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RESEARCH PAPER

Thyroid stimulating hormone levels and geriatric syndromes: secondary nested case–control study of the Mexican Health and Aging Study

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Key summary points

Aim Does geriatric syndrome have an association with subclinical hypothyroidism.
Findings This study showed a greater incidence of GS in subjects 50 years and older with sub-clinical hypothyroidism, when compared to those with normal thyroid function.
Message Endocrine assessment should be taken in account in frail individuals as part of an integral evaluation for patients.

Abstract

Purpose To determine the incidence of geriatric syndromes (GS) in community dwelling older adults with subclinical hypothyroidism.
Methods This is an analysis from the Mexican Health and Aging Study, of a subsample of 2089 subjects with TSH determination. From this last subsample, we included 1628 individuals with TSH levels in the subclinical range (4.5–10 μU/ml).
Results The multivariate analysis showed that when comparing data obtained from the 2012 wave with the 2015 wave results, there was a significant incidence of some GS such as falls (OR 1.79, CI 1.16–2.77, $p=0.0116$), fatigue (OR 2.17, CI 1.40–3.38, $p=0.0348$) and depression (OR 1.70, CI 1.06–2.71, $p=0.0246$) among the subclinical hypothyroidism group.
Conclusion This study showed a greater incidence of GS in subjects 50 years and older with sub-clinical hypothyroidism, when compared to those with normal thyroid function.

Keywords Thyroid stimulating hormone · Aging · Geriatric syndromes · Chronic disease · Subclinical hypothyroidism

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Introduction

Several studies have shown a progressive proportional increase in thyroid-stimulating hormone (TSH) levels with age [1], making it critically important to develop new methods to differentiate actual thyroid diseases from normal hormonal changes, especially in the older persons [2]. This leads to overdiagnosis of clinical and sub-clinical hypothyroidism, and subsequently to inappropriate prescription [3]; or treatment inadequacy for thyroid dysfunction [4, 5]. Moreover, a placebo-controlled study, that followed 368 older adults with subclinical hypothyroidism assigned to receive T4, did not show apparent benefits compared to those that did not receive treatment [6]. Notwithstanding, there is disagreement about the clinical therapeutic behavior when TSH levels persist between 7 and 10 μU/ml. In this respect, studies have shown that treating these patients with L-thyroxine, results in a significant improvement of cardiovascular (CV) risk factors as well as in other symptoms, including fatigue [7]. Finally, it is well known that in older adults, other conditions coexist and even share common nonspecific symptoms with some of the geriatric syndromes [8].

There is a clear association between thyroid dysfunction and chronic diseases that eventually lead to adverse outcomes, mainly mortality [9–11]. Geriatric syndromes, recognized as a sole manifestation with multifactorial causality, are frequent conditions in older adults that interact along each other and have higher probability of adverse outcomes (e.g., frailty, disability, dependency, institutionalization) [12, 13].

Previous reports have shown that chronic diseases are associated with geriatric syndromes [14], in particular, subclinical hypothyroidism (SCH) has shown to be related to depression and cognitive impairment [15].

Noteworthy, a recent systematic review showed that overt dementia is associated with SCH, without evidence of amelioration with the use of hormonal replacement [16]. To the best of our knowledge, there is no information on Latin American older adults about the association of geriatric syndromes and TSH concentration, a region with particular features and with a high burden of chronic diseases. Therefore, this study aims to estimate the incidence of geriatric syndromes in community dwelling older adults with SCH.

Methods

Design and sample

A nested in cohort case–control of the Mexican Health and Aging Study (MHAS) was conducted. MHAS is a prospective study based on Mexican 50-year or older Mexican individuals; the sample has a nation-level representativeness, and currently has four waves (2001, 2003, 2012 and 2015). The aim of MHAS is to identify and characterize demographic, social, health and functional factors that determine aging-related outcomes. Face to face interviews were performed to community-dwelling 50-year or older persons at their households by trained and standardized personnel. Complete procedures, aims and description of MHAS is available elsewhere [17, 18].

Every wave has a subset of individuals to whom anthropometric and physical performance measurements along with serum biomarkers are obtained [17]. In 2012 new biomarkers were incorporated into the set, including TSH levels. The survey in 2012 recruited 18,465 participants, including 12,569 follow-up respondents from 2001 wave and 5896 new participants (including spouses of the selected individual, regardless of age). The subsample of those with biomarkers included 2089 persons, only 60-year or older adults were included in this analysis, leaving a sample of 1144 individuals.

Cases and controls

Cases were defined as that individual having a particular geriatric syndrome: depression, cognitive impairment, falls, urinary incontinence, nutritional problems, or sleep problems. Controls were those persons without any geriatric syndrome. Controls were compared to cases, regarding to 2012 characteristics, in particular TSH-level categories. Cases were expected to have lower frequencies of euthyroid TSH levels, when compared to cases. Geriatric syndromes were selected according to previous works on the matter [12, 13] and availability in MHAS 2015 dataset.

Cases of depression were considered present whenever the MHAS questionnaire on depressive symptoms had a score of 5-points or higher, as previously established [19]. A modified version of the cross-cultural Cognitive Examination was used to establish cases of cognitive impairment, with previously reported methodology on processing subtests and cut-off values (according to age and years in school categories). Those individuals with a standardized score of − 1.5 standard deviations (SD) were considered to have cognitive impairment [20]. Those individuals answering yes to the question "Have you fallen in the past 2 years?" were considered cases for falls. Two questions regarding urinary incontinence are available in the MHAS dataset, answering yes to any of those questions was considered as a case for the urinary incontinence geriatric syndrome: "During the last 2 years have you frequently had urinary incontinence when coughing, sneezing, picking something up, or exercising?" or "During the last 2 years have you frequently had urinary incontinence when had the urge to urinate, but couldn't reach

the bathroom in time?" To define nutritional problems cases, those individuals who reported to had a weight decrease or increase (of 5 or more kilograms) in the last 2 years or have reported a diminished food intake "most of the time"; were considered to have nutritional problems. Finally, four questions about sleep quality were asked to determine those having sleeping problems (see Supplementary material for the complete set of questions and the definition).

To test if there was a quantitative association (sum of geriatric syndromes) with TSH concentration besides the qualitative association (individual geriatric syndromes), a composite variable was integrated, adding all the conditions to generate a score with a minimum of 0 and a maximum of 6.

Thyroid-stimulating hormone

TSH levels were categorized as follows: < 0.1 µU/mL (hyperthyroid levels), 0.1–4.49 µU/mL (euthyroid), 4.5–10 µ/mL (subclinical hypothyroidism) and > 10 µU/mL (overt hypothyroidism). From October to November 2012 blood samples were obtained through venipuncture performed by trained personnel in accordance with standardized protocols, the sample was take during the day, with no specific time frame, the patients could or could not be fasting at the time of the study. A total of 6 ml were obtained from each subject for all the biomarkers, whole blood sample was stored at 2–8 °C, within 30 min after the venipuncture, the samples collected were centrifuged at 2500 rpm for 15–20 min to separate serum from other blood components, and stored in 2 ml tubes to be transported to the processing center [21].

TSH levels were determined using the chemiluminescent microparticle immunoassay (CMIA), assay technique called Chemiflex (CMIA-Architect Abbott Laboratories. Abbott Park, IL, USA) [21, 22]. The interval of this CMIA ranged from 0.0109 to 127.9 µU/mL, the ARCHITECT TSH assay is designed to have a functional sensitivity of ≤ 0.01 µIU/mL, which meets the requirements of a third generation TSH assay.

Adjusting variables

To test the independent association of TSH concentration and geriatrics syndromes, some variables were included in the analysis (from the 2012 dataset), according to their potential impact in geriatric syndromes. Regarding, socio-demographic characteristics age, sex, marital status and completed years in school were included.

Health-related behaviors included for the analysis were: smoking status (currently smokers) and physical activity (considered to be physically active if responded yes to the following question: on average the last 2 years, have you exercised or done hard physical work three or more times per week in a row?). A sum of chronic diseases, from a list of seven available (hypertension, diabetes, cancer, lung disease, ischemic heart disease, stroke, articular disease) was included to reflect multimorbidity. Finally, disability defined as having difficulty in any activity of daily living (walking, bathing, eating, going to bed, using toilet, preparing meals, shopping and managing money and medicines), was also included.

Statistical analysis

In a first step, descriptive statistics were performed, categorical variables are presented using relative and absolute frequencies, for continuous variables means and SD are used. Afterwards, a bivariate analysis was performed; Chi-square tests were used for categorical variables, and one-way ANOVA was used for continuous variables; contrasting cases and controls according to their frequencies of TSH-concentration categories. Finally, in multivariate analysis, logistic regression models were adjusted to obtain the odds ratio (OR) with 95% confidence intervals (CI). These models used the TSH concentration with the euthyroid group as the reference category. For the sum of syndromes, a multiple linear regression was used to estimate beta-coefficients and their respective CI. Association measurements (OR and beta-coefficients) are presented with and without adjustment. The statistical level of significance was set at $p < 0.05$. Data were analyzed using STATA 14.2 SE® (StataCorp 4905 Lakeway Drive College Station, Texas 77,845 USA).

Ethical issues

The Institutional Review Board or Ethic Committee of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografia and the Instituto Nacional de Salud Puublica in Mexico, approved the study. All study persons signed informed consent. The study adhered to the ethical guidelines of the Declaration of Helsinki.

Results

From a total of 1144 60-year or older Mexican individuals, 55.2% ($n = 632$) were women and the mean age was of 69.6 years (± 7.6). The majority was married and the mean number of years in school was 4.7 (± 6.1). Only 11% ($n = 126$) are current smokers, and up to 39.1% ($n = 447$) of these individuals are physically active. On average they had 1.1 (± 0.9) chronic diseases and 27.8% ($n = 319$) were disabled (see Table 1).

Regarding the TSH-concentration categories, the euthyroid group was the largest (86.6%) followed by the

subclinical hypothyroidism group (10.1%). The average number of geriatric syndromes was 2.1 (±SD 1.4). Sleep problems was the most frequent geriatric syndrome (70.8%), followed by falls (48.3%), nutritional problems (40.6%), depression (30.6%), urinary incontinence (28.5%) and cognitive impairment (16.6%). According to the bivariate results, only falls, years in school and currently smoking were significantly different between groups of TSH levels ($p=0.025$) (see Table 1).

The unadjusted logistic regression models showed a significant association of subclinical hypothyroidism with depression (OR 1.53, 95% CI 1.03–2.29, $p=0.034$), falls (OR 1.69, 95% CI 1.04–2.7, $p=0.033$) and nutritional problems (OR 1.54, 95% CI 1.05–2.28, $p=0.027$). The other categories of TSH concentration had no significant association with individual geriatric syndromes in the unadjusted models. However, the sum of geriatric syndromes had a significant association with the subclinical hypothyroidism TSH concentration (beta-coefficient 0.46, 95% CI 0.16–0.77, $p=0.002$). The adjusted models were only significant for the association of subclinical hypothyroidism and falls (OR 1.7, 95% CI 1.04–2.7, $p=0.033$) for the individual geriatric syndromes and persisted significant for the sum of geriatric syndromes (beta-coefficient 0.43, 95% CI 0.11–0.75, $p=0.007$) (see Table 2).

Discussion

This case–control nested in a cohort study showed a significant and independent association of falls with subclinical hypothyroidism TSH concentration. The path that leads an individual from subclinical hypothyroid levels to falls, could be related to cardiometabolic issues. For example, cardiovascular problems have shown to be related both to subclinical hypothyroidism [7] and to geriatric syndromes; however, even when adjusting to other chronic diseases (including ischemic heart disease), the association was sustained. Moreover, a recent meta-analysis showed that the association of cardiovascular problems with subclinical hypothyroidism are age-dependent, and seem to be diluted in those 65-year or older [23].

According to our results, some geriatric syndromes could be independently associated with TSH levels corresponding to subclinical hypothyroidism, adding evidence to what is already known. However, the persistent association of incremental number of geriatric syndromes with TSH levels corresponding to subclinical hypothyroidism, adds to what is already known and points to a possible overt failure of complex systems in older adults. How could adding levothyroxine ameliorate the course of those with two or more geriatric syndromes is still to be defined.

Similar to our results, a study with a smaller sample, showed that subclinical hypothyroidism was associated with

Table 1 Characteristics of the sample according to TSH concentrations

Variable	Total ($n=1144$)	TSH levels				p value
		Euthyroid 86.6% ($n=991$)	<0.1 µU/mL 0.8% ($n=10$)	4.5–10 µU/mL 10.1% ($n=115$)	>10 uUI/mL 2.4% ($n=28$)	
Age, mean (SD)	69.6 (7.6)	69.5 (7.6)	70 (7.5)	69.8 (7.9)	70.7 (6.9)	0.853
Women, *n* (%)	632 (55.2)	540 (54.4)	7 (70)	69 (60)	16 (57.1)	0.532
Married, *n* (%)	645 (56.3)	572 (57.7)	6 (60)	56 (48.7)	11 (39.2)	0.076
Years in school, mean (SD)	4.7 (6.1)	4.8 (6.3)	3.7 (3.3)	3.9 (3.7)	3.5 (3.9)	<0.001
Currently smokes, *n* (%)	126 (11)	116 (11.7)	1 (10)	3 (2.6)	6 (21.4)	0.008
Exercises in the last two years, *n* (%)	447 (39.1)	386 (38.9)	2 (20)	49 (42.6)	10 (35.7)	0.518
Sum of comorbidities, mean (SD)	1.1 (0.9)	1.05 (0.97)	1.1 (1.1)	1.05 (0.97)	1.42 (0.9)	0.959
Any difficulty in ADL/IADL, *n* (%)	319 (27.8)	274 (27.6)	2 (20)	33 (28.7)	10 (35.7)	0.746
Geriatric syndromes						
Depression, *n* (%)	350 (30.6)	292 (29.4)	4 (40)	45 (39.1)	9 (32.1)	0.173
Cognitive impairment, *n* (%)	163 (16.6)	145 (17)	1 (11.1)	15 (15)	2 (10.5)	0.812
Falls, *n* (%)	473 (48.3)	397 (46.6)	7 (77.7)	59 (59.6)	10 (52.6)	0.025
Urinary incontinence, *n* (%)	279 (28.5)	234 (27.4)	1 (11.1)	36 (36.3)	8 (42.1)	0.089
Nutritional problems, *n* (%)	465 (40.6)	393 (39.6)	4 (40)	58 (50.4)	10 (35.7)	0.154
Sleep problems, *n* (%)	811 (70.8)	704 (71)	7 (70)	83 (72.1)	17 (60.7)	0.68
Geriatric syndromes sum, mean (SD)	2.1 (1.4)	2.1 (1.4)	2.2 (1.2)	2.5 (1.5)	2.6 (1.4)	0.54

Frequencies of THS-concentration columns are respect to the row

TSH Thyroid stimulating hormone, *SD* standard deviation, *n* number, *ADL* activities of daily living, *IADL* instrumental activities of daily living

Table 2 Multivariate analysis comparing TSH-concentration categories for each of the GS and for the sum of the GS, unadjusted and adjusted[a] models with the euthyroid group as reference (not shown)

Individual GS	TSH-concentration categories											
	< 0.1 µU/Ml				4.5–10 µU/mL				> 10 µU/mL			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Logistic regression models	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Depression	1.59 (0.4–5.69)	0.472	1.01 (0.24–4.18)	0.979	1.53 (1.03–2.29)	0.034	1.43 (0.92–2.2)	0.109	1.13 (0.5–2.53)	0.76	0.98 (0.42–2.29)	0.98
Cognitive impairment	0.6 (0.07–4.9)	0.642	0.78 (0.09–6.5)	0.821	0.87 (0.48–1.5)	0.639	0.8 (0.47–1.6)	0.745	0.57 (0.13–2.5)	0.461	0.56 (0.12–2.5)	0.456
Falls	4.01 (0.82–19.42)	0.084	6.5 (0.79–53.5)	0.081	1.69 (1.1–2.58)	0.015	1.7 (1.04–2.7)	0.033	1.27 (0.5–3.16)	0.603	1.01 (0.38–2.63)	0.984
Urinary incontinence	0.3 (0.04–2.65)	0.297	0.3 (0.04–2.7)	0.308	1.5 (0.97–2.3)	0.064	1.4 (0.85–2.3)	0.17	1.92 (0.76–4.8)	0.166	1.87 (0.69–5.04)	0.214
Nutritional problems	1.01 (0.28–3.61)	0.982	0.69 (0.17–2.81)	0.605	1.54 (1.05–2.28)	0.027	1.35 (0.8–2.1)	0.167	0.84 (0.3–1.85)	0.674	0.74 (0.32–1.69)	0.478
Sleep problems	0.95 (0.24–3.7)	0.943	0.82 (0.19–3.4)	0.791	1.05 (0.68–1.62)	0.79	0.9 (0.5–1.4)	0.676	0.63 (0.29–1.3)	0.24	0.68 (0.29–1.5)	0.362
Linear regression model	*ß* (95% CI)	*p*	*ß* (95% CI)	*p*	*ß* (95% CI)	*p*	*ß* (95% CI)	*p*	*ß* (95% CI)	*p*	*ß* (95% CI)	*p*
Sum of geriatric syndromes	0.12 (− 0.82, 1.07)	0.797	0.02 (− 0.92, 0.98)	0.953)	0.46 (0.16, 0.77)	0.002	0.43 (0.11, 0.75)	0.007	0.48 (− 0.17, 1.14)	0.152	0.29 (− 0.35, 0.93)	0.375

TSH thyroid stimulating hormone, *OR* odds ratio, *CI* confidence interval

[a]Adjusted for: age, sex, marital status, years in school, currently smoking, physical activity in the previous 2 years, sum of chronic diseases, any difficulty in activities of daily living or instrumental activities of daily living

disability and global deterioration of health status—in our study reflected in the incremental association with geriatric syndromes—impacted by thyroid function [24].

Our study supports the hypothesis of higher incidence of GS in persons with TSH in the subclinical hypothyroidism range [5]. GS are widely associated with frailty and functional decline in the older persons population, as well as an increase in hospitalizations, decreased quality of life, socio-economic problems and death [25].

Our results could also show the relationship between the loss of homeostasis that leads to abnormalities in the "weakest link" as hypothesized by Olde Rikkert; and with the manifestations of a geriatric syndrome [13].

According to the current definition of GS, subclinical hypothyroidism could be a piece of the multifactorial nature of these conditions, or the precipitant of the GS. However, when it comes to the sum of geriatric syndromes, the role of subclinical hypothyroidism could be in the multifactorial path leading to an older adult with overall not optimal health status. It is also important to be stressed, that similar conditions to GS may have one identifiable cause (e.g., urinary incontinence due to bladder problems); not every geriatric syndrome behaves with the "classic" presentation.

On the other hand, recent reports have shown that areas in Mexico considered to have a deficiency of iodine are in the south of the country, but public health strategies have ameliorated this situation. Mexico has a history of iodine supplementation, we cannot know the specific status, despite a mandatory salt iodination program established since the early 1960s, goiter is still found but we cannot know if it's related to diet or other factors. Mexico has been reported as a country with higher than recommended intake as iodine according to the only data available [26].

As mentioned before, there is increasing evidence about the importance of monitoring and controlling thyroid hormone serum levels, due to its important role in general metabolism, and therefore the impact it has on multiple systems [22]. Literature reports important physiological changes in TSH levels with aging, which apparently lead to overdiagnosis of hypothyroidism and subsequent inappropriate prescriptions of L-thyroxine supplementation [27].

The association between TSH levels and presence of GS such as sleep disturbances, falls, depression, alimentary disorders, fatigue, urinary incontinence, and memory complaints, has not been widely studied [28]. However, studies have shown that euthyroid individuals have fewer cardiovascular risk factors suggesting a beneficial effect associated to the administration of L-thyroxine in persons with TSH abnormal levels [7]. This situation has generated discussion about diagnosis and treatment recommendations. There are also some studies that reported no association between hypothyroidism and entities such as depression or cognitive impairment [29].

This study has some limitations: data were obtained through self-reported methods, which imply memory bias and a greater risk of missing reports among the evaluated variables. Additionally, we did not take into consideration the participants who were already receiving L-thyroxine supplementation at the beginning of the follow-up period; anyhow, there is great evidence that prevalence of treated hypothyroidism is actually low in the general population. One potential problem was the lack of power for those groups of TSH levels with a very low number. In particular the relation between falls and hyperthyroidism, seem to have a lack of power, and further research should elucidate this relationship. Moreover, even that a case–control design is still inappropriate to draw causal conclusions, is a step further in this matter. Another potential flaw is the fact that abnormal levels of TSH fluctuate, and can 'normalize' spontaneously [28], and the lack of information related to antithyroid antibodies, whom have been reported higher than the prevalence of people living with clinical and subclinical hypothyroidism [30]. Since we have only one measurement, some individuals could have normal TSH levels. These TSH levels in older adults in relation to geriatric syndromes merit further studies.

Despite these clear limitations, this study provides important results in a Mexican representative sample. There are no other Latin American studies describing or analyzing these variables, and obtained results are valuable for future population studies and clinical decisions focused in preventing adverse outcomes in older persons population.

The study results support the hypothesis that there is a greater incidence of GS in Individuals 50 years and older, with sub-clinical hypothyroidism compared to those with normal thyroid function. Based on these findings, we consider important to encourage further studies that confirm this association and, therefore, promote the formulation of public policies that aim to prevent adverse but preventable outcomes in persons with abnormal thyroid function.

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Data availability Data available from the MHAS.

Code availability None.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The Institutional Review Board or Ethic Committee of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografia and the Instituto Nacional de Salud Puublica in Mexico, approved the study. The study adhered to the ethical guidelines of the Declaration of Helsinki.

Consent for publication All authors have given consent for the publication of this manuscript.

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