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Original Research Article

Left ventricular diastolic and pulmonary dysfunction in patients with sub-clinical hypothyroidism; A case- control study

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ABSTRACT

Introduction: Subclinical hypothyroidism has been associated with adverse metabolic, cardiovascular, neuromuscular, and cognitive effects and has been shown to have a detrimental impact on quality of life. Though there are many literatures regarding the effect of hypothyroidism on pulmonary function but few studies revealing the influence of subclinical hypothyroidism on pulmonary functions are found.
Aim of the Study: To evaluate the left ventricular diastolic dysfunction in individuals with subclinical hypothyroidism and to evaluate their relation to (FEV1%, FVC%, FEF 25-75%).
Materials and Methods: This is a case-control study involving ninety five (95) subjects who were divided into 2 groups; 50 cases with higher than normal TSH (>4.5 mU/L) but lower than 10mU/L with normal FT3 and FT4 (group 1), group 2 with normal levels of TSH, FT3 and FT4. The following was done to all subjects; TSH, FT3 and FT4 by Eliza, echocardiography for left ventricular diastolic dysfunction assessment and spirometry.
Results: There was Lower TSH, FT3, reduced E wave velocity, E/A ratio with increased A wave velocity, prolonged deceleration time (DT) and intra-ventricular relaxation time (IVRT) , lower (FEV1, FVC, FEF25-75) % in group 1. TSH showed a negative correlation with E wave velocity, E/A ratio and the three pulmonary function indices with a strong positive correlation with IVRT. IVRT has a moderate negative correlation with FVC%. Correlations between other echocardiograpic parameters of LV diastolic dysfunction and pulmonary function indices were weak.
Conclusion: Subclinical hypothyroidism patients are more prone to left ventricular diastolic dysfunction so they should be screened by Doppler echocardiography for early diagnosis and management. Although the pulmonary function alterations in subclinical hypothyroidism are mild, they should not be ignored. Further studies are needed to decide whether these changes are enough to establish thyorxine replacement therapy.

1. Introduction

Hypothyroidism is the most common form of thyroid disorder throughout the world.[1] Subclinical hypothyroidism is a common endocrine disorder characterized by increased levels of thyroid stimulating hormone (TSH) with normal levels of free thyroxine (T4) and free triiodothyronine (T3) in serum. The signs and symptoms of SCH are usually subtle as compared with those of overt hypothyroidism, so it is difficult to detect. Thus, the diagnosis of SCH is a laboratory diagnosis.[2] As the values of thyroid hormone are normal, increased level of TSH represents a compensatory mechanism that stimulates the thyroid gland to produce sufficient amounts of thyroid hormones. The disorder can eventually progress to overt hypothyroidism which is characterized by increased values of TSH but reduced values of thyroid hormones.[3] The range of TSH for diagnosis of SCH is between 4.5 mIU /L-10 mIU /L. A study including 107 SCH patients reported progression to full blown hypothyroidism in 26.8% with higher TSH levels

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being a significant indicator.[4] However, a study reported 52% of SCH patients with TSH below 10, spontaneously recovered.[5] The prevalence of this condition in different population studies varied from 1% to 17%, with the highest prevalence in the elderly.[6]

The risk that subclinical hypothyroidism will progress to overt hypothyroidism in patients with TSH higher than 8 mIU /L is high, and in 70% of these patients, the TSH level rises to more than 10 mIU /L within 4 years. Early treatment should be considered if the TSH is higher than 7 or 8 mIU /L.[7]

Subclinical hypothyroidism has been associated with adverse metabolic, cardiovascular, neuromuscular, and cognitive effects and has been shown to have a detrimental impact on quality of life.[8] Mild and subclinical thyroid dysfunction is associated with an increased mortality in patients with cardiovascular disease.[9–11] A report indicated that patients with SCH (median 6.3 mIU /l) and pre-existing heart failure had a higher rate of mortality as compared with euthyroid candidates.[12]

The Respiratory system like other body systems and organs is affected by hypothyroidism though respiratory manifestations are seldom the major complaints in hypothyroidism.[13] Both hypothyroidism and hyperthyroidism cause respiratory muscle weakness and decrease pulmonary function. Lung volumes are usually normal, but studies have shown findings suggestive of restrictive pattern of impairment.[14]

This study was carried out with the objective to evaluate the left ventricular diastolic dysfunction in individuals with subclinical hypothyroidism. Also, to evaluate the relation between left ventricular diastolic dysfunction indices and thyroid hormones with some pulmonary function parameters (FEV1%, FVC%, FEF 25-75%).

2. Materials and Methods

This study was a case control study which was carried out in the period from February 2018 to August 2019. Ninety- five (95) subjects were enrolled in the study selected from those who visited Benha University hospital outpatient general Clinic for checkup. They were divided into 2 groups; 50 cases (group 1) and 45 controls (group 2).

2.1. Inclusion criteria

1. Higher than upper limit of normal TSH ($>$ 4.5 mU /L) but lower than 10 m U /L as this defines subclinical hypothyroidism state.
2. Normal levels of thyroxin (FT4) (9–16 pmol /L, and normal free triiodothyronine (FT3) level (3.7–6.5 pmol /L).
3. Age between 20 and 60 years (as above 60 years diastolic dysfunction can be present even in healthy subjects.[15]

2.2. Exclusion criteria

1. Absence of diabetes mellitus, hypertension, cardiac respiratory, liver or kidney disease. They were excluded by thorough history taking and necessary investigations.

2. Absence of smoking, alcoholism or drugs that affect the thyroid, cardiac or pulmonary function.

Control subjects were selected from age, sex and BMI matched healthy volunteers who were subjected to the same selection criteria as cases but with TSH level within normal range (0.4 to 4.2 m U /L).

This research was accepted by research ethics committee of Faculty of medicine, Benha University. All procedures performed in this study were in accordance with the ethical standards of the institutional and / or national research committee and with Helsinki declaration and its later amendments.

3. In both groups the following was performed:

3.1. Assessment of thyroid function

This was done in two occasions; at the beginning of the study and 6 weeks later. After an overnight fasting venous blood was withdrawn from both cases and controls. TSH, FT4 and FT3 were assayed using ELIZA reader (450 nm). The three thyroid hormones kits were supplied by Genzyme Diagnostics (1531, Industrial road, San Carlos, CA 94070 U.S.A).

3.2. Assessment of left ventricular diastolic dysfunction

Examination was done by a single cardiologist who was blinded about the study subject state (cases vs controls). A commercially available (Vivid 7; General Electric, Vingmed, Norway) echocardiography system was used in the study. At apical four chamber view a pulsed-wave Doppler was used to measure trans-mitral flow velocity. Diastolic trans-mitral peak velocity (E and A wave), E/A ratio, and deceleration time (DT) of mitral E wave were measured. At apical five-chamber view, continuous-wave Doppler was used to obtain IVRT, we took the average value of three consecutive beats to get the final value. Diastolic dysfunction was diagnosed if any of the following was present: (a) E/A $\leq$1.0, (b) IVRT $\geq$ 100 ms, or (c) DT $\geq$220 ms.[16]

3.3. Assessment of pulmonary function parameters

Examination was done by a single pulmonologist who was blinded about subject state (cases versus controls). Room temperature and pressure were entered along with the patient data [age (years), weight (kg), height (cm), and sex] to obtain results in the form of percent of-predicted (% predicted) except for FEV1 /FVC. A Sensor-medics Vmax series, 2130 spirometer, V 6200 Autobox, 6200 DL (Sensor Medics Corporation, California, USA) was used in the

study. Flow/volume loop was performed to all participants. Individuals with FEV1 /FVC less than 0.7 of predicted were excluded from the study.

3.4. Statistical analysis

The collected data were analyzed using SPSS version 18 for windows (IBM corporation, Chicago, USA). Quantitative variables were displayed as means and standard deviations. Independent T test was used to compare cases and control groups while Chi square test was used to compare qualitative variables. For correlation between variables, Pearson correlation co-efficient was used (r), $P < 0.05$ was considered significant statistically.

4. Results

This work was carried out on 95 subjects divided into; group 1 which included 50 patients with higher than normal TSH (subclinical hypothyroid group) and group 2 which included 45 healthy subjects with a normal TSH level as control. Table 1 showed a well-matched age and BMI between both groups. However, systolic and diastolic blood pressures were higher in group 1 than group 2 but still in the normal range for BP. in both groups the number of females were higher than males (P value 0.000).

In Table 2 despite FT3 and FT4 levels were normal in both groups, TSH was significantly higher in group 1 (P value 0.000). FT3 despite of being in the normal range, it was lower in group 1 (2.61±0.82) than in group 2 (3.61±0.74) P value 0.000. echocardiographic measurements have shown diastolic dysfunction in group 1 where peak E velocity was reduced (57.53±11.48 VS 71.43±3.69 In group 2) while peak A velocity was increased (67.30±4.61) compared to group 2 (54.81±8.22) P value 0.000. as a result, E/ ratio was found to be lower in group1 (0.85±0.18) compared to (1.54±1.73) in group 2 (p value 0.012). IVRT and DT were significantly longer in group 1 (119.51±4.70, 174.18±8.41 Respectively) than group 2 (70.26±4.43, 164.34±6.34 Respectively) (P value 0.000) pulmonary functional indices (FEV1, FVc, FEF25-75)% were all significantly lower in group 1 than in group 2 (P value 0.012, 0.000, 0.001 respectively). There were no gender differences in all the measured variables except for FVC which was lower in males than females in group 1 (P value 0.012). TSH was mildly lower in males than females in group 2 but the difference was not highly significant P value (0.047), Table 3.

TSH level was correlated with many of the study variables where it had a negative correlation with E wave velocity, E/A ratio and the three pulmonary function indices while it showed a strong positive correlation with IVRT (P value 0.000), Table 4. IVRT also has a moderate negative correlation with FVC% (r .487 p value 0.000). However, correlations between other echocadiograpic parameters of LV dysfunction and pulmonary function indices were weak, Table 5.

5. Discussion

The heart is very sensitive to alterations in serum thyroid levels.[17] Nonspecific histologic abnormalities have been demonstrated repeatedly in the hearts of myxoedema patients since first reported in 1888 in a report of a committee of the Chemical Society of London.[18]

It is known that clinically manifest hypothyroidism is associated with systolic and diastolic left ventricular disfunction.[17] However, studies investigating the systolic and diastolic function of the heart in SCH showed controversial results.[19]

In the current work, echocardiograpic measurements have shown diastolic dysfunction in group 1 where peak E velocity was reduced while peak A velocity was increased compared to group 2. As a result, E/ ratio was found to be lower than 1 (0.85±0.18) in group 1. IVRT and DT were significantly longer in group 1 than group 2. This was similar to a study done by Biondi et al.,[20] Kosar et al.,[21] Franzoni et al.,[22] and Nag et al.[23] However, the latter had measured Tei index and found a higher index in the subclinical hypothyroidism group. In contrast to our study and the study done by Kosar et al., and Biondi et al., NAg et al., found no prolongation of E wave velocity. Vitale et al.[24] Despite he did not find alterations in the above parameters they had diagnosed diastolic dysfunction in 20 subclinical hypothyroidism patients by increases in LV preejection period, preejection period/LV ejection time ratio, and isovolumic relaxation time (IVRT). Meena., et al.,[25] investigated 30 subjects with subclinical hypothyroidism with tissue doppler echocardiography. They found a decreased E wave velocity with decreased E/A ratio. Arnic et al.,[26] diagnosed diastolic dysfunction based on the significantly higher Septal annulus relaxation time in SCH group. Lateral annulus and myocardial relaxation times, precontraction /contraction ratios and precontraction times were also slightly higher. Septal, lateral annulus and lateral myocardial relaxation times were decreased after TRT.

In the current study TSH was moderately correlated negatively with E wave velocity while moderately correlated positively with IVRT and DT. T3 was moderately correlated with A wave velocity, in all the above correlations P value was significant. Malhotra et al.,[27] studied 67 patients with SCH by echocardiography. Their results showed that E/A ratio correlated significantly with thyroid stimulating hormone (TSH), free triiodothyronine (FT3) with echocardiographic indices for LVDD showed significant improvement after 6 months of L-thyroxine therapy. In Vitale et al.[24] Study, Myocardial precontraction time (PCTm) and myocardial relaxation time (RTm) were prolonged and PCTm/myocardial contraction time ratio was increased and positively correlated to serum TSH levels.

Table 1: Baseline characteristics of the study groups

	Group 1 (N =50)	Group 2 (N= 45)	P value
Age	48.46±6.12	47.93±6.42	0.68
Sex Males females	21 29	19 26	.000 .000
BMI	31.51±2.79	31.35±2.93	0.79
Systolic BP	136.96±5.58	131.42±10.06	0.002
Diastolic BP	83.1±4.96	79.02±5.306	.000
total	50	45	95

Table 2: Thyroid, echocardiographic and pulmonary function measurements in the study groups

	Group 1 (N=50)	Group 2 (N=45)	P value
TSH	6.35±1.58	2.79±0.85	.000
T3	2.61±0.82	3.61±0.74	.000
T4	12.55±1.81	12.68±1.74	0.727
Peak E velocity	57.53±11.48	71.43±3.69	.000
Peak A velocity	67.30±4.61	54.81±8.22	.000
E/A ratio	0.85±0.18	1.54±1.73	.012
IVRT	119.51±4.70	70.26±4.43	.000
DT	174.18±8.41	164.34±6.34	.000
FEV1%	81.74±6.30	84.6±5.71	.021
FVC%	83.3±4.76	88.53±4.05	.000
FEF25-75%	73.85±18.69	83.76±6.19	.001
Total	50	45	95

Table 3: Gender differences in the measured variables in the study groups

	Group 1		P value	Group 2		P value
	Males	Females		Males	Females	
TSH	6.09±1.32	6.54±1.74	.298	2.505±0.75	3.01±0.88	.047
E wave velocity	58.05±12.76	57.15±10.67	.794	71.43±3.17	71.43±4.08	.997
A wave velocity	66.46±5.13	67.89±4.18	.298	55.27±3.79	54.47±10.40	.719
E/A ratio	0.87±0.20	0.85±0.17	.594	1.30±0.11	1.71±2.28	.364
DT	175.13±8.71	173.45±8.26	.507	164.37±5.76	164.31±6.84	.974
IVRT	118.38±5.38	120.32±4.03	.172	70.35±3.51	70.18±5.07	.896
FEV1%	81.10±5.87	82.21±6.67	.536	85.05±5.97	84.31±3.77	.674
FVC%	81.19±5.44	84.83±3.57	.012	88.63±4.49	88.46±3.79	.894
FEF25-75%	78.24±4.12	70.68±23.96	.106	83.89±6.34	83.65±6.20	.900

Table 4: Correlation of thyroid hormones with other measured variables

	TSH		T3		T4	
	r	P	r	P	r	P
E wave velocity	-.435	0.000	-0.111	0.420	-0.018	0.898
A wave velocity	.549	0.000	-0.305	0.030	-0.138	0.338
E/A ratio	-.242	0.018	-0.018	0.899	0.031	0.829
DT	.455	0.000	0.008	0.957	0.228	0.111
IVRT	.796	0.000	0.124	0.392	0.138	0.339
FEV1%	-.154	.137	-0.124	0.390	-0.0819	0.572
FVC%	-.360	0.000	-0.031	0.828	-0.0585	0.686
FEF25-75%	-.234	.023	-0.063	0.660	0.152	0.294

Table 5: Correlation between pulmonary function and left ventricular diastolic function indices

	E wave velocity		**A wave velocity**		**E/A ratio**		**DT**		**IVRT**	
	r	P	r	p	r	P	r	P	r	P
FEV%	.161	.119	-.112	0.240	.099	0.342	-.112	0.281	-.218	0.034
FVC%	.383	0.000	-.251	.014	.092	.374	-306	0.003	-.487	0.000
FEF25-75%	.172	0.096	-.189	.067	.089	.392	-.251	0.014	-.329	0.001

In the absence of primary respiratory disease, the diminution of the respiratory function in the hypothyroid patients is not significant in most cases. Nevertheless, it does affect the respiratory system including respiratory muscle weakness, alveolar hypoventilation due to decreased hypoxic and hypercapnic ventilatory drives, upper airway obstruction, central and obstructive sleep apnea and even pleural effusion. Lung volumes are usually normal or mildly reduced, but maximal breathing capacity and diffusing capacity are usually reduced.[27] Though there are many literatures regarding the effect of hypothyroidism on pulmonary function, few studies revealing the influence of subclinical hypothyroidism on pulmonary functions are found.[28]

In our study FEV1%, FVC%, FEF25-75% though still in the normal range they were significantly lower in group 1 with moderate negative correlation between FVC and TSH however no significant correlation between the measured pulmonary function parameters and left ventricular diastolic dysfunction parameters except FVC and IVRT where there was a moderate negative correlation. Sutar and Mishra[29] compared spirometry in 70 subjects with subclinical hypothyroidism and 35 control ones, they found abnormal spirometry in 26% (18 out of 70) patients had abnormal spirometry findings. The most common spirometric abnormality was mild restrictive pattern i.e. decreased FVC% and FEV1% and increased FEV1/FVC%. This coincides with a study conducted by Valjevac et al.[30] who suggested that the causes for reduced respiratory function are decreased inspiratory muscle strength, hypoventilation, hypercapnia and it is related to the degree and duration of the thyroid disorders in hypothyroidism. Another study conducted by Cakmak et al[31] found a significantly lower FVC, FEV1, FEF25-75% and diffusing capacity of lung for carbon monoxide (DLCO) in patients with subclinical hypothyroidism. FEF25 -75% is an average Forced Expiratory Flow rate over the middle 50% of the FVC and it is said to be more sensitive than FEV1 for detecting early airway obstruction.[32] Cakmak et al (2007)[31] reported a significant decrease in FEF25-75% in subclinical hypothyroidism patients, this was in accordance with our study results. In our study, FEF 25-75% was weakly correlated with thyroid hormones and cardiac diastolic dysfunction parameters. In Contrary, Sutar and Mishra,[29] Sharon et al,[33] didn't find a significant decrease in FEF 25-75% in patients of SCH. They explained their results by the assumption that this parameter reflects a slowing in terminal part of airways. So, in their study they presumed no small airway obstruction in subclinical hypothyroids.

6. Conclusion

Sub-clinical hypothyroidism patients are more prone to left ventricular diastolic dysfunction. So, they should be screened by doppler echocardiography for early diagnosis and management. Although the pulmonary function alterations in sub-clinical hypothyroidism are mild, they should not be ignored. Further studies are needed to decide whether these changes are enough to establish thyorxine replacement therapy.

7. Conflicts of interest

None

8. Acknowledgments

None

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