Original article

Evaluation of sarcopenia in patients with hyperthyroidism

Asli Tufan[1], Ebru Engin[2], Onur Elbasan[3], Nurdan Senturk Durmus[1], Busra Can[1], Can Ilgin[4], Bulent Can[5]

[1]Department of Geriatrics, Marmara University School of Medicine, Istanbul, Turkey; [2]Department of Internal Medicine, Marmara University School of Medicine, Istanbul, Turkey; [3]Department of Endocrinology, Marmara University School of Medicine, Istanbul, Turkey; [4]Department of Public Health, Marmara University School of Medicine, Istanbul, Turkey; [5]Department of Endocrinology, Medeniyet University School of Medicine, Istanbul, Turkey

Abstract. *Background and aim:* Sarcopenia is a generalized skeletal muscle disease and thyroid hormones have regulatory effects on skeletal muscle metabolism. This study aims to evaluate the association between hyperthyroidism and sarcopenia. *Methods:* Thirteen patients with overt hyperthyroidism (OH), 13 patients with subclinical hyperthyroidism (SH) and 30 healthy volunteers were included. OH was defined as serum thyroid-stimulating hormone (TSH) <0.34 mU/L and free T4 (fT4) >1.12 ng/dL and/or free T3 (fT3) >4.37 ng/L; while SH was defined as TSH <0.34 when fT4 and fT3 were within the normal reference range (0.61–1.12 ng/dL for fT4; 2.6–4.37 ng/L for fT3). Handgrip strength (HGS) measurement and chair stand test were performed for muscle strength, while skeletal muscle mass index measurement with bioelectrical impedance analysis and calf circumference (CC) measurement were performed for muscle mass evaluation. *Results:* The median age was 44.9 (21–76), and 16 (61.5%) were female. HGS and CC were found to be significantly lower in the OH and SH groups than in the control group (p=0.007; p=0.008, respectively). Sarcopenia was more common in the OH and SH groups than in the control group (p=0.007), and the risk of sarcopenia was higher in the OH group than in the SH group (OR: 2.44, 95% CI: 0.26–31.87). In hyperthyroid patients, a high fT4 increased the possibility of sarcopenia (OR: 6.0 95% CI: 0.59–79.23). *Conclusions*: Sarcopenia is significantly more common in patients with hyperthyroidism.

Key words: Hyperthyroidisim, muscle, sarcopenia

Introduction

Sarcopenia is a progressive and generalized skeletal muscle disease associated with a risk of adverse outcomes, including falls, fractures, physical disability and mortality (1). To raise awareness and improve the provision of care to sarcopenia patients, the European Working Group on Sarcopenia in Older People (EWGSOP) updated its definition and diagnosis strategies in 2018, stating that sarcopenia is probable when low muscle strength is detected (1). A diagnosis of sarcopenia is confirmed through a quantitative measurement of muscle quantity or quality.

Skeletal muscle (SM) is an important target organ for thyroid hormones (2). Both overt and subclinical hyperthyroidism have been found to be associated with skeletal muscle mass and strength (3). Since the publication of the revised definition of sarcopenia (EWGSOP2), there have been no studies evaluating all the recommended diagnostic parameters of sarcopenia in patients with overt hyperthyroidism (OH) and subclinical hyperthyroidism (SH). In the present study, we aimed to investigate the relationship between hyperthyroidism and sarcopenia according to EWGSOP2 definition.

Methods

The research sample included 13 patients newly diagnosed with overt hyperthyroidism (OH) and 13 patients newly diagnosed with subclinical hyperthyroidism (SH) who presented to the General Internal Medicine outpatient clinic of a university hospital between February 2020 and August 2020. The control group consisted of 30 individuals without thyroid disease.

Included in the study were those aged 18 years or older who met the criteria and who gave their consent for participation in the study. Patients under the age of 18 with a history of active infection, a diagnosis of malignancy, a diagnosis of diabetes mellitus, a diagnosis of neuromuscular disease, a diagnosis of rheumatological/inflammatory disease with chronic inflammation, a disability/amputated extremity that could affect measurement, pregnancy, those using drugs that could affect body composition (such as diuretics, corticosteroids) or that could affect thyroid function tests (such as the beta-blockers, amiodarone), those with pacemakers, ICD (Implantable Cardioverter Defibrillator) or prostheses, and who declined to participate in the study were excluded. Demographic information of the study participants was recorded. The SARC-F questionnaire (4) was used for sarcopenia screening. The SARC-F is a 5-item questionnaire that garners data on strength, walking aid, getting up from a chair, climbing stairs and falling. The possible SARC-F scale scores are in the 0–10 range and are divided into two to represent symptomatic (4+) and healthy (0–3).

Muscle strength measurements included the handgrip strength (HGS) and the chair-stand test. HGS was measured using a Jamar Plus+ Digital Hand Dynamometer. Three measurements were taken in which the individual was seated with the shoulder in adduction, the elbow at 90° flexion and the forearm in the neutral position, and was asked to grasp the dynamometer with the dominant hand and squeeze it as firmly as possible. Separate anaylsis were performed for national (<22 kg in females, <32 kg in males) (5) and EWGSOP2 (<16 kg in females, <27 kg in males) criteria as handgrip strength cut-off values. For the chair stand test, the time taken for the individual to get up from a seated position five times without using his/her arms was measured with a stopwatch. A cut-off value of >15 seconds was considered significant.

Muscle mass was measured based on the skeletal muscle mass index (SMMI) and calf circumference (CC), with a bioelectrical impedance analysis (BIA) (Tanita BC 532). A 4-meter walking test was performed for the physical performance evaluation. Height was measured without shoes using a standard stadiometer, and body mass index (BMI) was calculated as weight (kg)/height squared (m^2). Skeletal muscle mass (SMM) was calculated using the equation: SMM (kg) = 0.566 x FFM (Fat Free Mass). The SMMI was measured using the SMM (kg)/height squared (m^2) equation (6). Based on the national cut-off values, an SMMI of <7.4 kg/m^2 for females and <9.2 kg/m^2 for males was considered significant for sarcopenia (5). CC was measured at the widest part of the calf using a non-stretchable tape while the participant was in a standing position. Again, CC was evaluated using both EWGSOP2 (<31 cm) and national (<33 cm) cut-off values. In the 4-meter walking test, a walking speed of ≤0.8 m/s was considered poor physical performance. Patients found to have low muscle strength were accepted as probable sarcopenia; those with low muscle strength accompanied by low muscle mass were diagnosed with confirmed sarcopenia; and those with low muscle strength, low muscle mass and low physical performance were diagnosed with severe sarcopenia.

The blood samples were collected after a 12-hour fast at initial presentation. OH was determined as TSH <0.34 mU/L, while free T4 (fT4) >1.12 ng/ dL and/or free T3 (fT3) >4.37 ng/L; and SH was determined as TSH <0.34, while fT4 and fT3 were within the normal reference range (0.61–1.12 ng/dLfor fT4; 2.6–4.37 ng/L for fT3). In the control group, all three parameters were within the normal reference range.

Approval for the study was granted by the Clinical Research Ethics Committee of the hospital, and all participants provided written consent for their inclusion. The study was performed in accordance with the Declaration of Helsinki.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics (Version 23.0. Armonk,

NY: IBM Corp.). The conformity of continuous data to normal distribution was evaluated with a Shapiro-Wilk test and a histogram graph. Median and minimum-maximum (min-max) values were given for non-normally distributed numerical data. A Mann-Whitney U test was used for the comparison of the numerical data of two groups; a Kruskal Wallis test was used for the comparison of the numerical data of three groups, and a p-value of <0.05 was considered significant. A Fisher's Exact test was used for the comparison of categorical data of the groups, and a p-value of <0.05 was considered significant. The Odds Ratio and confidence interval were given based on the Fisher's Exact test. A ROC analysis was performed for the relevant test sensitivity and specificity of the fT4 level above a certain threshold value.

Results

The study included 13 newly diagnosed OH patients, 13 newly diagnosed SH patients, and 30 healthy controls. The general characteristics of the OH, SH, and control groups are presented in Table 1.

As muscle strength is the first parameter to deteriorate in sarcopenia (7), patients with probable and severe sarcopenia were included in the sarcopenia group (n=6). The difference between the hyperthyroid group and the control group was statistically significant in terms of the presence of sarcopenia (p=0.007) (Table 2).

In the hyperthyroid group (OH and SH), six (23%) of the 26 patients were diagnosed with sarcopenia. The patients diagnosed with sarcopenia were older (69.1 vs. 42, p=0.051), although there was no difference in terms of gender (p=1.000). The risk of sarcopenia in OH patients was 2.44 times greater than in the SH patients (OR: 2.44 95% CI: 0.26–31.87). The rate of concomitant chronic disease (hypertension or osteoporosis) was higher in those with sarcopenia (p=0.010). The median fT4 was 1.33 ng/dL in hyperthyroid patients and above the normal range (>1.12 ng/dL) in sarcopenic patients. In the group without sarcopenia, the median fT4 (0.99) was within the normal range. The risk of sarcopenia was six times greater in the hyperthyroid patients with fT4 above the normal range (OR: 6.0 95% CI: 0.59–79.23). The characteristics of the two groups with and without sarcopenia are presented in Table 3.

In hyperthyroid patients, fT4 above the threshold value (>1.12 ng/dL) showed 66.7% sensitivity and 75% (50.9–91.3%) specificity for the presence of sarcopenia.

It was predicted that 88.2% (63.6–98.5%) of the patients with fT4 values within the normal range would not have sarcopenia.

In patients with OH and SH, a fT4 value of ≥1.22 showed 66.6% sensitivity and 73.9% specificity for completing the chair rise test in >15 seconds (AUC: 0.608) (LR+ =2.55) (CI=0.31–0.90).

In patients with OH and SH, a fT4 value of ≥1.44 could predict completion of the 4-meter walking test

Table 1. General characteristics of Overt Hyperthyroidism, Subclinical Hyperthyroidism and control groups and handgrip strength.

Parameter	Overt Hyperthyroidism (n = 13)	Sublinical Hyperthyroidism (n = 13)	Control group (n = 30)	p value
Sex (n, %)				
Women	6 (46.2%)	10 (76.9%)	21 (70%)	0.225
Men	7 (53.8%)	3 (23.1%)	9 (30%)	
Age (year)&	39.9 (21–76)	49.1(21–73)	32.3 (21–52)	**0.010**
Handgrip strength&	32.5 (16.6–54.1)	29.6 (20.6–49.5)	31.9 (23.5–68.2)	0.125
EWGSOP2 cut-off points				
Women <16 kg (n,%)	0	0	0	
Men <27 kg (n,%)	0	0	0	
Turkish cut-off points	4 (30.7%)	2 (15.3%)	0	**0.007**
Women <22 kg (n,%)	2 (33.3%)	2 (20%)	0	
Men <32 kg (n,%)	2 (28.6%)	0	0	

& median (minimum-maximum) values are given.

Table 2. Sarcopenia status in OH, SH and control groups.

Sarcopenia status	OH (n=13)	SH (n=13)	Control group (n=30)	Total (n=56)	P value
No sarcopenia	9 (69.2%)	11 (84.6%)	30 (100%)	50	**0.007**
Probable sarcopenia	3 (23.1%)	2 (15.4%)	0 (0%)	5	
Severe sarcopenia	1 (7.7%)	0 (0%)	0 (0%)	1	

Note: OH: Overt Hyperthyroidism, SH: Subclinical Hyperthyroidism

Table 3. Comparison of patients with and without sarcopenia.

Parameter	Sarcopenia (n=6)	No Sarcopenia (n=20)	P value
Age (years)§	**69.1 (21–76)**	**42 (21–67)**	**0.051**
Gender (n)			
Women	4 (66.7%)	12 (60%)	1.00
Men	2 (33.3%)	8 (40%)	
fT3 level (ng/L)§	3.73 (3.37–8.93)	4.14 (2.97–11.57)	0.273
fT4 level (ng/dL)§	1.33 (0.93–2.53)	0.99 (0.73–4.47)	0.180
fT4 > 1.12 ng/dL	4 (66.7%)	5 (25%)	0.138
fT4 normal€	2 (33.3%)	15 (75%)	

§ median (minimum-maximum) values are given. € fT4 normal: 0.61–1.12 ng/dL.

at ≤0.8 m/s with 100% sensitivity and 79.1% specificity (AUC: 0.791) (LR = + 4.80) (CI = 0.62–0.95).

We evaluated the relationship between the chair stand test and the 4-meter walking test results with fT3 values, and observed that the fT3 values of three patients who completed the chair rise test within >15 seconds were within the normal reference range. The fT3 values of two patients who completed the 4-meter walking test at ≤0.8 m/s were within the normal reference range. For this reason, a ROC analysis was not performed for either test, since an fT3 elevation would not be predictive of sarcopenia.

Discussion

In the present study, we have revealed a statistically significant relationship between hyperthyroidism and sarcopenia. The risk of sarcopenia was greater in OH patients than in SH patients.

Thyroid hormones play a role in the transcription of many genes, including myofibrils and calcium regulatory proteins (8). Skeletal muscle growth and regeneration are dependent on the proliferation and differentiation of satellite cells in a process known as myogenesis (9). Thyroid hormone receptor alpha plays an important role in maintaining the satellite cell pool, indicating that thyroid hormone signaling is crucial for skeletal muscle function, metabolism and skeletal muscle repair (10). Similarly, control of intracellular thyroid hormone levels is essential for myogenesis progression (9). Possibly due to the association between throid hormones and the muscle, we found the risk of sarcopenia to be higher in OH patients than in SH patients.

There have been studies suggesting that fT3 is protective for the muscle, but that fT3 levels decrease with aging (11). In our study, a negative correlation was noted between fT3 and age in the hyperthyroid group. Our SH patients were older than OH patients, which is consistent with the literature (12). Our female predominance is also in line with the literature (13).

The higher incidence of osteoporosis in the SH group can be explained by the fact that the SH group is older and has a higher prevalence of women, both of which are risk factors for osteoporosis (14).

Hypertension may also be a clinical finding of OH (15), which may be why hypertension is significantly more common in patients with OH.

Malnutrition is an essential component of sarcopenia (16). Among the biochemical parameters, serum albumin levels are known to be an important criterion of malnutrition. In the present study the albumin levels of all patients were found to be within the normal range.

Low vitamin-D levels have been associated with reduced muscle mass and strength (17). In the present study, no significant difference was observed in the vitamin-D levels of the hyperthyroid and control groups. The distribution of vitamin-D levels was also similar in the groups with and without sarcopenia, excluding the effect of vitamin-D as a possible confounder.

High-density lipoprotein (HDL) cholesterol levels decrease in hyperthyroidism due to increased transfer of cholesterol esters from HDL cholesterol to very low-density lipoprotein (VLDL) and hepatic lipase-mediated catabolism of HDL (18). In the present study, HDL cholesterol levels were found to be significantly lower in the OH group than in the SH group, as expected.

In our study, the results of the SARC-F scoring system used for sarcopenia screening was not in accordance with the prevalence of clinically diagnosed sarcopenia. Still, patients with suspected secondary sarcopenia should be screened as recommended (1).

To the best of our knowledge, this is the first study to evaluate the relationship between hyperthyroidism and sarcopenia using EWSOP2 criteria in newly diagnosed and untreated patients. As a further strength of our study, the significant results garnered from the measurement of muscle strength and calf circumference were found using normative data from our community, rather than the EWGSOP2 threshold values. That said, our study also has some limitations, the first of which relates to the small sample. The study is also limited by being conducted in a single center.

Conclusion

According to the findings of our study, sarcopenia is significantly more common in patients with hyperthyroidism when compared to a control group. The risk of sarcopenia is greater in the overt hyperthyroidism group than in the subclinical hyperthyroidism group. In hyperthyroid patients, a high fT4 increases the risk of sarcopenia, and fT4 elevation is more valuable than fT3 in predicting strength and performance impairment.

Conflict of Interest: No potential conflict of interest relevant to this article was reported by the authors.

References

1. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age and ageing. 2019;48(1):16-31.
2. Bousquet-Santos K, Vaisman M, Barreto ND, et al. Resistance training improves muscle function and body composition in patients with hyperthyroidism. Archives of physical medicine and rehabilitation. 2006;87(8):1123-30.
3. Brennan MD, Powell C, Kaufman KR, Sun PC, Bahn RS, Nair KS. The impact of overt and subclinical hyperthyroidism on skeletal muscle. Thyroid : official journal of the American Thyroid Association. 2006;16(4):375-80.
4. Malmstrom TK, Miller DK, Simonsick EM, Ferrucci L, Morley JE. SARC-F: a symptom score to predict persons with sarcopenia at risk for poor functional outcomes. Journal of cachexia, sarcopenia and muscle. 2016;7(1):28-36.
5. Bahat G, Tufan A, Tufan F, et al. Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. Clinical nutrition (Edinburgh, Scotland). 2016;35(6):1557-63.
6. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. The journals of gerontology Series A, Biological sciences and medical sciences. 2002;57(12):M772-7.
7. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Frontiers in physiology. 2012;3:260.
8. Klein I, Ojamaa K. Thyroid (neuro)myopathy. Lancet (London, England). 2000;356(9230):614.
9. Bloise FF, Cordeiro A, Ortiga-Carvalho TM. Role of thyroid hormone in skeletal muscle physiology. The Journal of endocrinology. 2018;236(1):R57-r68.
10. Milanesi A, Lee JW, Yang A, et al. Thyroid Hormone Receptor Alpha is Essential to Maintain the Satellite Cell Niche During Skeletal Muscle Injury and Sarcopenia of Aging. Thyroid : official journal of the American Thyroid Association. 2017;27(10):1316-22.

11. Borba VZC, Costa TL, Moreira CA, Boguszewski CL. MECHANISMS OF ENDOCRINE DISEASE: Sarcopenia in endocrine and non-endocrine disorders. European journal of endocrinology. 2019;180(5):R185-r99.
12. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nature reviews Endocrinology. 2018;14(5):301-16.
13. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid : official journal of the American Thyroid Association. 2016;26(10):1343-421.
14. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone. 2006;38(2 Suppl 1):S4-9.
15. Berta E, Lengyel I, Halmi S, et al. Hypertension in Thyroid Disorders. Frontiers in endocrinology. 2019;10:482.
16. Sieber CC. Malnutrition and sarcopenia. Aging clinical and experimental research. 2019;31(6):793-8.
17. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. The Journal of clinical endocrinology and metabolism. 2003;88(12):5766-72.
18. Rizos CV, Elisaf MS, Liberopoulos EN. Effects of thyroid dysfunction on lipid profile. The open cardiovascular medicine journal. 2011;5:76-84.

Correspondence:
Asli Tufan, MD
Marmara University Department of Geriatrics,
Pendik, 34893
Istanbul, Turkey
Phone: 0555 5771118
Fax number: 0216 777 55 01
E-mail: aslitufan@yahoo.com