NOTE

Does low-normal serum TSH level adversely impact cognition in elderly adults and might methimazole therapy improve outcomes?

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Abstract. Serum thyroid stimulating hormone (TSH) levels increase with age. This elevation has been associated with better outcomes in very elderly subjects; however, little is known about the relationship between TSH below the lower limit of the reference range and health-related outcomes. Here, we investigated the association between cognitive impairment or depressive symptoms and low-normal serum TSH (<1.0 $\mu\text{IU/mL}$, in the reference range) in elderly subjects and whether the use of methimazole in subjects without dementia but with low-normal TSH could affect cognition or depressive symptoms. From 293 healthy adults ≥ 65 years old with normal TSH included in the sectional phase, only subjects without dementia were prospectively analyzed: 1) TSH ≥ 1.0 $\mu\text{IU/mL}$ (observation; untreated); 2) TSH <1.0 $\mu\text{IU/mL}$ (observation; untreated); and 3) TSH <1.0 $\mu\text{IU/mL}$ (methimazole therapy). Cognition was assessed, using the Mini Mental State Examination (MMSE) and depressive symptoms (at MMSE ≥ 13) by the Geriatric Depression Scale (GDS). Age >80 years was the sole independent factor associated with dementia (OR=2.89; confidence interval [CI] 1.72-4.86; $p<0.01$). Prospectively, 93 completed follow-up, with 7.5% (7) receiving methimazole intervention. Untreated subjects with lower TSH showed the greatest declines in MMSE scores during follow-up that was not observed in those with serum TSH ≥ 1.0 $\mu\text{IU/mL}$. Lower MMSE score reductions were associated with elderly subjects receiving methimazole. There were no significant changes in depressive symptoms and GDS scores among those with serum TSH <1.0 $\mu\text{IU/mL}$. In this study, low-normal TSH was not associated with higher prevalence of dementia. However, in elderly subjects without dementia, low TSH was associated with worsening cognition.

Key words: Elderly, Cognition, Depression, TSH

IT has been shown that thyroid hormone concentrations changes with age, and elevated serum thyroid stimulating hormone (TSH) level is viewed as part of physiologic process of aging [1, 2]. In fact, slight elevations of serum TSH portend better outcomes in the elderly in different studies [3-5]. Seniors with subclinical hypothyroidism (SCH) have demonstrated

better mobility and less decline of walking ability in a 2-year period than those whose serum TSH levels fell within normal range [3]. Likewise, reduced mortality [4, 5] and fewer declines in functionality [4] were associated with states of SCH, compared with euthyroid status. Despite concordant consensus to do not treat elderly people with SCH and serum TSH <10.0 $\mu\text{IU/mL}$ [6, 7], discordant results have been reported, concerning cardiovascular risk and mortality related to SCH, by recent studies, even in patients aged 70 years old [8, 9]. In the other hand, subclinical hyperthyroidism (SCHyper), even with serum TSH 0.1-0.4 $\mu\text{IU/mL}$, in the elderly, has been associated with cardiovascular risk [10].

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Besides possible protective effect of SCH, a possible hypothesis is that these results may be due to the inclusion of individuals with misdiagnosed SCHyper in the group of subjects with “normal” serum TSH levels, and by this way those elderly subjects with serum TSH levels near the lower limit of normal range might have worse outcomes. Diverse sources have documented an association between lower TSH levels and dementia in elderly [11-18].

Recent population-based studies have strengthened this hypothesis, claiming adverse effects in terms of depressive symptoms, cognition, and hip fractures in elderly subjects with serum TSH <1.0 $\mu\text{IU/mL}$, even if values fall within the reference range [19-21].

Based on that, the purpose of this study was to evaluate in a group of elderly subjects, if there is association between cognitive impairment, depressive symptoms and low levels of serum TSH (<1.0 $\mu\text{IU/mL}$) within the reference range. Furthermore, to assess prospectively if in elderly subjects without dementia who have TSH level in the lower limit of the reference range, the use of methimazole, in order to elevate serum TSH levels to the upper limit of the reference range, positively impact cognitive function and/or depressive symptoms.

Materials and Methods

Study design and population

A preliminary cross-sectional study was conducted on an outpatient basis; examining male and female elderly subjects ≥ 65 years of age, whose had serum TSH levels within the reference range, according to their age (0.4-6.7 $\mu\text{IU/mL}$) [22]. All subjects were recruited from outpatient geriatric and endocrine clinics at Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Brazil, between 2010 and 2013.

Exclusion criteria were as follows: 1) recent hospitalization (<3 months before evaluation), 2) use of levothyroxine, 3) ongoing or prior thyroid disease, and 4) use of amiodarone or any medication interfering with thyroid function. Individuals with serum free thyroxine (FT4) levels below or upper the reference range, were also excluded.

Thereafter, a controlled, not blinded, longitudinal study was performed, after exclusion of subjects with dementia. Three groups were generated and followed through the time, assigning subjects by baseline TSH

level and strategy as follows: 1) TSH ≥ 1.0 $\mu\text{IU/mL}$ (observation; untreated); 2) TSH <1.0 $\mu\text{IU/mL}$ (observation; untreated); and 3) TSH <1.0 $\mu\text{IU/mL}$ (methimazole therapy). The intervention with methimazole, at initial dosage of 5 mg/day, was used with intention to raise TSH levels to upper normal reference range (>2.5 $\mu\text{IU/mL}$). Only after achieving this target serum TSH, the period of time on follow-up was considered for the research purpose. The major aim was to reevaluate the outcomes, defined as the variations on scores for depressive symptoms and cognition, in the treated patient, after six months of achieving and maintaining target serum TSH levels. Serum TSH was measured at each 2 months intending to perform dosage adjustments of methimazole. Liver enzymes and blood cells count were assessed at baseline and at each visit. Patients with abnormal liver enzymes, anemia or leucopenia were not included in the prospective phase of the study. All patients underwent regular clinical visits to assess serum TSH and methimazole dosage adjustment and also to assess possible adverse effects of drug prescription. The median follow-up period of methimazole use was 11 months. The group of patients that did not received treatment was followed under observation and also underwent regular visits to general clinical evaluation at each 3/4 months. This last group underwent reevaluation of the outcomes in the second year of follow-up, with median follow-up period of 16 months.

The local ethics committee approved the study protocol (040/11-CEP), in accordance with the ethical standards of the institutional and National Research Committee and with the 1964 Helsinki Declaration. All participants provided written consent before study enrolment. The study protocol has been registered at Clinicaltrials.gov (NCT 01849861).

Clinical and functional evaluation

All eligible subjects were clinically evaluated through targeted interviews, and all medical records were reviewed by one of the researchers of the study. At the same day of the interview, cognition function and depressive signals and symptoms were assessed.

Cognition function was gauged through the Mini Mental State Examination (MMSE) [23]. Cut-off points for cognitive impairment adjusted to educational level of Brazilian population were 24/30 for those with formal education (≥ 1 year of schooling) and 18/30 for those who were unschooled [24].

Concerning depressive symptoms assessment, two methods were applied at baseline, since cognition influences the interpretation of results in different scales evaluating depressive symptoms in the elderly. At MMSE scores ≥ 13 , the Brazilian validated 15-item version of the Geriatric Depression Scale (GDS) was engaged [25, 26]. GDS scores $\geq 6/15$ suggested depressive disorders. At MMSE scores < 13 , the Cornell Scale for Depression in Dementia (CSDD) was utilized [27, 28], with scores ≥ 10 indicating probable depressive disorder.

In the prospective study phase, whose patients with dementia were excluded, and the GDS was the exclusive instrument to assess depressive symptoms.

Laboratory tests

Serum TSH, FT4, and anti-thyroperoxidase antibody (TPO-Ab) assays were performed on blood samples, using a third-generation chemiluminescence kit (Immulite 2000; Diagnostic Products Corp, Los Angeles, CA, USA). Respective reference ranges were 0.4-5.8 $\mu\text{IU/mL}$ [22], 0.8-1.9 ng/dL, and $< 35 \text{ UI/mL}$.

Statistical analyses

All analyses were relied on standard software (SPSS v. 13.0 for Windows; SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation (median). The Kolmogorov-Smirnov test with Lilliefors correction was applied to assess Gaussian nature of pattern distributions.

Scores of functional scales were assessed as continuous and categorical variables. Proportional comparisons were achieved using Chi-square or Fisher's exact test. The Spearman correlation index was invoked to evaluate correlations between serum TSH level and other variables (age, BMI, MMSE and GDS scores).

For the cross-sectional study, comparisons between two groups were made using Mann-Whitney test and among three groups *via* Kruskal Wallis. Multivariate analysis (*via* binary logistic regression) was applied twice, to detect variables independently associated with presence of dementia or presence of depressive symptoms. In both instances, outcomes constituted dependent variables, treating the following parameters as potentially related variables: diabetes mellitus (DM), high blood pressure (HBP), stroke, acute myocardial infarction (AMI), age > 80 years, presence of depressive syndrome (if analyzing dementia as dependent or outcome), presence of dementia (if analyzing depres-

sive syndrome as dependent), and finally, serum TSH $< 1.0 \mu\text{IU/mL}$ as the variable of higher interest.

Absolute changes in different variables during the follow-up period were calculated and comparisons between groups were performed. Paired analysis was also applied to detect significant variations in each followed group, by Wilcoxon test.

Multivariate linear regression was applied, in two models, to detect which variables were independently associated with changes in MMSE scores throughout the time. First, it was applied to those patients followed without intervention, where the group subjected to methimazole intervention was excluded from the analysis. The endpoint or dependent variable was the Δ MMSE scores and the baseline serum TSH $< 1.0 \mu\text{IU/mL}$ was the variable of major interest, combining with two other important confounding variables: age > 80 years old and time of follow-up > 12 months. In the second model, other important variables possible related to this endpoint were added (DM, HBP, stroke, AMI and depressive syndrome) to the analysis.

Furthermore, these two models of multivariate regression were also applied to those patients with serum TSH $< 1.0 \mu\text{IU/mL}$ to assess which possible variables were independently associated with the same endpoint (change in MMSE scores throughout the time). In this analysis, including only patients in the lowest levels of serum TSH, the variable of major interest was methimazole use.

Finally, the same design of multivariate analysis was applied to detect possible variables independently related to Δ GDS scores during the study. The selected variables included were: DM, HBP, stroke, AMI, worsening of MMSE score during the study, age > 80 years old, time of follow-up > 12 months and one of the two variables of major interest ("baseline serum TSH $< 1.0 \mu\text{IU/mL}$ " for the subgroup under observation or "methimazole use" evaluating those patients with serum TSH $< 1.0 \mu\text{IU/mL}$).

Statistical significance was stated at $p < 0.05$.

Results

Cross-sectional study

A total of 293 elderly adults met the inclusion criteria for this preliminary study, with women accounting for 74% (217) (Fig. 1). Of this total, 45% (132) were > 80 years old. Baseline clinical characteristics and laboratory data are shown in Table 1. A total of 27

Fig. 1 Flowchart of participants

* All of them had serum TSH in the upper range.

Table 1 Baseline characteristics of all enrolled elderly subjects - Cross-Sectional Study Phase – Comparisons among groups according to baseline TSH range and correlations with serum TSH levels

	Whole group (n=293)	TSH <1.0 (n=27)	TSH ≥1.0 (n=266)	p-value ⁺	r * (p-value)
Female, n (%)	217 (74.1%)	17 (63.0%)	200 (75.2%)	0.167	NE
Age (years)	78.4 ± 7.3 (78.0)	77.0 ± 6.6 (77.0)	78.5 ± 7.4 (78.5)	0.334	+0.135 (p=0.01)
>80y (%)	132 (45.1%)	8 (29.6%)	124 (46.6%)	0.106	NE
BMI (kg/m ²)	27.4 ± 4.6 (27.1)	27.1 ± 4.1 (27.5)	27.4 ± 4.7 (27.0)	0.869	0.05 (p=0.49)
TSH (µIU/mL)	2.3 ± 1.2 (2.0)	0.7 ± 0.1 (0.7)	2.5 ± 1.2 (2.2)	0.000	NA
FT4 (ng/dL)	1.1 ± 0.2 (1.1)	1.2 ± 0.2 (1.1)	1.1 ± 0.2 (1.1)	0.127	-0.10 (p=0.05)
DM (%)	78 (26.6%)	5 (18.5%)	73 (27.4%)	0.317	NA
HBP (%)	229 (78.2%)	22 (81.5%)	207 (77.8%)	0.661	NA
AMI (%)	18 (6.1%)	1 (3.7%)	17 (6.4%)	0.729	NA
Stroke (%)	40 (13.7%)	2 (7.4%)	38 (14.3%)	0.309	NA
Depressive Sy.**, n (%)	89 (30.4%)	7 (25.9%)	82 (30.8%)	0.618	NA
GDS	4.4 ± 3.2 (4.0)	3.6 ± 2.7 (2.5)	4.5 ± 3.2 (4.0)	0.224	+0.101 (p=0.13)
Cornell	7.5 ± 5.7 (7.0)	7.0 ± 4.5 (6.5)	4.5 ± 3.2 (4.0)	NA	+0.148 (p=0.35)
MMSE	20.8 ± 8.1 (23.0)	21.4 ± 8.6 (25.0)	20.7 ± 8.1 (22.5)	0.443	0.100 (p=0.49)
Dementia, n (%)	141 (48.1%)	12 (44.4%)	129 (48.5%)	0.888	NA

Continuous variables were expressed as mean ± standard deviation (median). Significant comparisons were expressed by boldfaced underlined values. NA, not applicable; TSH, thyroid stimulating hormone; BMI, body mass index; FT4, free thyroxine; AMI, acute myocardial infarction; HBP, high blood pressure; DM, diabetes mellitus; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination. ⁺ Comparisons between TSH <1.0 vs ≥1.0 µIU/mL. * Correlation with serum TSH. ** Depressive syndrome according to Geriatric Depression Scale or Cornell score.

(9.2%) subjects had lower levels of serum TSH (TSH <1.0 μ IU/mL). Subjects of both TSH subsets had similar mean FT4 values. The groups were also comparable with respect to gender, age, body mass index (BMI), comorbidities, ie, DM, HBP and stroke, frequency of depressive symptoms or dementia, and mean GDS and MMSE scores (Table 1).

It was detected a slightly positive correlation between serum TSH and age (Table 1). Serum TSH levels and MMSE scores displayed no correlation in the whole group, as shown in Table 1.

Multivariate analysis (Table 2) was performed with presence of dementia as dependent variable and the following factors as possible confounders: age >80 years, TSH <1.0 μ IU/mL, depressive syndrome, HBP, DM, AMI and stroke. Age >80 years was identified as the only independent risk factor ($p < 0.01$) for dementia (OR=2.89; confidence interval [CI]: 1.72-4.86). The presence of diabetes also tended to be independently associated with this endpoint (OR=1.78; CI: 0.99-3.21; $p = 0.06$) as shown in Table 2.

In multivariate analysis, we found that depressive syndrome was not independently associated with comorbidities, TSH range or age (Table 2). However, a tendency for positive association between the presence of AMI and depressive syndrome was detected (OR=3.04; CI: 0.99-9.35; $p = 0.05$).

Longitudinal study

Of 152 eligible subjects without dementia, 110 agreed to participate in the prospective phase of the study. There were 15 participants with baseline serum TSH <1.0 μ IU/mL. Seven of these subjects were offered methimazole (on an investigational basis) as a manner of raising TSH levels to the upper limit of the

reference range.

Throughout the time, there were missings of follow-up, as demonstrated in Fig. 1. A total of 93 (84.5%) seniors concluded the study, being 80 (86%) subjects in the group with serum TSH ≥ 1.0 μ IU/mL, whose were followed-up under observation. Regarding those patients with serum TSH <1.0 μ IU/mL, six concluded the follow-up period of treatment under methimazole therapy and seven were followed without intervention, being solely observed throughout the time.

Baseline characteristics of the participants that concluded the study according to the three groups of follow-up, and the corresponding variations in cognition and depressive symptoms during the course of this prospective longitudinal study are shown in Table 3. Also, the time period of follow-up is shown in this table. The two groups under observation (TSH <1.0 and TSH ≥ 1.0 μ IU/mL) were comparable regarding all demographic variables and the frequency of depressive syndrome. However, analyzing the methimazole use group with low-level TSH (<1.0 μ IU/mL) we detected that those subjects were younger than the untreated subjects in the same TSH range (71 vs 77 years old). In Table 3 it is also demonstrated that the time period of follow-up was smaller in the treated patients than in those only followed without intervention (11.0 vs 16.0 months). However, the two groups followed under observation had similar time of follow-up, irrespective to baseline serum TSH (<1.0 or ≥ 1.0 μ IU/mL).

In evaluating temporal changes in MMSE score, in paired analyses, the only group that showed significant changes, consisted of elderly subjects with the lowest levels of serum TSH (<1.0 μ IU/mL), regarding those untreated and followed by observation only (medium variation: -4.0; $p = 0.017$). Methimazole-treated sen-

Table 2 Multivariate analysis, by binary logistic regression, evaluating variables associated with the outcomes “dementia” and “depressive syndrome” in the sectional study

	Dementia			Depressive Syndrome		
	OR	CI	<i>p</i> -value	OR	CI	<i>p</i> -value
Age >80 yo	2.89	1.72-4.86	<0.001	1.16	0.67-2.00	0.596
DM	1.78	0.99-3.21	0.060	0.782	0.42-1.44	0.782
HBP	0.80	0.42-1.51	0.497	0.894	0.52-1.87	0.960
AMI	1.41	0.45-4.40	0.552	3.04	0.99-9.35	0.050
Stroke	2.02	0.93-4.29	0.075	1.42	0.67-3.02	0.356
TSH <1.0 μ IU/mL	1.26	0.53-3.00	0.607	0.771	0.31-1.93	0.580
Dementia	NA	NA	NA	1.16	0.68-2.01	0.576
Depressive syndrome	1.16	0.68-2.01	0.577	NA	NA	NA

Significant comparisons were expressed by boldfaced underlined values. OR, odds ratio; CI, confidence interval; DM, diabetes mellitus; AMI, acute myocardial infarction; HBP, high blood pressure; TSH, thyroid stimulating hormone; yo, years old; NA, not applicable.

Table 3 Characteristics of the subjects without dementia completing prospective study phase (overall and by TSH range)

	Total (n=93)	Whole group	TSH <1.0 (n=7) observation	TSH <1.0 (n=6) methimazole use	TSH ≥1.0 (n=80) observation	p-value #	p-value ###	p-value ###
Female, n (%)		71 (76.3%)	5 (71.4%)	4 (66.7%)	61 (76.3%)	0.846	0.540	0.657
Age (years)		76.1 ± 6.2 (76.0)	78.4 ± 4.5 (77.0)	71.0 ± 4.7 (71.0)	78.3 ± 5.8 (79.0)	0.024	0.956	0.008
>80y (%)		36 (38.7%)	2 (28.6%)	0 (0.0%)	34 (42.5%)	0.101	0.384	0.269
BMI (kg/m ²)		28.3 ± 4.8 (27.7)	28.1 ± 4.8 (27.84)	28.5 ± 5.2 (28.8)	29.4 ± 5.3 (27.5)	0.928	0.840	0.923
TSH (μIU/mL)		2.3 ± 1.2 (2.2)	0.77 ± 0.2 (0.8)	0.7 ± 0.2 (0.7)	2.7 ± 1.1 (2.6)	0.000	0.000	0.838
FT4 (ng/dL)		1.1 ± 0.2 (1.1)	1.2 ± 0.2 (1.13)	1.2 ± 0.2 (1.3)	1.1 ± 0.1 (1.1)	0.052	0.122	0.366
DM (%)		22 (23.7%)	2 (28.6%)	0 (0.0%)	20 (25.0%)	0.362	0.570	0.269
HBP (%)		75 (80.6%)	7 (100.0%)	5 (83.3%)	64 (80.0%)	0.420	0.228	0.462
Stroke (%)		12 (12.9%)	1 (14.3%)	0 (0.0%)	11 (13.8%)	0.652	0.665	0.538
AMI (%)		4 (4.3%)	1 (14.3%)	0 (0.0%)	3 (3.8%)	0.363	0.202	0.335
Depressive Sy.*, n (%)		35 (37.6%)	3 (42.9%)	5 (83.3%)	49 (61.3%)	0.329	0.297	0.179
MMSE		26.9 ± 2.8 (28.0)	25.9 ± 4.4 (27.0)	28.3 ± 2.2 (29.0)	26.3 ± 3.0 (27.0)	0.171	0.820	0.295
GDS		4.7 ± 3.5 (5.0)	5.1 ± 3.8 (0.0)	-0.7 ± 2.2 (-1.5)	-0.6 ± 2.8 (-0.5)	0.503	0.718	0.366
Period of follow-up (Months)		16.5 ± 4.8 (16.0)	19.2 ± 6.6 (18.0)	11.0 ± 3.2 (11.0)	16.9 ± 4.6 (16.0)	0.003	0.484	0.001
Worsening GDS** (%)		29 (31.2%)	2 (28.6%)	2 (33.3%)	25 (31.3%)	0.982	0.625	0.657
Δ GDS ^Φ		-0.7 ± 2.8 (-1.0)	-1.7 ± 3.9 (0.0) <i>P</i> =0.223 ^Φ	-0.7 ± 2.2 (-1.5) <i>P</i> =0.459 ^Φ	-0.6 ± 2.7 (0.0) <i>P</i> =0.073 ^Φ	0.758	0.509	0.776
Worsening MMSE** (%)		47 (50.5%)	7 (100.0%)	3 (50.0%)	37 (46.3%)	0.034	0.040	0.103
Δ MMSE		-1.2 ± 3.7 (-1.0)	-3.8 ± 2.4 (-4.0) <i>P</i> =0.017 ^Φ	-0.8 ± 3.9 (-0.5) <i>P</i> =0.680 ^Φ	-1.0 ± 3.7 (0.0) <i>P</i> =0.091 ^Φ	0.031	0.009	0.100

Continuous variables were expressed as mean ± standard deviation (median). Significant comparisons were expressed by boldfaced underlined values. AMI, acute myocardial infarction; TSH, thyroid stimulating hormone; SD, standard deviation; BMI, body mass index; FT4, free thyroxine; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination. * Depressive syndrome according to Geriatric Depressive Scale. ** Any positive (GDS) or negative (MMSE) variation throughout the time of follow-up. # Comparisons among the three groups. ### *p*-values comparing groups observed in follow-up with serum TSH ≥1.0 vs <1.0 mIU/mL. #### *p*-values comparing two groups followed with serum TSH <1.0 μIU/mL (observation vs methimazole use). ^Φ Paired analysis evaluating the significance of variation in the studied group (Wilcoxon test).

iors in the same TSH range displayed less worsening of MMSE score (medium variation of -0.5; *p*=0.680) that, however, did not differed from that observed in untreated group (*p*=0.100). Also, a slight non-significant reduction in MMSE score was detected in subjects with serum TSH ≥1.0 μIU/mL (-1.0 ± 3.7 [0.0]; *p*=0.091).

In comparing the two groups followed without intervention (TSH lower or ≥1.0 μIU/mL), negative changes in MMSE of subjects with lower TSH levels differed significantly from that seen in seniors with serum TSH ≥1.0 μIU/mL (*p*=0.009).

Multiple regression model in its first model, showed that, among the patients under observation, serum TSH <1.0 μIU/mL was independently associated with MMSE changes (B=-0.333; *t*=-3.24 [IC:-5.61/-1.34; *p*=0.002]). Time of follow-up (B=-0.054; *t*=-0.520

[IC:-1.69/+0.004; *p*=0.604]) and age >80 years (B=-1.115; *t*=-1.111 [IC:-1.83/+0.49; *p*=0.270]) were not independently associated with changes in MMSE. In the second model, adding those other variables probably related to the endpoint, it was detected that serum TSH <1.0 μIU/mL was still independently associated with changes in MMSE (B=-0.309; *t*=-3.03 [IC:-5.34/-1.1; *p*=0.003]). Past history of stroke was associated with positive changes in MMSE during the study (B=+0.242; *t*=+2.32 [IC:+0.264/+0.416; *p*=0.023]). None of other tested variables were independently associated with changes in MMSE throughout the time in the group of patients under observation (*p*>0.100).

Additionally, multivariate analysis of those patients in the lowest level of serum TSH detected that methimazole use (B=+0.852; *t*=+2.77 [IC:+1.05/+10.37; *p*=0.022]) and time of follow-up (B=+0.788; *t*=+2.56

[IC: +0.62/+9.95; $p=0.031$]) were independently associated with MMSE changes, in the first model. However, in the second model, no variable was independently associated with changes in MMSE scores ($p>0.100$), even methimazole use ($B=+0.983$; $t=+1.52$ [IC: -5.44/+18.62; $p=0.203$]) or time of follow-up ($B=+0.965$; $t=+1.68$ [IC: -4.19/+17.14; $p=0.168$]).

There were no significant changes in depressive symptoms and GDS scores among the groups (Table 3). Multivariate analysis indicated that among patients under observation no variable was significantly associated with changes in GDS, independently of the applied model. Even serum TSH <1.0 was not related to this outcome ($B=-0.036$; $t=-0.335$ [IC: -2.8/+2.0; $p=0.739$] and $B=-0.015$; $t=-0.125$ [IC: -2.79/+2.45; $p=0.901$] regarding respectively to the first and second model). Finally, evaluating those patients with the lowest levels of serum TSH, no variable was independently related to changes in GDS during the study ($p>0.100$), even methimazole use ($B=+0.914$; $t=+1.13$ [IC: -8.2/+19.5; $p=0.319$]).

Two models of multivariate analysis are shown in Supplementary Tables 1 and 2.

Discussion and Conclusions

Clinical significance

Recently, more attention has been given on the relationship between low, but normal, serum TSH levels and health-related outcomes in the elderly [21, 29, 30].

The present study demonstrated that elderly subjects with serum TSH <1.0 $\mu\text{IU/mL}$ who were followed without intervention, experienced the greatest negative variations in MMSE scores, despite the lack of a significant association between dementia and low-normal levels of TSH in the sectional phase of study. At baseline, multivariate analysis detected that "age >80 " was the only variable independently associated with the diagnosis of dementia, with serum TSH <1.0 being only slightly associated with this diagnosis. The prospective study phase expressly excluded those candidates with dementia to ensure homogeneity of groups, exercising the same methods in evaluating depressive syndrome. The CSDD scale is considered better by some authors, for assessing these symptoms in the elderly with dementia [26].

In our subgroup of seniors with low-level serum TSH given methimazole therapy (boosting serum TSH to upper limits of normal range), worsening of MMSE

scores was significantly less significant, in paired analysis. A hypothesis is that methimazole therapy might be beneficial in these patients, preventing cognitive deterioration. Furthermore, there is also the possibility of misdiagnosed SCHyper in these elderly adults with the lowest levels of serum TSH. SCHyper has been linked with dementia and various negative outcomes in the elderly, including cardiac arrest and death [31-33].

Recently, an association between cognitive decline and serum TSH <1.0 $\mu\text{IU/mL}$ (even if within normal range) was documented in a sizeable cohort ($N=1503$) of elderly adults. During 8 years of follow-up monitoring, those patients with low-normal TSH levels ($N=365$) registered more concurrent depressive symptoms and were at substantially increased risk of developing a depressive syndrome in subsequent years. This investigation suggests that low-normal TSH level is an important risk factor for depression in the elderly, although methimazole intervention (which was not done) is a missing element [19].

To the author's knowledge, this is the first study to use methimazole in elderly adults without thyroid disease (but with low-normal serum TSH levels [<1 $\mu\text{IU/mL}$]), for the express purpose of evaluating temporal changes in cognition and depressive symptoms.

In a recent extensive review of longitudinal and cross-sectional studies, a relationship between SCHyper and cognition was emphasized, drawing attention as well to the potential liability of a low-normal serum TSH level in this context. However, none of the studies incorporated anti-thyroid drug administration [11, 12, 16-18, 34, 35].

In our hands, cognition and depressive symptoms were both addressed. Impairment in cognition is related to advanced age; and coexisting depressive symptoms are common accompaniments of cognitive impairment, potentially affecting multiple domains (ie, attention, memory, and executive function). Depression may be implicated as both a manifestation of and a risk factor for cognitive decline, heightening long-term risk of dementia [36]. Of note, cognitive impairment is predictive of a poor response to antidepressants [27, 37]. Even with remission of depression, deficits may persist and carry a high risk of dementia, although this was not evident in the present study.

Strengthening the results, we attempted to include different variables potentially related to changes in cognition in models of multivariate analysis. It was demonstrated that lower levels of TSH was inde-

pendently associated with negative variations in MMSE throughout the time. Surprising, past history of stroke was associated with positive variations in MMSE during the study and we hypothesize that an improvement in cognition might have occurred in the first months after a stroke, as occurs in some motor deficits. This hypothesis is plausible since we did not assess the true moment of the stroke diagnosis.

Limitations and future perspectives

This study was not randomized or blinded, and we used a sample of convenience in selecting participants. One single measurement of serum TSH at the inclusion was a limitation, but this was a common inadequacy, also reported by other researchers [20, 21, 29]. Furthermore, the three groups prospectively monitored were not homogeneous with respect to age, influencing the comparisons among some of them, since those patients that were followed under treatment with methimazole were younger than other two followed groups. However, it is important to notice that the two groups followed under observation (untreated) showed comparable ages and also other demographic characteristics, which might minimize those differences in comparing variations in outcomes between untreated groups (TSH <1.0 vs ≥ 1.0 $\mu\text{IU/mL}$). Multivariate analysis was another approach to evaluate the impact of such differences in the results and did demonstrate that the association between low serum TSH levels and cognitive decline occurred independently from other possible conditions influencing the endpoint. Also, the period of follow-up differed between treated and untreated patients (11 vs 16 months), but it was not different between the two groups followed under observation and probably not impacting the results concerning the comparisons between outcomes of patients with serum TSH $<$ or ≥ 1.0 $\mu\text{IU/mL}$ through the time. Again, multivariate analysis showed that it did not influence major findings. Also, we showed that the smaller follow-up time and the comparative reduced age were not probably important influencers of better outcomes in methimazole use group.

Another important limitation was the small number of subjects with serum TSH <1.0 $\mu\text{IU/mL}$, especially concerning those two groups followed in the prospective phase. It would be expected to include those subjects, since it is known that the majority of elderly people have serum TSH above this cut-off and have higher serum TSH [1, 22]. Furthermore,

the exclusion of subjects with dementia, to homogenize the group, also contributed to the small sample size at the end of the study. Finally, we anticipate, giving emphasis to the preliminary of presented results. As exposed, this is the first intervention study to evaluate the impact of rising serum TSH to the upper reference range in cognition and depressive symptoms of elderly. The assessment of the impact in reducing levothyroxine doses during the treatment of hypothyroidism, intending to achieve upper reference range of serum TSH in elderly subjects is being evaluated in a large active study protocol [38] (Wilkes, *Trials*, 2013) but the results are still awaited. We agree that future studies in this subject are needed and that the present results will possibly stimulate this perspective.

Our findings admittedly are tentative, requiring corroboration through randomized controlled interventional trials to evaluate the impact of treating elderly adults with low-normal serum TSH levels. In other words, it still remains to be seen whether therapeutic intervention truly prevents cognitive decline as shown in the present study and in recent publications [15, 19].

Ultimately, it is necessary to ascertain if low serum TSH does lead to dementia through extremes activity of central nervous system by thyroid hormonal action. There are situations which can alter TSH, and influence cognition, which must be considered first. Some drugs, for example, such as metformin and dopamine, may blunt the rise of serum TSH and thereby worsen cognition [39].

This scenario may be a secondary event or a marker of comorbidities or drugs that more directly exact worse outcomes, such as dementia or disabilities. Further studies are needed to better clarify and define the relationship between lower “normal” levels of TSH in the elderly and its relation to dementia and depression.

Summarizing, in the sample studied, TSH levels in the lower limit of the reference range was not associated with higher prevalence of dementia. However, in elderly without dementia, was associated with worsening cognition, an outcome that did not occur in patients with serum TSH >1.0 $\mu\text{IU/mL}$ and also in those under methimazole therapy to increase serum TSH to the upper limit of the reference range. Further studies are needed to evaluate if methimazole treatment, for elderly patients with serum TSH <1.0 $\mu\text{IU/mL}$, could be a strategy to be adopted in order to prevent or minimize cognitive impairments, commonly observed in this population.

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Disclosure Statement

The authors have no potential conflict of interest to disclose.

Supplementary Table 1 Variations in Mini Mental State Examination

	Δ MMSE					
	Patients under observation			Patients with serum TSH <1.0		
	Beta	t	IC	Beta	t	IC
First model						
TSH <1.0 OR metimazole use	-0.333	-3.24	-5.61/-1.34	+0.852	+2.77	+1.05/+10.37
Age >80	-1.115	-1.111	-1.83/+0.49	-0.362	-1.49	-8.4/+1.7
Time of follow-up >12 months	-0.054	-0.520	-1.69/+0.004	+0.788	+2.56	+0.62/+9.95
Second model						
TSH <1.0 OR metimazole use*	-0.309	-3.03	-5.34/-1.1	+0.983	+1.52	-5.44/+18.62
Age >80	-0.141	-1.38	-1.84/0.33	-0.476	+1.02	16.5/+7.6
Time of follow-up >12 months	-0.081	-0.75	-1.9/+0.87	0.965	+1.68	-4.2/+17.14
DM	+0.178	1.71	-0.179/2.34	0.171	+0.366	-10.1/+13.6
HBP	-0.145	-1.4	-2.39/+0.50	-2.77	-0.906	-14.14/+7.19
AMI	-0.108	-1.025	-4.0/+1.28	0.047	+0.091	-17.3/+18.5
Stroke	+0.242	+2.32	+0.264/+0.416	0.249	+0.561	-12.3/+18.5
Depressive syndrome	-0.069	-0.638	-1.54/+0.79	-0.017	-0.041	-7.99/+7.76

Two models of MMSE variation throughout the time of follow-up. Comparing groups observed in follow-up with serum TSH ≥ 1.0 vs <1.0 mUI/mL (observation vs methimazole use). DM, diabetes mellitus; HBP, high blood pressure; AMI, acute myocardial infarction; TSH, thyroid stimulating hormone; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination.

Supplementary Table 2 Variations in Geriatric Depression Scale

	Δ GDS					
	Patients under observation			Patients with serum TSH <1.0		
	Beta	t	IC	Beta	t	IC
First model						
TSH <1.0 OR metimazole use	-0.036	-0.335	-2.8/+2.0	+0.750	+2.23	-0.7/+9.4
Age >80	+0.171	+1.57	-0.26/+2.24	+0.529	+1.99	-0.61/+9.65
Time of follow-up >12 months	+0.056	+0.515	-1.1/+1.9	+0.540	+1.61	-1.3/+8.1
Second model						
TSH <1.0 OR metimazole use*	-0.015	-0.125	-2.79/+2.45	+0.914	+1.13	-8.2/+19.5
Age >80	+0.212	+1.85	-0.9/+2.5	+0.856	+2.08	-2.4/+17.1
Time of follow-up >12 months	+0.043	0.382	-1.3/+1.89	+0.484	+0.694	-8.9/+14.9
DM	-0.02	-0.16	-1.6/+1.38	+0.506	+1.22	-5.5/+14.12
HBP	+0.116	1.01	-0.83/+2.54	-0.086	-0.231	-12.9/+10.99
AMI	-0.069	-0.61	-3.99/+2.12	-0.431	+0.818	-21.9/+11.9
Stroke	-0.079	-0.69	-2.5/+1.23	-0.345	-0.926	-15.9/+7.9
Worsening MMSE during study	-0.161	-1.37	-2.42/+0.45	0.182	+0.378	-8.4/+11.12

Two models of GDS variation throughout the time of follow-up. Comparing groups observed in follow-up with serum TSH ≥ 1.0 vs <1.0 mUI/mL (observation vs methimazole use). DM, diabetes mellitus; HBP, high blood pressure; AMI, acute myocardial infarction; TSH, thyroid stimulating hormone; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination.

References

1. Bremner AP, Feddema P, Leedman PJ, Brown AJ, Beilby JP, et al. (2012) Age-Related Changes in Thyroid Function: A Longitudinal Study of a Community-Based Cohort. *J Clin Endocrinol Metab* 97: 1554-1562.
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: 4575-4582.
3. Simonsick EM, Newman AB, Ferrucci L, Satterfield S, Harris TB, et al. (2009) Subclinical hypothyroidism and functional mobility in older adults. *Arch Intern Med* 169: 2011-2017.
4. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, et al. (2014) Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 292: 2591-2599.
5. Atzmon G, Barzilai N, Hollowell JG, Surks MI, Gabriely I (2009) Extreme Longevity Is Associated with Increased Serum Thyrotropin. *J Clin Endocrinol Metab* 94: 1251-1254.
6. Das G, Ojewuyi TA, Baglioni P, Geen J, Premawardhana LD, et al. (2012) Serum thyrotrophin at baseline predicts the natural course of subclinical hyperthyroidism. *Clin Endocrinol (Oxf)* 77: 146-151.
7. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, et al. (2014) Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 24: 1670-1751.
8. Pasqualetti G, Tognini S, Polini A, Caraccio N, Monzani F (2013) Is subclinical hypothyroidism a cardiovascular risk factor in the elderly? *J Clin Endocrinol Metab* 98: 2256-2266.
9. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, et al. (2010) Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 304: 1365-1374.
10. Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, et al. (2015) The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. *Eur Thyroid J* 4: 149-163.
11. Annerbo S, Lökk J (2013) A Clinical Review of the Association of Thyroid Stimulating Hormone and Cognitive Impairment. *ISRN Endocrinol* 2013: 856017.
12. Vadiveloo T, Donnan PT, Cochrane L, Leese GP (2011) The thyroid epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab* 96: 1344-1351.
13. Forti P, Olivelli V, Rietti E, Maltoni B, Pirazzoli G, et al. (2011) Serum thyroid-stimulating hormone as a predictor of cognitive impairment in an elderly cohort. *Gerontology* 58: 41-49.
14. Joffe RT, Pearce EN, Hennessey JV, Ryan JJ, Stern RA (2013) Subclinical Hypothyroidism, Mood, and Cognition in the Elderly: A Review. *Int J Geriatr Psychiatry* 28: 111-118.
15. Gan EH, Pearce SH (2012) The thyroid in mind: cognitive function and low thyrotropin in older people. *J Clin Endocrinol Metab* 97: 3438-3449.
16. Yeap BB, Alfonso H, Chubb SA, Puri G, Hankey GJ, et al. (2012) Higher free thyroxine levels predict increased incidence of dementia in older men: the health in men study. *J Clin Endocrinol Metab* 97: E2230-2237.
17. Bensenor IM, Lotufo PA, Menezes PR, Scazufca M (2010) Subclinical hyperthyroidism and dementia: the Sao Paulo ageing & Health study (SPAH). *BMC Public Health* 10: 298.
18. Ceresini G, Lauretani F, Maggio M, Ceda GP, Morganti S, et al. (2009) Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. *J Am Geriatr Soc* 57: 89-93.
19. Medici M, Direk N, Visser WE, Korevaar TI, Hofman A, et al. (2014) Thyroid function within the normal range and the risk of depression: a population-based cohort study. *J Clin Endocrinol Metab* 99: 1213-1219.
20. Moon JH, Ahn S, Seo J, Han JW, Kim KM, et al. (2014) The effect of long-term thyroid-stimulating hormone suppressive therapy on the cognitive function of elderly patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 99: 3782-3789.
21. Leader A, Ayzenfeld RH, Lishner M, Cohen E, Segev D, et al. (2014) Thyrotropin levels within the lower normal range are associated with an increased risk of hip fractures in euthyroid women, but not men, over the age of 65 years. *J Clin Endocrinol Metab* 99: 2665-2673.
22. Fontes R, Coeli CR, Aguiar F, Vaisman M (2013) Reference interval of thyroid stimulating hormone and free thyroxine in a reference population over 60 years old and in very old subjects (over 80 years): comparison to young subjects. *Thyroid Res* 6: 13.
23. Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189-198.
24. Lourenço RA, Veras RP (2006) Mini-Mental State Examination: psychometric characteristics in elderly outpatients. *Rev. Saude Publica* 40: 712-719 (In Portuguese).
25. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, et al. (1983) Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 17: 37-49.

26. Almeida OP, Almeida SA (1999) Reliability of the Brazilian version of the Geriatric Depression Scale (GDS) short form. *Arq Neuropsiquiatr* 57: 421-426 (In Portuguese).
27. Alexopoulos GS, Abrams RC, Young RC, Shamoian CA (1988) Cornell scale for depression in Dementia. *Biol Psychiatry* 23: 271-284.
28. Carthery-Goulart MT, Areza-Fegyveres R, Schultz RR, Okamoto I, Caramelli P, et al. (2007) Brazilian version of the Cornell depression scale in dementia. *Arq de Neuropsiquiatr* 65: 912-915 (In Portuguese).
29. Moon JH, Park YJ, Kim TH, Han JW, Choi SH, et al. (2014) Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment in elderly: Korean Longitudinal Study on Health and Aging (KLoSHA). *J Clin Endocrinol Metab* 99: 424-432.
30. Ritchie M, Yeap BB (2015) Thyroid hormone: Influences on mood and cognition in adults. *Maturitas* 81: 266-275.
31. Roberts LM, Pattison H, Roalfe A, Franklyn J, Wilson S, et al. (2006) Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Ann Intern Med* 145: 573-581.
32. Almeida OP, Alfonso H, Flicker L, Hankey G, Chubb SA, et al. (2011) Thyroid hormones and depression: the Health in Men study. *Am J Geriatr Psychiatry* 19: 763-770.
33. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, et al. (2014) Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. *J Clin Endocrinol Metab* 99: 2372-2382.
34. de Jong FJ, Masaki K, Chen H, Remaley AT, Breteler MM, et al. (2009) Thyroid function, the risk of dementia and neuropathologic changes: the Honolulu- Asia aging study. *Neurobiol Aging* 30: 600-606.
35. Tan ZS, Beiser A, Vasan RS, Au R, Auerbach S, et al. (2008) Thyroid function and the risk of Alzheimer disease: the Framingham study. *Arch Intern Med* 168: 1514-1520.
36. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, et al. (2010) Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology* 75: 35-41.
37. Sheline YI, Pieper CF, Barch DM, Welsh-Bohmer K, McKinstry RC, et al. (2010) Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry* 67: 277-285.
38. Wilkes S, Pearce S, Ryan V, Rapley T, Ingoe L, et al. (2013) Study of Optimal Replacement of Thyroxine in the Elderly (SORTED): protocol for a mixed methods feasibility study to assess the clinical utility of lower dose thyroxine in elderly hypothyroid patients: study protocol for a randomized controlled trial. *Trials* 14: 83.
39. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, et al. (2012) Clinical Practice Guidelines For Hypothyroidism In Adults: Cosponsored By The American Association Of Clinical Endocrinologists And The American Thyroid Association. *Endocr Pract* 18: 988-1028.