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ORIGINAL ARTICLE

Endocrine

Elevated serum thyrotropin levels and endothelial dysfunction in a prospective hemodialysis cohort

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Abstract

Introduction: Thyroid dysfunction is a highly prevalent yet under-recognized complication in hemodialysis patients. In the general population, hypothyroidism has been associated with endothelial dysfunction due to impaired vasodilator synthesis and activity. Little is known about the association of serum thyrotropin (TSH), the most sensitive and specific single biochemical metric of thyroid function, with endothelial function in hemodialysis patients.

Methods: In a secondary analysis of 99 patients from the Anti-inflammatory and anti-oxidative nutrition in hypoalbuminemic dialysis patients (AIONID) trial, we examined measurements of serum TSH and endothelial function ascertained by fingertip digital thermal monitoring (DTM), a novel method used to measure micro-vascular reactivity, collected within a 90-day period. DTM was used to measure changes in fingertip temperature during and after an ischemic stimulus (blood pressure cuff occlusion) as an indicator of changes in blood flow, and two DTM indices were assessed, namely adjusted (a) Temperature Rebound (TR), defined as the maximum temperature rebound post-cuff deflation, and adjusted (b) Area Under the Temperature Curve (TMP-AUC), defined as area under the curve between the maximum

and minimum temperatures. We examined the relationship between serum TSH with impaired TR (separately) and TMP-AUC (both defined as less than the median level of observed values) using multivariable logistic regression.

Findings: In unadjusted and case-mix analyses, higher serum TSH levels (defined as the three highest quartiles) were associated with lower (worse) TR (ref: lowest TSH quartile): ORs (95% CI) 2.64 (1.01–6.88) and 2.85 (1.08–7.57), respectively. In unadjusted and case-mix analyses, higher TSH levels were associated with lower (worse) TMP-AUC: ORs (95% CI) 2.64 (1.01–6.88) and 2.79 (1.06–7.38), respectively.

Discussion: In HD patients, higher serum TSH levels were associated with worse micro-vascular reactivity measured by DTM. Further studies are needed to determine if thyroid hormone supplementation improves endothelial function in hemodialysis patients with lower levels of thyroid function.

KEYWORDS
dialysis, endothelial function, hypothyroidism, thyroid, thyrotropin

INTRODUCTION

Hypothyroidism is a common endocrine complication in chronic kidney disease (CKD) patients, including those receiving dialysis.[1–4] Epidemiologic data from the Third National Health and Examination Survey have shown a graded association between the prevalence of hypothyroidism ascertained by biochemical tests with increasingly lower kidney function: 5%, 11%, 20%, and 23% of participants with estimated glomerular filtration rates (eGFRs) of >90, 60–89, 45–59, and ≤44 ml/min/1.73 m^2, respectively.[5] In a large population-based study of over 460,000 US Veterans with stages 3–5 CKD, approximately one-quarter of patients had hypothyroidism defined by elevated serum thyrotropin (TSH) levels and/or use of thyroid hormone supplementation, with heightened risk of thyroid dysfunction observed with incrementally impaired lower eGFR.[6]

Studies in the general population suggest that hypothyroidism is associated with a higher risk of endothelial dysfunction, atherosclerosis, and heart failure.[7–9] Given the exceedingly high cardiovascular morbidity and mortality of dialysis patients (~40% of deaths[10]), there has been increasing interest in thyroid dysfunction as a potential novel risk factor for cardiovascular disease and death in CKD.[2–4] Indeed, a growing body of evidence has shown that elevated serum TSH levels even in the high-normal range are associated with higher mortality risk across multiple diverse CKD cohorts.[11–14]

Among dialysis-dependent CKD patients, endothelial dysfunction is common[15,16] and has been associated with adverse cardiovascular sequelae and death.[17–19] Despite their high prevalence of thyroid dysfunction and increasing recognition of the cardiovascular sequelae of hypothyroidism, there have been few studies that have examined the relationship between thyroid status and endothelial function in advanced CKD patients. Existing studies provide limited evidence owing to (a) utilization of thyroid function metrics (i.e., serum triiodothyronine [T3] levels) that are highly sensitive to illness, malnutrition, and uremia, and may thus be confounded by non-thyroidal illness,[20,21] and (b) reliance on endothelial function assessment methods that are subject to high inter-session variability (i.e., flow-mediated vasodilation).[22–24] To address these limitations, we conducted a study examining the relationship between serum TSH, the most sensitive and specific single biochemical metric of thyroid function[25,26] that is less influenced by non-thyroidal illness,[20,21] with endothelial function in a secondary analysis of patients from the prospective *Anti-inflammatory and anti-oxidative nutrition in hypoalbuminemic dialysis patients* (AIONID) trial.[27] To provide robust and accurate measurement of endothelial function, we utilized fingertip digital thermal monitoring (DTM) given its standardized, automated, and operator-independent methods and low inter-session variability compared with other vasoreactivity tests.[28–32]

MATERIALS AND METHODS

Source cohort

We conducted a secondary analysis of the association between thyroid status and endothelial function

measured by fingertip DTM among hemodialysis patients from the AIONID trial (Clinicaltrials.gov# NCT00561093) who were recruited across 12 outpatient dialysis units in the Southern California region over the period of June 2008 to June 2010.[27] The AIONID study was a pilot-feasibility, double-blind randomized controlled trial using a two-by-two factorial design in which patients were randomly assigned to (a) either a nutrition supplement (e.g., Nepro) plus Anti-inflammatory anti-oxidant supplement (e.g., Oxepa) versus placebo, and (b) an Anti-inflammatory appetite stimulator (e.g., pentoxifylline) versus placebo. These interventions were administered during routine thrice-weekly hemodialysis treatments over a period of 16 weeks in order to test feasibility and improvements in serum albumin concentrations.

In the present study, patients were included provided that they were (a) ≥18 years of age, (b) received thrice-weekly in-center hemodialysis for at least four consecutive weeks, (c) had serum albumin levels <4.0 g/dl over a 3-month period, and (d) signed a local institutional review board approved consent form (i.e., eligibility criteria for the parent AIONID trial); (e) underwent DTM measurement during the pre-trial phase of the AIONID study; and (f) had available sera collected within 90 days of their DTM measurements. Patients were excluded if they (a) had a TSH level below the reference range (i.e., TSH level <0.5 mIU/L), (b) were actively receiving peritoneal dialysis, or (c) had a terminal disease (e.g., stage IV cancer). The study was approved by the institutional review boards of the Lundquist Institute (previously known as the Los Angeles Biomedical Research Institute) at Harbor UCLA Medical Center and the University of California Irvine (UCI).

Exposure ascertainment

The primary exposure of interest was thyroid status as defined by serum TSH level. Serum TSH was measured from thawed serum samples that were collected pre-dialysis at weekday hemodialysis treatments during the baseline period of the AIONID trial (i.e., prior to randomization) and subsequently stored at −80°C. Serum TSH was measured using second generation chemiluminescent immunoassay tests (Beckman Coulter, Chaska, MN; reference range 0.5–5.0 mIU/L) in the Clinical Pathology Laboratory of the UCI Medical Center.

In primary analyses, serum TSH was categorized as "higher TSH level," defined as the three highest quartiles of observed TSH values (i.e., TSH Quartiles 2 + 3 + 4) versus "lower TSH level," defined as the lowest quartile of TSH levels (i.e., TSH Quartile 1). The higher vs. lower TSH categories corresponded to TSH levels of >1.19 to 10.0, and ≤1.19 mIU/L, respectively. In secondary analyses, we examined varying serum TSH thresholds in which patients were parsed into TSH Tertiles 2 + 3 versus Tertile 1, corresponding to TSH levels of >1.41 versus ≤1.41 mIU/L. In sensitivity analyses, we examined additional thyroid markers from thawed samples including serum anti-thyroid peroxidase (anti-TPO) antibody levels ascertained by the "two-step sandwich" method (Beckman XL, Brea, California; reference range <35 U/ml) in the UCI Clinical Pathology Laboratory.

Outcome ascertainment

The outcome of interest was endothelial function measured by fingertip DTM (VENDYS-5000, Endothelix Inc., Houston, Texas)[28–32] on non-hemodialysis treatment days at Harbor UCLA Medical Center under the oversight of an experienced cardiologist (MJB). DTM was selected for endothelial function measurement given its noninvasive, automated, and operator-independent methods[28–32]; low inter-session variability versus other vasoreactivity tests (i.e., flow mediated vasodilation, reactive hyperemia peripheral arterial tonometry)[29,33–35]; and associations with cardiovascular disease in the dialysis and non-dialysis populations.[29–32] DTM is based on the principle that changes in fingertip temperature during and after an ischemic stimulus (i.e., blood pressure cuff occlusion) reflect changes in blood flow; in normal endothelial function, cuff inflation results in a 1–3°C temperature decline, followed by rapid temperature rise to above baseline during cuff deflation due to compensatory vasodilation. In this study, DTM measurements were performed after an overnight fast of at least 10 h and abstinence from tobacco, alcohol, caffeine, vasoactive medications, exercise, high-fat foods and vitamin C at a temperature between 23.5 and 25.0°C, and finger temperature was measured 5-min before cuff inflation, during a 2-min blood pressure cuff inflation, and 5-min after cuff deflation in the non-vascular access arm of the dialysis patients.

We examined two DTM metrics namely (a) adjusted *Temperature Rebound*, defined as [(Post-deflation-Baseline temperature)/Baseline temperature] * 100 and (b) adjusted *Area Under the Temperature Curve (TMP-AUC)*, defined as area under the curve between the maximum and minimum temperatures post-deflation.[28–32] Adjustments were applied to both indices to account for variations in testing conditions and patient characteristics. In primary analyses, we examined the association between thyroid status and decreased levels of Temperature Rebound and TMP-AUC (i.e., indicating impaired endothelial function) defined as less than the median of

observed values. In sensitivity analyses, we examined varying thresholds of decreased Temperature Rebound and TMP-AUC as indicators of "severely impaired" endothelial function, defined as less than the lowest tertile of observed values.

Socio-demographic, comorbidity, medication, and laboratory covariates

Information on socio-demographics, comorbid conditions, medications, and dialysis treatment characteristics (i.e., vascular access type) were collected at study entry by AIONID research coordinators. Dialysis vintage was defined as the time between the date of study entry and the date of hemodialysis initiation. Routine dialysis laboratory measurements were performed by the outpatient dialysis laboratories using automated methods.

Statistical analyses

Baseline characteristics between exposure groups were compared using chi-squared, analysis of variance, and Kruskal-Wallis tests, according to variable type. We examined cross-sectional associations between serum TSH and adjusted Temperature Rebound and TMP-AUC (separately) using logistic regression models using two incremental levels of covariate adjustment:

1. *Unadjusted model: Included serum TSH level as the primary exposure of interest*;
2. *Case-mix adjusted model: Adjusted for age, sex, and race (White vs. Non-White).*

We a priori defined the case-mix model as our primary model, which forced into the model core socio-demographic measures. To explore the impact of other potential confounders, we also conducted expanded case-mix and expanded case-mix + vintage adjusted models as sensitivity analyses given the high number of parameters relative to the number of cases:

1. *Expanded case-mix adjusted model: Adjusted for covariates in the case-mix model, as well as diabetes and vascular access type (arteriovenous fistula [AVF]/ arteriovenous graft [AVG] vs. catheter)*;
2. *Expanded case-mix + vintage adjusted model: Adjusted for covariates in the expanded case-mix model, as well as dialysis vintage.*

Analogous analyses were conducted in examining the relationship between additional exposure definitions for serum TSH and anti-TPO antibody levels with the DTM endpoints. There were no missing values for any of the covariates. Analyses and figures were generated using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), Stata version 13.1 (Stata Corporation, College Station, Texas), and SigmaPlot Version 12.5 (Systat Software, San Jose, California).

RESULTS

Study population

Among 99 patients who met the eligibility criteria (Figure S1), the mean ± SD, median (IQR), and minimum-maximum baseline serum TSH values were 2.28 ± 1.91, 1.73 (1.19, 2.72), and 0.14 to 10.02 mIU/L, respectively. Among this cohort, all 99 patients underwent anti-TPO antibody measurements.

Baseline characteristics of the cohort stratified by serum TSH levels are shown in Table 1. Compared with patients with lower TSH level (i.e., TSH Quartile 1), those with higher TSH level (i.e., TSH Quartiles 2 + 3 + 4) were more likely to be male and White; had a longer dialysis vintage; were more likely to have an AVF/AVG as their vascular access; and were more likely to have diabetes, although these differences were not statistically significant. Baseline characteristics of the cohort stratified by TSH quartiles are shown in Table S1.

Serum thyrotropin levels and adjusted temperature rebound

In the overall cohort, the mean ± SD and median (IQR) adjusted Temperature Rebound levels were 1.6 ± 2.1 and 0.99 (0.31, 2.43), respectively. There were a total of 49 patients in the overall cohort who had decreased adjusted Temperature Rebound levels, defined as less than the median of observed values. When examined across serum TSH categories, lower adjusted Temperature Rebound levels were observed in 41 versus 8 patients with higher vs. lower serum TSH levels, respectively.

In unadjusted and case-mix adjusted analyses, higher TSH levels were significantly associated with lower adjusted Temperature Rebound levels (ref: lower TSH levels): ORs (95% CI) 2.64 (1.01–6.88) and 2.85 (1.08–7.57), respectively (Figure 1 and Table S2). In expanded case-mix and expanded case-mix + vintage adjusted analyses, point estimates suggested higher TSH levels were associated with lower adjusted Temperature Rebound, but associations did not achieve statistical significance: ORs (95% CI) 2.60 (0.96–7.00) and 2.45 (0.90–6.68),

TABLE 1 Baseline characteristics according to thyroid status defined as the lowest versus three highest serum thyrotropin (TSH) quartiles

	Serum thyrotropin (TSH) level			
	Overall	**Quartile 1**	**Quartiles 2–4**	***P*-value**
Number of patients	99	25	74	N/A
TSH level (min-max)	0.14–10.02	0.14–1.19	1.21–10.02	N/A
Age (years), mean ± SD	59 ± 13	60 ± 14	58 ± 12	0.54
Female, %	53	56	51	0.69
Race, %				0.36
White	64	56	66	
Non-White	36	44	34	
Hispanic ethnicity, %	55	52	55	0.77
Vintage (months), mean ± SD	33 ± 33	26 ± 27	36 ± 35	0.09
Vascular access, %				0.55
AVF/AVG	80	84	78	
Catheter	20	16	22	
Diabetes, %	68	54	73	0.09
Anti-TPO antibody level, median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.90

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; anti-TPO, anti-thyroid peroxidase.

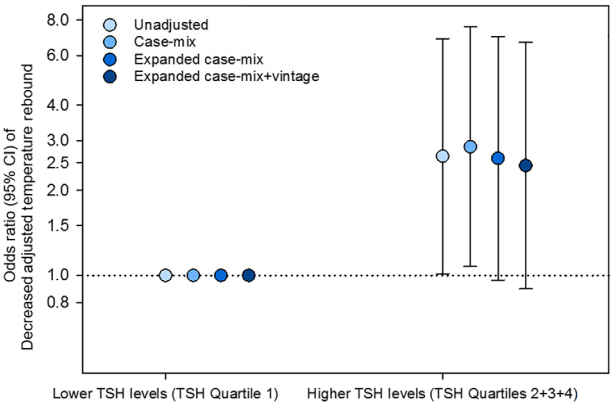

FIGURE 1 Association between higher serum thyrotropin (TSH) levels (defined as TSH quartiles 2–4) and decreased adjusted temperature rebound (defined as less than median levels) using logistic regression (ref: TSH quartile 1) in unadjusted, case-mix, expanded case-mix, and expanded case-mix + vintage adjusted models [Color figure can be viewed at wileyonlinelibrary.com]

respectively. Other adjustment covariates considered in analyses of the association between serum TSH tertiles and DTM indices are presented in Table S3.

In analyses examining even lower adjusted Temperature Rebound thresholds as an indicator of severe endothelial dysfunction (i.e., defined as less than the lowest tertile of observed values), point estimates suggested that higher TSH levels were significantly associated with severely decreased adjusted Temperature Rebound levels but did not achieve statistical significance (ref: lower TSH levels): ORs (95% CIs) 3.02 (0.94, 9.71), 3.06 (0.94, 9.96), 2.89 (0.87, 9.59), and 2.86 (0.86, 9.55) in unadjusted, case-mix, expanded case-mix, and expanded case-mix + vintage adjusted analyses, respectively (Figure S2 and Table S4). In sensitivity analyses examining varying TSH thresholds, we found that the highest two TSH tertiles (i.e., TSH Tertiles 2 + 3) were significantly associated with severely reduced adjusted Temperature Rebound in unadjusted analyses (ref: TSH Tertile 1): ORs (95% CIs) 2.74 (1.00–7.57) (Table S4). Following adjustment for case-mix, expanded case-mix, and expanded case-mix + vintage covariates, point estimates were slightly attenuated with associations narrowly missing statistical significance: ORs (95% CIs) 2.66 (0.96, 7.40), 2.66 (0.94, 7.52), and 2.65 (0.93, 7.50), respectively.

Serum thyrotropin levels and adjusted area under the temperature curve

In the overall cohort, the mean ± SD and median (IQR) adjusted TMP-AUC levels were 170.7 ± 181.6 and 102.2 (33.8, 269.5), respectively. There were a total of 49 patients in the overall cohort who had decreased adjusted TMP-AUC levels, defined as less than the median of observed values. When examined across serum TSH categories, decreased adjusted TMP-AUC levels were observed in

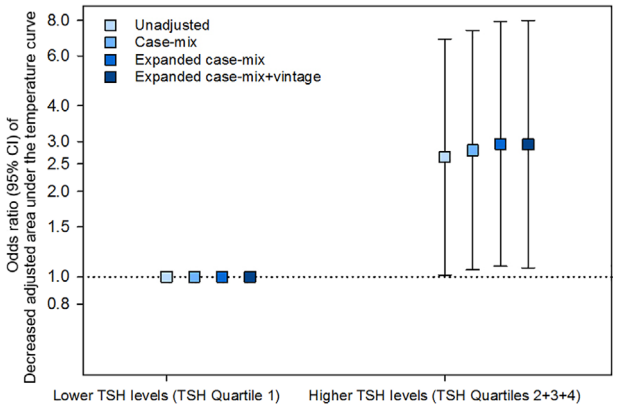

FIGURE 2 Association between higher serum thyrotropin (TSH) levels (defined as TSH quartiles 2–4) and decreased adjusted area under the temperature curve (TMP-AUC; defined as less than median levels) using logistic regression (ref: TSH quartile 1) in unadjusted, case-mix, expanded case-mix, and expanded case-mix + vintage adjusted models [Color figure can be viewed at wileyonlinelibrary.com]

41 versus 8 patients with higher vs. lower serum TSH levels, respectively.

In unadjusted analyses, higher TSH levels were significantly associated with lower adjusted TMP-AUC levels (ref: lower TSH levels): OR (95% CI) 2.64 (1.01–6.88) (Figure 2 and Table S5). Following adjustment for case-mix, expanded case-mix, and expanded case-mix + vintage covariates, stronger associations between higher TSH levels with lower adjusted TMP-AUC were observed (ref: lower TSH levels): ORs (95% CIs) 2.79 (1.06–7.38), 2.94 (1.09–7.94), and 2.93 (1.07–7.99), respectively.

In analyses examining even lower adjusted TMP-AUC thresholds as an indicator of severe endothelial dysfunction (i.e., defined as less than the lowest tertile of observed values), higher TSH levels were significantly associated with severely decreased adjusted TMP-AUC in unadjusted, case-mix, and expanded case-mix models (ref: lower TSH levels): ORs (95% CIs) 3.20 (0.99–10.27), 3.23 (0.99, 10.48), and 3.31 (1.00, 10.90), respectively (Figure S3 and Table S6). Following adjustment for expanded case-mix + vintage covariates, point estimates were slightly attenuated with associations narrowly missing statistical significance: ORs (95%CIs) 3.12 (0.94, 10.38). In sensitivity analyses examining varying TSH thresholds, the highest two TSH tertiles (i.e., TSH Tertiles 2 + 3) were significantly associated with severely reduced adjusted Temperature Rebound across all adjustment levels (ref: TSH Tertile 1): ORs (95% CIs) 2.93 (1.06, 8.06), 2.91 (1.05, 8.11), 3.06 (1.08, 8.65), and 3.03 (1.07, 8.59) in unadjusted, case-mix, expanded case-mix, and expanded case-mix + vintage adjusted analyses, respectively (Table S6).

Anti-thyroid peroxidase antibody, direct free thyroxine levels, and endothelial function

In secondary analyses, we examined serum anti-TPO antibody levels as an indicator of thyroid autoimmunity. Examination of serum anti-TPO antibody levels did not show associations with decreased adjusted Temperature Rebound (Tables S2 and S4) nor decreased adjusted TMP-AUC levels (Tables S5 and S6).

DISCUSSION

In a well-defined cohort of hemodialysis patients who underwent rigorous assessment of serum thyroid markers and fingertip DTM as a novel tool to assess microvascular reactivity, we found that serum TSH levels in the high-normal to high range (i.e., three highest TSH quartiles) were associated with worse parameters of endothelial function. Compared with patients with TSH levels in the lowest quartile, those in three highest quartiles were more likely to have decreased (i.e., impaired) adjusted Temperature Rebound levels independent of socio-demographic characteristics. In case-mix adjusted analyses, we also found that higher TSH levels were independently associated with decreased and severely decreased adjusted TMP-AUC levels.

In the general population, hypothyroidism, even in mild subclinical form, has been associated with multiple traditional risk factors for cardiovascular disease and progression.[7–9] Lower levels of thyroid function are known to cause endothelial dysfunction due to impaired vasodilator (e.g., nitric oxide, adrenomedullin) synthesis and activity,[36–39] as well increased systemic vascular resistance and diastolic hypertension. Indeed, clinical studies have shown that "mild" subclinical hypothyroidism as well as high-normal TSH levels are associated with impaired endothelial function using various methods of assessment (e.g., flow-mediated vasodilation,[40] coronary microvascular and epicardial endothelial function[41]). Furthermore, several clinical trials have shown that thyroid hormone supplementation (i.e., levothyroxine) over a 3–6 month period reverses endothelial dysfunction in patients with subclinical hypothyroidism.[38,42]

To date, a growing body of evidence suggests that alterations in thyroid markers are associated with worse endothelial function in advanced CKD and ESRD patients. In a study of 137 hemodialysis patients, lower free triiodothyronine (FT3) levels were associated with higher (i.e., worse) carotid-femoral pulse wave velocities.[22] Similarly, in a study of 213 stage 3 to 4 CKD patients, low circulating FT3 was associated with lower

(i.e., worse) flow-mediated vasodilation and higher levels of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase.[24] In another study of 57 peritoneal dialysis patients, lower FT3 levels and high-normal TSH levels were associated with greater arterial stiffness as measured by pulse wave analysis indices (e.g., augmentation index and subendocardial viability ratio).[23]

To our knowledge, ours is the first study to examine the association between thyroid status and endothelial function measured by DTM in a prospective dialysis cohort. In both dialysis and non-dialysis patients, fingertip DTM has been shown to correlate with burden of coronary atherosclerosis, and also provides an inexpensive, automated, and convenient method of direct vascular function measurement.[28–32] In contrast with other methods of endothelial function assessment that have inherently large inter-session variations (e.g., flow-mediated vasodilation, reactive hyperemia peripheral arterial tonometry),[33–35] DTM also provides a standardized, operator-independent technique with lower inter-session variability.

Building upon the aforementioned studies of thyroid status and endothelial function in CKD, our study also focused on serum TSH as a more reliable indicator of thyroid status than circulating T3 levels. Given that T3 is largely derived from the peripheral deiodination of T4-to-T4,[21,43] a process highly sensitive to inflammation, malnutrition, and non-thyroidal illness,[20,21,44–46] lower T3 levels may be more indicative of underlying ill health as opposed to low thyroid function in the dialysis population. In contrast, TSH is considered the single most sensitive and specific biochemical metric of thyroid function given its negative logarithmic association with thyroid hormone levels (i.e., small changes in T3 and T4 lead to exponential changes in TSH).[25,26] Using serum TSH as a robust indicator of thyroid status and endothelial function, we found that TSH levels in the high-normal to high range were associated with worse endothelial function for the first time. Given that thyroid dysfunction is a common and modifiable endocrine complication, and considering the ill effects of endothelial dysfunction on the development of cardiovascular disease and death in dialysis patients, further studies including clinical trials are needed to determine the impact of thyroid hormone replacement on the vascular health of this population.

The strengths of our study include its well-characterized cohort of hemodialysis patients who underwent thyroid status evaluation with "gold-standard" metrics; rigorous assessment of endothelial function using fingertip DTM as a robust indicator of microvascular reactivity; and comprehensive availability of detailed patient-level data on socio-demographics, comorbidities, and laboratory data collected in the ambulatory setting. However, several limitations of our study bear mention. First, given that the serum samples in which thyroid tests were conducted and DTM measurements were concurrently collected within a 90-day period, we cannot confirm a longitudinal relationship nor causal association between thyroid status and endothelial function from the present study. Second, the limited sample size of our cohort may have precluded the ability to conduct extensive adjustments and to detect significant associations between some of the thyroid markers (i.e., anti-TPO antibody) and Temperature Rebound and TMP-AUC levels. Third, as our study was a secondary analysis of participants from a clinical trial, it is possible that patients who agreed to participate in the AIONID study may have been healthier than the broader US hemodialysis population; however, patients were required to have low serum albumin as part of the AIONID eligibility criteria and may have therefore had worse nutritional status. Lastly, given that our recruitment was restricted to 12 outpatient dialysis units in Southern California, our findings may not be generalizable to other geographic regions in which patients' case-mix characteristics and dialysis practice patterns may differ.

In conclusion, we observed that lower levels of thyroid function ascertained by serum TSH levels in the high-normal to high range were significantly associated with worse endothelial function in hemodialysis patients. Given the high prevalence of thyroid dysfunction and cardiovascular disease in CKD patients, further studies are needed to confirm findings and determine whether thyroid hormone replacement ameliorates endothelial dysfunction and its downstream consequences in this population.

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CONFLICT OF INTEREST

None of the authors declare conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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