SHORT REPORTS

Thyrotropin and Free Thyroxine Concentrations Do Not Affect Cardiovascular Disease and Mortality in Euthyroid Peritoneal Dialysis Patients

Few studies have assessed the relationship of thyroid function with cardiovascular disease (CVD) and mortality in dialysis patients (1–3). Low triiodothyronine (T3) has been associated with inflammation, malnutrition, and mortality in dialysis (1,2); subclinical hypothyroidism may influence cardiac dysfunction in peritoneal dialysis (PD) patients; and even an euthyroid state is possibly linked to atherosclerosis in these population (3). We investigated the relationship of thyrotropin (TSH) and free thyroxine (fT4) levels with CVD and mortality in this population.

METHODS

We studied a retrospective cohort of all end-stage renal disease (ESRD) patients more than 18 years of age who had entered the PD program at the Hospital Universitario La Paz from 1981 to 2007 ($n = 302$). One measurement of TSH during the first 6 months and at least 3 months' duration on PD were required. Patients with overt thyroid dysfunction or those receiving drugs known to affect TSH secretion were excluded. Baseline data also included cardiovascular risk factors, PD parameters, and prevalent CVD. Follow-up data included annual TSH and fT4 values and incident CVD. Subjects were considered euthyroid if their TSH was in the range 0.45 – 4.50 mU/L. Eligible patients were allocated to groups based on TSH and fT4 levels. The TSH euthyroid groups were defined as normal-low (0.46 – 1.00 mU/L, $n = 46$), normal (1.01 – 3.50 mU/L, $n = 201$), and normal-high (3.51 – 4.50 mU/L, $n = 31$). The fT4 euthyroid groups were defined as normal-low (≤ 0.98 ng/dL, $n = 89$), normal (0.99 – 1.20 ng/dL, $n = 84$), normal-high (≥ 1.21 ng/dL, $n = 89$). Subclinical hypothyroidism was defined as a TSH level of 4.5 mU/L or higher, with a normal fT4 concentration ($n = 15$); and subclinical hyperthyroidism, as a TSH level of 0.45 mU/L or less, with a normal fT4 concentration ($n = 9$).

For comparisons between groups, we used one-way analysis of variance and Kruskal–Wallis analysis of variance. Kaplan–Meier curves and the log-rank method were used to compare survival times. To investigate the association of annual of TSH and fT4 values with CVD and mortality during follow-up, hazard ratios and 95% confidence intervals were estimated through univariate and multivariate Cox regression with time-dependent covariant models. Data were adjusted for other baseline risk factors or potential confounding factors, mainly age, sex, prevalent CVD, and atrial fibrillation.

RESULTS

Baseline Characteristics and Thyroid Function: At study entry, 278 (92.05%) of the 302 eligible subjects were euthyroid, 15 (4.96%) had subclinical hypothyroidism, and 9 (2.98%) had subclinical hyperthyroidism. Among the euthyroid subjects, 46 (16.54%) were classified normal-low TSH; 201 (72.30%), normal TSH; and 31 (11.15%), normal-high TSH. No statistical differences in cardiovascular risks factors, PD parameters, or prevalent CVD were observed between the three euthyroid groups or between the euthyroid and subclinical thyroid disease groups (data not shown).

Incidence Rates for CVD and Mortality: Patients in the euthyroid normal-low TSH group had higher incidence rates of dyslipidemia, atrial fibrillation, and overall CVD. In contrast, the incidence rates of hypertension and of all-cause and cardiovascular mortality were higher in the euthyroid normal-high TSH group (Table 1). Based on fT4 concentration, incidence rates were higher for diabetes in the normal group, for hypertension in the normal-high group, and for CVD in the normal-low group. All-cause and cardiovascular mortality were higher in the normal-low fT4 group (data not shown).

Survival Analysis: Of the euthyroid patients, 82 (29.49%) died, most of them of CVD ($n = 67$, 81.70%). Survival curves for all-cause and cardiovascular mortality were not different between the euthyroid groups (Figure 1) nor between the euthyroid and subclinical thyroid disease groups (data not shown).

TABLE 1
Mortality, Cardiovascular Events, and *De Novo* Cardiovascular Risk Factor Incidence Rates^a in Patients
Classified by Thyrotropin (TSH)

Variable	Normal-low (0.46–1.00 mU/L)	TSH level Normal (1.01–3.50 mU/L)	Normal-high (3.51–4.50 mU/L)
Patients (n)	46	201	31
Death (%)			
All-cause	13.85	9.53	16.25
Cardiovascular disease	11.08	7.85	13.30
Cardiovascular event (%)	10.39	8.04	5.91
Coronary artery disease	6.23	5.60	4.43
Cerebrovascular disease	4.16	2.05	2.95
Peripheral vascular disease	4.85	3.18	0
Diabetes (%)	1.38	13.08	2.95
Hypertension (%)	0	0.56	1.48
Hyperlipidemia (%)	10.39	6.91	7.40
Atrial fibrillation (%)	1.38	1.12	0

^a Events per 100 patient-years.

Figure 1 — Kaplan-Meier curves for all-cause (panels A and C) and cardiovascular (panels B and D) mortality by levels of thyrotropin [TSH (in milliunits per liter)] and free thyroxine [fT4 (in nanograms per deciliter)] in euthyroid patients on peritoneal dialysis.

Impact of Annual Variations of TSH and fT4 on CVD and Mortality: No relationship was found for annual TSH

(Table 2) and fT4 concentrations (data not shown) with incident CVD in euthyroid patients. When calculating time to all-cause and cardiovascular death in this population, we observed that the euthyroid normal-high TSH subgroup had a higher risk of mortality during follow-up although values did not reach statistical significance.

DISCUSSION

To our knowledge, few studies have investigated TSH and fT4 in PD patients and their relationships with traditional cardiovascular risk factors, CVD, and mortality. None evaluated the association of annual TSH and fT4 values with incident CVD and mortality. Our study shows such results for first time.

We found no significant relationships of basal TSH and fT4 with sex, age, hypertension, diabetes, body mass index, total cholesterol or triglycerides, or prevalent CVD between the euthyroid groups or between the euthyroid and subclinical thyroid groups. Few studies of the possible implications of thyroid function within the euthyroid range with respect to such metabolic alterations have so far been reported in these populations. High TSH in euthyroid PD patients has been recently associated with a lower subendocardial viability ratio, which was used to assess arterial stiffness as a cardiovascular risk factor (4). A cross-sectional study recently performed in Taiwan in 122 PD patients showed that prevalent CVD was not higher in patients with subclinical thyroid disease than in euthyroid patients (5).

TABLE 2
Impact of Annual Serum Thyrotropin (TSH) on Cardiovascular Disease and Mortality

Variable	Analysis [hazard ratio (95% confidence interval)] ^a	
	Univariate	Multivariate
Cardiovascular event	0.90 (0.68 to 1.20)	0.88 (0.64 to 1.21)
Death	0.82 (0.67 to 1.02)	0.84 (0.67 to 1.06)
Cardiovascular death	0.81 (0.65 to 1.03)	0.82 (0.64 to 1.64)

^a Calculated using Cox regression models.

When investigating mortality, we found that baseline TSH and fT4 levels within the euthyroid range in PD patients were not related to all-cause and cardiovascular mortality. In a clinically euthyroid HD population, Zoccali *et al.* (1), found that low T3 was an independent risk factor for mortality, but that TSH and fT4 were not associated with death. Those authors did not assess the various causes of mortality or the incidence of CVD. In clinically stable euthyroid incident end-stage renal disease patients, Carrero *et al.* (6) did not find that TSH and fT4 were significant predictors of all-cause mortality, but found significance for fT3 and borderline significance for T4. In a prospective cohort study by Enia *et al.* (2), low levels of T3 were linked to low-grade inflammation and death in PD patients. During the follow-up period, fT3 levels were lower in patients who died; fT4 and TSH levels were not different.

None of the studies performed in PD patients so far have investigated annual TSH and fT4 values during follow-up and their influence on incident CVD and mortality. Our study is the first to show lack of any relationship of annual TSH and fT4 values with incident CVD or mortality in euthyroid PD patients. In addition, when analyzing all patients on PD, including those with subclinical hypothyroidism and subclinical hyperthyroidism, we observed no significant relationships.

Some limitations of our study have to be addressed. The statistical power for analyzing the subclinical thyroid disease population is low because the limited number of cases. The lack of measurements of thyroid autoantibodies and serum T3, and variations in laboratory procedures over a period of more than 30 years could also have reduced the statistical power.

CONCLUSIONS

Our data support the hypothesis that serum concentrations of TSH and fT4 within the normal range are not associated with prevalent or incident CVD, all-cause and CVD mortality, or the incidence of risk factors for CVD.

Furthermore, annual TSH and fT4 values are not associated with increased cardiovascular events and mortality in euthyroid PD patients.

DISCLOSURES

The authors declare that they have no financial conflicts of interest.

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