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ORIGINAL ARTICLE

Hypothyroidism in hospitalized elderly patients: a sign of worse prognosis

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Abstract
Purpose Overt hypothyroidism has adverse clinical consequences and might worsen prognosis in critically ill elderly patients. However, the difficult interpretation of thyroid function tests (TFT) due to non-thyroidal illness (NTI) has led to discouragement of screening for thyroid dysfunction. Our aim was to determine the prevalence of TFT compatible with hypothyroidism and to study its influence on mortality among hospitalized elderly patients.
Methods In this prospective study we consecutively included all patients ≥60 years admitted by the Internal Medicine Department to the hospital ward ($n = 451$) of the Cesar Milstein Hospital in Buenos Aires, Argentina. TFT were done on day 1 and 8. Thyroid function categories were defined as overt and subclinical hypothyroidism, overt and subclinical hyperthyroidism, euthyroidism and NTI. Stage of chronic kidney disease (CKD), Adult Comorbidity Evaluation (ACE)-27, and intra-hospital mortality were recorded. The association between mortality and TFT categories was studied by Cox regression.
Results Out of 451 patients (77.0 ± 7.9 years, 54% females) 76% were categorized as NTI, 4% as overt hypothyroid, 10% as subclinical hypothyroid, 1% as subclinical hyperthyroid and 9% as euthyroid. Overt hypothyroid patients showed significantly higher mortality than the rest of the groups (25%, $p < 0.05$) while ACE-27 was similar among all of them ($p = 0.658$). In addition, patients within the overt hypothyroid category showed a higher mortality rate than NTI in a model adjusted by Stage 5-CKD, ACE-27, sex and age [HR 3.1 (1.14–8.41), $p < 0.026$].
Conclusion Overt hypothyroidism during hospitalization was associated with elevated mortality. Further studies would reveal if TFT alterations compatible with hypothyroidism should be diagnosed/treated in hospitalized elderly patients.

Keywords Hypothyroidism · Thyroid function tests · Elderly · Non-thyroidal disease · Hospitalization

Introduction

According to population studies, the values of TSH slightly increase as age advances [1, 2]. Nevertheless, this has not been associated to a deficit of thyroid hormones but to a possible adaptation of the thyroid axis in the elderly. Major controversies arose from several reports of lack of adverse effects [3–5] and prolonged life span [6, 7] in old age individuals with abnormally high levels of TSH. Such results have led to important changes in the treatment recommendations for these patients. Most of the treatment guidelines [8–10] recommend against treating this special segment of the population when TSH values are below 10 mU/L and

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free T4 is within the reference range. Such recommendation is issued despite the lack of randomized controlled trials assessing the cost-effectiveness of levothyroxine replacement in elderly population.

On the other hand, it is widely recognized that with age the prevalence of thyroid autoimmunity raises [11], with the consequent increase in hypothyroidism and a detrimental impact in the cardiovascular and neurocognitive areas [8]. Considering the influence of medications and comorbidities in this period of life together with the above explained changes in the thyroid profile, it is quite understandable why it is so difficult to interpret thyroid function tests (TFT) and to identify true thyroid pathology in the elderly.

In elderly hospitalized patients, the scenario is even worse due to the use of drugs that interfere on the measurement of TFT and, most importantly, to the presence of the non-thyroidal illness (NTI) [12, 13]. In particular, the use of contrast solutions, amiodarone, heparin, corticoids and of other medications that interfere with the absorption of levothyroxine, all hamper the evaluation of thyroid function in hospitalized patients [14] Therefore, the diagnosis of hypo or hyperthyroidism in this particular population is a difficult task; thus, the screening for thyroid pathology is discouraged in these patients [15]. Nevertheless, this strategy underestimates the potential detrimental effect of a true state of hyper or hypothyroidism on the evolution of hospitalized patients.

There are scarce data on the possible effect of hypothyroidism on the evolution of elderly in-patients. A former retrospective study has shown that higher baseline TSH values during hospital admission were related to a worse long-term prognosis in older patients [16]. In addition, Maldonado et al. [17] reported in a series of 116 critically ill patients that high TSH was independently associated with mortality. These findings challenge the notion of a possible protective effect of hypothyroidism in this period of life [6, 7] and also contrast with other studies that did not report excess mortality in hypothyroid patients [15, 18, 19].

Our aim was to evaluate the prevalence of TFT compatible with hypothyroidism and to study its influence on mortality in a population of hospitalized elderly patients.

Materials and methods

Population

The study was conducted in a hospital for the elderly in Buenos Aires during a 12-month period, from January 2013 to January 2014. Eligible subjects were 504 patients who were consecutively admitted to the clinical ward of our institution by the Internal Medicine Department. Exclusion criteria were: age <60 years, myxedema coma, thyroid cancer, incomplete clinical or biochemical data and refusal to participate in the study. The study population comprised 451 patients. The study protocol was approved by the Ethics Committee of the Cesar Milstein Hospital.

Informed consent

"Informed consent was obtained from all individual participants included in the study."

Clinical evaluation

The main cause of admission and the medications taken before admission were registered. At day 1 of the hospital stay, the usage of drugs that may interfere with TFT was registered. Comorbidities at day 1 were assessed by the Adult Comorbidity Evaluation (ACE-27) [20]. Geriatric assessment was obtained with the Karnofsky performance scale (KPS) that allows patients to be classified according to their functional impairment [21]. During the hospital stay, changes in medications, intensive care unit (ICU) requirement, hospital discharge, and intra-hospital mortality were recorded.

Biochemical assays

Every blood extraction was done between 8.00 and 9.00 a.m. Serum samples were stored at −20° C until assayed for TFT on the same run at the end of the recruitment period. An automated immunoassay system was used (Immulite1000, Siemens Healthcare Diagnostics, Llanberis, UK). The methodologies used for the different hormones were: TSH: two-site solid-phase chemiluminescent immunometric assay, and TT4 and T3: solid-phase competitive chemiluminescent enzyme immunoassay. We preferred to determine total T4 instead of free T4 analog-based immunoassays, since in the context of NTI, albumin is abnormal and can affect free T4 values. Similarly, if the patients receive drugs, such as phenytoin, carbamazepine, furosemide, or heparin, that displace T4 from the thyroxine binding globulin (TBG), thyroid function evaluation with TSH + total T4 has been recommended [8]. Intra-assay coefficients of variation for TSH, TT4 and T3 were: 4.5–6.2%; 6.3–8.4%; 5.4–13.2%, respectively. Inter-assay coefficients of variation for TSH, TT4 and T3 were: 5.7–8.3%; 5.7–10.6%; 5.6–11.6%, respectively. Laboratory defined reference values are: TSH: 0.3–5.0 mU/L, TT4: 4.5–13 µg/dL, T3: 80–190 ng/dL. Samples for TFT evaluation were drawn at day 1 ($n = 451$) and at day 8 ($n = 194$).

Overt hyperthyroidism was diagnosed when TT4 was over 13 µg/dL and/or T3 over 190 ng/dL and TSH below

0.3 mU/L. Subclinical hyperthyroidism was diagnosed when TT4 (4.5–13 μg/dL) and T3 (80–190 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 80–190 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 80–190 ng/dL with TSH over 5 mU/L. NTI was diagnosed when T3 levels were below 80 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 any of the previously defined categories.

General biochemical parameters were evaluated by standardized methods. The stage of chronic kidney disease (CKD) of each patient was evaluated using age and serum creatinine to calculate the glomerular filtration rate (CKD-EPI formula). CKD stages were defined according to international guidelines.

Clinical outcomes

The primary outcome was defined as intra-hospital mortality.

Statistical analysis

Data were expressed as mean and standard deviation or median and interquartile range (IQR) as appropriate according to data distribution. ANOVA or the Kruskall–Wallis test was used to compare data between the groups. To compare categorical variables between the groups a *Z*-test with the Bonferroni correction for multiple comparisons was employed. Associations among TFT categories and mortality were evaluated by COX regression. All variables included in the model were graphically tested to meet the proportional hazard assumption. The group of patients with subclinical hyperthyroidism was excluded from COX regression analysis due to its low number of patients. Similarly, euthyroid patients were excluded from COX analysis because no deaths were registered in this group. Potential confounders/predictors that were included in the COX model were: sex, age (divided by tertiles), ACE-27 score, CKD stages and TFT categories. $P < 0.05$ was used to consider statistical significance. SPSS® 17.0 software (Chicago, Ill) was used in all the statistical analyses.

Results

Baseline clinical characteristics and TFT results

The studied population consisted of 243 women (54%) and 208 (46%) men, aged 77 (71–83) years old. The overall prevalence of previous thyroid disease was 17.5%. Most of these cases (96%) were due to previous hypothyroidism. Among these patients, levothyroxine was unintentionally discontinued in 12% of the cases at the first day of hospitalization. According to TFT results the study population was categorized as NTI (76%), overt hypothyroidism (4%), subclinical hypothyroidism (10%), subclinical hyperthyroidism (1%) and euthyroidism (9%).

Clinical characteristics and outcomes according to TFT categories are shown in Table 1. Patients classified as overt hypothyroidism were older and presented higher ICU requirement and mortality than the other TFT categories. The prevalence of history of hypothyroidism and levothyroxine use was higher in the patients categorized as subclinical hypothyroid. Most likely, these results suggest sub medication as a leading cause of high TSH values among patients within this group (Table 1). TSH and thyroid hormones results and the proportion of positive TPOab patients according to TFT categories are shown in Supplementary Table 1. Significantly higher prevalence of positive TPOab was observed in the subclinical hypothyroid group. The rest of significant differences among TFT categories were in line with the selection criteria employed.

Causes of admission according to TFT categories are shown in Table 2. The leading cause of hospitalization was infectious disease (22%), followed by respiratory (19%) and hematological disease (18%). Differences in the causes of admission among TFT categories were only significant for hematological and tumoral diseases (Table 2). Overt hypothyroid and euthyroid groups showed a larger number of patients with hematological diseases than the NTI category. In addition, in the subclinical hypothyroid group a higher number of patients were admitted by tumoral diseases in comparison with the NTI and euthyroid groups.

In regards to geriatric assessment no differences in functional status were found among the groups with the KPS. The possible presence of cognitive impairment and consequent potential onset of delirium (a well-known risk factor for short term mortality), was assessed as part of the ACE score and no differences were observed when hypothyroid patients were compared with the rest of the groups.

We also compared the number of patients in each CKD stage among the groups and found that euthyroid patients presented a lower number of patients at stage 5-CKD (Table 1).

Changes in categories in day 8

Out of 451 patients, 194 remained at the hospital and had their TFT reevaluated at day 8. Figure 1 shows TFT categories at day 1 and day 8 according to baseline TSH values. Those patients whose baseline TSH level was 0.3–5.0 mU/l as well as those classified as NTI and

Table 1 Clinical characteristics of patients in the study according to the TFT categories

	NTI ($n = 345$)	oh ($n = 20$)	sch ($n = 44$)	SCH ($n = 3$)	Eu ($n = 39$)	Total ($n = 451$)	*P*
Age (years)	77 (71–83)[a]	81 (71–86)[a]	78 (73–84)[a]	74 (62-76)[a, b]	71 (67–79)[b]	77 (71–83)	0.017
Hospital stay (days)	7 (4–12)	8 (5–12)	8 (4–18)	6 (16–27)	6 (3–15)	7 (4–13)	0.301
Females (%, *n*)	54 (182)	60 (12)	64 (28)	100 (3)	46 (18)	54 (243)	0.258
History of hypothyroidism (%, *n*)	15 (51)[a]	25 (5)[a, b]	43 (19)[b]	–	5 (2)[a]	17 (77)	<0.001
History of hyperthyroidism (%, *n*)	1 (2)	5 (1)	–	–	–	0.6 (3)	0.971
Discontinuation of LT4 (%, *n*)	14 (48)	5 (1)	7 (3)	–	5 (2)	12 (54)	0.578
LT4 at day 1 (%, *n*)	13 (43)[a]	15 (3)[a]	32 (14)[b]	–	5 (2)[a]	14 (62)	0.004
Amiodarone (%, *n*)	6 (20)	5 (1)	9 (4)	–	–	6 (25)	0.823
Corticoid (%, *n*)	14 (49)	35 (7)	14 (6)	33 (1)	10 (4)	15 (67)	0.090
Omeprazol (%, *n*)	56 (194)	55 (11)	61 (27)	67 (2)	54 (21)	56 (255)	0.953
ICU (%, *n*)	5 (18)[a]	15 (3)[b]	2 (1)[a]	33 (1)	3 (1)[a]	5 (24)	0.044
Mortality (%, *n*)	10 (35)[a]	25 (5)[b]	11 (5)[a]	33 (1)	–	10 (47)	0.026
Previous admission (%, *n*)	25 (88)	15 (3)	25 (11)	67 (2)	23 (9)	25 (114)	0.411
ACE-27 (%, *n*)							
1	22 (75)	15 (3)	12 (5)	–	22 (9)	21 (92)	0.658
2	27 (92)	30 (6)	23 (11)	33 (1)	23 (10)	26 (120)	
3	51 (179)	55 (11)	65 (28)	67 (2)	55 (19)	53 (239)	
CKD (%, *n*)							
1	18 (61)	20 (4)	11 (5)	–	28 (11)	18 (81)	0.010
2	34 (116)	25 (5)	46 (20)	–	60 (23)	36 (164)	
3	25 (88)	30 (6)	27 (12)	–	0 (0)	24 (106)	
4	15 (53)	10 (2)	11 (5)	33 (1)	10 (4)	14 (65)	
5	8 (27)[b]	15 (3)[b]	5 (2)[a, b]	66 (2)[b]	2 (1)[a]	8 (35)	

Quantitative variables are expressed as median (IQ range). Different letters depict statistically significant differences between the groups

TSH thyrotrophin, *TT4* total thyroxine, *T3* triiodothyronine, *NTI* non-thyroidal illness, *oh* overt hypothyroidism, *sch* subclinical hypothyroidism, *SCH* subclinical hyperthyroidism, *Eu* euthyroid, *LT4* levothyroxine, *ICU* intensive care unit, *ACE* adult comorbidity evaluation, *CKD* chronic kidney disease

Table 2 Major causes of admission in the studied population and according to TFT categories

Main cause of admission	NTI *n*: 345	oh *n*: 20	sch *n*: 44	Eu *n*: 39	Total *n*: 451	*P*
Infectious	23 (80)	15 (3)	16 (7)	26 (10)	22 (100)	0.570
Respiratory	21 (71)	15 (3)	1 (5)	13 (5)	19 (84)	0.389
Hematological	15 (52)[a]	25 (5)[b]	–	31 (12)[b]	18 (70)	0.025
Gastric	14 (48)	25 (5)	4 (6)	13 (5)	14 (64)	0.643
Tumoral	8 (29)[a]	15 (3)[a, b]	23 (10)[b]	8 (3)[a]	10 (47)	0.001
Neurological	7 (24)	15 (3)	–	–	6 (27)	0.075
Cardiac	4 (15)	–	7 (3)	–	4 (18)	0.872

Values are expressed as % (*n*). Different letters depict statistically significant differences between the groups. Patients with subclinical hyperthyroidism were not included in Table ($n = 3$). There were 41 patients in which the main cause of admission could not be correctly established

NTI non-thyroidal illness, *oh* overt hypothyroidism, sch subclinical hypothyroidism, *Eu* euthyroid

subclinical hypothyroidism in day 1 were the ones in which most of the TFT category switches took place. It was remarkable that most of the patients initially classified as overt hypothyroid remained in the same TFT category by day 8.

Mortality according to TFT groups

Mortality was compared among the NTI, overt hypothyroid and subclinical hypothyroid categories. None of the euthyroid patients had died during their hospital stay; thus, this group was not included in the analysis.

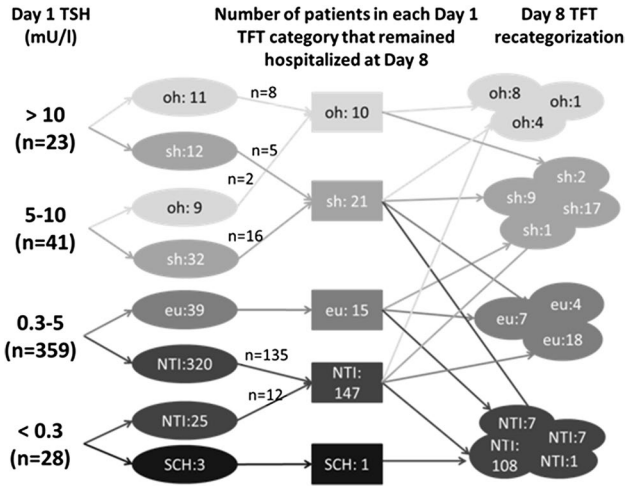

Fig. 1 Sequence of patients in each TFT category from day 1 to day 8 according to TSH values in day 1 ($N = 194$). *NTI* non-thyroidal illness, *oh* overt hypothyroidism, *sch* subclinical hypothyroidism, *SCH* subclinical hyperthyroidism, *eu* euthyroid

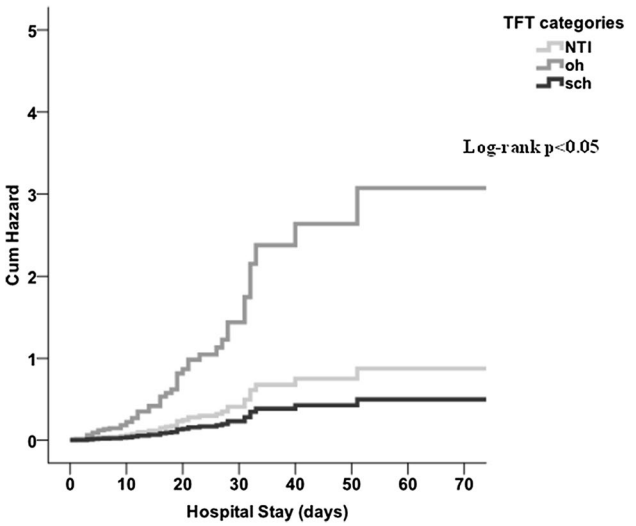

Fig. 2 Mortality in each TFT category during hospital stay. *NTI* non-thyroidal illness, *oh* overt hypothyroidism, *sch* subclinical hypothyroidism, *SCH* subclinical hyperthyroidism, *ACE* adult comorbidity evaluation. None of the euthyroid patients died during their hospital stay and the whole category was excluded from the analysis. Likewise, as there were only three patients classified as subclinical hyperthyroid, they were not included in the analysis

Regarding the potential interference of severe pathological conditions, we accounted for the presence of important clinical parameters such as albuminemia, natremia, glomerular filtration rate.

Hypoalbuminemia (albumin <3.5 g/dl) (HR 1.79 95% CI 0.87–3.69, $p = 0.112$) and hyponatremia (sodium <130 mEq/l) (HR 1.11 95% CI 0.59–2.07, $p = 0.75$) were not associated with mortality and thus, were not included in the statistical analyses.

As euthyroid patients presented a lower number of patients at stage 5-CKD, the stages of CKD were included in the survival analysis. However, CKD-stage as an ordinal variable (HR 1.14, 95% CI 0.88–1.48, $p = 0.314$) and stage 5-CKD as a dichotomic variable (yes/no) (HR 2.5, 95% CI 0.995–6.27, $p = 0.051$), were not significantly associated with mortality either.

Patients classified as overt hypothyroid presented significantly higher mortality hazard than NTI patients (Fig. 2 and Supplementary Table 2). On the other hand, no significant differences were observed between NTI and subclinical hypothyroid patients. Such result remained statistically significant even when the model was adjusted by age, sex, ACE-27 score and Stage 5-CKD (Fig. 2).

Discussion

Our study showed that TFT compatible with hypothyroidism is a frequent finding in the elderly in-patient population and that it can go unnoticed during the hospital stay. This finding is clinically relevant as patients classified as hypothyroid showed an increased mortality in comparison to patients with other thyroid function alterations, even when adjusted by age, sex, stage 5-CKD and a comorbidity score.

In regards to hospitalized patients, the role of hypothyroidism has recently become a controversial issue. Indeed, TF testing is discouraged unless there is a clear suspicion of thyroid dysfunction [8, 9]. These recommendations are based on the interference created by drugs and the presence of NTI that hamper the interpretation of TFT in this setting [15]. Although this strategy can be cost effective, it is at the expense of under-diagnosing true thyroid dysfunction. In fact, in a retrospective study it was observed that out of 56 adult patients with newly diagnosed primary overt hypothyroidism admitted from the Emergency Department, only in 12 (21%) there was a correct initial impression of primary overt hypothyroidism [22].

A few studies that have explored TFT in admitted elderly patients confirmed that NTI is the most frequent cause of TFT abnormalities. Iglesias et al. [18] found about three quarters of patients with alterations in TFT and the reduction of FT3 values was a powerful predictor for mortality during hospitalization in their cohort of elderly patients. In another study that excluded patients admitted to ICU, NTI prevalence was only 31.9% and in this group mortality rate was also significantly higher [19]. Similarly, De Alfieri et al. [23] included 450 very old (mean age: 84 years) hospitalized patients admitted for an acute disease in their study, and reported that low T3 syndrome was associated with an excess mortality risk during the hospital stay.

Although all these studies are in coincidence with the ample evidence about low T3 and T4 values as predictors of poor survival in critically ill patients [16, 24], the clinical significance of impaired TSH values at admission still remains undetermined. In the present study, in line with Iglesias et al. [25], the large majority of the population had NTI. However, patients with overt hypothyroidism presented an even worse prognosis during hospitalization than NTI. A possible interpretation to these data is that we excluded ICU patients, therefore, sicker patients with low T3 values. Moreover, our group of overt hypothyroid patients was larger in comparison with that found in the study of Iglesias et al. [25]. In the study by De Alfieri et al. [23], hypothyroidism did not reveal any difference in survival compared to the rest of the population. However, these authors defined hypothyroidism as patients taking replacement therapy, and included patients with subclinical hypothyroidism apart from purely overt hypothyroid patients as in the present study.

With regards to the rest of the studies that have explored the effects of TSH alterations as predictors of survival in hospitalized patients, an earlier one [26] performed in 200 patients admitted to the ICU showed that subnormal TSH values (<0.4 mU/L) were associated to much higher mortality rates than patients with TSH serum levels >5 mU/L. These results differ to the present findings since every patient with high TSH in the study of Rothwell et al. [26] had T4 values within the normal range and most of these patients returned to normal TSH values on repeated measurements. Although doubts had been casted on the diagnostic value of TSH levels <10 mU/L [15], we observed that most of the patients initially classified as hypothyroid still remained in the same category by day 8 when the TFT were reassessed. Therefore, it can be possible that elderly in-patients with a minor increase of TSH levels (TSH: 5–10 mU/L) might present a true hypothyroidism in this particular setting.

On the other hand, in another study where only ICU patients were included a high mortality rate (55%) was found among the patients who were retrospectively found to be hypothyroid [17]. Furthermore, in the mentioned study, higher TSH values were still associated to mortality after excluding the group of hypothyroid patients. In line with these data, we previously found in a retrospective cohort of elderly admitted patients, that hypothyroidism was associated to increased morbi-mortality. Nonetheless, this study was limited to a population of elderly patients with a clinical suspicion of thyroid dysfunction [16]. In a recent study of 1662 hospitalized patients with type 2 diabetes, hypothyroidism was related to increased cerebrovascular disease compared with euthyroidism after adjustment for age and gender [27]. In further agreement with our findings, Laulund et al. [28] also reported excess mortality for hospitalized patients with overt hypothyroidism. However, this association disappeared when patients with no registered comorbidities were only included for the analysis reflecting that lack of thyroid hormones might have a detrimental influence particularly in those patients who are critically ill.

Another interesting finding of our study is related to subclinical hypothyroid patients. Although all had higher than normal TSH values, 32% of these patients were on levothyroxine treatment at admission in coincidence with history of previous hypothyroidism in almost half of this group. During their stay in the hospital some of these patients developed overt hypothyroidism and it was also observed that 40% of patients who were taking levothyroxine on day 1 were not taking it on day 8. These findings are in line with those of Vaisman et al. [29], showing that a significant number of hypothyroid patients taking thyroid hormones are not in the therapeutic range and with those of Imberti et al. [30] who reported a series of cases on hypothyroid in-patients whose thyroid status worsened due to unintended discontinuation of levothyroxine or malabsorption secondary to other drugs frequently administered during hospitalization.

Spencer et al. [15] found the TSH concentration to be above 20 mU/L in only 1.6% of unselected in-patients. During follow-up they showed that in only 50% of these cases, thyroid disease could be diagnosed. Since overt hypothyroid patients in our study did not exhibit very high TSH values despite low T3 and T4 values, miscategorization of NTI as hypothyroidism cannot be discarded. It could be speculated that this group of hypothyroid patients may also be under the effects of NTI, thus explaining the low levels of T4 and T3 with TSH levels that do not escalate accordingly. However, it has to be acknowledged that the effect of glucocorticoids or dopamine, drugs often used during hospitalization are a possible explanation to this discrepancy between thyroid hormones and TSH [14]. Another plausible explanation rely in an age-effect as it was reported that hypothyroid elderly subjects show lower TSH values than younger ones at similar T4 values [31]. In addition, it could be possible that during the study our hypothyroid patients presented a diminished TSH secretion during acute stress as it has been previously reported [32].

In the present cohort, from the 13 patients classified as hypothyroid at day 8, eight patients were already identified as hypothyroid in day 1. Such result supports that thyroid dysfunction found early during hospitalization in elderly patients may be persistent and of clinical relevance. In this regard, a limitation of our study is the lack of intervention to observe possible effects of levothyroxine treatment in the patients found to be hypothyroid. However, this was an observational study and the results of TFT were blinded until the end of the recruitment phase.

It has been previously recommended against screening for thyroid dysfunction in hospitalized patients since NTI, although associated to higher mortality, is usually not worth of treatment. Moreover, hypo or hyperthyroidism are difficult to identify in this context. However, according to our findings we would suggest to reconsider screening the elderly population in whom hypothyroidism was frequently found and was also associated to a worse prognosis. Although it seems reasonable that those hypothyroid patients identified through screening deserve levothyroxine treatment, we still need a RCT proving the efficacy of levothyroxine replacement in hospitalized elderly patients.

In conclusion, we found a large proportion of overt hypothyroid in-patients with a worse prognosis when compared to the rest of the population admitted to our clinical ward. These findings warn about the misdiagnosis of potentially treatable cases of thyroid dysfunction and also show that hypothyroidism may serve as a marker of bad prognosis among hospitalized elderly patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Our research involved human participants from whom we obtained the informed consent.

Informed consent "Informed consent was obtained from all individual participants included in the study."

References

1. Surks MI, Boucai L (2010) Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab 95(2):496–502. doi:10.1210/jc.2009-1845
2. Surks MI, Hollowell JG (2007) Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 92(12):4575–4582. doi:10.1210/jc.2007-1499
3. Blum MR, Wijsman LW, Virgini VS, Bauer DC, den Elzen WP, Jukema JW, Buckley BM, de Craen AJ, Kearney PM, Stott DJ, Gussekloo J, Westendorp RG, Mooijaart SP, Rodondi N (2016) Subclinical thyroid dysfunction and depressive symptoms among the elderly: a prospective cohort study. Neuroendocrinology 103(3–4):291–299. doi:10.1159/000437387
4. Meuwese CL, Gussekloo J, de Craen AJ, Dekker FW, den Elzen WP (2014) Thyroid status and renal function in older persons in the general population. J Clin Endocrinol Metab 99(8):2689–2696. doi:10.1210/jc.2013-3778
5. Virgini VS, Wijsman LW, Rodondi N, Bauer DC, Kearney PM, Gussekloo J, den Elzen WP, Jukema JW, Westendorp RG, Ford I, Stott DJ, Mooijaart SP (2014) Subclinical thyroid dysfunction and functional capacity among elderly. Thyroid 24(2):208–214. doi:10.1089/thy.2013.0071
6. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG (2004) Thyroid status, disability and cognitive function, and survival in old age. JAMA 292(21):2591–2599. doi:10.1001/jama.292.21.2591
7. Pearce SH, Razvi S, Yadegarfar ME, Martin-Ruiz C, Kingston A, Collerton J, Visser TJ, Kirkwood TB, Jagger C (2016) Serum thyroid function, mortality and disability in advanced old age: the Newcastle 85+ study. J Clin Endocrinol Metab 101(11):4385–4394. doi:10.1210/jc.2016-1935
8. Brenta G, Vaisman M, Sgarbi JA, Bergoglio LM, de Andrada NC, Bravo PP, Orlandi AM, Graf H (2013) Clinical practice guidelines for the management of hypothyroidism. Arq Bras Endocrinol Metabol 57(4):265–291
9. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA (2012) Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American thyroid association. Thyroid 22(12):1200–1235. doi:10.1089/thy.2012.0205
10. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, Wemeau JL (2013) 2013 ETA guideline: management of Subclinical hypothyroidism. Eur Thyroid J 2(4):215–228. doi:10.1159/000356507
11. Morganti S, Ceda GP, Saccani M, Milli B, Ugolotti D, Prampolini R, Maggio M, Valenti G, Ceresini G (2005) Thyroid disease in the elderly: sex-related differences in clinical expression. J Endocrinol Invest 28(11 Suppl Proceedings):101–104
12. Stockigt JR, Lim CF (2009) Medications that distort in vitro tests of thyroid function, with particular reference to estimates of serum free thyroxine. Best Pract Res Clin Endocrinol Metab 23(6):753–767. doi:10.1016/j.beem.2009.06.004
13. Sanai T, Okamura K, Kishi T, Miyazono M, Ikeda Y, Kitazono T (2015) Importance of specific reference values for evaluation of the deteriorating thyroid function in patients with end-stage renal disease on hemodialysis. J Endocrinol Invest 38(1):47–56. doi:10.1007/s40618-014-0121-6
14. Fliers E, Alkemade A, Wiersinga WM (2001) The hypothalamic-pituitary-thyroid axis in critical illness. Best Pract Res Clin Endocrinol Metab 15(4):453–464. doi:10.1053/beem.2001.0163
15. Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S, Nicoloff J (1987) Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. Clin Chem 33(8):1391–1396
16. Mingote E, Merono T, Rujelman R, Marquez A, Fossati P, Gurfinkiel M, Schnitman M, Brites F, Faingold C, Brenta G (2012) High TSH and low T4 as prognostic markers in older patients. Hormones (Athens) 11(3):350–355
17. Maldonado LS, Murata GH, Hershman JM, Braunstein GD (1992) Do thyroid function tests independently predict survival in the critically ill? Thyroid 2(2):119–123
18. Iglesias P, Munoz A, Prado F, Guerrero MT, Macias MC, Ridruejo E, Tajada P, Diez JJ (2009) Alterations in thyroid function tests in aged hospitalized patients: prevalence, aetiology and clinical outcome. Clin Endocrinol (Oxf) 70(6):961–967. doi:10.1111/j.1365-2265.2008.03421.x
19. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M, Monzani F (2010) Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing 39(1):46–50. doi:10.1093/ageing/afp197
20. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr (2004) Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 291(20):2441–2447. doi:10.1001/jama.291.20.2441

21. Crooks V, Waller S, Smith T, Hahn TJ (1991) The use of the Karnofsky performance scale in determining outcomes and risk in geriatric outpatients. J Gerontol 46(4):M139–144
22. Chen YJ, Hou SK, How CK, Chern CH, Lo HC, Yen DH, Huang CI, Lee CH (2010) Diagnosis of unrecognized primary overt hypothyroidism in the ED. Am J Emerg Med 28(8):866–870. doi:10.1016/j.ajem.2009.04.024
23. De Alfieri W, Nistico F, Borgogni T, Riello F, Cellai F, Mori C, Nante N, Di Bari M (2013) Thyroid hormones as predictors of short- and long-term mortality in very old hospitalized patients. J Gerontol A Biol Sci Med Sci 68(9):1122–1128. doi:10.1093/gerona/glt012
24. De Groot LJ (2006) Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin 22(1):57–86, vi. doi:10.1016/j.ccc.2005.10.001
25. Iglesias P, Ridruejo E, Munoz A, Prado F, Macias MC, Guerrero MT, Tajada P, Garcia-Arevalo C, Diez JJ (2013) Thyroid function tests and mortality in aged hospitalized patients: a 7-year prospective observational study. J Clin Endocrinol Metab 98(12):4683–4690. doi:10.1210/jc.2012-3849
26. Rothwell PM, Udwadia ZF, Lawler PG (1993) Thyrotropin concentration predicts outcome in critical illness. Anaesthesia 48(5):373–376
27. Song F, Bao C, Deng M, Xu H, Fan M, Paillard-Borg S, Xu W, Qi X (2016) The prevalence and determinants of hypothyroidism in hospitalized patients with type 2 diabetes mellitus. Endocrine. doi:10.1007/s12020-016-1095-2
28. Laulund AS, Nybo M, Brix TH, Abrahamsen B, Jorgensen HL, Hegedus L (2014) Duration of thyroid dysfunction correlates with all-cause mortality. The OPENTHYRO register cohort. PLoS One 9(10):e110437. doi:10.1371/journal.pone.0110437
29. Vaisman F, Coeli CM, Ward LS, Graf H, Carvalho G, Montenegro R Jr, Vaisman M (2013) How good is the levothyroxine replacement in primary hypothyroidism patients in Brazil? Data of a multicentre study. J Endocrinol Invest 36(7):485–488. doi:10.3275/8810
30. Imberti R, Ferrari M, Albertini R, Rizzo V, Tinelli C (2010) Increased levothyroxine requirements in critically ill patients with hypothyroidism. Minerva Anestesiol 76(7):500–503
31. Carle A, Laurberg P, Pedersen IB, Perrild H, Ovesen L, Rasmussen LB, Jorgensen T, Knudsen N (2007) Age modifies the pituitary TSH response to thyroid failure. Thyroid 17(2):139–144. doi:10.1089/thy.2006.0191
32. Hooper MJ (1976) Letter: diminished TSH secretion during acute non-thyroidal illness in untreated primary hypothyroidism. Lancet 1(7949):48–49