). Animal models have shown that thyroid hormones influence noradrenergic and serotonergic neurotransmission in the pathogenesis of depression (11–17). In humans, functional brain imaging studies have shown that thyroid hormone affects brain metabolism in patients with hypothyroid and mood disorders (18). Although population-based studies of thyroid dysfunction and depression have yielded mixed findings, thyroid hormone supplementation has been used in clinical practice to augment or accelerate response to antidepressants among patients with depressive disorders (10,12,19). In addition to mental health impairments, untreated hypothyroidism has been associated with overall reductions in health-related quality of life (HRQOL) (20).

These observations bear particular relevance to patients on dialysis who disproportionately suffer from impaired HRQOL and depression compared with the general population (21–25). Left untreated, these disorders may lead to higher risk of cardiovascular disease, hospitalization, and mortality (26–29). Recognizing its importance, the US Center for Medicare Services Conditions for Coverage mandates that dialysis facilities perform routine measurements of HRQOL (30,31). Hence, there is compelling need to identify novel and modifiable risk factors for reduced quality of life (QOL) and depression in patients on dialysis.

Although multiple factors concomitantly contribute to the morbidity and mortality of patients on dialysis, there are remaining knowledge gaps in how endocrine disorders influence their health and survival. Despite the high prevalence of hypothyroidism in patients on dialysis, no studies have examined the association of thyroid status with patient-centered outcomes, such as HRQOL and mental health, in this population. Thus, we sought to determine whether thyroid status, defined by serum TSH levels measured at baseline and longitudinally, is associated with reduced HRQOL and depression over time in a prospective hemodialysis cohort.

Materials and Methods

Source Cohort

The study cohort consisted of adult patients on incident and prevalent hemodialysis from the Malnutrition, Diet and Racial Disparities in CKD (MADRAD) Study (ClinicalTrials.gov NCT01415570), an ongoing prospective cohort study examining the differential association between dietary factors and nutritional status among racial/ethnic hemodialysis subgroups (30). Every 6 months (semesters), participants underwent protocolized collection of information on sociodemographics, comorbidities, medications, and dialysis treatment characteristics; administration of questionnaires; serum collection; and laboratory testing during routine outpatient hemodialysis treatments.

In this MADRAD Substudy, patients were recruited from 17 outpatient dialysis facilities in southern California from May of 2013 to May of 2015. Patients were included if they underwent at least one or more serum TSH measurement (s), were age 18 years old or older at the time of study entry (defined as the time of the first TSH measurement), received thrice-weekly in-center hemodialysis for at least 4 consecutive weeks, and signed an institutional review board–approved consent form. For analyses of QOL, patients were required to have underwent a TSH measurement and Short Form-36 (SF-36) questionnaire administration during the same semester, the first instance of which was designated as the baseline semester (SF-36 cohort). For analyses of mental health, patients were required to have undergone a TSH measurement and Beck Depression Inventory-II (BDI-II) questionnaire administration during the same semester (BDI-II cohort). Patients were excluded if they were actively receiving peritoneal dialysis, had a life expectancy <6 months, or were unable to provide consent without a proxy. The study was approved by the institutional review committees from Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles and the University of California Irvine Medical Center.

Exposure Ascertainment

The exposure of interest was thyroid status defined by TSH. First, we examined the association of baseline TSH with outcomes, in which serum TSH levels were assessed at study entry. Second, because the effect of time-dependent exposure on outcomes may differ from the effect of baseline TSH at study entry, we also examined the association of time-dependent TSH with outcomes, in which time-updated TSH levels were used to account for changes in thyroid function over time. Each semester, all study patients underwent protocolized TSH testing of fresh serum samples obtained predialysis during weekday outpatient hemodialysis treatments that were largely nonfasting, which chronologically coincided with routine blood tests conducted at the dialysis facilities. All TSH measurements were conducted at a centralized laboratory in the University of California Irvine Medical Center Clinical Pathology Laboratory (second generation chemiluminescent immunoassay; Beckman Coulter, Chaska, MN; reference range =0.5–5.0 mIU/L).

Given that the normal TSH range in patients on dialysis remains undefined, in coprimary analyses, we examined TSH (*1*) categorized into tertiles of observed baseline values (defined as <1.28, ≥ 1.28–2.11, and >2.11 mIU/L) and (*2*) as a continuous variable. Other routine dialysis laboratory measurements were performed by the large dialysis organization's central laboratory based in Deland, Florida on a monthly or quarterly basis using automated methods.

Outcome Ascertainment

We examined the association of baseline and time-dependent thyroid function with two coprimary outcomes, namely (*1*) HRQOL ascertained using SF-36 surveys and (*2*) depression ascertained using BDI-II. The SF-36 is a patient-reported QOL assessment instrument validated in the general and hemodialysis populations (20,28) consisting of 36 questions grouped into eight domains/subscales (minimum to maximum score of 0–100 for each domain, with higher scores indicating a better state of health): physical functioning, role limitations due to physical health, pain, general health, energy/fatigue, social functioning, role limitations due to emotional problems, and emotional wellbeing. Because the objective of our study was to examine the effect of thyroid function on specific QOL domains, we examined the association of TSH with each individual subscale defined as continuous outcomes.

We analogously examined the association of thyroid function with the BDI-II score as a continuous outcome. The BDI-II is a psychometric test used to measure depression severity consisting of 21 multiple choice questions (minimum to maximum score range of 0–63) that has been validated in patients on hemodialysis (22,24,32). The total score for BDI-II surveys in which $<50\%$ of questions were unanswered was rescaled as follows: rescaled BDI-II score = (actual BDI-II score $\times$ total number of questions)/number of answered questions. The BDI-II surveys in which $>50\%$ of questions were unanswered were excluded from analysis.

Statistical Analyses

Baseline patient characteristics were presented for the SF-36 cohort (n=450). The baseline characteristics for the BDI-II cohort (n=444) were essentially the same and thus, were not provided. Multivariate linear mixed effects analyses were performed to examine the association of baseline and time-dependent TSH as categorical and continuous variables with SF-36 and BDI-II scores. The association between TSH and each outcome was examined using three nested linear mixed effects models: (*1*) unadjusted model: TSH level and time (month from baseline); (2) case mix model: unadjusted model covariates plus baseline case mix covariates consisting of age, sex, race, ethnicity, diabetes, and vintage; and (*3*) expanded case mix plus laboratory model: case mix model covariates plus expanded case mix covariates (body mass index, marital status, and insurance) and baseline laboratory measurements (serum albumin, normalized protein catabolic rate [nPCR], serum creatinine, and single-pool Kt/V).

In this study, we present results from the expanded case mix plus laboratory models in more detail, because results from unadjusted and case mix models were similar. In analyses of TSH as a continuous variable, to account for possible nonlinear associations (particularly at lower TSH ranges [<0.5 mIU/L]) with outcomes, we conducted sensitivity analyses that only considered patients in the euthyroid (TSH=0.5–5.0 mIU/L) and hypothyroid (TSH>5.0 mIU/L) ranges (*i.e.*, excluded 22 patients with TSH<0.5 mIU/L). We also examined for effect modification by sequentially adding interaction terms of each covariate and TSH level to the expanded case mix plus laboratory model. Modifier effects of all covariates were examined using baseline and time-dependent TSH as the main exposure variables.

Sensitivity analyses were conducted to examine the robustness of the main results after (*1*) excluding patients with exogenous thyroid hormone supplementation (thyroxine [T4], tri-iodothyronine [T3], and combination T4/T3 therapy; n=28) and (2) incremental adjustment for antidepressants (Supplemental Table 1) in addition to expanded case mix plus laboratory covariates. There were no instances of receipt of thyroid hormone suppressive therapy.

Baseline missing data were imputed using multiple imputation methods with ten imputed datasets. Missing baseline covariates included body mass index, serum albumin, nPCR, serum creatinine, and single-pool Kt/V (13%, 18%, 14%, 19%, and 16% of data). Analyses were implemented in SAS 9.4 PROC MIXED, MI, and MIANALYZE (SAS Institute, Cary, NC). Two-sided tests with P<0.05 were considered statistically significant after false discovery rate (FDR) adjustment was used to account for multiple comparisons (33).

Results

Study Cohort Characteristics

The final study cohort consisted of 450 patients who underwent at least one TSH measurement and the SF-36 survey during the same semester (SF-36 cohort), whereas 444 patients underwent both TSH and BDI-II testing during the same semester (BDI-II cohort) (Supplemental Figure 1). Approximately 35%, 45%, and 20% of patients in the SF-36 and BDI-II cohorts underwent one, two, and three repeated measurements, respectively, over time; one patient underwent four repeated measurements. Baseline characteristics of the SF-36 cohort showed that, compared with patients in the lowest TSH tertile, those in the highest tertile were less likely to be black, were more likely to be Hispanic, and had longer dialysis vintage (Table 1). The study cohort's mean±SD and minimum to maximum TSH values on the basis of baseline measurements were 2.20±2.90 and 0.07–39.4 mIU/L, respectively.

Thyroid Status Categorized as TSH Tertiles, QOL, and Depression

In the overall cohort, 35% of patients (n=156) had baseline data only. Among the remaining patients (n=294) who had at least two visits, the median (interquartile range) follow-up time was 12.4 (6.0–18.5) months. In baseline analyses, the highest TSH tertile was associated with a five-point lower SF-36 domain score for energy/fatigue versus the lowest tertile (P=0.04) (Table 2). In time-dependent analyses, the highest TSH tertile was associated with a five-point lower score for physical function (P=0.03) and showed a trend toward a lower energy/fatigue score versus the lowest tertile (β=−3.0; P=0.10). We did not observe a significant association between TSH tertiles and BDI-II score after FDR adjustment, although the overall association trends were similar to the main analyses.

Thyroid Status as a Continuous Variable, QOL, and Depression

Thyroid status examined as a continuous variable was also associated with several important QOL domains. Figure 1 and Table 3 summarize the estimates from the model fit, which are to be interpreted as the average change in SF-36 domain score associated with a 1-mIU/L change in TSH level. Higher baseline TSH level (+Δ1 mIU/L) was associated with a lower pain score (estimate [β]=−1.4; P=0.002). Thus, a 1-SD increase in TSH level on the basis of all repeated measure values (approximately +Δ3.4 mIU/L) was associated with a five-point decline in pain score, considered to be a clinically relevant difference in the SF-36 domain score (34). Higher baseline TSH was also associated with lower scores for role limitations due to physical health (β=−1.3; P=0.04) and energy/fatigue (β=−0.8; P=0.03). In addition, there was a trend toward an association between higher baseline TSH level (+Δ1 mIU/L) and lower scores for role limitations due to emotional problems (β=−1.3; P=0.06) and social functioning (β=−0.8; P=0.08). Similar findings were observed in analyses restricted to patients with euthyroid- and hypothyroid-range TSH values on study entry (Supplemental Table 2).

Similar to the baseline analyses, time-dependent TSH levels over time were negatively associated with scores for role limitations due to physical health. For example, a 1-mIU/L increase in TSH level over time was associated with a one-point decline in the SF-36 domain score for role limitations due to physical health (β=−1.0; P=0.03). Equivalently, a 1-SD increase in TSH on the basis of all repeated measure values (approximately +Δ3.4 mIU/L) was associated with a three-point decline in the SF-36

Q : 6

Table 1. Baseline characteristics of the Short Form-36 cohort according to serum thyrotropin tertiles (*n*=450)

Characteristics	TSH Tertiles				*P* Value
	Overall	Tertile 1	Tertile 2	Tertile 3	
Age mean±SD, yr	54.7±14.5	54.6±13.2	54.7±14.7	54.9±15.7	0.66
Women, %	46	46	45	47	0.98
Race, %					
Black	68	59	70	73	0.02
Nonblack	32	41	30	27	
Ethnicity, %					
Hispanic	51	59	53	41	<0.01
Non-Hispanic	49	41	47	59	
Diabetes, %	55	52	57	55	0.66
Vintage, mo, %					
<12	16	18	79	89	0.04
≥12	84	82	20	10	
Marital status, %					
Married	43	43	47	39	0.37
Nonmarried	57	57	53	61	
Primary insurance, %					
Medicare or Medicaid	77	76	74	81	0.60
Private	11	11	14	8	
Other/unknown	12	12	12	11	
Body mass index mean±SD, kg/m^2	28.0±6.8	27.8±5.9	27.8±6.5	28.4±7.8	0.98
Serum albumin mean±SD, g/dl	4.0±0.4	4.0±0.3	4.0±0.3	4.0±0.4	0.12
nPCR mean±SD, g/kg per day	1.0±0.3	1.0±0.3	1.0±0.3	1.0±0.3	0.92
Serum creatinine mean±SD, mg/dl	10.0±3.0	10.4±2.9	9.7±3.2	9.8±3.0	0.18
spKt/V mean±SD	1.65±0.34	1.62±0.30	1.68±0.36	1.65±0.35	0.39
Thyroid hormone supplementation use, %	3	7	6	6	0.95
Antidepressant medication use, %	3	1	5	3	0.26
Outcome measures at baseline					
BDI-II	11±9	11±10	11±8	12±9	0.34
Physical function	52±29	56±28	52±29	49±31	0.17
Role limitations due to physical health	40±42	42±43	38±39	41±43	0.69
Role limitations due to emotional problems	57±44	59±44	57±45	56±44	0.85
Energy/fatigue	50±22	52±24	51±21	46±22	0.05
Emotional wellbeing	72±19	73±20	73±18	71±19	0.72
Social functioning	65±27	64±27	67± 26	64±27	0.64
Pain	61±29	63±28	60±29	58±31	0.33
General health	47±21	48±21	45±19	46±23	0.41

TSH, thyrotropin; nPCR, normalized protein catabolic rate; spKt/V, single-pool Kt/V; BDI-II, Beck Depression Inventory-II.

domain score for role limitations due to physical health. There was also a trend toward an association between higher TSH levels over time (+Δ1 mIU/L) and lower scores for physical function (β=−0.5; P=0.06) and pain (β=−0.5; P=0.09). In analyses restricted to patients with euthyroid and hypothyroid TSH ranges on study entry, similar findings were observed, although associations between time-dependent TSH and role limitations due to physical health were no longer statistically significant (P=0.58) (Supplemental Table 2).

We did not observe a significant association between baseline or time-dependent TSH and the BDI-II score in expanded case mix plus laboratory models (Supplemental Table 3). Similar findings were observed in analyses restricted to patients with euthyroid and hypothyroid TSH ranges on study entry (Supplemental Table 2).

Adjustment covariates found to be important in the relationship between the main exposure, thyroid status, and the coprimary outcomes, SF-36 and BDI-II scores, are presented in Supplemental Tables 3 and 4, respectively (all covariates with P values <0.10 in the expanded case mix and laboratory model). We did not find that QOL or depression outcomes changed significantly over time after study entry (within 24 months of follow-up), except for the SF-36 domain energy/fatigue score, in which there was a statistically significant but modest effect size (β=+0.2; P=0.003).

Q : 3

Effect Modification of the Association between Thyroid Status and Outcomes

Age was found to be a potential effect modifier of the association of TSH level with the BDI-II score, emotional wellbeing, and general health (P interaction =0.05, P interaction <0.01, and P interaction =0.07, respectively) (Table 4). However, after FDR adjustment for multiple comparisons, interactions were no longer significant.

Table 2. Association between baseline thyrotropin and time-dependent thyrotropin categorized as tertiles and outcomes

Outcome and TSH Tertile Comparison or Parameter	Estimate (β)	95% CI		*P* Value
		Lower	Upper	
Baseline TSH				
BDI-II score				
Medium versus low	−0.1	−2.1	1.8	0.89
High versus low	1.4	−0.6	3.4	0.18
Physical function				
Medium versus low	−1.8	−7.5	4.0	0.55
High versus low	−4.1	−10.0	1.7	0.17
Role limitations due to physical health				
Medium versus low	−3.9	−12.2	4.4	0.36
High versus low	−3.0	−11.5	5.5	0.49
Role limitations due to emotional problems				
Medium versus low	−2.9	−11.5	5.7	0.51
High versus low	−5.4	−14.2	3.4	0.23
Energy/fatigue				
Medium versus low	−0.8	−5.4	3.9	0.75
High versus low	−5.1	−9.8	−0.4	0.04
Emotional wellbeing				
Medium versus low	0.1	−3.9	4.1	0.95
High versus low	−2.7	−6.7	1.4	0.20
Social functioning				
Medium versus low	2.6	−2.9	8.2	0.36
High versus low	−1.3	−6.9	4.4	0.66
Pain				
Medium versus low	−2.8	−8.8	3.2	0.37
High versus low	−4.9	−11.1	1.2	0.12
General health				
Medium versus low	−2.2	−6.6	2.3	0.34
High versus low	−2.4	−7.0	2.1	0.30
Time-dependent TSH				
BDI-II score				
Medium versus low	−0.3	−1.6	1.0	0.66
High versus low	1.1	−0.3	2.5	0.13
Physical function				
Medium versus low	−3.3	−7.3	0.7	0.11
High versus low	−4.9	−9.3	−0.5	0.03
Role limitations due to physical health				
Medium versus low	−1.4	−8.4	5.6	0.69
High versus low	−3.9	−11.2	3.5	0.30
Role limitations due to emotional problems				
Medium versus low	−3.2	−10.5	4.1	0.39
High versus low	−4.6	−12.3	3.1	0.24
Energy/fatigue				
Medium versus low	−0.2	−3.4	3.1	0.92
High versus low	−3.0	−6.6	0.6	0.10
Emotional wellbeing				
Medium versus low	−1.0	−4.0	2.0	0.51
High versus low	−1.5	−4.7	1.7	0.37
Social functioning				
Medium versus low	2.3	−2.0	6.6	0.29
High versus low	−1.1	−5.6	3.5	0.65
Pain				
Medium versus low	0.7	−3.7	5.0	0.76
High versus low	−3.9	−8.6	0.9	0.11
General health				
Medium versus low	−0.9	−4.0	2.1	0.55
High versus low	−0.5	−3.8	2.9	0.78

Q : 7 TSH, thyrotropin; 95% CI, 95% confidence interval; BDI-II, Beck Depression Inventory-II.

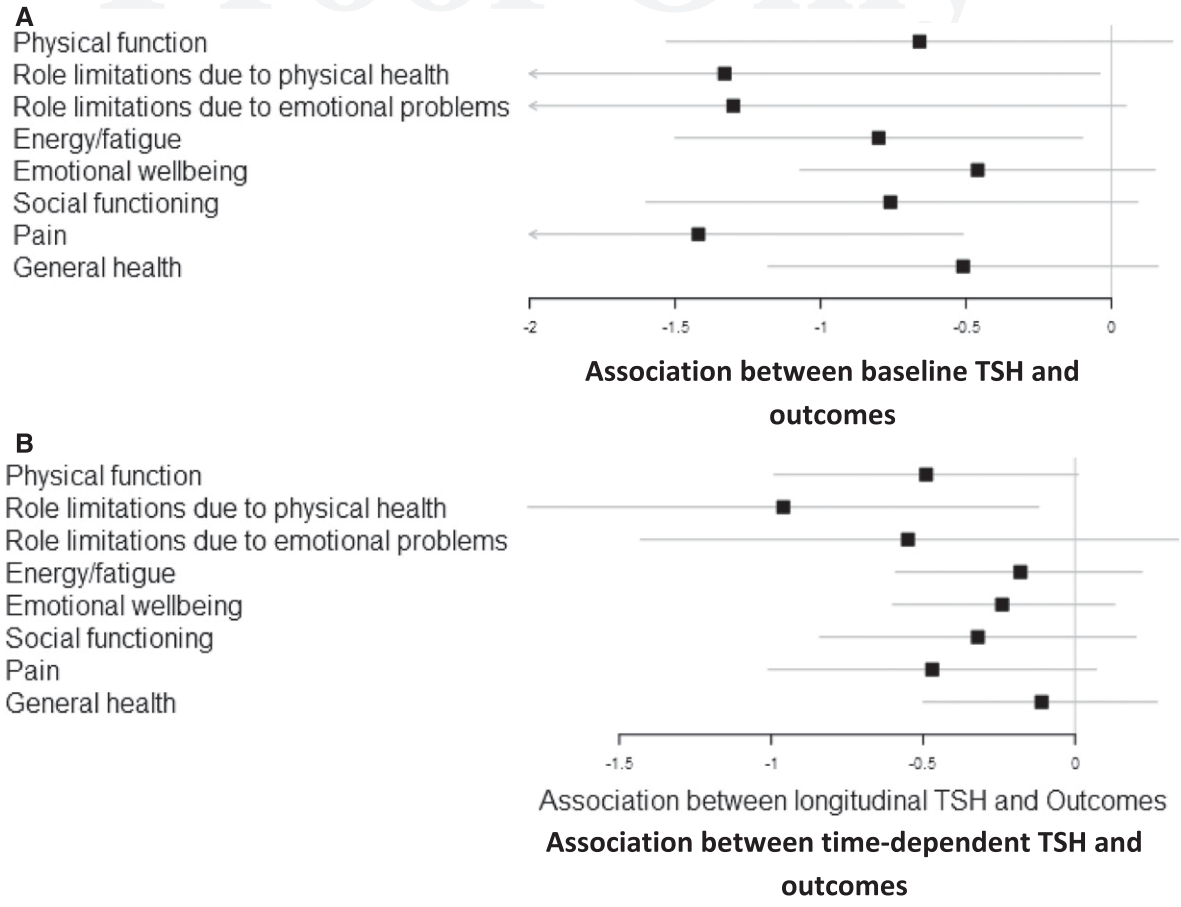

Figure 1. | **Associations between (A) baseline thyrotropin (TSH) levels and (B) time-dependent TSH levels as continuous variables with Short Form-36 domain scores.** The *x* axis denotes the point estimates and 95% confidence intervals for the change in Short Form-36 domain scores associated with a 1-mIU/L higher TSH level. Analyses were adjusted for time (month from baseline TSH), age, sex, race, ethnicity, diabetes, dialysis vintage, body mass index, marital status, insurance, and baseline laboratory measurements (serum albumin, normalized protein catabolic rate, serum creatinine, and single-pool Kt/V).

Q : 5

Thyroid Hormone Supplementation and Antidepressant Use

In analyses that excluded patients receiving thyroid hormone replacement therapy (n=28), higher baseline TSH level was significantly associated with lower scores for energy/fatigue and pain (Supplemental Table 5). Higher time-dependent TSH level was significantly associated with lower scores for role limitations due to physical health observed in the overall cohort as well as physical function, energy/fatigue, and pain.

In analyses that incrementally adjusted for antidepressant use, higher baseline TSH level was significantly associated with lower scores for role limitations due to physical health, energy/fatigue, and pain and trended toward an association for role limitations due to emotional problems and social functioning (Supplemental Table 5). Higher time-dependent TSH level was significantly associated with lower scores for role limitations due to physical health and trended toward an association with lower scores for physical function and pain.

Discussion

Among a prospective cohort of patients on hemodialysis who underwent protocolized thyroid testing every 6 months, higher TSH levels were associated with impairments across multiple HRQOL domains. Higher baseline and time-dependent TSH tertiles were associated with lower (worse) HRQOL domain scores for energy/fatigue and physical function, respectively. When examined as a continuous variable, higher baseline TSH levels were associated with worse scores for role limitations due to physical health, energy/fatigue, and pain and trended toward an association with worse scores for social functioning and role limitations due to emotional problems. In analyses of time-dependent TSH as a continuous variable, we similarly observed that higher TSH levels were significantly associated with impairments in role limitations due to physical health and trended toward an association with worse physical function and pain.

In the general population, there has been increasing recognition of the effect of thyroid function on patient-centered outcomes, such as physical and mental health (12,19,35). Some but not all studies have documented an association between thyroid status and self-reported

Table 3. Association between baseline thyrotropin and time-dependent thyrotropin as continuous variables with quality of life outcomes

Outcome	Estimate (β)	95% CI Lower	95% CI Upper	*P* Value
Baseline TSH				
Physical function	−0.6	−1.5	0.2	0.14
Role limitations due to physical health	−1.3	−2.6	0.0	0.04
Role limitations due to emotional problems	−1.3	−2.6	0.1	0.06
Energy/fatigue	−0.8	−1.5	−0.1	0.03
Emotional wellbeing	−0.5	−1.1	0.2	0.14
Social functioning	−0.8	−1.6	0.1	0.08
Pain	−1.4	−2.3	−0.5	0.002[a]
General health	−0.5	−1.2	0.2	0.14
Time-dependent TSH				
Physical function	−0.5	−1.0	0.0	0.06
Role limitations due to physical health	−1.0	−1.8	−0.1	0.03
Role limitations due to emotional problems	−0.6	−1.4	0.3	0.23
Energy/fatigue	−0.2	−0.6	0.2	0.37
Emotional wellbeing	−0.2	−0.6	0.1	0.21
Social functioning	−0.3	−0.8	0.2	0.23
Pain	−0.5	−1.0	0.1	0.09
General health	−0.1	−0.5	0.3	0.56

TSH, thyrotropin; 95% CI, 95% confidence interval.
[a]*P* value remained significant after false discovery rate adjustment.

HRQOL ascertained by the SF-36 questionnaire (19,36,37). In a cross-sectional study of 2057 Brazilian patients with hypothyroidism treated with levothyroxine for at least 6 months by Vigário *et al.* (37), those who were undertreated reported lower levels of HRQOL across physical function, role-physical, vitality, and role-emotional domains compared with adequately treated patients. In contrast, there were no differences in any of the HRQOL domain scores among overtreated versus adequately treated patients. In a double-blinded, randomized, crossover study of 33 patients with hypothyroid receiving usual-dose (designated as the euthyroid arm) versus higher-dose levothyroxine (designated as the subclinical thyrotoxicosis arm), those with subclinical thyrotoxicosis had slightly worse physical component summary and general health subscale scores compared with those in the euthyroid arm (19). However, in a study of 9000 participants in The Netherlands who underwent TSH and SF-36 testing, HRQOL scores were

Table 4. Potential effect modifiers of the association between baseline thyrotropin and time-dependent thyrotropin as continuous variables on outcomes

Main Exposure and Modifier	Outcome	Estimate (β)	95% CI Lower	95% CI Upper	*P* Value
Baseline TSH					
Age at baseline	Physical function	0.1	0.0	0.2	0.07
BMI	BDI-II	0.1	0.0	0.1	0.08
Serum albumin	Physical function	−2.1	−4.2	−0.1	0.04
nPCR	Physical function	−1.8	−3.7	0.1	0.07
spKt/V	Pain	−4.1	−8.2	0.0	0.05
Time-dependent TSH					
Age at baseline	BDI-II	0.0	0.0	0.0	0.05
Age at baseline	Emotional wellbeing	−0.1	−0.1	0.0	<0.01
Age at baseline	General health	0.0	−0.1	0.0	0.07
Vintage ≥12 versus <12 mo	Physical function	1.3	−0.1	2.6	0.06
Vintage ≥12 versus <12 mo	Emotional wellbeing	0.9	0.0	1.9	0.06
BMI	BDI-II	0.1	0.0	0.1	0.04
Serum albumin	Physical function	−1.7	−3.7	0.3	0.10

95% CI, 95% confidence interval; TSH, thyrotropin; BMI, body mass index; BDI-II, Beck Depression Inventory-II; nPCR, normalized protein catabolic rate; spKt/V, single-pool Kt/V.

indistinguishable between those with normal and elevated TSH levels (36).

To our knowledge, our study is the first study to examine the association between thyroid status and HRQOL in patients on dialysis. Similar to the study by Vigário *et al.* (37), we observed that higher TSH levels were associated with worse levels of physical function, specifically energy/fatigue, physical function, and role limitations due to physical health, across several primary and secondary analyses. These findings may have important implications on the health and survival of patients on dialysis for several reasons. First, routine assessment of the HRQOL of patients on dialysis as well as interventions that improve their functional status and overall wellbeing have become a major emphasis of the United States ESRD program and clinical practice (30,31). To date, few interventions have been identified that result in significant improvements in HRQOL (30,38,39), and thyroid functional disease may be a potentially modifiable factor for reduced QOL in this population. Second, this is the first study in patients on dialysis to document an association between higher TSH levels and low levels of physical function, a strong predictor of death in this population (40–42). Although multiple coexisting mechanisms may lead to impaired physical function in patients on dialysis (*e.g.*, older age, comorbidities, and inflammation) (43), it is plausible that myalgia, reduced muscle strength, higher oxygen requirements during physical activity, and refractory anemia ensuing from hypothyroidism may be potent yet underrecognized contributors (8,44–48). Indeed, it is established that thyroid hormones have direct action in nearly every tissue, including the skeletal muscle, bone and cartilage, and the heart, and emerging data indicate suggest TSH may have extrathyroidal effects on these end organs given the presence of TSH receptors in skeletal muscle, bone, and brain (49–51). Because levothyroxine replacement has been shown to improve certain aspects of physical function in the general population (*e.g.*, strength and cardiopulmonary exercise performance) (46,52), future studies are needed to determine whether correction of thyroid status with exogenous thyroid hormone improves physical function in patients on dialysis. A third novel finding of our study was the observed association between higher TSH levels and worse levels of pain. Although chronic pain is a common complaint among patients on dialysis, there has been little research regarding its causative factors and consequences (30,53,54). Further studies are needed to characterize the association between thyroid function and pain in patients on dialysis.

Whereas our study observed a trend toward an association of thyroid status with worse levels of role limitations due to emotional health, we did not find a significant association between TSH and depressive symptoms ascertained by the BDI-II scores. Although a relationship between hypothyroidism and depression in the general population has been presumed for many years, the true nature of this association has been difficult to define due to conflicting studies, which may relate to heterogeneous study populations, definitions of thyroid functional status, and methods of depression ascertainment (*e.g.*, diagnostic codes, validated questionnaires, or self-report) (12). The absence of an observed association between thyroid function and depressive symptoms in our cohort may be due to the large proportion of patients with milder depressive symptoms suggested by the low prevalence of antidepressant use (14% of patients); measurement of self-reported depressive symptoms using the BDI-II questionnaires in lieu of objective measures of clinical depression, which are defined using standard Diagnostic and Statistical Manual of Mental Health Disorders IV criteria (24,55); true absence of a biologic association; or type 2 error. Further studies are needed to elucidate the association of thyroid status with mental health using alternative measures of depression in patients on dialysis.

The strengths of our study include its well characterized cohort of patients on hemodialysis who underwent protocolized TSH testing and the SF-36 and the BDI-II surveys at 6-month intervals; examination of repeated measures of thyroid function, HRQOL, and depressive symptoms; and comprehensive availability of patient-level data on sociodemographics, comorbidities, medications, and laboratory data collected in the outpatient setting. However, several limitations of our study bear mention. First, we defined thyroid status using serum TSH only as the most sensitive and specific single metric of thyroid function in the general population given its inverse logarithmic association with serum T3 and T4 levels (56) and its robust characteristics in the setting of nonthyroidal illness and uremia. In contrast, routinely used free T4 assays are hormone protein binding dependent and may result in spurious results in conditions where serum protein levels are low (*e.g.*, malnutrition) or circulating substances impair hormone protein binding (*e.g.*, uremia) (57). Furthermore, although T3 has gained recognition as an important metric of thyroid status in cardiovascular outcome studies, given that cardiac myocytes are unable to locally generate T3 from its T4 precursor, the vast majority of circulating T3 is derived from the peripheral conversion of T4 to T3, which is highly sensitive to inflammation, malnutrition, and cortisol levels. Consequently, low T3 may be observed in mild illness independent of thyroid functional status, whereas TSH is typically normal in mild to moderate illness and is not suppressed until developing severe critical illness. Second, although we cannot exclude residual confounding by protein energy wasting, we adjusted for proxies of inflammation and nutritional status (*e.g.*, serum albumin, creatinine, and nPCR). Third, our study used generic surveys of HRQOL and depressive symptoms in lieu of disease-specific instruments (*e.g.*, Kidney Disease Quality of Life survey) (20). Although disease-specific instruments show greater sensitivity, we opted to administer generic measures to allow for comparison across various populations. Fourth, given the moderate sample size of our cohort, we accounted for specific medications that were most potently associated with thyroid status, HRQOL, and depressive symptoms to avoid overadjustment. Fifth, as with all observational studies, our findings do not confirm causal associations. Although a global relationship between thyroid status and HRQOL was robust, the individual associations were tempered, and interventional studies examining the effect of thyroid hormone replacement on these patient-centered outcomes are needed.

In conclusion, our study found that higher TSH levels were independently associated with impaired HRQOL,

particularly across the domains of physical health, energy/fatigue, and pain, in a prospective hemodialysis cohort. Given the high prevalence of thyroid functional disease and strikingly low levels of QOL, further studies are needed to determine the underlying mechanisms by which thyroid functional disease impairs functional status and wellbeing in patients on dialysis and whether thyroid hormone replacement improves HRQOL in this population.

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