HORMONES 2012, 11(3):350-355

Research paper

High TSH and low T4 as prognostic markers in older patients

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ABSTRACT

OBJECTIVE: To examine the association between thyroid profile and morbidity/mortality (MM) in hospitalized older patients. DESIGN: This is a retrospective study of patients over the age of 60yr admitted to the Dr. Cesar Milstein Hospital between 2009 and 2010 and who had thyroid function tests (TFT). The patients were grouped as per their thyroid tests and their clinical characteristics and MM was associated with their TFT. High MM was defined as mortality, intensive care unit (ICU) requirement or prolonged hospital stay (>18 days, *75th percentile*), and mortality assessed during an 18-month follow-up period after their hospital discharge. RESULTS: Out of 2599 older patients admitted to our hospital, 7% had TFT performed for various reasons. The patients who had TFT were mostly women and presented in a more serious clinical condition compared to the rest of the patients. The patients were grouped as per their thyroid values as follows: 61% of them had a non-thyroidal illness, 25% were euthyroid, 7% had overt hyperthyroidism, 5% overt hypothyroidism and 1% had subclinical hyper- or hypothyroidism. The hypothyroid patients had a worse clinical outcome compared to the others. Patients with increased MM exhibited higher TSH and lower TT4 ($p<0.005$). Short-term MM (OR=2.0,95%CI=1.1-3.6, $p<0.01$) was associated with the decrease of TT4 adjusted by age, sex, T3 and TSH, while for long-term MM the increase in TSH (OR=1.6,95%CI 1.1-2.3, $p<0.05$) was also significant. CONCLUSION: Among hospitalized older patients who had TFT tests, low TT4 and high TSH were associated with a worse prognosis. We propose that TFT be used as an additional tool in assessing MM in elderly hospitalized patients.

Key words: Elderly patients, Hypothyroidism, Hospitalization, Non-thyroidal illness, Thyroid hormones

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Received 02-04-12, Revised 09-05-12, Accepted 18-06-12

INTRODUCTION

Thyroid hormones change with age. In old age, serum triiodothyronine (T3) levels tend to decrease, while tetraiodothyronine (T4) values remain unchanged.[1] With regard to thyrotropin (TSH) levels,

the literature is controversial. According to some authors, TSH values may be lower in older adults than in the whole population.[2] However, it has recently been reported that aging shifts the TSH distribution curve and the 97.5th percentile to higher TSH concentrations.[3] All these alterations create a major disadvantage for the correct interpretation of thyroid status in the elderly.

With regard to hospital older patients, the prevalence of thyroid laboratory tests abnormalities, even without previous thyroid disease, is quite high. While the diagnosis of hypothyroidism has been reported in about 2% of this population,[4] non-thyroidal illness (NTI), also known as euthyroid sick syndrome, is the main finding.[5] The laboratory parameters of NTI usually include low serum levels of T3 and normal or low serum levels of T4 and TSH. Iglesias et al.[5] reported that out of 447 elderly hospitalized patients, 332 (74.3%) had some kind of alteration of TSH and/or thyroid hormones. This last group was mainly represented by NTI (n:278, 62.2%). In contrast, Tognini et al,[6] excluding patients requiring intensive care unit facilities, found only 31.9% of 301 hospitalized older adults with this syndrome. Although higher hospital mortality has been linked to NTI,[5,6] it is still unclear whether it is involved in the progression of disease or simply represents a marker of worse outcome for patients during hospitalization.[7] On the other hand, the impact of true hypothyroidism present in a critically ill patients has not been explored, speculation being that in the elderly it might even be protective.[8]

While alterations of thyroid function in hospitalized elderly patients are very frequent, routine testing is not at present recommended.[4,9] Unless there is a specific clinical reason for suspecting that thyroid dysfunction may be contributing to the clinical condition, thyroid diagnostic tests should be delayed until the resolution of the disease. If primary hypothyroidism has been ruled out, higher TSH levels rather than lower serum T4 levels are more reliable for diagnosis.[10]

The aim of the present study was to define the characteristics of those older patients in whom thyroid function testing (TFT) was requested during hospitalization, and secondly, to analyze the possible association between hospital morbidity/mortality (MM) and thyroid abnormalities present in these patients.

METHODS

Population

This is a retrospective study conducted in a Hospital for the elderly in Buenos Aires over a 6-month period, from August 2009 to January 2010. Out of the 2599 patients aged 60yr or older who were admitted to our institution, 180 had their TFT measured for a variety of reasons. The clinical notes were recalled from the computer system of the laboratories. Clinical characteristics of this group (TFT) were compared with the whole population and also with a selected group (control) of admitted patients without TFT matched for gender, age and reason for admission. All patients signed informed consent to participate in the study and the study protocol was approved by the Ethics Committee of the Dr. Cesar Milstein Assistance Unit.

The specific clinical indications for TFT were identified and the patients were classified according to thyroid hormones and thyrotropin (TSH) values into different categories: euthyroidism (Eu), non-thyroidal illness (NTI), subclinical (SH) and overt hyperthyroidism (OH); and subclinical (sh) and overt hypothyroidism (oh). The current treatment of every patient included in the study was recorded. High MM was defined as a composite endpoint of mortality, intensive care unit (ICU) requirement or prolonged hospital stay (>18 days, *75th percentile*). Long-term MM was defined with the addition of the data concerning mortality at 18 months after discharge.

Hormonal assays

In 68% and 80% of the cases, serum samples were obtained before day 5 and 10 of admission, respectively. Every extraction was done between 8:00 and 9:00 am. Samples were assayed using an automated assay system (Immulite 1000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). The methodologies used for the different hormones were: TSH: two-step immunometric assay, and TT4 and T3 competitive immunoassay. The intra-assay and inter-assay coefficients of variation (CVs) were: TSH= 1.6 and 7.6 %, TT4= 3.2 and 9.1% and T3= 3.3 and 7.6%. Reference values: TSH 0.3-5 mU/l, TT4 4.5-13 μg/dl, T3 0.8-1.9 ng/dl.

Criteria for diagnosis

Overt hyperthyroidism was diagnosed when TT4 was over 13 μg/dl and/or T3 over 1.9 ng/dl and TSH below 0.3 mU/l. Subclinical hyperthyroidism was diagnosed when TT4 (4.5-13 μg/dl) and T3 (0.8-1.9 ng/dl) were normal and TSH below 0.3 mU/l. Euthyroidism was diagnosed when all hormones were within their normal range: TSH 0.3-5 mU/l, TT4 4.5-13 μg/dl, and T3 0.8-1.9 ng/dl. Overt hypothyroidism was diagnosed when TT4 was below 4.5 μg/dl and TSH over 5 mU/l. Subclinical hypothyroidism was diagnosed with normal levels of TT4 4.5-13 μg/dl and T3 0.8-1.9 ng/dl with TSH over 5 mU/l. NTI was diagnosed when T3 levels were below 0.8 ng/dl and the rest of the hormones within their normal range or in any case where the combination of hormones would not fit in the previous categorization.

Statistical analysis

Data were expressed as mean and standard deviation or median and interquartile range (IQR) as appropriate. Mann-Whitney and Kruskall Wallis tests were used to compare data between two and among multiple groups, respectively. The Fisher test was used to compare proportions between two groups, and when more than two were compared a Z-test with the Bonferroni method for multiple comparisons was employed. Associations among hormone levels and in-hospital and long-term morbimortality were evaluated by multiple logistic regressions. Potential confounders/predictors that were tried in the multiple logistic regression as covariates include: gender, drugs, $\log_e$-transformed TSH concentration and the standardized concentration of TT4 and T3 levels. $p<0.05$ was used to consider statistical significance. SPSS ® 17.0 software (Chicago, Ill) was used in all statistical analyses.

RESULTS

Clinical characteristics of TFT patients

Out of the 2599 patients admitted to our Hospital 180 (7%) had TFT. In our Institution TFT are not prescribed routinely. Indications to measure TFT were the following: hyponatremia (30%), cardiologic evaluation (21.6%), previous history of thyroid illness (21.6%), clinical hyperthyroidism (6.6%), anemia (5%), use of amiodarone (3%), anasarca edema and ascites (3%), goiter (3%), weight loss (1.5%) and scheduled thyroidectomy (1.5%). Most TFT were ordered by the Internal Medicine Department (62%) followed by Cardiology (18%), Neurology (10%) and Endocrinology (4%). In 6% of patients we were not able to determine which Department had made the order.

As in 80 out of the 180 cases the medical records were judged incomplete, the TFT patients group finally included only 100 subjects whose clinical characteristics and outcome were first compared to that of the entire population (n=2419). Patients with TFT presented a higher prevalence of female gender (70 *vs.* 58%, $p<0.05$) and an older age (75 (70-82) *vs.* 73 (67-80) years, respectively; $p<0.0001$) than the others. In addition, they were more severely ill as evidenced by a longer hospital stay (8 (5-18) *vs.* 2 (1-6) days, $p<0.0001$), and higher ICU requirement (13 *vs.* 5%, $p<0.0001$) and mortality (15 *vs.* 4%, $p<0.0001$).

Considering these differences, TFT patients were compared to an age-, gender- and reason for admission-matched group of in-patients from the total cohort (control patients, n=100). Clinical outcome for TFT and control patients is shown in Figure 1. While no significant differences were observed as to hospital stay and mortality, TFT patients still presented a more deteriorated health condition as evidenced by a higher requirement for ICU hospitalization and also higher MM.

TFT patients were subsequently classified according to TSH and thyroid hormone levels. Sixty-one percent of the patients were included as NTI, 25% as Eu, 7% as SH, 5% as oh and 1% as both sh and OH. Age was not different among groups. TFT mean values for each thyroid status category are depicted in Table 1. Considering the clinical indication for TFT, we found that of all the patients with hyponatremia, only 5.5% had oh, with arrhythmia and cardiopathies, 15% were SH, and out of all patients in whom TFT was requested because there was a history of hypothyroidism, 23% were actually found oh. Twenty-nine percent of TFT patients had hypothyroidism diagnosed prior to admission and were receiving levothyroxine. Only 4% of patients had a history of previous hyperthyroidism.

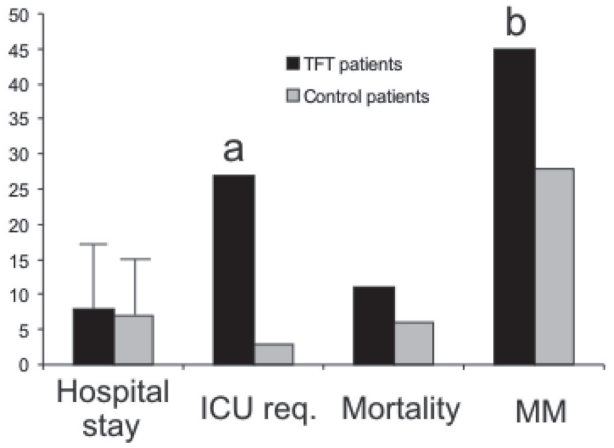

Figure 1. Clinical outcome of TFT and control patients. ICU req., intensive care unit requirement; MM, morbimortality. Every bar shows the percentage of patients, with the exception of hospital stay in which the bars stand for days. a = p<0.0001; b = p<0.01.

Table 1. TSH and thyroid hormones concentration from TFT patients classified according to thyroid status categories

Category of TFT	TSH (mU/l) Median (Q1-Q3)	TT4 (µg/dl) mean±SD	T3 (ng/dl) mean±SD
Total (n=100)	1.7 (0.9-3.2)	7.7 ± 2.2	0.76 ± 0.34
OH (n=1)	0.2 (NA)	11 ± NA	0.98 ± NA
SH (n=7)	0.2 (0.04-0.3)	7.7 ± 2.2	1.07±0.15
Eu (n=25)	1.5 (1.0-2.5)	8.6 ± 1.9	1.08±0.26
oh (n=5)	8.8 (6.8-20.8)	4.16±0.68	0.49±0.21
sh (n=1)	8.6 (NA)	6.2 ± NA	1.1 ± NA
NTI (n=61)	1.7 (0.9-3.5)	7.54±2.24	0.61±0.28

OH and SH: overt and subclinical hyperthyroidism; oh and sh: overt and subclinical hypothyroidism; Eu: euthyroid; NTI: non-thyroidal illness; n: number of patients; NA: not available; SD: standard deviation.

Association of thyroid status with clinical outcome and morbimortality in TFT patients

The clinical outcome of TFT patients within each thyroid status category was analyzed and significant differences were found among groups. Hypothyroid (oh and sh) and NTI patients presented a statistically significantly longer hospital stay than the Eu and hyperthyroid (OH and SH) patients (hypothyroid: 28[19-40], NTI: 11 [6-18], Eu: 6 [3-11] and hyperthyroid: 4 [2-11] days, $p<0.01$ for hypothyroid against all other patient categories and for NTI against Eu and hyperthyroid patients). Moreover, the hypothyroid patients presented the highest prevalence of ICU requirement (hypothyroid: 83%, NTI: 25%, Eu: 22% and hyperthyroid: 13%, $p<0.05$), and of mortality (hypothyroid: 50%, NTI: 10%, Eu: 10%, and hyperthyroid: 0%, $p>0.05$), though the latter did not attain statistical significance.

Furthermore, when TSH and thyroid hormone concentrations were compared within TFT patients classified according to MM, the high MM patients vs the low MM were characterized by higher TSH (2.5 [0.9-6.4] vs. 1.3 [0.8-2.6] mU/l, respectively, $p<0.05$) and lower TT4 concentration (6.9 ±2.4 vs. 8.3±2.0 µg/dl, $p<0.005$), while no difference was observed in T3 plasma levels (0.71±0.34 vs. 0.79±0.35 ng/dl, $p>0.05$).

Accordingly, by multiple logistic regression the decrease of TT4 was the only TFT associated with higher short-term MM (Table 2) adjusted by age, gender, T3 and TSH concentration. However, when long-term MM was analyzed employing the same model, the increase in TSH concentration also attained statistical significance (Table 3).

Table 2. Multiple logistic regression analysis of variables associated with high morbidity/mortality (MM) in TFT patients

	OR (CI 95%)	*p*
Gender	1.3 (0.5-3.5)	0.815
Age	1.0 (0.9-1.1)	0.579
Ln TSH	1.3 (0.9-1.9)	0.190
T3 (per 1-SD decrease)	0.9 (0.6-1.5)	0.727
TT4 (per 1-SD decrease)	2.0 (1.1-3.6)	0.019

SD: standard deviation. High MM was defined as a composite endpoint of mortality, intensive care unit requirement or prolonged hospital stay. T3-SD: 0.34 ng/dl and TT4-SD: 2.2 µg/dl.

Table 3. Multiple logistic regression analysis of variables associated with long-term morbimortality in TFT patients

	OR (CI 95%)	*p*
Gender	1.7 (0.6-4.6)	0.476
Age	1.01 (0.96-1.06)	0.646
Ln TSH	1.6 (1.1-2.3)	0.020
T3 (per 1-SD decrease)	0.6 (0.4-1.0)	0.071
TT4 (per 1-SD decrease)	1.8 (1.1-3.2)	0.041

SD: standard deviation; Long-term MM was defined as high MM with the addition of the data concerning mortality at 18 months after being dismissed; T3-SD: 0.34 ng/dl and TT4-SD: 2.2 µg/dl.

DISCUSSION

The present study highlights the fact that among older patients with TFT measurement, only those who feature low TT4 levels or high TSH levels had a worse prognosis compared to our whole population.

During prolonged critical illness, several tissue responses could be interpreted as compensatory to low thyroid hormone availability, although they might also be in fact reflecting a maladaptive response to stress.[11]

In spite of the fact that the association between mortality and the decline of TT4 levels in critically ill patients is well recognized, the role of TSH levels in prediction of clinical outcomes still remains a matter of debate.[12] Low levels of TSH are known to accompany NTI and also be a consequence of medication in sick patients.[13,14] High levels of TSH, by contrast, found in ambulatory elderly subjects have been related to increased longevity.[9] However, in critically ill elderly patients in whom thyroid disease is suspected, the prognostic value of higher TSH levels has not as yet been evaluated. In this context, it is worth mentioning our finding of a relationship between the progressive augment of a $\log_e$ unit (from 1 to 2.1 mU/l, from 2.1 to 7.4 mU/l, and so on) of TSH concentration with a higher risk for a worse clinical outcome in the TFT group. Specifically, increasing levels of TSH were associated with a 1.3 and a 1.6-fold rise in the risk of short- and long-term MM, respectively, being only statistically significant for long-term MM. Furthermore, the results from the present study agree with previous ones confirming the influence of low TT4 levels over MM,[12,13] as the progressive decrease in 2.2 μg/dl of TT4 concentration (1SD unit) was associated with a 2.0 and 1.8-fold increase in the risk of short- and long-term MM, respectively. With regard to the possible effect of medication on our results, several drugs were considered as confounders in the multivariate logistic regression. However, since the effects on short- and long-term MM were for every drug non-significant (including corticosteroids, levothyroxine, etc), and the T4 and TSH association remained unaffected by its inclusion, the statistical analyses were carried out excluding drug treatments.

An entire body of literature[4-9] has been devoted to the difficulties in clearly differentiating between hypothyroidism and NTI in hospitalized patients, and our study forms no exception. Judging by the low T3 and T4 values with moderately elevated TSH values found in the overt hypothyroid group, it might be inferred that the worse outcome observed in these patients could be explained by the presence of NTI superimposed in a preexisting hypothyroid condition. However, in contrast to NTI, in which high TSH levels reflect recovery of the disease,[7] our patients with high TSH levels presented a worse clinical course. Although patient-misclassification might be biasing these results, and increased TSH may be simply the result of the acute illness, the use of the thyroid hormones levels as continuous variables in the logistic regression models, instead of thyroid function categories that imply the choice of specific cut-off values, tended to minimize any misinterpretation of the results. In fact, the association between worse prognosis and high TSH levels found in the present study agrees with what has been recently reported by Iglesias et al.[15] In this study the authors established that higher serum TSH values in elderly patients found at the beginning of hospitalization were related to a thyroid profile of persistent NTI, while the lowest TSH values were associated with recovery of thyroid function after one month of discharge. Furthermore, in our study most TSH values were assessed at the beginning of their hospitalization, while high TSH levels in the context of NTI have been described once the patient has succeeded in recovering from disease.[7] Considering also that the TFT group had a very high proportion of previously hypothyroid patients, it is possible that the worse prognosis associated with increased TSH levels might in reality reflect the impact of the lack of thyroid hormones in the tissues. Therefore, the cause of the high mortality in patients having higher TSH values could be explained by the well recognized detrimental effects of hypothyroidism, such as increased systemic vascular resistance, decreased cardiac contractility, decreased cardiac output and accelerated atherosclerosis and coronary artery disease.[16] We acknowledge, though, that ATPO or thyroid ultrasound assessment would have proved useful to confirm hypothyroidism; however, due to the retrospective nature of the study this was not possible.

While there is controversy as to the frequency of NTI in hospitalized older patients,[5,6] our findings agree

with what had been previously reported by Iglesias et al.[5] However, unlike these authors, we found a higher proportion of hypothyroidism and hyperthyroidism. This may be explained by the design of our case finding study. Surprisingly, most patients in the oh category had a history of hypothyroidism and were currently on levothyroxine. The observation of increased levothyroxine requirements in hypothyroid critically ill patients has recently been reported by Imberti et al.[17] A possible explanation for our findings may be that the drug was probably interrupted at admission to the hospital or that it was malabsorbed during the patient's stay. On the other hand, and in agreement with the literature,[18] almost one third of the patients classified as SH were on supraphysiological doses of levothyroxine.

The lack of association between low T3 levels and worse clinical outcome was unexpected. However, when analyzing TFT patients characteristics, the T3 levels were indeed low normal on our reference scale. In effect, 75% of the population exhibited T3 concentrations ranging between 0.46-0.89 ng/dl. This feature might account for the lack of association between T3 levels and MM.

In conclusion, in older patients with TFT, whether NTI or hypothyroid, low TT4 or high TSH were associated with higher short- and long-term MM. The increased morbid-mortality in older patients found to be hypothyroid in the context of acute illness and the exact role of high TSH levels necessitate further study.

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