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ORIGINAL ARTICLE

Physical activity in women with subclinical hypothyroidism

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Abstract

Purpose Physical activity is associated with many health-related benefits. However, there is a shift towards inactive lifestyles around the world. Subclinical hypothyroidism (SCH) may have adverse effects similar to hypothyroidism. The presence of symptoms and reduced physical performance in SCH may contribute to an inactive lifestyle. Therefore, the present study aimed to compare physical activity levels (PALs) between women with subclinical hypothyroidism and healthy controls.

Methods Thirty-two women with newly diagnosed SCH and 28 healthy women were enrolled in this cross-sectional study. Arterial stiffness was evaluated by pulse wave velocity (PWV). Neuromuscular symptoms were questioned. Participants wore a physical activity monitor (SenseWear® Armband) for 4 consecutive days. Handgrip and quadriceps muscle strength were assessed by dynamometer. Functional exercise capacity was assessed by 6-minute walk test (6MWT).

Results There was no significant difference in sociodemographic variables between the groups. PWV was significantly higher in the SCH group ($P=0.006$). Physical activity duration and number of steps were significantly lower in the SCH group ($P<0.05$). There was significant difference in neuromuscular symptoms, handgrip and quadriceps muscle strength, and 6MWT distance between the groups ($P<0.05$).

Conclusions This study demonstrates that women with SCH had lower PALs compared to healthy controls. Women with SCH should participate in exercise programs to increase physical activity and muscle strength to achieve adequate PALs.

Keywords Subclinical hypothyroidism · Physical activity · Arterial stiffness · Six-minute walk test · Women

Introduction

Subclinical hypothyroidism (SCH) is an early stage of thyroid dysfunction characterized by elevated levels of thyroid-stimulating hormone (TSH), normal free thyroxine (FT4), and free triiodothyronine (FT3) [1]. Community-based studies have shown that the prevalence of SCH in the adult population is 4–10% [2, 3]. A Colorado prevalence study reported TSH was elevated in 9.5% of all subjects and SCH is more common in women than in men [4]. Approximately, 2–5% of SCH patients may progress to overt hypothyroidism each year [2]. Studies suggest that the adverse effects of overt hypothyroidism may also occur in SCH [5, 6].

Thyroid hormone has both gene transcriptional effects that result from binding to receptors in the cell nucleus as well as nongene-related cellular effects. Therefore, thyroid hormone influences many systems including the nervous, cardiovascular, respiratory, and musculoskeletal systems [7]. Heart and skeletal muscle are the specific targets of thyroid hormone. SCH is characterized by diastolic dysfunction and impaired systemic vascular resistance [8]. In addition, neuromuscular symptoms are common in this population [9, 10]. Abnormal cardiovascular function and impaired mitochondrial activity in patients with SCH may cause exercise intolerance [5, 11].

Cardiovascular disease (CVD) is a major cause of mortality and morbidity [12]. Atherogenic profile, altered

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coagulation parameters, endothelial dysfunction, and arterial stiffness can yield cardiac dysfunction, and several studies have demonstrated similar changes in these parameters in SCH. It is known that overt hypothyroidism is associated with hyperlipidemia, which is the major risk factor for atherosclerotic diseases. However, SCH has also been associated with some cardiovascular risk factors, though this is still controversial [8]. Arterial stiffness, which represents the viscoelastic properties of the vessel wall and vascular damage, is an indicator of atherosclerosis. Increased arterial stiffness is associated with presence of many diseases such as coronary artery disease, peripheral arterial disease, and cerebrovascular disease [13, 14].

Physical activity (PA) is any bodily movement that causes energy consumption over basal metabolism [15]. Physical inactivity is also an independent risk factor for CVD, while increased PA is associated with positive changes in cardiovascular risk factors [16, 17]. Scientific evidence indicates that physical inactivity is a modifiable risk factor for variety of chronic diseases such as CVD, type 2 diabetes, and cancer [18]. Studies have used various self-reported or objective methods to measure PA in healthy individuals and different patient groups [19, 20].

The presence of neuromuscular symptoms and exercise intolerance in SCH can lead to impaired daily activities and an inactive lifestyle [5]. In the literature, there is a paucity of data regarding physical activity levels (PALs) in patients with SCH. Therefore, the aim of this study was to compare PALs between women with SCH and healthy controls and investigate factors associated with PA.

Methods

Design and participants

Participants with SCH and healthy volunteers were included in this cross-sectional study. The study was performed between April 2017 and February 2018. Women with SCH were recruited from the Endocrinology Department of Dokuz Eylül University Hospital. SCH was defined as increased serum TSH levels (> 4.0 mUI/l) with normal levels of serum free thyroxine (FT4) and free triiodothyronine (FT3) [1]. Healthy participants who had normal serum TSH, FT4, and FT3 levels were randomly selected from relatives of patients and the university and hospital staff. Participants with cardiovascular, respiratory, neurological, or other systemic disease, cognitive disorders, and orthopedic problems were excluded. In addition, both patient and healthy participants who used any drugs that would influence thyroid function were excluded.

Assessments

All participants were questioned about neuromuscular symptoms including muscle cramps, myalgia, weakness, and fatigue. Symptoms that occurred in the last month and interfered with participants' daily activities were noted.

Aortic pulse wave velocity (AoPWV) is commonly used to measure arterial stiffness. In the present study, AoPWV was assessed non-invasively using the SphygmoCor Xcel system (AtCor Medical, Sydney, NSW, Australia). Xcel system is a valid, reliable and useful tool for measuring AoPWV [21]. All measurements were carried out after 10 min of supine rest in a temperature-controlled room. To assess AoPWV, a partially inflated cuff was placed over the femoral artery between the hip and knee and femoral pulse waves were obtained while simultaneously measuring carotid pulse waves by applanation tonometry.

PA was objectively measured using the SenseWear Armband Mini (SWA) (BodyMedia Inc, Pittsburgh, USA), which is a valid activity monitor consisting of a skin temperature sensor, heat flux sensor, galvanic skin response sensor, and tri-axis accelerometer. The tri-axis accelerometer measures motion using a microelectromechanical sensor [22]. The SWA provides information about estimated energy expenditure, active energy expenditure, physical activity duration, number of steps, average metabolic equivalents (METs), lying and sleep duration, and duration on-body. The SWA was fixed to the lateral part of the triceps muscle with an elastic band and PA was measured for 4 consecutive days. Data were analyzed using SenseWear Professional version 7.0 software (BodyMedia) and summarized daily.

Handgrip and quadriceps muscle strength were evaluated as indicators of peripheral muscle strength. Handgrip strength was evaluated with a valid and reliable hydraulic hand dynamometer (Jamar, Nottinghamshire, UK) [23]. The test was performed according American Society of Hand Therapists recommendations [24]. Participants were seated with their shoulder adducted and neutrally rotated, elbow flexed at 90° and the forearm and wrist in neutral position. The second handle position of the dynamometer was used during the test. Three consecutive trials were conducted with a 30-s break interval between each trail, and the average value was calculated. Manual Muscle Tester (Lafayette, Indiana, USA) was used to measure quadriceps muscle strength. Participants were seated with hip and knee at 90° flexion and a dynamometer was placed on anterior surface of leg proximal to the ankle joint. The participants pushed maximally against the plate and the piston of the hand-held dynamometer for 4–5 s. The test was performed three times [25].

Functional exercise capacity was assessed with the 6-minute walk test (6MWT). The 6MWT was performed

as recommended by the American Thoracic Society [26]. The distance walked in 6 min (6MWD) was recorded. Enright and Sherrill reference equations were used to calculate percent predicted 6MWD [27].

Statistical analysis

All data analyses were performed using IBM SPSS software (Version 23.0, IBM Corp., Armonk, NY, USA). Normality of distribution was checked using Shapiro–Wilk tests and histograms. Mann–Whitney *U* test was used to compare the differences between two groups for non-normally distributed data and independent samples *t* test was used to compare differences in normally distributed data between two groups. Comparisons of categorical variables between the two groups were done using Chi-square test. Continuous variables were reported as median and interquartile range or mean and standard deviation, while categorical variables were expressed as number and percent. Strength of correlation was interpreted as weak for $r = 0.00–0.249$, moderate for $r = 0.250–0.499$, strong for $r = 0.500–0.749$, and very strong for $r > 0.750$ [28]. Statistical significance was set at $P < 0.05$.

Results

Thirty-seven patients with SCH met the inclusion criteria. Five patients were not willing to participate. Therefore, thirty-two women with SCH and twenty-eight healthy women were included in the study. Etiology of SCH was chronic autoimmune thyroiditis (positive thyroid autoantibodies) in 28 patients, partial thyroidectomy due to benign nodule in 3 patients, and atrophic thyroiditis in 1 patient.

Comparisons of demographic and clinical features are shown in Table 1. There were no significant differences in age, body mass index, menopausal status, or employment status between the groups. Both TSH and FT4 were significantly different between the groups ($P < 0.05$). Total cholesterol, triglyceride, and LDL-cholesterol levels were higher in the SCH group than in the healthy group, but the differences were nonsignificant. There were significant differences between the groups in PWV and pulse transit time (PTT) ($P < 0.05$) as well as muscle cramps, myalgia, weakness, and fatigue ($P < 0.05$).

Data related to the participants' PA are presented in Table 2. There were significant differences in PA duration and number of steps between the groups ($P < 0.05$). Active energy expenditure and METs were lower in the SCH group than the healthy group. Lying down and sleep duration were

Table 1 Sociodemographic and clinical features of women with SCH and healthy controls

	SCH ($n = 32$)	Healthy controls ($n = 28$)	*P* value
Age (years)	43.1 ± 9.9	43.1 ± 9.3	0.986
BMI (kg/m^2)	26.5 ± 3.7	25.8 ± 3.5	0.463
Menopausal status			
Pre-menopausal, *N* (%)	24 (75.0)	22 (78.6)	0.744
Post-menopausal, *N* (%)	8 (25.0)	6 (21.4)	
Working Status, *N* (%)	15 (46.9)	16 (57.1)	0.427
Serum FT4 (ng/dl)	0.7 ± 0.1	0.8 ± 0.1	0.006*
Serum TSH (μIU/ml)	11.2 ± 7.4	1.6 ± 0.8	< 0.001*
Total cholesterol (mg/dl)	213.8 ± 48.96	195.6 ± 33.5	0.178
Triglyceride (mg/dl)	128.2 ± 65.7	99.90 ± 31.9	0.092
LDL-C (mg/dl)	134.1 ± 40.5	124.68 ± 45.4	0.501
HDL-C (mg/dl)	54.2 ± 12.6	56.2 ± 9.6	0.567
PWV (m/s)	7.2 ± 1.5	6.0 ± 1.3	0.006*
PTT (ms)	73.7 ± 21.0	91.6 ± 29.3	0.008*
Muscle cramps, *N* (%)	24 (75.0)	1 (3.6)	< 0.001*
Myalgia, *N* (%)	18 (56.3)	2 (7.1)	< 0.001*
Weakness, *N* (%)	18 (56.3)	0 (0)	< 0.001*
Fatigue, *N* (%)	29 (90.6)	1 (3.6)	< 0.001*

Data were expressed as mean ± SD or number (percentage)

SCH subclinical hypothyroidism, *BMI* body mass index, *FT4* free T4, *TSH* thyrotropin hormone, *LDL-C* LDL-cholesterol, *HDL-C* HDL-cholesterol, *PWV* pulse wave velocity, *PTT* pulse transit time

*Statistically significant difference ($P < 0.05$)

Table 2 Physical activity of women with SCH and healthy controls

	SCH ($n=32$)	Healthy controls ($n=28$)	P value
Total energy expenditure (kcal/day)	2250.4 ± 355.2	2319.3 ± 374.9	0.452
Physical activity duration (min/day) (> 3 METs)	65.8 ± 49.8	103.6 ± 74.9	0.025*
Active energy expenditure (kcal/day) (> 3 METs)	307.9 ± 258.2	418.7 ± 305.4	0.096
Daily number of steps	6189.7 ± 3021.9	9370.4 ± 4545.7	0.002*
METs	1.3 ± 0.3	1.5 ± 0.3	0.066
Lying duration (min/day)	489.6 ± 123.9	459.9 ± 100.6	0.120
Sleep duration (min/day)	419.0 ± 106.8	384.9 ± 105.3	0.291

Data were expressed as mean ± SD

SCH subclinical hypothyroidism, *METs* metabolic equivalent of task

*Statistically significant difference ($P<0.05$)

Table 3 Physical features of women with SCH and healthy controls

	SCH ($n=32$)	Healthy controls ($n=28$)	P value
Handgrip strength (kg)	21.8 ± 5.5	24.9 ± 5.6	0.038*
Quadriceps strength (kg)	15.2 ± 3.6	17.9 ± 3.8	0.009*
6MWD (m)	476.0 ± 67.3	557.0 ± 62.5	< 0.001*
Percent predicted 6MWD (%)	79.5 ± 8.2	92.8 ± 10.0	< 0.001*

Data were expressed as mean ± SD

SCH subclinical hypothyroidism; *6MWD* six-minute walk test distance

*Statistically significant difference ($P<0.05$)

also higher in the SCH group than in the healthy group, but the differences were not statistically significant.

Physical parameters of the participants are summarized in Table 3. Handgrip strength and quadriceps strength were significantly lower in the SCH group than in the healthy group ($P<0.05$). The SCH group also showed significantly lower 6MWD and percent predicted 6MWD compared to the healthy group ($P<0.05$).

Correlations between PA and other variables among women with SCH are presented in Table 4. PA duration was positively correlated with fatigue ($p=0.047$, $r=0.366$) and 6MWD ($P<0.001$, $r=0.601$). Moderate positive correlations were observed between active energy expenditure and fatigue ($P=0.03$, $r=0.390$) and 6MWD ($P=0.01$, $r=0.453$). MET value was moderately negatively correlated with weakness ($P=0.018$, $r=-0.422$) and strongly positively correlated with 6MWD ($P=0.004$, $r=0.500$).

Discussion

To the best of our knowledge, this is the first study exploring PALs and associated factors in women with SCH compared to healthy controls. The main findings of this study indicate that PA duration and number of steps were significantly lower in women with SCH than in healthy controls. In addition, arterial stiffness was significantly increased, whereas handgrip strength, quadriceps muscle strength, and functional exercise capacity were significantly decreased in women with SCH compared to the healthy controls.

Table 4 Spearman correlation coefficients of physical activity with other variables in women with SCH

	Physical activity duration (min/day) (> 3 METs)	Active energy expenditure (kcal/day) (> 3 METs)	Daily number of steps	METs
PWV	−0.067	−0.029	0.215	−0.020
Cramps	−0.205	−0.190	−0.124	−0.175
Myalgia	−0.004	0.051	0.058	−0.044
Weakness	−0.355	−0.181	−0.014	−0.422*
Fatigue	0.366*	0.390*	−0.110	0.222
HGS (kg)	−0.081	0.008	−0.115	−0.040
QS (kg)	0.178	0.201	0.070	0.188
6MWD (m)	0.601*	0.453*	0.036	0.500*

SCH subclinical hypothyroidism, *METs* metabolic equivalent of task, *PWV* pulse wave velocity, *QS* quadriceps strength, *HGS* handgrip strength, *6MWT* six-minute walk test distance

*Statistically significant difference ($P<0.05$)

The possible link between CVD and SCH has been evaluated in several studies. A meta-analysis showed an increased prevalence of CVD in patients with SCH compared to euthyroid subjects [29]. In addition, another meta-analysis found that risk of CVD is associated with severity of thyroid hormone deficiency and high TSH levels [30]. A recent meta-analysis reported that the relationship between CVD and SCH is TSH-dependent and that patients with TSH levels above 10 μIU/ml are at higher risk for CVD [8]. The high values of TSH (> 10 μIU/ml) are related to the atherogenic lipid profile. Based on this, a study by Teixeria et al. supported the link between SCH and abnormal lipid profile, especially total cholesterol and LDL-cholesterol [31]. In our study, the mean TSH level was over 10 μIU/ml. Of the patients, 21 had mild SCH and 11 had severe SCH. In accordance with the literature, the total cholesterol and LDL-cholesterol values of our SCH patients were above the reference range. However, although levels of total cholesterol, triglyceride, and LDL-cholesterol were higher among SCH patients than the healthy controls, there was no significant difference between the groups. This may be due to the fact that these values were close to the upper limit of the reference range in our healthy control group.

Arterial stiffness is an independent predictor of cardiovascular conditions and all-cause mortality [13]. Owen et al. used pulse wave analysis to assess arterial stiffness in patients with SCH [32]. Nagasaki et al. also used brachial-ankle PWV to measure arterial stiffness in patients with SCH [33]. These studies showed increased arterial stiffness in patients with SCH. In our study, we used AoPWV to assess arterial stiffness. Consistent with previous studies, our study also found increased arterial stiffness in patients with SCH.

Studies have reported that direct measures of PA are superior in terms of validity and reliability than self-reported measures. Among the PA measures, the SWA has the highest accuracy in populations diagnosed with cardiovascular and chronic obstructive pulmonary disease [34, 35]. We also used the SWA to measure participants' PAL in our study and found significant differences in PA duration and daily number of steps between the SCH and healthy groups.

Tudor-Locke and Bassett used a pedometer to classify PA in healthy adults. According to current evidence, they defined less than 5000 steps per day as 'sedentary lifestyle index', 5000–7499 steps per day is defined as 'low active', 7500–9999 is defined as 'somewhat active' and over 10,000 steps per day is defined as 'active' [36]. In our study, SWA data showed the daily number of steps of patients with SCH was 6189.9, while the daily number of steps of healthy controls was 9370.4. In this context, the PA of patients with SCH and healthy controls were 'low active' and 'somewhat active', respectively. These results showed that patients with SCH had lower PALs than healthy controls. Saglam et al. showed that only 18% of university students in the Turkish population were physically active [37]. Similarly, in our study, only 36% of healthy controls were classified as active. These findings suggest that the PALs of healthy individuals in the Turkish population are lower than expected, and that activity counseling would benefit both SCH patients and healthy controls. In addition, although the PALs of women with SCH were lower, their total energy expenditure was similar to that of healthy controls. This suggests that SWA is effective in measuring PALs, but may underestimate energy expenditure at low walking speeds and during high-intensity exercise [38].

Inactive lifestyle has been identified as a risk factor for CVD [17]. PA is one of the non-pharmacological strategies for managing and preventing CVD as it increases musculoskeletal fitness, improves physiological parameters, alleviates symptoms, and reduces morbidity [39]. Every 10% increase in time spent in moderate–vigorous intensity PA was reported to cause a 5% reduction in risk of death in patients with type 2 diabetes mellitus [40]. In addition, individuals who take more than 10,000 steps/day have less arterial stiffness than those who take less than 6000 steps a day [41]. As shown in our study, patients with SCH had abnormal lipid profile, increased arterial stiffness, decreased PALs, and increased risk of CVD.

Previous studies have shown that neuromuscular symptoms are more common in patients with SCH compared to healthy controls [9, 10]. The authors suggested that these neuromuscular symptoms may arise due to abnormal serum calcium balance and surface electromyography in this population. Consistent with these reports, we also found that neuromuscular symptoms were more frequent in patients with SCH. The prevalence of muscle cramps, myalgia, weakness, and fatigue among the SCH patients were 75%, 56.3%, 59.3% and 90.6%, respectively. There was a significant inverse association between weakness and METs. Fatigue was related to physical activity duration and active energy expenditure. According to our data, fatigue increased as PA duration and active energy expenditure increased in patients with SCH. Therefore, fatigue avoidance may be a factor limiting PAL in our SCH patients.

Grip strength provides information about not only hand strength but also all upper extremity strength [42]. A recent study showed a tendency toward lower handgrip strength in SCH patients, although the difference compared to healthy controls was not significant [43]. In our study, we evaluated handgrip and quadriceps muscle strength with a dynamometer. There was a significant difference in handgrip and quadriceps muscle strength between the groups, with SCH patients exhibiting lower muscle strength. However, it is not clear whether this weakness is due to sedentary lifestyle or myopathic state, because the study did not include serum enzyme analysis. Our results showed no association between

handgrip and quadriceps muscle strength and PA in patients with SCH, which may be because in general, both PA and muscle strength were lower.

In the present study, functional exercise capacity was assessed using the 6MWT, which is widely used in many different populations because it is reliable, simple, and inexpensive. In a previous study examining the physical performance of patients with hypothyroidism, 6MWD was reported to be decreased in both overt hypothyroidism and SCH patients compared to healthy controls [43]. In our study, mean 6MWD was 476.0 ± 67.3 m in the SCH group and 557.0 ± 62.5 m in the healthy control group, indicating lower functional exercise capacity in patients with SCH. This may be due to mitochondrial activity damage leading to impaired oxygen utilization [11]. In addition, 6MWD of the SCH patients in our study was significantly associated with PA duration, active energy expenditure, and METs.

Patients with SCH may have reduced PAL due to weakness, fatigue, and reduced functional exercise capacity. Moreover, reduction in PAL may result in decreased muscle strength and functional exercise capacity. This vicious cycle must be broken by increasing PA through behavioral modifications and individualized exercise programs.

Our study has strengths and limitations. The main strength is the use of an objective method to measure PAL. A limitation of this study is the small sample size. Another limitation is cross-sectional design, which does not allow evaluation of causal relationships between PA and related factors. Furthermore, all of the study participants were women, which may reduce the generalizability of our results to the entire SCH population. Therefore, future larger studies should investigate causality between PA and related factors in both female and male patients with SCH.

Conclusion

This study demonstrates that PALs are lower in women with SCH and PA was associated with weakness, fatigue, and functional exercise capacity. Women with SCH should participate in exercise programs to increase physical activity and muscle strength to achieve adequate PALs. Activity counseling is recommended for both healthy individuals and those with SCH.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

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