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LEFT VENTRICULAR DYSFUNCTION IN HYPOTHYROID PATIENTS

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ABSTRACT

Background: The heart is a very sensitive organ to thyroid hormones, any change in thyroid function can cause adverse cardiovascular effects. **Aim & Objective:** studying the effects of overt and subclinical hypothyroidism on left ventricle (LV) systolic & diastolic functions. **Material & Methods:** A total of 43 cases of recently diagnosed hypothyroidism patients (28 overt and 15 subclinical) with 43 age sex matched healthy control subjects were included in this study. Serum TSH, FT3, and FT4 hormones levels were measured and both those with hypothyroidism and healthy subjects underwent for 2D Echocardiography and the same was done for the controls. **Results:** Systolic function of LV in hypothyroid patients was mostly normal without any statistical significance when compared to with control group. Diastolic dysfunction was noticed in patients groups with both types of hypothyroidism. In overt hypothyroidism, there was a statistically significant increase in IVRT [98.92±12.5 ms] VS. [78.32±9.9 ms] in control group ($P<0.05$), and a statistically significant increase in E/e' ratio [9.55±3.6] VS. [5.87±1.2] in control group ($P<0.05$). In subclinical hypothyroid patients, there was a statistically significant increase in IVRT [92.33±11.3] VS. [78.33±10.9] in control group ($P<0.05$). We noticed a statistically significant increase in Myocardia performance Index(MPI) in both overt hypothyroid patients [0.47±0.04] VS. [0.39±0.04] in control group ($P<0.05$), and subclinical hypothyroid patients [0.45±0.03] VS. [0.38±0.03] in controls ($P<0.05$). **Conclusion:** In patients with hypothyroidism, in addition to compromised LV diastolic function, MPI was also increased which reflect both systolic and diastolic LV dysfunction.

KEYWORDS: Overt Hypothyroidism; Subclinical Hypothyroidism; Left Ventricular function; Doppler Echocardiography.

INTRODUCTION

The heart affects all other organs in human body and is affected by them at the same time. One of the most important organs that affects the heart is thyroid gland. The thyroid gland secretes triiodothyronine (T3) and thyroxin (T4). The production of thyroid hormones is regulated by thyroid stimulating hormone (TSH), which is released by the anterior pituitary gland. TSH is in turn regulated by thyrotropin-releasing hormone (TRH), produced by the hypothalamus.[1]

Hypothyroidism is a common disease. Iodine deficiency is the most common cause worldwide, whereas Hashimoto's autoimmune disease is the most common cause in the United States.[2] Hypothyroidism is classified into two types: Overt and subclinical hypothyroidism.

In overt hypothyroidism, thyroid hormones levels are decreased which cause a positive feedback effect causing an increase in TSH level, whereas in subclinical hypothyroidism, thyroid hormones levels are normal but TSH levels are increased.[3]

Subclinical hypothyroidism can be asymptomatic, but it is associated with disturbances in lipids metabolism and cardiovascular problems.[3]

Overt hypothyroidism is characterized by fatigue, loss of energy, decreased appetite, weight gain, cold intolerance, dry skin, edema, lethargy, constipation, mental impairment, and depression. Cardiovascular manifestations are important in this disease like bradycardia, pericardial effusion, systolic and diastolic dysfunction.[4]

Thyroid hormones and especially T3 affects the heart by attaching linked to thyroid hormone nuclear receptors TREs causing genomic and non-genomic effects on cardiac cells.[4] (Table1)

Table 1. Thyroid hormones effects on cardiac gene expression.

Positively Regulated	Negatively Regulated
α-Myosin heavy chain	β-Myosin heavy chain
Sarcoplasmic reticulum Ca^{2+} -ATPase	Phospholamban
β -Adrenergic receptors	Adenylyl cyclase catalytic subunits
Na^{+}/K^{+} -ATPase	Thyroid hormone receptor α1
Atrial natriuretic hormone	Na^{+}/Ca^{2+} exchanger
Voltage-gated potassium channels (Kv1.5, Kv4.2, Kv4.3)	

Since thyroid hormones are decreased in hypothyroidism, this will cause negative effects on the heart which are mentioned in (Table2). [5]

Table 2. Cardiovascular and hemodynamic effects of hypothyroidism.

Cardiovascular and Hemodynamic effects of Hypothyroidism
Narrow pulse pressure
Increased diastolic pressure
Bradycardia
Pericardial effusion
Decreased preload, stroke volume, blood volume, and cardiac output
Reduction in exercise tolerance
Prolongation of QT interval
Diastolic and systolic dysfunction
Increased peripheral vascular resistance
Increased collagen and GAG contents in the heart
Increased total cholesterol, LDL, CRP, and Homocysteine

AIM OF STUDY

This study aims to highlight the cardiovascular manifestations in hypothyroid patients of both types overt and subclinical.

MATERIAL AND METHODS

This case-control study was conducted at the Cardiology and Endocrinology outpatient clinics in Tishreen University Hospital, between January 2020 and April 2021, and included 43 patients(9 males and 34 females) with recently diagnosed overt and subclinical hypothyroidism, who were compared with 43 healthy participants (9 males and 34 females) as a control group. The two groups were matched in terms of age, gender, and cardiovascular risk factors. We excluded patients with ischemic heart diseases, rheumatic heart diseases, valvular heart diseases, endocarditis, diabetes mellitus, hypertension, chronic kidney disease, and pregnant patients. The two groups were scrutinized for Transthoracic echocardiography and systolic and diastolic functions of left ventricle and MPI measurements were performed. Bi-dimensional, pulsed Doppler, M-mode, and color flow Doppler echocardiographic examinations were performed. Using Siemens Acuson x300 premium ultrasound machine, the LV diastolic function was evaluated according to the recommendations of the American Society of Echocardiography 2016, the LV systolic function was evaluated using modified Simpson method, and Myocardial Performance index (MPI) which is a Compound index of LV systolic and diastolic functions.

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Statistical assessment of our study was performed by using IBM Statistical Package for Social Sciences (SPSS) for Windows, version 20, manufactured by IBM Corp., located in Armonk, N.Y., USA and summarized as frequencies and proportions. $P<0.05$ value was accepted to be statistically significant. The results were indicated in average ±SD and in percentage (%). One-way ANOVA was used for comparing groups. The independent-samples *t* test was used for comparing the 2 groups, and the *t* test was used for variables.

Definitions

Mitral E/A ratio: Mitral valve E velocity divided by A-wave velocity, it is used to identify the filling patterns:

normal, impaired relaxation (grade I), pseudonormal (grade II), and restrictive filling (grade III).

IVRT: Isovolumic relaxation time is the Time between aortic valve closure and MV opening. IVRT is=<70 ms in normal subjects and is prolonged in patients with impaired LV relaxation but normal LV filling pressures. When LAP increases, IVRT shortens and its duration is inversely related to LV filling pressures in patients with cardiac disease.

Mitral E/é: MV E velocity divided by mitral annular é velocity. é velocity can be used to correct for the effect of LV relaxation on mitral E velocity, and E/é ratio can be used to predict LV filling pressures.[6]

MPI: Myocardial performance index (MPI), or Tei index, is a Doppler echocardiographic parameter defined as the sum of the isovolumic contraction and relaxation times divided by the ejection time. It is considered a reliable parameter for global left ventricular function.[7]

Hormone measurements

In our hospital, Thyroid Stimulating Hormone (TSH), free thyroxin (FT4), free triiodothyronine (FT3) are assessed by Immuno Enzymometric Assay method using TOSOH AIA-360 Automated Immunoassay Analyzer. According to the kits used in our hospital, the ranges of 0.38-4.31 uIU/mL, 0.82-1.63 ng/dL, and 2.17-3.34 pg/mL were accepted as normal values in terms of TSH, FT4, and FT3 respectively for euthyroid state in our patients.

RESULTS

A total of 43 hypothyroid patients (28 overt hypothyroid patients + 15 subclinical hypothyroid patients) and 43 healthy controls were included into the study. Patients were divided into two groups to be studied: overt hypothyroidism **group A** (28 overt hypothyroid patients + 28 matched healthy controls), and subclinical hypothyroidism **group B** (15 subclinical hypothyroid patients +15 matched healthy controls).

The mean age of all patients was 43.4±6.4 years, and sex ratio (F:M) was 3.8:1.

The mean age and sex ratio of the controls groups were similar to those in patients groups.

The laboratory data of both overt hypothyroidism (Group A) we noticed statistically significant decrease in FT3 and FT4 levels and an increase in TSH levels in cases as compared to controls (Table 3), and in subclinical hypothyroidism (Group B) we noticed a statistically significant increase in TSH compared to controls without any significant changes in FT3 or FT4 levels compared to controls. (Table 4)

Table 3: Laboratory differences between overt hypothyroid patients and controls in our study.

Laboratory Data	Overt hypothyroidism (Group A)		p-value
	Cases	Controls	
FT3 (pg/mL)	1.42±0.4	2.82±0.3	0.0001
FT4 (ng/dL)	0.62±0.2	1.24±0.2	0.0001
TSH (uIU/mL)	18.68±7.1	3.19±1.1	0.0001

Table 4: Laboratory differences between subclinical hypothyroid patients and controls in our study.

Laboratory Data	Subclinical hypothyroidism (Group B)		p-value
	Cases	Controls	
FT3 (pg/mL)	**3.22±1.6**	**2.67±0.3**	**0.2**
FT4 (ng/dL)	**1.18±0.4**	**1.22±0.2**	**0.6**
TSH (uIU/mL)	**14.69±4.8**	**2.71±1.2**	**0.0001**

When we studied left ventricle systolic function of both groups, we noticed a decrease in ejection fraction (EF) in both group A (Table 5) and group B (Table 6) compared to their control groups but this decrease was not statistically significant.

Table 5: Left Ventricle systolic function differences between overt hypothyroid patients and controls in our study.

LV Systolic Function	Overt hypothyroidism (Group A)		p-value
	Cases	Controls	
LVEDV(mL)	102.75±10.9	107.14±8.7	0.1
LVESV(mL)	38.21±3.4	41.82±8.8	0.2
EF(%)	59.17±6.8	63.57±4.2	0.06

Table 6: Left Ventricle systolic function differences between subclinical hypothyroid patients and controls in our study.

LV Systolic Function	Subclinical hypothyroidism (Group B)		p-value
	Cases	Controls	
LVEDV(mL)	95.06±11.04	107.66±6.9	0.09
LVESV(mL)	34.40±2.6	38.86±2.9	0.8
EF(%)	63.40±3.5	64.06±1.7	0.2

When we studied left ventricle diastolic function in overt hypothyroid patients (Group A), we noticed statistically significant changes in LV diastolic function parameters changes in cases compared to their controls, we also noticed a statistically significant increase in Isovolumic relaxation time IVRT 98.92±12.5 ms as compared to their controls 78.32±9.9 ms (p-value=0.04), and a a statistically significant increase in E/e' ration in patients 9.55±3.6 compared to controls 5.87±1.2 (p-value=0.02), but we did not notice any statistically significance in E/A ration in cases compared to their controls.(Table 7)

In subclinical hypothyroid patients (Group B), we noticed a statistically significant increase in IVRT 92.33±11.3 ms in cases compared to controls 78.33±10.9 ms (p-value=0.001). (Table8)

Table 7: Left Ventricle diastolic function differences between overt hypothyroid patients and controls in our study.

LV Diastolic Function	Overt hypothyroidism (Group A)		p-value
	Cases	Controls	
E/A	1.16±0.5	1.30±0.2	0.1
IVRT (ms)	98.92±12.5	78.32±9.9	0.04
E/e´	9.55±3.6	5.87±1.2	0.02

Table 8: Left Ventricle diastolic function differences between subclinical hypothyroid patients and controls in our study.

LV Diastolic Function	Subclinical hypothyroidism (Group B)		p-value
	Cases	Controls	
E/A	**0.87±0.2**	**1.34±0.2**	**0.8**
IVRT (ms)	**92.33±11.3**	**78.33±10.9**	**0.001**
E/e´	**7.28±2.6**	**5.98±1.2**	**0.09**

After we studied Myocardia Performance Index (MPI) in both groups compared to controls, we noticed a statistically significant increase in MPI in overt hypothyroid patients (Group A) 0.47±0.04 vs. 0.39±0.04 in their controls (p-value=0.01), and in subclinical hypothyroid patients (Group B) 0.45±0.03 compared to controls 0.38±0.03 (p-value=0.03). (Table9)

Table 9: Myocardial Performance Index (MPI) differences between hypothyroid patients (overt and subclinical) and controls in our study.

MPI	Cases	Controls	p-value
Overt hypothyroidism (Group A)	0.47±0.04	0.39±0.04	0.01
Subclinical hypothyroidism (Group B)	0.45±0.03	0.38±0.03	0.03

DISCUSSION

Overt hypothyroidism causes left ventricular dysfunction. It causes diastolic dysfunction firstly, then systolic dysfunction will also be developed in a long-tem, non-treated hypothyroid state. Thyroid hormones deficiency and especially low levels of T3 low levels will cause LV dysfunction through multiple mechanisms. Thyroid hormones have effects on cardiac gene expression, and their decrease in overt hypothyroidism will cause increased expression of β-Myosin heavy chain (slow twitch) in cardiac muscle fibers, increased expression of phospholamban which inhibits sarcoplasmic reticulum Ca^{2+} -ATPase, and down regulation of β-adrenergic receptors in the heart and blood vessels.[4] Overt hypothyroidism causes endothelial dysfunction and decreased endothelial nitric oxide production. All of that will increase systemic vascular resistance SVR and decrease the arterial compliance, which in turn leads to an increase diastolic pressure and afterload. Together, this will cause a reduction in the cardiac output. Thyroid hormones also impact the renin-angiotensin-aldosterone system (RAAS) because T3 stimulates renin synthesis in liver. Normochromic, normocytic anemia is often found in hypothyroidism, because erythropoietin secretion is stimulated by T3. In addition, overt hypothyroidism results in decreased

expression of hepatic LDL receptors and reduced activity of cholesterol-α-monooxygenase, which breaks down cholesterol, resulting in decreased LDL clearance.[5]

A study which was done in 2009 on the heart of the rats after inducing experimental hypothyroidism, showed increased content of both GAG and collagen, regardless of the method of its induction. Structural integrity of the heart is determined by its connective tissue. Moreover, connective tissue binds the myocytes to capillaries, and helps to maintain the forward flow during systole. Excess accumulation of the collagen and glycosaminoglycans in the heart will cause a decrease in its compliance. Glycosaminoglycans (GAG) are heteropolysaccharides consisted of the disaccharide repeating sequences. Increased GAGs in interstitial spaces, will cause an increase in osmotic pressure, which in turn, will lead to water retention and cardiac muscle edema.[8]

Our results showed decreased left ventricle ejection fraction (LVEF) in overt hypothyroid patients (Group A) compared to controls, but these results were not statistically significant because most of our patients presented to the hospital in early stages of the disease, and a relatively longer period is needed for LV systolic dysfunction to be developed. At the same time, we noticed a significant increase in detecting LV diastolic dysfunction in those patients (Group A). We noticed a statistically significant increase in both IVRT and E/e' ratio in patients compared to their controls, but E/A ratio was decreased in patients because most of them had grade I diastolic dysfunction compared to normal values of E/A ratio in most of their healthy controls. Myocardia performance index (MPI) values which reflect both systolic and diastolic functions of left ventricle in patients (Group A) showed a statistically significant increased compared to controls., which reflects a global left ventricular dysfunction.

Left ventricular function was recently studied in subclinical hypothyroid patients. In our study, we evaluated both systolic and diastolic left ventricular function. We noticed a statistically significant increase in IVRT in subclinical hypothyroid patients (Group B) compared to their controls, and an increase in E/e' ratio but without a statistical significance. Evaluating E/A ratio showed decreased values in patients (Group B) as most of the patients had grade I diastolic dysfunction, but without any statistical significance. We did not notice any significant changes between subclinical hypothyroid patients (Group B) and their controls, regarding LV systolic function, but we noticed a significant increase in MPI in subclinical hypothyroid patients (Group B) compared to controls because it reflects both LV systolic function at the same time with its diastolic function which was abnormal in our patients especially when TSH values are severely increased (>10 uIU/mL) compared to their controls.

Subclinical hypothyroidism affects cardiovascular system through several mechanisms.

It causes endothelial dysfunction and decreased nitric oxide production. Functional TSH receptors were found in cardiomyocytes,[10] and as TSH levels are increased in subclinical hypothyroid patients, this will cause impaired LV diastolic dysfunction. High levels of TSH affect sarcoplasmic reticulum Ca^{2+} -ATPase activity and cellular calcium transport in cardiomyocytes. TSH inhibits SERCA2a activity and its expression by binding to TSH receptors in cardiomyocyte membranes and inhibiting the protein kinase A/phoshpolamban (PKA/ PLN) signaling pathway. SERCA2a is crucial for calcium cycle because its role in restoring cytosolic calcium concentrations during cardiac relaxation and contraction in cardiomyocytes.[11]

TSH receptors were also found in bone marrow cells and adipocytes, TSH increase will induce IL-6 and TNF-α secretion, suggesting a possible link between high levels of TSH and low-grade inflammation and oxidative stress[12]. All of previous mechanisms will cause LV dysfunction in non-treated subclinical hypothyroid patients with time.

CONCLUSION

In patients with both types of hypothyroidism, overt and subclinical, in addition to compromised left ventricular diastolic function, Myocardial Performance Index (MPI) was also abnormally increased, which reflects both systolic and diastolic left ventricular dysfunction compared to healthy subjects matched of in age, gender, and cardiovascular risk factors.

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