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THE INCIDENCE OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN PATIENTS AFFECTED WITH SUBCLINICAL HYPOTHYROIDISM.

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Abstract.

Background:

Numerous studies have identified the presence of adverse cardiovascular effects associated with hypothyroidism. The timely detection of individuals presenting with sub-clinical hypothyroidism has the potential to facilitate prompt intervention, consequently yielding a beneficial impact on cardiovascular morbidity and mortality rates.

Objectives: The primary aim of this study is to investigate the potential correlation between subclinical hypothyroidism and left ventricular dysfunction. Additionally, we aim to explore the relationship between systolic and diastolic dysfunction in patients with subclinical hypothyroidism.

Materials and Methods:

In this study, a total of 60 cases of subclinical hypothyroidism, as well as 30 age- and sex-matched healthy control subjects, were included. Serum levels of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) were assessed, and individuals exhibiting subclinical hypothyroidism were subsequently subjected to a two-dimensional echocardiogram (2DEcho).

Results:

A statistically significant decrease was observed in peak early filling velocity (PE) ($p<0.001$) and early filling time velocity integral (Ei) ($p<0.001$). The statistical analysis revealed a significant reduction in the ratio of early and late peak velocities (PE/PA) ($p<0.001$), the ratio of time velocity integral of early and atrial filling (Ei/Ai) ($p<0.001$), and the ratio of the early peak to average velocity (PE/M) ($p<0.001$). The mean ejection fraction (EF) for the hypothyroid patients was 54.88 5.54, which was slightly lower compared to the control subjects who had a mean EF of 55.66 3.45.

Conclusion:

In conclusion, the findings of this study indicate that sub-clinical hypothyroidism is associated with notable diastolic dysfunction, while systolic function remains largely unaffected.

Recommendation:

TSH and T4 need to be repeated at least once after 2-3 months. TPO antibodies which indicate an autoimmune etiology of hypothyroidism should be measured.

Keywords: Left ventricular diastolic dysfunction, Subclinical hypothyroidism, Cardiac dysfunction, Diastolic, Echocardiographic evaluation, Submitted: 2023-09-15, Accepted: 2023-09-20

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1. INTRODUCTION.

The cardiac manifestations observed in individuals with subclinical hypothyroidism primarily consist of systolic dysfunction [1]. The identification of adverse cardiovascular effects associated with hypothyroidism has been well-documented in numerous studies. The majority of the investigations have primarily concentrated on the assessment of systolic and diastolic dysfunction in individuals with hypothyroidism [2-6]. Subclinical hypothyroidism (SCH) is characterized by an elevation in serum thyroid stimulating hormone (TSH) levels that surpass the upper threshold of normal while maintaining normal levels of serum-free thyroxine. The prevailing etiology of this condition is commonly attributed to autoimmune thyroid disease [7]. Subclinical hypothyroidism (SCH) is a frequently encountered medical condition, exhibiting a prevalence ranging from 3% to 8% among individuals without a documented history of thyroid pathology. The prevalence of the condition increases proportionally with advancing age and exhibits a higher incidence among the female population. The presence of antithyroid antibodies has been observed in approximately 80% of patients diagnosed with subclinical hypothyroidism (SCH). In the context of subclinical hypothyroidism (SCH), it is observed that approximately 80% of patients exhibit a serum thyroid-stimulating hormone (TSH) level below 10 μIU/L [8]. Subclinical hypothyroidism (SCH) has the potential to advance into overt hypothyroidism, thereby giving rise to systemic manifestations of hypothyroidism. These manifestations include cardiac dysfunction, adverse effects on fetal development, neuromuscular impairments, psychiatric disturbances, cognitive dysfunction, elevation in serum total cholesterol levels, as well as increased levels of low-density lipoprotein cholesterol (LDL-C) [9]. The impact of SCH on the cardiovascular system has been evaluated through the examination of diastolic function, characterized by decelerated myocardial relaxation and compromised ventricular filling. The presence of this cardiac abnormality may potentially hurt the prognosis due to its association with isolated left ventricular diastolic dysfunction (LVDD), which is correlated with heightened morbidity and mortality rates in the overall population [10]. Diastolic dysfunction possesses crucial therapeutic implications and can aid physicians in formulating prompt intervention strategies [11]. The yearly probability of advancing to overt hypothyroidism is estimated to be around 5% in cases where subclinical hypothyroidism (SCH) is present alongside elevated levels of autoantibodies in the bloodstream. Subacute combined hyperhomocysteinemia (SCH) manifests with a clinical presentation that lacks specificity and is commonly confirmed through laboratory investigations [12]. The assessment of diastolic dysfunction can be accomplished through the utilization of pulsed-wave Doppler (PWD) for the measurement of mitral inflow velocities and tissue Doppler echocardiography (TDE) for the measurement of mitral annular velocities [13]. The timely detection of individuals presenting with sub-clinical hypothyroidism holds the potential to initiate prompt intervention, consequently yielding a beneficial impact on cardiovascular morbidity and mortality rates. The present study has been designed to investigate the impact of sub-clinical hypothyroidism on left ventricular diastolic functions.

1.1. Objectives.

- *To investigate the potential correlation between subclinical hypothyroidism and left ventricular dysfunction.*
- *To investigate the correlation between systolic and diastolic function in the selected patient population.*

2. MATERIALS AND METHODS.

The study was carried out within the Non-invasive cardiology laboratory situated at IGIMS, Patna. The study encompassed a total of 60 cases of subclinical hypothyroidism, accompanied by 30 age- and sex-matched healthy control subjects. The study exclusively encompassed

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cases in which the diagnosis of subclinical hypothyroidism was established using standard criteria. Exclusion criteria encompassed various conditions that have been associated with left ventricular dysfunction, including but not limited to advanced age (greater than 70 years), elevated heart rate (above 100 beats per minute), conditions leading to left ventricular hypertrophy, conditions resulting in myocardial stiffness such as hemochromatosis, amyloidosis, alcoholism, diabetes mellitus, sarcoidosis, and other infiltrative diseases. Additionally, individuals with overt hypothyroidism and the presence of any chronic medical or surgical condition that may independently detrimentally impact left ventricular function were also excluded from the study. Serum levels of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) were assessed, and individuals exhibiting subclinical hypothyroidism were subsequently subjected to a two-dimensional echocardiogram (2DEcho). Informed consent was obtained from all patients before they participated in the study.

3. RESULTS.

The average age of patients was 46.9 ± 6.92 years, whereas, for the control group, it was 47.4 ± 5.96 years. In a cohort of 60 cases, the proportion of female patients was 76.66%, while the proportion of male patients was 23.33%. Out of the total sample size of 54 cases, representing 90% of the population, the majority exhibited no clinical manifestations indicative of hypothyroidism. However, a small subset of 2 cases (3.3%) presented with a dull expression, while another 2 cases displayed sparse hair. Additionally, 6 cases (10%) were found to be associated with prolonged relaxation of the Achilles tendon reflex. No electrocardiographic abnormalities were observed in any of the patients (Table 1).

In the present study, a total of 52 individuals (86.66%) exhibited no evidence of dyslipidemia, while 8 cases (13.3%) demonstrated an association with elevated levels of total cholesterol. Additionally, 4 cases (6.6%) were found to be associated with increased levels of triglycerides, as depicted in Table 1.

The Doppler evaluation reveals a substantial decrease in the peak early filling velocity (PE) ($p<0.001$) and early filling time velocity integral (Ei) ($p<0.001$), indicating a significant impairment in cardiac diastolic function. The ratio of early and late peak velocities (PE/PA) demonstrated a statistically significant decrease ($p<0.001$). Similarly, the ratio of time velocity integral of the early and atrial filling (Ei/Ai) exhibited a significant reduction ($p<0.001$). Additionally, the ratio of the early peak to average velocity (PE/M) was found to be significantly decreased ($p<0.001$). The mean ejection fraction (EF) of the hypothyroid patients was 54.8 ± 5.54, which was compared to the EF of the control subjects, which was 55.6 ± 3.45. The difference between the two groups was not statistically significant, with a T value of 0.48. However, there was a significant presence of diastolic dysfunction in the hypothyroid patients, as indicated by the mean Ei/Ai ratio of 1.34±0.52. In comparison, the control group subjects had a mean Ei/Ai ratio of 2.12 ± 0.47. The difference between the two groups in terms of the Ei/Ai ratio was highly statistically significant, with a T value of 5.22 (Table 2).

4. DISCUSSION.

Conflicting evidence exists concerning the phenomenon of subclinical hypothyroidism. According to the research conducted by Cappola et al., as published in a study, it has been determined that subclinical hypothyroidism, when left undetected, does not pose a risk factor for cardiovascular health [14]. The study on cardiovascular health revealed no discernible elevation in cardiovascular risk among individuals with thyroid-stimulating hormone (TSH) levels below 10.0 milliunits per liter (mU/l) [15]. In a separate investigation, Rodondi et al. postulated that patients exhibiting a thyroid-stimulating hormone (TSH) level exceeding 7 mIU/L may potentially face an elevated susceptibility to heart failure. However, no other notable cardiovascular incidents were observed in this cohort [16]. Based on the

Table 1: **Study population characteristics**

	Controls	**Patients**
Mean age* (± SD) Years	47.4 ± 5.96	46.9 ± 6.92
Sex		
Male	10 (33.33)	14 (23.33)
Female	20 (66.66)	46 (76.66)
Signs/Symptoms		
Constipation	-	6 (10)
Lethargy	-	6 (10)
Menstrual disorder	-	6 (10)
Increase in weight	-	6 (10)
Prolonged relaxation of deep tolerance reflex	-	6 (10)
Decreased appetite	-	4 (6.66)
Sparse hair	-	2 (3.33)
Dull expressionless face	-	2 (3.33)
Cold intolerance	-	2 (3.33)
Lipid proftle		
HDL cholesterol (<66 mg%)	-	0 (0.0)
LDL cholesterol (>155 mg%)	-	0 (0.0)
Total cholesterol (>250 mg%)	-	8 (13.3)
Triglyceride (>180 mg%)	-	4 (6.6)
Within normal limit	30 (100)	52 (86.66)

data that has been reviewed, it is recommended to refrain from implementing routine treatment for subclinical hypothyroid disease in cases where the thyroid-stimulating hormone (TSH) level falls within the range of 4.5–10.0 mIU/L [12]. In contrast, Biondi et al. discovered an association between subclinical hypothyroidism and left ventricular systolic and diastolic dysfunction, as well as an increased risk for atherosclerosis and myocardial infarction. This association is based on the observation that the heart exhibits a response to minimal, yet persistent alterations in thyroid hormone levels, which are characteristic of subclinical hypothyroidism [17]. There is also compelling evidence about the heightened arterial stiffness observed in this pathological condition [18]. Several studies have provided evidence of diastolic dysfunction in individuals with subclinical hypothyroidism. These findings have led researchers to suggest that treatment with levothyroxine may potentially alleviate this diastolic dysfunction over a certain duration of time [19-21].

A research study has revealed the presence of notable diastolic dysfunction in the left ventricle among patients diagnosed with subclinical hypothyroidism, while the systolic function remains unaltered. A notable augmentation in mitral peak A velocity, diminished E/A ratio, and elongation of isovolumic relaxation time (IVRT) were observed in the Doppler echocardiography findings. The mitral peak E velocity remains unchanged. Subclinical hypothyroidism exhibits a notably elevated Tei index in comparison to individuals with normal thyroid function. The present observations bear resemblance to the aforementioned findings reported by Biondi et al., albeit without the inclusion of Tei index measurements [22]. The present study provides additional evidence that aligns with the findings of Kosar et al., indicating a notable decrease in the E/A ratio and elongation of the isovolumic relaxation time (IVRT) in both the left and right ventricles. However, it is important to note that this study did not encompass an assessment of right ventricular dysfunc-

Table 2: **Comparative analysis was conducted to assess the left ventricular diastolic and systolic function in two distinct groups: control subjects and sub-clinical hypothyroid patients**

	Indices of LV function	**Patient**	**Control**	**t**	**P**
		(mean ± SD)	(mean ± SD)		
LV Systolic function					
1	EF	54.8 ± 5.54	55.6 ± 3.45	-0.48	
LV Diastolic function	**Indices of LV function**	**Patient**	**Control**	**t**	**P**
1	PE	0.51 ± 0.11	0.65 ± 0.07	-4.55	<0.001
2	PA	0.53 ± 0.11	0.52 ± 0.08	-0.05	
3	M	0.33 ± 0.09	0.30 ± 0.06	0.32	
4	Ei	4.21 ± 0.79	7.53 ± 1.61	-6.19	<0.001
5	Ai	3.50 ± 1.48	3.60 ± 0.77	-0.29	
6	Ti	9.78 ± 2.36	13.16 ± 2.91	-3.15	<0.01
7	%AC	35.54 ± 10.26	27.58 ± 2.84	3.23	<0.01
8	1/3FF	38.23 ± 6.67	47.02 ± 4.18	-4.41	<0.001
9	P%T	0.09 ± 0.04	0.12 ± 0.02	-2.78	<0.01
10	Time E	0.09 ± 0.02	0.11 ± 0.03	-3.04	<0.01
11	PE/PA	0.98 ± 0.23	1.28 ± 0.15	-3.87	<0.001
12	PE/M	1.64 ± 0.40	2.28 ± 0.36	-4.29	<0.001
	Ei/Ai	1.34 ± 0.52	2.12 ± 0.27	-5.22	<0.001

tion [23]. The incidence of cardiovascular disease (CVD) has been documented to be lower in the female population compared to males before the onset of menopause. This disparity is believed to be associated with a diminished accumulation of abdominal adipose tissue in women [24]. The mean body mass index (BMI) observed in this study was slightly elevated, approaching the upper threshold of the normal range, consistent with findings reported in previous studies [10, 25, 26]. A notable correlation has been observed between body mass index (BMI) and subclinical hypothyroidism (SCH) [27]. SCH, also known as subclinical hypothyroidism, is a thoroughly characterized medical condition exhibiting a comprehensive array of clinical manifestations and symptoms [28].

The presence of diastolic dysfunction has been associated with a higher prevalence of diabetes, hypertension, and dyslipidemia in patients [29]. In the presence of abnormal myocardial relaxation, there is an observed increase in the ratio of mitral annular motion during atrial systole to total diastolic annular motion [30]. The precise characterization of the impact of modified diastolic function in individuals with compromised systolic function remains to be definitively established, albeit its potential significance cannot be understated. Primary diastolic dysfunction, in the absence of systolic dysfunction, represents a significant and progressively acknowledged medical condition.

5. CONCLUSION.

In this study, it was observed that sub-clinical hypothyroidism exhibited notable diastolic dysfunction while not significantly affecting systolic function, as evidenced by the measurement of Ejection Fraction.

6. LIMITATIONS.

The limitations of this study include a small sample population who were included in this study. The findings of this study cannot be generalized for a larger sample population. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

7. RECOMMENDATION.

TSH and T4 need to be repeated at least once after 2-3 months. TPO antibodies which indicate an autoimmune etiology of hypothyroidism should be measured.

8. ACKNOWLEDGEMENT.

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9. LIST OF ABBREVIATIONS.

TSH- thyroid-stimulating hormone
T4- thyroxine
T3- triiodothyronine
2DEcho- two-dimensional echocardiogram
PE- peak early
EF- ejection fraction
TPO- Thyroid peroxidase
SCH- Subclinical hypothyroidism
LDL- low-density lipoprotein cholesterol
LVDD-left ventricular diastolic dysfunction
PWD- pulsed-wave Doppler
TDE- tissue Doppler echocardiography
HDL- high-density lipoprotein
IVRT- isovolumic relaxation time
BMI- Body mass index

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11. Conflict of interest.

The authors report no conflicts of interest in this work.

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