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Original Research Article

Cardiopulmonary Dysfunction in Patients with Subclinical Hypothyroidism

Dr. Tauseef Nabi[1], Dr. Nadeema Rafiq[2], Dr. Quratul-Ain- Arifa[3]

[1]DM Endocrinology, Department of Endocrinology, Govt. Medical College, Srinagar, J&K, India
[2]MD Physiology, Department of Physiology, Govt. Medical College, Baramulla, J&K, India
[3]MD SPM, Department of Community Medicine, Govt. Medical College, Baramulla, J&K, India

Corresponding Author: Dr. Tauseef Nabi

ABSTRACT

Background: Subclinical Hypothyroidism (SCH) represents the earliest stage of hypothyroidism. SCH is defined biochemically as a high serum thyroid-stimulating hormone (TSH) and normal serum free thyroxine (fT4) and triiodothyronine (fT3) concentrations. Cardiopulmonary fitness reflects the overall capacity of the cardiovascular and respiratory system. VO2 max, also known as maximal oxygen uptake, is the measurement of the maximum amount of oxygen a person can utilize during intense exercise.
Objective: The aim of this prospective observational case-control study was to evaluate the cardiopulmonary fitness of patients diagnosed with SCH.
Methods: The study comprised of 140 participants (80 patients with SCH and 60 healthy controls) in the age-group of 18-55 years. VO2 max was estimated indirectly by following the protocol of Queen's College Step Test (QCT) method to assess cardiopulmonary fitness
Results: The patients of SCH and Controls were comparable for age, gender, weight, waist circumference, BMI and hemodynamic parameters. TSH was significantly elevated in SCH than controls while fT4 and fT3 were comparable. The patients of SCH showed a significant reduction VO2 max as compared to controls 46.4±8.6 and 49.8±9.8 ml/kg/min respectively (P=0.029). VO2 max was significantly reduced in female SCH than male SCH (P=0.001).
Conclusion: Cardiopulmonary functions were affected in patients with SCH. A mild cardiopulmonary dysfunction was seen in patients with SCH particularly in females.

Keywords: Subclinical hypothyroidism (SCH); Cardiopulmonary fitness; VO2 max; Queen's College Step Test (QCT)

INTRODUCTION

Subclinical Hypothyroidism (SCH) is defined as an elevation in serum Thyroid Stimulating Hormone (TSH) above the upper limit of the reference range with normal free thyroxine (fT4) and triiodothyronine (fT3) concentrations and with few or no signs and symptoms of hypothyroidism. [1] The incidence of SCH varies between 4 and 10% depending upon the gender, age and population studied. [2,3] SCH poses an enormous burden in India as the prevalence rates of SCH in India exceed those in the developed nations. Indian studies have reported varying prevalence, which varies with geographical area and iodine status as 11.3%, [4] 8.02% [5] and 21.5%. [6] The prevalence increases with age and is more common in females than males. [6, 7] SCH can be reversible or it can progress to overt hypothyroidism. The annual risk of progression of SCH to overt hypothyroidism is 2-5%. [1] Etiologically, most cases of persistent SCH are due to autoimmune

thyroiditis (AIT); however, germline loss of function mutations in the TSH receptor account for a small proportion of cases. [8]

The consequences of SCH are variable at several levels and may depend on the duration and the degree of elevation of the serum TSH. Since heart, vasculature, lungs, and muscles are target organs for thyroid hormones; a reduction of their performance in SCH is expected and has already been documented. [9-12] It has been reported in many studies that patients with SCH have increased frequency of hyperlipidemia, increased inflammatory markers, diabetes, hypertension and increased cardiovascular risk or mortality as compared with a euthyroid population. [13-16]

VO2 max is the measurement of the maximum amount of oxygen a person can utilize during intense exercise. It is a common measurement used to establish the aerobic endurance of an athlete prior to or during the course of training. It is one of several tests used to determine an athlete's cardiovascular fitness and performance capacity. Cardiorespiratory endurance is the level at which your heart, lungs, and muscles work together when you are exercising for an extended period of time. This shows how efficiently your cardiorespiratory system functions.

The VO2 max can be estimated using maximal or submaximal tests, by direct or indirect methods. The most commonly used tests are walking/running tests followed by cycling and step tests other are Astrand Treadmill and Rockport Mile Walk test. [17-21] Among various indirect protocols, the Queen's College step test (QCT) is the simplest one and validated. [22, 23] VO2 max is often used as a marker of physical fitness and considered the best indicator of aerobic fitness. [24] VO2 max estimation by step test is one such test and is considered to be a practical field test for assessing individual aerobic fitness. [25] Physical fitness is considered as the degree of ability to execute a physical task under various ambient conditions. Physical fitness is presently considered one of the most important health markers, as well as a predictor of morbidity and mortality for cardiovascular disease (CVD) and for all causes. [26]

There are not many studies to report the influence of SCH on cardiopulmonary fitness. [27-30] The impairment of cardiopulmonary function may be considered as the indication for initiation of L-thyroxine at the subclinical stage of hypothyroidism. [31-33] Hence, the present study was aimed to assess the cardiopulmonary fitness by Queens College step tests in patients of SCH to find out impairment if any.

MATERIALS AND METHODS

This was a prospective observational case-control study of adults with SCH. This study was carried out in the Department of Endocrinology and Department of Physiology of GMC Srinagar, Jammu and Kashmir, India. The study was approved by the institutional ethical committee.

STUDY SUBJECTS

Total of 80 patients with newly diagnoses of SCH attending the outpatient department of Endocrinology, who fulfilled eligibility criteria were recruited in the study. We also recruited 60 randomly selected healthy euthyroid controls standardized for age and gender for the comparison. This study was conducted over a period of 10 months from August 2018 to May 2019. Informed consent was obtained from all the recruited subjects. Information regarding various demographic characteristics was taken through well-structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations blood glucose fasting (BGF), and Thyroid function test (TFT) were carried out.

Eligibility criteria:

Inclusion criteria included patients having age >18years and Subclinical hypothyroidism was defined as biochemical evidence of elevated TSH levels (>4.3 to ≥ 10 mIU/ml) and normal fT3 and fT4 values.

In patients with SCH, laboratory tests were performed 1-3 days before treatment if required acute. Exclusion criteria include i) Hypertension, ii) Smokers, iii) Coronary artery disease, iv) Diabetes, v) Other chronic diseases like heart failure, respiratory disease, hepatic or renal dysfunction, vi) Drugs like estrogen supplements, Levothyroxine, diuretics, antihypertensive, or hypolipidemic drugs and vii) Subjects under-going regular physical training.

MEASUREMENT OF TFT

TFT comprising of TSH, fT3 and fT4 levels was carried out by electrochemiluminescence immunoassay (ECLIA) method using a fully automatic analyzer ECLIA 2010 (Roche Diagnostic Germany).

SCH Group: 80 patients who fulfilled the eligibility criteria were tested for cardiopulmonary fitness level.

Control Group: 60 euthyroid subjects were also tested for cardiopulmonary fitness level.

STUDY PROCEDURE

Initial explanation about the aim and purpose of the study, test procedure and instructions on how to perform the test was given. All the subjects were tested under similar laboratory conditions in a comfortable environment. Before the test, the subjects were instructed not to indulge in any activities. Subjects were also instructed not to have heavy meals/tea/coffee at least 2 hours before the test. Detailed history was taken and clinical examination was done. Before commencement of the test, the subjects were asked to rest, then all basal parameters like heart rate, blood pressure and respiratory rate were measured. Body Mass Index (BMI) was calculated as Body weight in kilograms divided by square root of Body height in meter, using Quetelet's index. Normal weight was defined as BMI 18.5 to ≤ 22.9, Under weight as BMI < 18.5, Overweight as BMI 23 to ≤ 24.9 and Obesity as BMI ≥ 25 kg/m^2, as per revised body type classification for Indian Population recommended by Health ministry and Diabetes Foundation of India in 2008.

VO2 max was estimated indirectly by following the protocol of Queen's College Step Test (QCT) method. [34] The test has been well validated in the Indian population. [22] Compared to the Harvard Step Test, this version has a lower step height, slower cadence, shorter test and more simple analysis. The step test was performed using a tool of 16.25 inches in height. Stepping was done for a total duration of 3 minutes at the rate of 24 steps up per minute for males and 22 steps up per minute for females which were set by a metronome. After completion of the exercise, the carotid pulse rate was measured from the fifth to the twentieth second of recovery period. The 15 seconds pulse rate was converted into beats per minute and the following equation was used to predict VO2 max.

For males: VO2 max = 111.33 – [0.42 × pulse rate (beats/min)]

For females: VO2 max= 65.81– [0.1847×pulse rate (beats/min)] [ml/kg/min]

STATISTICAL ANALYSES

In univariate analysis, the categorical variables were compared in the two groups by using $\chi 2$ test or Fisher exact test where appropriate. For continuous variables, the independent sample t test was used. *P* values <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

RESULTS

A total of 140 patients (80 cases and 60 controls) who met the inclusion criteria were included in the study. Table 1 shows the baseline parameters of the study population. The mean ages of SCH patients and Euthyroid controls were 36.4±9.3 and 34.8±8.6 years respectively. The two groups were comparable in age, gender, BMI, waist circumference and hemodynamic

parameters. Serum TSH levels were significantly higher in SCH patients compared to control group with TSH of 10.72±2.38 and 3.66±1.22 respectively (*P*<0.001). The means fT4 in SCH and controls were 1.15±0.46 and 1.23±0.38 ng/dl respectively (*P*=0.275) and means fT3 in SCH and controls were 2.56±0.62 and 2.70±0.74 pg/ml respectively (*P*=0.226). Thus fT4 and fT3levels were comparative between two groups. On comparison of VO2 max between SCH and controls which represents cardiopulmonary fitness was significantly lower in SCH than controls 46.4±8.6 and 49.8±9.8 ml/kg/min respectively (*P*=0.029).

Table 1: Baseline parameters of study participants (Subclinical Hypothyroidism and Controls)

Parameters	Euthyroid Controls N = 60	Subclinical Hypothyroidism N = 80	*P-value
Female, n (%)	40 (67%)	52 (65%)	0.805
Age (years)	34.8±8.6	36.4±9.3	0.300
Weight (kg)	62±8	64±10	0.205
Height (cm)	166±16	164±14	0.433
BMI (kg/m2)	23.7±4.8	24.4±4.1	0.355
Waist circumference (cm)	90±9	92±8	0.167
Resting Heart rate (beats/min)	76±12	74±10	0.284
SBP (mmHg)	128±12	130±14	0.376
DBP (mmHg)	82±7	84±8	0.125
TSH (µIU/mL)	3.66±1.22	10.72±2.38	<0.001
fT4 (ng/dl)	1.23±0.38	1.15±0.46	0.275
fT3 (pg/ml)	2.70±0.74	2.56±0.62	0.226
VO2 max (ml/kg/min)	49.8±9.8	46.4±8.6	0.029

*P-value <0.05 is considered statistically significant Categorical variables [n (%)] Continuous variables [mean ± SD] N = Number; SD = Standard deviation

Table 2 shows the comparison of characteristics of subclinical hypothyroidism patients on the basis of gender. The two genders were comparable in age, gender, BMI, waist circumference, hemodynamic parameters and thyroid function test. Comparison of VO2 max between female and male SCH was significantly lower in female SCH than males SCH 42.6±8.2 and 49.3±9.3 ml/kg/min respectively (*P*=0.001).

Table 2: Characteristics of Subclinical Hypothyroidism patients on the basis of Gender

Parameters	Females SCH N = 52	Males SCH N = 28	*P-value
Age (years), mean ± SD	34.8±8.6	36.4±9.3	0.442
Weight (kg)	69±10	67±8	0.365
Height (cm)	162±16	168±14	0.099
BMI (kg/m2)	24.4±4.1	23.7±4.8	0.494
Waist circumference (cm)	92±8	90±9	0.310
Resting Heart rate (beats/min)	73±6	75±8	0.210
SBP (mmHg)	132±14	128±12	0.204
DBP (mmHg)	84±8	82±7	0.269
TSH (µIU/mL)	10.8±5.56	9.1±4.84	0.176
fT4 (ng/dl)	1.13±0.44	1.23±0.34	0.299
fT3 (pg/ml)	2.23±0.78	2.43±0.61	0.243
VO2 max (ml/kg/min)	42.6±8.2	49.3±9.3	0.001

*P-value <0.05 is considered statistically significant

DISCUSSION

The maximum oxygen uptake (VO2 max), an internationally accepted parameter to evaluate the cardiopulmonary fitness reflects the amount of oxygen utilized by working muscles during maximal exercise. It is the best index of aerobic capacity and the gold standard for cardiopulmonary fitness. So in a person, the more is the maximum oxygen consumption capacity, the more will be his/ her aerobic capacity. VO2max is the measure of the functional limit of the cardio-respiratory system and the single most valid index of maximal exercise capacity. [35]

The current study utilized a simple and non-invasive QCT method to evaluate cardiopulmonary fitness in patients with

SCH. Many researchers have found impaired cardiopulmonary function while other studies suggested normal cardiopulmonary fitness in patients with SCH, hence the involvement of cardiopulmonary function in SCH is still not very clear. [29, 36]

In our study, the patients of SCH showed a significant reduction VO2 max as compared to controls 46.4±8.6 and 49.8±9.8 ml/kg/min respectively (*P*=0.029). VO2 max was significantly reduced in female SCH than male SCH (*P*=0.001). Thus reduction of VO2 max in the study points to a mild cardiopulmonary dysfunction. Similar to the present study Pawaria S *et al*., also found significantly reduced cardiorespiratory fitness in subjects with hypothyroidism (36.19±3.55) as compared to euthyroid subjects (45.76± 2.912). [28]

Our results are consistent with results of Xiang GD *et al*. [37] and Caraccio N *et al*., [38] they also observed a significant reduction in VO2 max in patients with SCH. Contrary to current findings, Amati F *et al*., found before training, no significant differences in VO2 max between patients with SCH and controls were found. [36] The study done by Reuters VS *et al*., also found comparable VO2 max between patients with SCH and controls. [39]

The significant reduction in cardiopulmonary function test values, found in SCH patients in the present study, may be attributed to respiratory muscle weakness. Low VO2 max in hypothyroid patients is justified by the decrease in myocardial contractile force. [40] This reduction in the heart's pumping function decreases cardiac output, an important factor in determining the level of cardiopulmonary fitness.

CONCLUSION

The current study suggests that cardiopulmonary functions were affected in the patients with SCH. A mild cardiopulmonary dysfunction was seen in patients with SCH particularly in females.

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