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Prognostic impact of subclinical thyroid dysfunction in heart failure

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ABSTRACT

Background: Therapeutic and prognostic implications of subclinical thyroid dysfunction in patients with heart failure (HF) are unclear. We compared the prognostic impact of euthyroidism, subclinical thyroid dysfunction, and euthyroid sick syndrome (ESS) in systolic HF.
Methods: We included 1032 patients hospitalized for systolic HF (left ventricular ejection fraction [LVEF] ≤40%) who participated in a randomized trial assessing the effects of a HF disease management program. Patients with incomplete thyroid function tests or thyrotropic medication were excluded. In the remaining 758 subjects, the risk of all-cause death was estimated based on TSH only, or full thyroid function profile. Changes of thyroid function after six months were assessed in 451 subjects.
Results: Subclinical thyroid dysfunction was present in 103 patients at baseline (14%). No differences were found between groups regarding NYHA class (P = 0.29), and LVEF (P = 0.60). After a median follow-up of three years patients with ESS (n = 13) had a 3-fold age-adjusted increased risk of death compared to euthyroid patients (P = 0.001). However, neither subclinical hyperthyroidism (HR 1.18, 95%CI:0.82–1.70) nor hypothyroidism (HR 1.07, 95%CI:0.58–1.98) were associated with increased age-adjusted mortality risk. Subclinical thyroid dysfunction had normalized spontaneously at follow-up in 77% of patients. However, persistent subclinical thyroid dysfunction was also not associated with worse outcome.
Conclusions: In this large well-characterized HF cohort, subclinical thyroid dysfunction did not predict an increased mortality risk. Thus, in patients with moderate to severe HF, further diagnostic and therapeutic procedures for subclinical thyroid dysfunction appear dispensable. ESS was an infrequent but important indicator of a poor prognosis in HF.
Clinical trial registration: URL: http://www.controlled-trials.com. Unique identifier: ISRCTN23325295.

1. Introduction

Heart failure is a frequent clinical syndrome representing the common final pathway of various heart diseases of different etiology [1,2]. It has been acknowledged that comorbidities are important modifiers of disease progression and outcome in heart failure [3,4]. Thyroid dysfunction represents a frequent comorbid condition exhibiting heterogeneous clinical manifestations [5,6].

Both overt hyper- and hypothyroidism are known to profoundly impact on cardiac function. Tachycardia is the dominant clinical feature and pathophysiological force driving heart failure in patients with Grave's disease (autoimmune hyperthyroidism) and thyroid autonomy [7–9]. Low thyroid hormone levels were shown to reduce cardiac contractility and output by various mechanisms [5,10]. Correspondingly, bradycardia and left ventricular heart failure are common in overt hypothyroidism [11]. The euthyroid sick syndrome (ESS) is defined by low levels of circulating triiodothyronine (T3) in patients with normal or slightly decreased thyroid stimulating hormone (TSH) and tetraiodothyronine (T4) concentrations and viewed as adaptive response to serious clinical impairment rather than genuine thyroid disease. Comorbid ESS in patients with heart failure has been reported to indicate a particularly grave prognosis [12].

Subclinical thyroid dysfunction is characterized by altered TSH but normal thyroid hormone levels. With a prevalence of up to 20% of the normal population aged 60–80 years it is much more frequent than overt thyroid dysfunction [13,14]. There is an ongoing debate whether or not subclinical thyroid diseases are really clinically inapparent or whether they possess prognostic relevance [14–17].

Several studies investigated the prognostic impact of subclinical thyroid dysfunction in heart disease. However, the data are inconclusive and partly conflicting [15,18,19]. One major limitation comparing studies on the association between thyroid function and clinical

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outcome in patients with cardiac disease is that selection of populations and definitions of thyroid disorders were heterogeneous, with several studies using only TSH as an indicator of thyroid dysfunction [4,16,17,19–21]. It has, thus, remained unclear whether subclinical thyroid dysfunction is a clinically and prognostically relevant entity in heart failure requiring specific diagnostic and therapeutic measures.

We, therefore, investigated whether

(i) Subclinical thyroid dysfunction has an impact on overall survival in systolic heart failure;
(ii) The full thyroid profile including free T3 (fT3) and free T4 (fT4), in comparison to TSH only, confers better differential appraisal of thyroid function and, hence, incremental prognostic relevance;
(iii) Repeating thyroid function tests after 6 months improves the diagnostic and prognostic accuracy of these measurements.

2. Methods

2.1. Patients

Between March 2004 and December 2008, 1032 patients hospitalized for heart failure were included in the Interdisciplinary Network Heart Failure study (INH study). The original study investigated in 715 patients the effects of a telephone-based nurse intervention on clinical outcome and enrolled consecutive adults hospitalized for decompensated cardiac failure at nine hospitals in South Germany. Details of the study design have been reported elsewhere [22]. In brief, inclusion criteria were left ventricular ejection fraction (LVEF) ≤40%, clinical signs and symptoms of heart failure at the time of inclusion, and written informed consent. Approval of the INH study protocol was obtained from local Ethics Committees.

2.2. Data collection and follow-up

Prior to discharge, patients underwent standardized evaluation including detailed medical history, physical examination, blood chemistry, 12-lead electrocardiogram, and echocardiography. All assessments were repeated six months after discharge from hospital on an outpatient basis. Patients unable to attend the follow-up visit underwent a structured telephone-based questionnaire. Survival status after 1.5 and 3 years was ascertained by contacting the patients themselves or their general physician. Follow-up was 100% complete.

2.3. Thyroid hormone sampling and measurement

Thyroid function was assessed at baseline and after six months. Thyroid hormones were either measured immediately after sampling or, using the same method, in batches of samples stored at −80 °C. TSH, fT3, and fT4 were measured using an automated chemiluminescence assay (Immulite 2000; Siemens, Erlangen, Germany) at the laboratory of the Endocrine and Diabetes Unit at the University Hospital of Würzburg under regular external quality control. The assay received regulatory approval based on data showing an analytical sensitivity of 0.004 μIU/ml for TSH, 1.5 pmol/l (1.0 pg/ml) for fT3, and 1.67 pmol/l (0.13 ng/dl) for fT4, respectively. For all assays, the intra- and inter-assay coefficients of variation were ≤12.5% and ≤12.5%, respectively. Reference intervals in our laboratory are: TSH 0.30–4.0 mIU/l, fT3 2.7–7.6 pmol/l (1.76–4.95 pg/ml), and fT4 11.0–23.0 pmol/l (0.85–1.79 ng/dl).

2.4. Definition of thyroid status

Patients with incomplete or implausible thyroid tests (e.g. patients with elevated fT4 values but normal TSH and fT3 without levothyroxine intake) and patients on medication interacting with thyroid function (amiodarone, thyreostatic agents, corticosteroids equivalent to 10 mg prednisone/d or more) were excluded. However, treatment with thyroid hormones was allowed.

There is no commonly accepted classification of subclinical thyroid dysfunction. In clinical routine, screening is frequently performed using TSH only. In accordance with this approach, subjects were divided into three groups according to TSH at baseline:

(1) 'Normal TSH': TSH within the reference range;
(2) 'Suppressed TSH': TSH <0.3 mIU/l;
(3) 'Elevated TSH': TSH >4.0 mIU/l.

In a second approach, the patients were categorized into six groups using the full information of thyroid hormones:

(1) 'Euthyroidism': TSH, fT3 and fT4 all within reference ranges;
(2) 'ESS': fT3 <2.7 pmol/l and TSH and fT4 low or within normal ranges;
(3) 'Subclinical hyperthyroidism': TSH <0.3 mIU/l and normal fT3/fT4;
(4) 'Subclinical hypothyroidism': TSH >4.0 mIU/l and normal fT3/fT4;
(5) 'Overt hyperthyroidism': TSH <0.1 mIU/l and elevated fT3 and/or fT4;
(6) 'Overt hypothyroidism': TSH >4.0 mIU/l and decreased fT3 and/or fT4.

It is well known that slightly altered thyroid tests may normalize over time without intervention [23]. In order to differentiate transient from persistent thyroid dysfunction, we made use of thyroid tests repeated six months after baseline. Accordingly, the patients were then divided into persistent and transient functional states:

(1) 'Persistent euthyroidism';
(2) 'Persistent subclinical hyperthyroidism';
(3) 'Transient subclinical hyperthyroidism' (i.e, euthyroidism at follow-up);
(4) 'Persistent subclinical hypothyroidism';
(5) 'Transient hypothyroidism'.

Patients with newly diagnosed thyroid dysfunction at six months were excluded from this subanalysis due to missing confirmatory data.

2.5. Data analysis

Data are expressed as mean (standard deviation), median (quartiles, range), or n (%), as appropriate. Group-wise comparisons were performed using Fisher's exact test, chi-square test, Mann–Whitney U-test or Kruskal–Wallis test, as appropriate. The association between thyroid dysfunction and survival was examined using Cox proportional hazards regression. Hazard ratios (HR) with 95% confidence intervals (CI) and the Wald statistic (i.e., the ratio of the coefficient to its SE squared; the higher the Wald statistic, the more a variable contributes to the model) are reported. The assumption of proportionality was checked by visual inspection, and no violation was found. Patients with euthyroidism served as the referent. Potential confounders were sought by examining the association of each variable reported in Table 1 with both the exposure (i.e., thyroid dysfunction) and the outcome (all-cause death; P<0.05 for inclusion). Kaplan–Meier plots with log rank P-values are also shown. Reported P-values are two-sided. For group-wise comparisons in Table 1 the Bonferroni-corrected alpha is reported. Otherwise, P-values <0.05 were considered statistically significant. All tests were performed using commercial software (SPSS Inc, Chicago, IL, version 19.0.1).

3. Results

3.1. Baseline characteristics

Of the 1032 patients included in the INH study, 274 patients had to be excluded for incomplete (n = 176) or implausible (n = 9) results of thyroid tests or the intake of amiodarone, thyreostatic agents or corticosteroids (Fig. 1). Baseline characteristics of the remaining 758 patients (mean age 68 ± 12 years; range: 20–95 years; 29% female) are presented in Table 1. No differences were found regarding most baseline characteristics between patients with euthyroidism (n = 628), subclinical hyperthyroidism (n = 69), subclinical hypothyroidism (n = 34) and ESS (n = 13). Levothyroxine treatment was frequent and differed between groups: subclinical hyperthyroidism (20%) and subclinical hypothyroidism (27%; P = 0.001 for respective comparison to 7% in euthyroidism). Patients with subclinical hyperthyroidism were slightly older (72 ± 9 years vs. 67 ± 13 years in euthyroidism; P = 0.002) and more often female (45% vs. 27% in euthyroidism; P = 0.002). On average, patients with ESS were older (75 ± 10 years; P = 0.014) than euthyroid patients and had a higher prevalence of comorbid burden, as anemia and renal dysfunction.

3.2. Prognostic impact of thyroid function and impact of confounding variables

The median duration of follow-up in survivors was 37 months (quartiles: 18, 43 months). Overall, 264 patients (34%) died during follow-up. In 153 of them (58%) the cause of death was judged as cardiac, whereas the others died due to malignancy (7%), sepsis (5%), stroke (2%) or other known (12.5%) and unknown reasons (15.5%).

3.2.1. TSH-based analysis

Of the 758 patients, 641 patients (85%) had normal TSH, 77 (10%) had suppressed TSH (<0.3 mIU/l) and 40 (5%) had an elevated TSH (>4.0 mIU/ml). Univariate analysis revealed no prognostic impact of elevated TSH (HR 0.97, 95%CI:0.55–1.69, P = 0.901), whereas for patients with suppressed TSH a trend towards worse outcome was observed (HR 1.35, 95%CI:0.95–1.91, P = 0.094; Table 2). Searching for potential confounding factors using the variables reported in Table 1 (which also includes factors known from the literature) we