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Physical Performance in Elderly Outpatients with Subclinical Hypothyroidism Compared with Euthyroid Counterparts

Abraham A. Vázquez-García[1], Lilia Cárdenas- Ibarra[2*], Jesús Z. Villarreal-Pérez[2], Sandra Meza[1], Daniel Gamez[1], Jorge Platt[1], Guillermo Guajardo-Álvarez[1], David Saucedo[1] and Francisco Torres-Pérez[1]

[1]*Geriatric Service, Universidad Autonoma de Nuevo Leon, University Hospital Dr. Jose E. Gonazalez, Monterrey, Mexico*

[2]*Endocrinology Service, Department of Internal Medicine, Universidad Autonoma de Nuevo Leon, Hospital Universitario Dr. Jose E. Gonazalez, Monterrey, MexicoA*

Abstract

Background: There continues to be controversy on the clinical relevance of elderly mild subclinical hypothyroidism (SH), defined as a TSH elevation (4.0-9.99 μIU/L) with normal free thyroxin levels.

Objective: To compare physical performance (PP) in elderly individuals with a TSH level above normal range versus normal counterparts.

Design: Case-control study of ambulatory patients enrolled between January 2009 and December 2010.

Setting: Outpatient geriatric service.

Participants: Elderly individuals 65-84 years old (y/o) with SH and without conditions known to affect physical mobility.

Measurements: The Short Physical Performance Battery (SPPB) was performed. The statistical analysis used the Mantel-Haenszel odds ratio (M-H-OR) method and Student's t test with an alpha of 0.05. Results: Of the 183 individuals screened, 28 (15.3%) had SH. The study response was 89.3%, thus 25 individuals with SH were compared to 27 euthyroid controls matched by age and sex. Gender and age influence SPPB, increased age was associated with <4 points balance: 13.8% in 65-74 y/o vs. 44.0% in 75-84 y/o, χ^2=6.1, p<0.05; strength of dominant leg and SPPB score were higher in men than women (both, p<0.05). Body mass index was higher in SH than controls in men (29.3 ± 2 vs. 23.4 ± 3, t=3.2, <0.02). Women with SH had a worse SPPB score than the control group, M-H-OR=8.4, p<0.05. Confidence intervals of mean gait speed were 0.73-0.95 vs. 0.98-1.14 m/s, respectively with results in men lacking significance. Chair stands were longer in SH than controls: 13.5 ± 2.4 vs. 10.0 ± 1.7 seconds for men and 20.6 ± 12.6 vs. 14.8 ± 2.9 seconds for women, both p<0.05.

Conclusions: These data suggests an association between SH and lower physcial performance. This warrants further study to define if T4 supplementation improves physcial performance, thus preventing frailty.

Keywords: Hypothyroidism; Elderly; Physical performance; Gait

Introduction

Subclinical hypothyroidism (SH) is diagnosed as a serum level of thyroid stimulating hormone (TSH) above normal with a normal free thyroxin level (FT4) [1]. Hypothyroidism is the most common thyroidal illness in the elderly [2] with a prevalence of 27% in our setting [3].

Thyroid hormones affect muscle function by modulating mitochondrial activity [4]. This effect is clinically evident in full hypothyroidism as muscle weakness, predominantly in proximal muscles, fatigue, exercise intolerance, muscle pain, and cramps [5]. These symptoms frequently affect physical activity and cause weakness, physical limitations that are difficult to treat in individuals with hypothyroidism [6]. There are no previous reports of this kind in elderly.

Physical performance and mobility are two of the primary capabilities necessary for preserving quality of life and survival. In fact, all quality of life questionnaires in the elderly include aspects of mobility [7]; however, objective physical performance measures provide more information. The main causes of difficulties in mobility in old age are musculoskeletal disorders. Among these, decreased muscle mass or other changes that result in a reduction of strength and endurance even in healthy elderlies, findings that contribute to a loss of self-sufficiency and independence [8]. The decrease in muscle mass in the normal elderly can range from 20% to 40%, and over 50% after 80 years of age [9]. The level of muscle function is related to mobility and is accentuated in the elderly, also affecting their quality of life.

Almost all existing studies perform indirect measurements of metabolic parameters of muscle function in adults and include none or few individuals over 65 years of age. The review by Biondi and Cooper [10] states that muscle dysfunction in SH is partially known and that impaired muscle energy metabolism correlates with SH duration. In a study of cases and controls, Monzani et al. [11], measured pyruvate and lactate in both groups during exercise and concluded that these energy metabolism parameters are altered in patients with subclinical hypothyroidism. Similarly, a randomized double-blind

***Corresponding author:** Lilia Cárdenas-Ibarra, Endocrinology Service, Department of Internal Medicine, University Hospital Dr. Jose E. Gonazalez and Faculty of Medicine, Universidad Autonoma de Nuevo Leon. Av. Madero s / n, Colonia Mitras Centro, Monterrey, Nuevo Leon, Mexico C.P. 64460, Tel: 528183487871; E-mail: dralilia@gmail.com

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study by Caraccio et al. [12], in young adult patients with subclinical hypothyroidism, measured CO_2 and VO_2 during and after exercise to assess tolerance and biochemical parameters; both were altered and did not improve after one year of restoring euthyroid levels. Thus, there is enough indirect evidence with biochemical parameters that there is altered muscle function in not so old adult patients with subclinical hypothyroidism. There are few studies that specifically analyze objective physical performance and SH in the elderly in a clinical setting. Gussekloo et al. [13] studied thyroid status and performance in the very old and did not find a correlation, suggesting treatment could be unfavorable but they assessed disability, an advanced deterioration of performance by questionnaire on activities of daily living. It is important to determine the functional impact of subclinical hypothyroidism in the elderly, since it is the group that is most vulnerable to dependency, physical disability, and frailty [14]; and has the highest prevalence of SH [2,3]. Therefore, we sought to determine if elderly patients with SH have a lower physical performance than euthyroid patients.

Methods

Setting and subjects

This is a case-control study that compares individuals with SH and age and sex-matched euthyroid controls. Men and women 65 to 84 years of age, attending a regional outpatient center for the study of the elderly were screened between January 2009 and December 2010. The protocol was previously reviewed and approved by the Ethics Committee of the UANL University Hospital and School of Medicine (registration no. GE051).

Outpatients who provided written informed consent and were in good health by physical examination were included. SH and control subjects that had diseases with a functional impact such as uncontrolled arthordial, neuromuscular, cardiovascular, neurological or advanced lung disease, a significant psychiatric affliction, hospitalization during the previous 3 months, a broken hip or knee in the previous six months, acute disease with prostration in the previous 30 days, significant changes in physical activity, or taking any of the following medications: neuroleptics, anabolics, thyroid hormones, amiodarone, beta blockers, iodine and lithium were excluded (Figure 1).

The assessment of each patient included clinical history, neurological examination, thyroid profile, an electrocardiogram, a cognitive test (mini-mental-state-examination), independence scales (Katz and Lawton-Brody), depression scale (GDS), and for physical mobility performance, the Short Physical Performance Battery (SPPB). A description, and the reliability and validation of the SPBB were reported by Guralnik et al. [15], Guralink et al. [16], and Markides et al. [17] Procedures were carried out by trained staff who did not know the patient´s TSH levels.

The variables studied were age, gender, body mass index (BMI), press strength of the dominant leg (SDL), physical performance (PP) by SPPB, TSH, and free thyroxin (FT4). For this study SH was defined as a TSH level between 3.9 and 10 μIU/L exclusive, with a FT4 level within normal range (0.93-1.7 ng%). An SPPB score of 12 to 9 was regarded as acceptable with good mobility and a score less than 9 was considered a deterioration of mobility.

TSH and FT4 determinations were performed in the endocrinology laboratory at the same hospital using an electrochemiluminescence immunoassay (ECLIA) on a Roche Elecsys 2010 analyzer (Roche Diagnostic GmbH, Mannheim, Germany) with a TSH detection range of 0.005-100 μIU/L, and of FT4 0.023-7.77 ng/dL.

Statistical analysis

Baseline data of patients with SH and controls (euthyroid subjects matched by age and gender) were evaluated using SPSS version 12.0. For group comparison, Student's t test and ANOVA were used; for continuous variables the Mann-Whitney test and χ^2 for non-normally distributed data. Men and women were analyzed separately since they differ significantly in several variables and we had a limited number of subjects. To overcome the confounding effect of age, the odds ratio Mantel-Haenszel χ^2 test was used; thus a SPPB global score <9 and subscales <4 were coded 1, poor PP; otherwise they were coded 0 for acceptable PP; for age 65-74 yrs=1, and 75-84 yrs=2. Also, in the stepwise linear regression for SPPB (points), the independent variables were gender (men=1, women=2), age (years) assignment (SH=1, control=2), BMI (kg/m^2), SDL (kilos) and free thyroxin (FT4 ng%). An alpha probability less than 0.05 was considered significant.

Results

During the study period 183 screening tests were carried out with 126 (70.5%) showing TSH levels below 4.0 μIU/ml and 54 (29.5%) over this limit. Of the patients with hyperthyrotropinemia, 15 (27.8%) had a level ≥ 10 μIU/ml and 39 (72.2%) were identified as SH with a TSH between 4.1-9.9 μIU/ml. Eleven patients with SH had exclusion criteria, three of the 28 eligible did not accept to participate, thus the study had a response of 89.3% (25 subjects with SH). Of the 126 euthyroid subjects, 27 without exclusion criteria were recruited as controls matched by age and gender with the SH patients.

The characteristics by thyroid status and gender are shown in Table 1. Similarity of age confirms matching, and a significant difference in TSH between SH and controls verifies assignment (5.7 ± 1.0 vs. 2.4 ± 0.9 μUI/mL). Most of the participants did not complete basic schooling (up to 4th grade) similarly across groups; this was likewise for marital status and living arrangements. Interestingly, free thyroxin was statistically lower in SH than controls (1.06 ± 0.14 vs. 1.22 ± 0.22, t=2.6, df=49, p<0.05) although all were within normal range. BMI was higher in SH participants than controls reaching statistical significance in men.

Some characteristics were influenced by gender: press strength of the dominant leg (SDL) was 51 ± 25 kg in men vs. 22 ± 13 kg in women, t=5.3, df=50, p<0.05, but indifferent between SH and controls; SPPB was also significantly higher in men than women (11.2 ± 1 vs. 9.1 ± 2 points, respectively, M-W z=3.43, p=0.001) and each gender showed a clear tendency to have a lower SPPB score in SH (both p<0.1). In fact, men scored top coded points on balance and gait speed, only chair stands showed decreased scores in 4 of 6 men with SH versus 1 of 5 control subjects (χ2=2.4, gl=1, p=0.12), a tendency that is due to the small numbers and the cutoff point used.

The influence of age on SPPB is evaluated in Table 2. Ranked scores for each of the three components are displayed by two age groups. The ranked scores for five chair stands was indifferently distributed among the two age groups but balance showed a statistically significant linear association of lower scores at a greater age. A similar tendency was observed in gait speed p=0.12. In fact, the table clearly shows that fewer older subjects versus less old subjects obtained maximum points, 15/23 vs. 27/29 subjects, χ2 = 6.42, df=1, p<0.05.

PP, total SPPB and its components by age and TSH group are shown in Table 3. The numbers of subjects having sub-top scores were the numerator and the subgroup total was the denominator. The proportion of subjects with a poor PP was greater in SH than controls. The subscale, gait speed, and total SPPB each reached statistical significance.

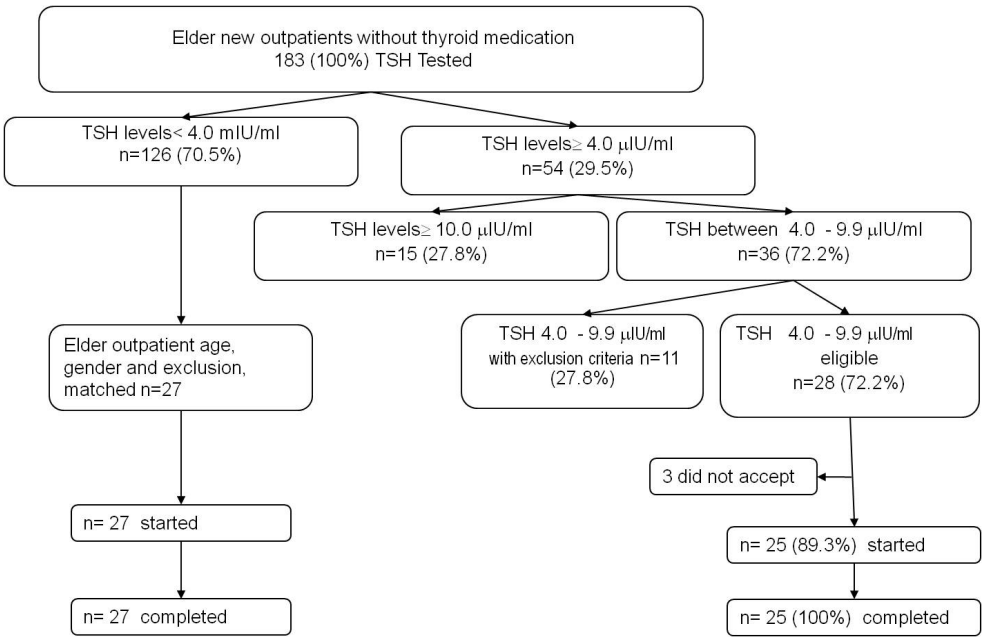

Figure 1: Patient flow diagram.

	Characteristic	SH (n=19) Mean ± SD	Control (n=22) Mean ± SD	t	d.f.	significance
Women	Age (yrs)	74.6 ± 5.4	73.4 ± 5.7	0.7	39	>0.05
	BMI kg/m²	27.7 ± 5.3	26.8 ± 4.6	0.57	38	>0.05
	SDL kg	21.8 ± 12.8	22.6 ± 13.1	-0.20	39	>0.05
	Free T4 (ng%)	1.10 ± 0.1	1.24 ± 0.23	-2.3	38	**<0.05**
	SPPB (max 12)	8.6 ± 2.3	9.7 ± 1.5	-1.9	29	**0.072**
		SH (n=6)	**Control (n=5)**			
Men	Age (yrs)	70.7 ± 4.5	72.2 ± 5.6	-0.5	9	>0.05
	BMI kg/m²	29.3 ± 2.0	23.4 ± 3.6	3.20	8	**<0.02**
	SDL, kg	59.5 ± 28.5	40.5 ± 17.0	1.3	9	>0.05
	Free T4 (ng%)	1.06 ± 0.16	1.16 ± 0.16	-1.7	9	0.12
	SPPB (max 12)	10.7 ± 1.2	11.8 ± 0.5	-2.1	7	**0.074**

SH: Subclinical Hypothyroidism; SDL: Strength of the Dominant Leg (press); SPPB: Short Physical Performance Battery, maximum score 12. Men scored significantly higher than women on SDL 51 ± 25 vs. 22 ± 13 kg, t=3.7, df=11, P<0.01, and on SPPB 11.2 ± 1.08 vs. 9.2 ± 1.97 points, t=4.4, df=29.8, P<0.00; d.f. degrees of freedom. Non-parametric analysis gave congruent results.

Table 1: Characteristics according to gender with and without SH.

	Age	Score					Linear Association	p
		0	1	2	3	4		
Chair stands	65-74 (n=29)	1	6	7	9	6 (20.7%)	1.7	>0.05
	75-84 (n=23)	0	9	7	4	3 (13.0%)		
Balance	65-74 (n=29)	0	0	1	3	25 (86.2%)	4.25	**<0.05**
	75-84 (n=23)	0	1	2	6	14 (60.9%)		
Gait Speed	65-74 (n=29)	0	1	1	0	27 (93.1%)	2.44	0.12
	75-84 (n=23)	0	0	3	5	15 (65.2%)		

SPPB: Short Physical Performance Battery
Values are number of patients; only the highest score shows its percentage. Gait speed significantly fewer older subjects obtained the max score x^2=6.42, df=1, P<0.05.

Table 2: SPPB subscales in all subjects by age (over or under 75 years).

Uncategorized gait speed permits seeing a more clear difference between individuals with SH and controls. Table 4 shows the mean ± standard deviation by gender and assignment. Men were significantly faster than women in both assignments, SH and control, with a mean difference (mdiff) of 0.53 ± 0.12 with a 95% CI 0.28 to 0.79 m/s, and of 0.46 with a 95% CI 0.24 to 0.68 m/s, respectively. Patients with SH

		Observed			Expected			M-H	
		SH n=25	Control n=27	Total	SH n=25	Control n=27	Total Exp.	OR	p
SPPB <9	65-74	2/14	0/15	2/29	1	1	2	8.4	**<0.05**
	75-84	6/11	2/12	8/23	3.8	4.2	8		
Chair stands <4	65-74	11/14	11/15	22/29	10.6	11.4	22	2.6	>0.05
	75-84	11/11	9/12	20/23	9.6	10.4	20		
Balance <4	65-74	2/14	2/15	4/29	1.9	2.1	4	1.4	>0.05
	75-84	5/11	4/12	9/23	4.3	4.7	9		
Gait speed <4	65-74	2/14	0/15	2/29	1	1	2	25.2	**<0.01**
	75-84	7/11	1/12	8/23	3.8	4.2	8		
Numerator: n patients with low score (as noted); Denominator: subgroup total. TSH: Thyroid-stimulating hormone; SH: Subclinical Hypothyroidism; M-H: Mantel-Haenszel test.									

Table 3: Display physical performance of patients grouped by age and TSH level.

	Characteristic	SH (n=19) Mean ± SD	Control (n=22) Mean ± SD	t	d.f.	significance
Woman	5 stand up (s)	19.7 ± 9.6	14.8 ± 2.9	2.1	19.5	**<0.05**
	Rapid Gait (m/s)	0.8 ± 0.25	1.1 ± 0.19	-3.3	38	**<0.002**
	5 Up plus 2 gait (s)	31.6 ± 16.0	22.9 ± 4.0	2.24	18.7	**<0.05**
		SH (n=6)	Control (n=5)			
Men	5 stand up (s)	13.5 ± 2.4	10.0 ± 1.7	2.8	9	**<0.05**
	Rapid Gait (m/s)	1.36 ± 0.29	1.52 ± 0.32	-0.9	9	>0.05
	5 Up plus 2 gait (s)	19.71 ± 3.1	15.7 ± 2.1	2.4	9	**<0.05**
SPPB: Short Physical Performance Battery.						

Table 4: Timed subscales of SPPB.

Dependent	SPPB (score)	R^2=0.44	F=11.73	<0.001
Independent	SDL (K)	β=0.05 ± 0.012	t=4.06	<0.001
	Age (years)	β=-0.13 ± 0.04	t=-3.2	<0.004
	Assg (SH=1, C=2)	β=1.3 ± 0.5	t=2.9	<0.006
No predictor	Gender, BMI, FT4			
Dependent	*Chair stands (s)	R^2=0.29	F=9.3	<0.001
Independent	SDL (K)	β=-0.14 ± 0.04	t=-3.4	<0.001
	Assg (SH=1, C=2)	β=-5.12 ± 1.7	t=-3.0	<0.005
No predictor	Gender, Age, BMI, FT4			
Dependent	Balance (score)	R^2=0.22	F=6.7	<0.005
Independent	Age (y)	β=-0.05 ± 0.016	t=-2.8	<0.008
	SDL (K)	β=0.01 ± 0.005	t=2.1	<0.05
No predictor	Gender, Assg, BMI, FT4			
Dependent	Rapid Gait (m/s)	R^2=0.54	F=17.7	<0.001
Independent	Gender	β=-0.4 ± 0.1	t=-4.02	<0.001
	Assg (SH=1, C=2)	β=0.22 ± 0.07	t=3.4	<0.001
	SDL (K)	β=0.004 ± 0.002	t=2.06	<0.05
No predictor	Age, BMI, FT4			
Assg: Assignment (SH: Subclinical Hypothyroidism, C: Control), y: Years, K: Kilogram, s: seconds, m/s: meters per second, BMI: Body Mass Index, FT4: Free Thyroxin.				

Table 5: Linear Regression Physical Performance in elderly (25 with SH and 27 controls).

were slower than controls; women with SH and controls showed a mean difference of gait speed -0.23 ± 0.07, 95% CI -0.37 to -0.09 m/s. Men with SH were in agreement not reaching statistical significance 0.16 ± 0.18, 95% CI -0.58 to 0.26 m/s.

The uncategorized time for repeated chair stands was also explored. Most women with or without SH showed impaired coded scores; nonetheless, the row data show that it took longer to complete the task for women with SH than controls (4.9 ± 2.2, 95% CI 0.6 to 9.3 seconds, Table 4); thus by changing the cutoff from 12 to 19 seconds, we found eight out of nineteen women with SH versus one of 22 controls with slower chair stands ($\chi2$=8.4, df=1, p<0.05). In men the values were 4.0 ± 1.2, 0.3 to 7.7 seconds; thus with a small adjustment in the cutoff point (12.4 instead of 12.0), we found four of six men with SH versus none of five control subjects with slower chair stands ($\chi2$=5.24, df1, p<0.05). Therefore, both women and men with SH were slower to stand repeatedly compared with their euthyroid counterparts. Moreover, the time for five stands plus the time in the two attempts to walk four meters as fast as the patient could, showed slowness in SH in both genders (SH vs. controls in men, 4.0 ± 1.7, 0.27 to 7.7 s, and for women 8.7 ± 3.9 s, 0.6 to 16.8).

The regression analysis for PP is described in Table 5. Candidate independent variables were assignment (SH or C), gender (m=1, f=2), age (years), BMI (kg/m2), SDL (kg), FT4 (ng%). SH was a predictor for all but the balance subscale; SDL was a predictor for SPPB and each subscale. Only BMI and FT4 did not reach significance for any of them; however, excluding assignment (SH or C), FT4 showed an inverse association with time to complete five chair stands, lower levels required longer time; also more adiposity was associated with more time for chair stands (Table 5).

Discussion

This study in Hispanic elderly, carefully selected to avoid confounders, evaluates physical function at the clinical level, analyzing SPPB as structured by Guralink et al. [15], plus an in-depth examination of uncategorized time to perform two subscales of SPPB (gait and repeated chair stands). The data suggest an association between lower physical performance and SH, independently of age and gender. It also indicates the need for gender specific cutoff points for the timed subscales of SPPB. Despite having fewer men subjects, the time to complete repeated chair stands showed an association between SH and a lower PP.

This study disagrees with Moon et al. [18] who reported no difference in muscle strength and SPPB between individuals with SH and euthyroid subjects, but they could not rule out an association between SH and a higher prevalence of sarcopenia in their studied women. In our study, we find no difference in strength (press with dominant leg) but the SPPB total score, gait speed, and the time to complete repeated chair stands showed an association between SH and lower physical performance. The lack of association in Moon et al. [18] might be due to cutoff points unsuitable for Korean population as occurred with our studied subjects. This was overcome by directly analyzing the time to complete chair stands and gait speed. The need for gender specific cutoff points was clear, revealing longer time to complete repeated chairs stands in both women and men with SH. Guralink et al. [15] also observed systematic differences in PP related to gender.

The results of this study contrast with the observations by Simonsick et al. [19] who reported no association between PP and SH, but their study population did not include Mexican-Americans and the subjects were already in their second year participating in a Health study "Aging and Body Composition". Thus, it is not surprising that 55.8%, 64.4% and 60% of euthyroid, mild SH, and moderate SH subjects, respectively, walked more than 30 minutes a week. Although in the controls in this study (men and women pooled for comparison), the best gait speed from two tryouts to go as fast as they could was 1.15 ± 0.28 m/s, this was significantly lower than the rapid gait speed 1.56 ± 0.31, t=-7.6, df=26, $p<0.001$ of the studied subjects of Simonsick et al. [19]. In our study the subjects who habitually exercised were the exception thus lacking the benefit of routine exercise suggested by Paterson et al. [20].

Studies in highly functional nonagenarians in developed countries suggest a favorable outcome in those with mild TSH elevations [21-23]; but in our region the nonagenarian population is small and requires support. Pearce et al. [22] reported in their nonagenarians' a mean FT4 of 15.2 pmol/L which is similar to our control group (men and women pooled) of 15.72 ± 2.8 pmol/L (t=0.88, $p>0.1$); but our SH group was significantly lower (14.02 ± 1.2 pmol/L, t=-3.5, $p<0.002$). This finding of a lower FT4 in elderly with SH was in agreement with Cardenas et al. [3] in the same region, which was formerly goitrous, although this has currently remitted with iodinated salt. Regression for chair stands, normal but lower FT4 and a higher BMI were associated with longer time, only if assignment was omitted as variable, since FT4 and BMI correlate with assignment.

The prevalence of sarcopenia has been reported as accentuated in Hispanic elderly in comparison to non-Hispanic elderly whites by Baumagartner et al. [9]. More recently Tyrvolas et al. [24] reported a prevalence of sarcopenia of 16.7% in Mexicans over 64 years; two thirds of this being sarcopenic obesity. Sarcopenia associates with impairment [8]. In our study, decreased strength was found in a third of men, SDL was <35 kg, and in two thirds of women, SDL was <20 kg but this seamed indifferent to assignment; however, the regression analysis showed SDL as a predictor for PP (Table 5). Proximal weakness and slowness are part of the clinical picture of hypothyroidism. Also, being overweight was higher in SH reaching significance in men (SH vs. controls).

The subscale gait speed undoubtedly distinguished women with SH having a more deteriorated performance than controls. Following Guralink´s [16] recommendation to evaluate mobility by gait speed in meters per second (m/s) we found that in our studied women the 95% confidence interval of the mean of gait speed was 0.73 to 0.95 m/s in SH vs. 0.98 to 1.14 m/s in controls. This suggests that patients with SH are in the range associated with increased mortality as reported by Studenski et al. [25]. Also, mortality risk was elegantly reported by Stanaway et al. [26] who calculated the gait speed of the mythological figure Grim Reaper to be 0.82 m/s, which is within the SH 95% CI and not in that of the control group. SH increases risk for all-cause and cardiovascular mortality according to Imaizumi et al. [27] and Walsh et al. [28]; however, not all have found an association between SH and increased mortality as in Rodondi, et al. [29] who reported an association only with heart failure; also the above mentioned studies were in highly functional nonagenarians.

Study Limitations

The cross-sectional design could not establish causality, but an association is required to find it. The sample did not include subjects older than 84 because there were very few and these had exclusion criteria. Also, few men were included. Nevertheless, our findings are compelling, even for men, significantly longer times for chair stands were associated with SH. Slower gait times in SH did not reach statistical significance. In addition, men with SH had significantly higher BMI than controls, as is expected in hypothyroidism. A larger sample size is desirable to allow enough power for further adjustment by multivariate statistic tools. The inclusion and exclusion criteria help to control confounding and interacting variables, careful data collection and an appropriate statistic tool (Manthel-Hheazal χ^2) allow discerning internally valid differences among elderly with and without SH. Lineal regression analysis draws congruent conclusions.

Conclusions

This study in Elderly Hispanics suggests an association between SH and low physical performance. Data also pointed out the need for gender specific cutoff points. Finally, it was clear that uncategorized speeds were more sensitive to differentiate SH from controls. A clinical trial is needed to determine if thyroxin substitution can improve physical performance and thus quality of life.

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