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Research Article

CARDIOVASCULAR PROFILE IN PATIENTS OF SUBCLINICAL HYPOTHYROIDISM: A CROSS-SECTIONAL STUDY AMONG HOSPITAL ATTENDEES IN WESTERN ODISHA

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A R T I C L E I N F O

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A B S T R A C T

Background: Subclinical hypothyroidism (SCH) has a prevalence of 4-20%. Although overt hypothyroidism is linked to cardiovascular dysfunctions, there are mixed results when it comes to degree of abnormalities in subclinical hypothyroidism. Since the management remains controversial it would be appropriate to study the cardiovascular abnormalities to initiate timely treatment of patients with mild thyroid failure to prevent cardiac involvement also progression to overt hypothyroidism. The aim of the current study was to assess the cardiovascular abnormalities in subclinical hypothyroidism and evaluate the association between thyroid-stimulating hormone (TSH) and cardiovascular effects among mild and severe subclinical hypothyroidism patients.

Materials and Methods: The observational study was conducted in VIMSAR, Burla, among 210 hospital attendees who were diagnosed with subclinical hypothyroidism selected by consecutive sampling. Cardiovascular profile of these patients were assessed by clinical examination, ECG, lipid profile, hs-CRP, 2D and tissue Doppler echocardiography and compared between mild (TSH<10) and severe (TSH>10) subclinical hypothyroidism using Chi-square and student T-tests.

Results: Doppler-derived indices of left ventricular (LV) diastolic filling showed diastolic dysfunction, as indicated by significant prolongation of the isovolumic relaxation time and significant reduction of the early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A) ratio. The findings are more significant in patients with TSH>10 ($p<0.001$). The correlation between TSH and LDL, hs-CRP and anti-TPO antibody was also significant.

Conclusion: Subclinical hypothyroidism is a common condition and affects diastolic function. Although the decision to treat with levothyroxine (LT4) remains controversial, this abnormality may be reversed by levothyroxine substitutive therapy.

INTRODUCTION

Cardiovascular system is considered as one of the primary targets for the action of thyroid hormone. Subclinical hypothyroidism (SCH) holds clinical importance because of its high prevalence, future risk of progression to clinical hypothyroidism and its association with increased risk of cardiovascular diseases. Altered thyroid function can causes remarkable changes in parameters of cardiovascular function such as heart rate, left ventricular (LV) systolic and diastolic function, blood volume, arterial pressure, cardiac output, and systemic vascular resistance[1,2] .

Patients with treated overt thyroid failure often end up having subclinical hypothyroidism[3-5] because of inadequate thyroid hormone supplementation, poor adherence, drug interactions, or inadequate monitoring of treatment[6]. The clinical presentation of SCH is nonspecific, and the symptoms are usually subtle, as compared to those of overt hypothyroidism, probably in relation to the intensity and the duration of thyroid hormone deficiency and the age of the patients[6]. Quality of life, anxiety, symptoms of depression, cognitive function, and memory can be altered in patients with subclinical hypothyroidism. Cardiovascular changes of arterial compliance, diastolic blood pressure, endothelial dysfunction, and dyslipidemia that are noted with overt hypothyroidism can also occur in subclinical hypothyroidism, but are less frequently studied than those of overt hypothyroidism[6].

Considering the high prevalence of SCH and preventive aspect of cardiac consequences of altered thyroid status, the present study investigated whether SCH caused cardiovascular abnormalities which were assessed using non-invasive methods.

MATERIAL AND METHODS

The current study was a hospital based cross-sectional, observational study conducted over a period of two years from November 2019 to 2021 at the post-graduate Department of

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General Medicine, Veer Surendra Sai institute of medical sciences and research (VIMSAR), Burla, Odisha. The study aimed at evaluating the effects of subclinical hypothyroidism on cardiovascular system. The primary objective was to evaluate the association between thyroid-stimulating hormone (TSH) and cardiovascular effects and the secondary objective was to assess the prevalence of anti-thyroid antibody (anti-TPO) among patients with mild and severe subclinical hypothyroidism. Ethical clearance was obtained from the Institutional Ethics Committee of VIMSAR, Burla prior to the start of the study. Written informed consent was taken from all the participants before enrolling them into the study and strict confidentiality over relevant patient information was maintained throughout the study. The study was executed in accordance with the principles of ICH-GCP and Declaration of Helsinki.

Patients diagnosed with subclinical hypothyroidism visiting the outpatient department of General Medicine comprised the study population. Patients aged 20-70 years of either gender diagnosed with mild (TSH=4.5-9.9mIU/L) or severe (TSH=≥10 mIU/L) subclinical hypothyroidism[1] with stable TSH and thyroid hormone levels for at least 6 months were included in the study. Those on thyroid replacement therapy prior to 3 months of study or with overt hypothyroidism, chronic kidney disease, type-2 diabetes mellitus, hypertension, obesity, cardiovascular diseases and pregnant women were excluded from the study. Non-probability convenience sampling method was used to recruit the patients. The sample size was calculated using the formula: $n=[DEFF*Np(1-p)/ [(d^2 /z^2_{1-\alpha/2} *(N-1) + p(1-p)]$. Considering a prevalence (p) of cardiovascular abnormality in subclinical hypothyroidism as 20%[2,6-7] and precision (α) of 5% for a confidence interval of 95%, the sample size was calculated to be 210. A detailed medical history was taken, physical examination and routine blood investigation done for all the study participants. The cardiovascular parameters were obtained using electrocardiography (ECG) and 2D-echocardiography.

The data were entered into Microsoft Excel and analyzed using SPSS v2.1 software. Quantitative variables are expressed as mean±standard deviations (SD). Chi-square test and student T-test were applied as appropriate to compare the categorical data. Results were considered significant at p-value less than 0.05.

Observations

A total of 210 patients diagnosed with subclinical hypothyroidism were studied. Among them, 40 (19%) had severe subclinical hypothyroidism (TSH: ≥10 m IU/L) and 170 (81%) had mild subclinical hypothyroidism (TSH: 4.5-9.9mIU/L). The TSH levels ranged from 5.6-46 mIU, with an average value being 9.1±5.8 mIU. Majority of the patients or 33.3% were aged between 20 to30 years (Table 1). There is a significant relation between age and TSH (p=0.001) i.e. the increase in TSH levels was directly proportional to the age. The incidence of hypothyroidism was significantly higher in females (p=0.005). In men, there was a significant relationship between body surface area and TSH in men (p=0.019).

Table 1 Demographic variables. *p value was calculated by Chi-square test, p<0.05 considered as statistically significant. [BSA=Body surface area]

	TSH group		
	Mildly elevated (n=170)	**Severely elevated (n=40)**	**p-value***
Age distribution			
20-30	67(39.4%)	3(7.5%)	
30-40	38(22.4%)	5(12.5%)	
40-50	40(23.5%)	10(25.0%)	0.001
50-60	15(11.8%)	21(40.0%)	
>60	4(2.9%)	7(15.0%)	
Gender distribution			0.005
Male	18(10.6%)	11(27.5%)	
Female	152(89.4%)	29(72.5%)	
BSA Men (m^2)			
<1.9	18(100%)	8(72.7%)	0.019
>1.9	0	3(27.3%)	
BSA Women (m^2)			
<1.6	49(32.2%)	9(31.0%)	0.899
>1.6	103(67.8%)	20(69.0%)	

There was no significant relation of TSH with blood pressure, heart rate, haemoglobin, serum urea, creatinine, RBS or ESR (Table 2). However, there was a significant association of TSH with total cholesterol (p=0.001), serum triglycerides (p=0.001), VLDL (p=0.001) and LDL (p=0.001). As the TSH level increases, there was an increase in total cholesterol, triglycerides, VLDL, and LDL.

Table 2 Clinical and laboratory variables. *p value was calculated by independent Student-T test, p<0.05 considered as statistically significant. [ESR=erythrocyte sedimentation rate, VLDL=very low density lipoprotein, LDL= low density lipoprotein, HDL=high density lipoprotein]

	TSH group		
	Mildly elevated (n=170)	**Severely elevated (n=40)**	**p-value***
Heart rate	74.43±7.413	76.05±4.761	0.189
Systolic blood pressure	119.16±14.717	116.10±14.884	0.238
Diastolic blood pressure	73.38±9.219	73.50±6.320	0.936
Hemoglobin	11.034±1.993	11.470±1.607	0.199
Urea	20.76±6.264	20.53±6.148	0.831
Creatinine	0.888±0.235	0.977±0.31	0.044
Random blood sugar	89.91±15.190	93.23±22.143	0.260
ESR	19.92±11.84	18.00±14.152	0.394
Total cholesterol	169.81±45.905	234.73±29.526	0.001
Triglyceride	153.79±39.482	223.38±32.155	0.001
VLDL	24.829±7.679	32.250±11.022	0.001
LDL	120.43±29.811	162.25±42.292	0.001
HDL	37.66±10.093	35.25±9.586	0.171

A reduction in the ejection fraction was noted (within the normal range for the age) in both the groups of study participants (Table 3). There was a significant relation of reduction of EF with rise in TSH (p=0.001). There was a significant reduction of E (p=0.001) and increase of A (p=0.092) with the rise of TSH levels. The resulting decrease in the E/A ratio, and increase in isovolumetric relaxation time describe the impaired diastolic filling resulting in diastolic dysfunction (Table 3).

Table 3 ECHO variables. *Independent Student-T test, #Chi-square test, p<0.05 considered as statistically significant. [LVESD=left ventricular end systolic diameter, IVST= interventricular septal thickness, PWT=posterior wall

thickness, EF=ejection fraction, FS=fractional shortening, PAFV=peak aortic flow velocity, E=e wave, A=a wave, IRT= isovolumic relaxation time]

	TSH group		
	Mildly elevated (n=170)	**Severely elevated (n=40)**	**p-value***
Systolic 2D variables			
LVESD	27.70±5.514	27.53±7.204	0.865
IVST	10.49±5.024	10.25±1.354	0.761
PWT	9.19±2.076	10.18±2.707	0.012
EF	64.60±7.346	55.15±7.238	0.001
FS	7.238±4.407	40.65±3.085	0.015
PAFV	8.25±1.494	10.50±1.177	0.021
Diastolic 2D variables			
E	0.724±0.212	0.521±0.044	0.001
A	0.757±0.137	0.795±0.083	0.092
E/A	0.971±0.314	0.655±0.057	0.001
IRT	91.69±14.899	115.82±10.735	0.001
ECHO Variables			**p-value#**
E/A			
<1	76(44.7%)	0(0.0%)	0.001
>1	94(55.3%)	40(100%)	
IRT			
<70	45(26.5%)	0(0.0%)	0.001
>70	125(73.5%)	40(100%)	

There was a positive association of CRP with TSH, which was significant (p=0.001). As the TSH level increased, there was an increase in the CRP level as well. The findings of this study show that subclinical hypothyroidism is a pro-inflammatory state (Table 4). Also, there is a statistically significant association between diastolic dysfunction and CRP (p=0.001). As the CRP levels increased there was higher chances of diastolic dysfunction (reduction in E/A ratio) among the study participants.

Table 4 Correlation between CRP levels and other parameters. *p value was calculated by Chi-square test, p<0.05 considered as statistically significant. [CRP=C-reactive protein]

		CRP levels		
	Types	**<10**	**>10**	**p-value***
TSH group	Mildly elevated	119(70.0%)	51(30.0%)	0.001
	Severely elevated	4(10.0%)	36(90.0%)	
Diastolic dysfunction	E>A	63(82.9%)	13(17.1%)	0.001
	A>E	60(44.8%)	74(55.2%)	

Prevalence of anti-thyroid peroxidase antibody (anti-TPO) in our study is 25.7%. Out of 210 patients, 54 were positive for anti-TPO. There was a statistically significant association between anti-TPO and TSH levels (p=0.001) which suggested that subclinical hypothyroidism patients with anti-TPO antibodies have raised TSH levels (Table 5 and Figure 1).

Table 5 Anti-TPO antibody. *p value was calculated by chi square test, p<0.05 considered as statistically significant.

Anti-TPO	**TSH group**		**Total**
	Mildly elevated	Severely elevated	
Positive	18(10.6%)	36(90.0%)	54(25.7%)
Negative	152(89.4%)	4(10.0%)	156(74.3%)
Total	170(100%)	40(100%)	210(100%)
Chi square test; p value:0.001			

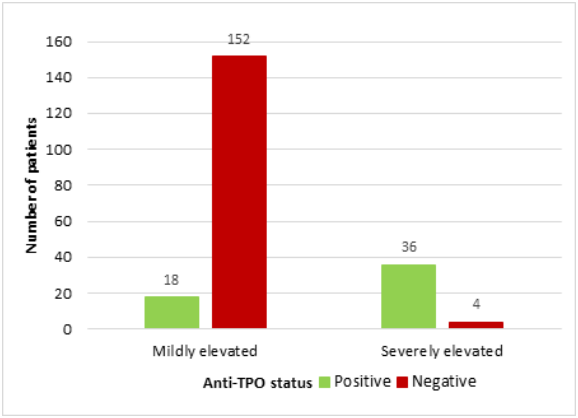

Figure 1 Distribution of anti-TPO antibody among mild and severe subclinical hypothyroidism (p=0.001)

DISCUSSION

The results of the present study demonstrated abnormal diastolic function which is quantified by E/A ratio and IRT. We found that there was a significant reduction in E/A ratio, increase in IRT suggestive of slowed relaxation time, which had a significant relation with TSH. There was no significant reduction in the systolic parameters except ejection fraction in severely elevated TSH patients. There was a significant increase in total cholesterol, triglycerides, LDL and VLDL with rise in TSH levels. CRP levels were directly related to TSH levels and inversely related to the diastolic function. All patients with severe subclinical hypothyroidism had anti-TPO positivity.

Two large population-based screening studies have provided important epidemiological data about subclinical hypothyroidism (SCH): the Whickham Survey[8], and NHANES III[9]. A third important large study-the Colorado Thyroid Prevalence Study[6], was not truly population based. In the Whickham Survey [2779 subjects], SCH, defined by serum TSH levels above 6 mIU/litre, was identified in 7.5% of females and 2.8% of males[8]. In our study females (86%) and young population (58%) were the most affected. Subclinical hypothyroidism seems to be less symptomatic in elderly people[10-13]. In two large cross-sectional community-based studies, subclinical hypothyroidism was not associated with cognitive dysfunction, anxiety, or depression in patients aged 65 years or older. In our study, SCH was also most prevalent in the younger age group between 20 to 30 years.

In the present study, we performed a strict selection of patients with stable SCH, excluding patients with confounding factors particularly affecting the cardiovascular system. The impaired diastolic function in this group of patients suggests that SCH is a condition of minimal tissue hypothyroidism rather than a compensated state. Such patients should be considered as potential candidates for therapy with levothyroxine (LT4)[14]. Several factors could likely contribute to arterial stiffness and endothelial dysfunction which ultimately results in diastolic dysfunction in subclinical hypothyroidism, including hyperlipidaemia and a pro-inflammatory state[15-17]. In the Rotterdam Study, aortic calcification and the prevalence of myocardial infarction was higher in patients with subclinical hypothyroidism who were positive for thyroid autoantibodies than in those with Subclinical hypothyroidism alone[18]. Both hyperlipidaemia and thyroid antibodies are thought to reduce expression of endothelial nitric oxide synthase, thereby

impairing vasodilation[19]. Similar to our study, Recently, Christ-Crain *et al*.[20] found that C-reactive protein was significantly increased in women with SH compared with euthyroid control individuals.

In the cross-sectional Rotterdam survey[21] a greater percentage of women with SH, defined as TSH levels >4.0 mU/L, had aortic atherosclerosis and a history of myocardial infarction, compared with euthyroid women [approximately 70% vs 56% and 15% vs 7%, respectively]. If properly monitored to maintain a normal serum TSH level, LT4 therapy is almost certainly safe[22]. It would be reasonable to recommend LT4 for those patients with SCH, especially women who are at increased risk of developing overt thyroid failure, those with anti-thyroid antibodies and/or serum TSH levels >6mU/L and/or a history of radioiodine ablation for Graves' disease and/or a history of external radiation therapy for non-thyroidal malignancies and/or on chronic lithium treatment] and/or; an increased risk of cardiovascular events i.e. those with clinically relevant hypercholesterolemia and/or hypertension and/or a habit tobacco use and/or diabetes and/or a cardiac defect with mainly diastolic dysfunction.

Subclinical hyperthyroidism is associated with mild LV hypertrophy (LVH), whose well-known deleterious consequences on diastolic function [31] may prevail over the enhanced relaxation induced by excess thyroid hormone [23]. On the other hand, SCH may impair diastolic function directly by reducing sarcoplasmic calcium ATPase activity, with consequent impairment of ventricular diastolic function[24]. Among the indices of systolic function, only mean aortic acceleration was significantly reduced in the group of patients with SCH in various studies in contrast to ours where we got reduced ejection fraction. Therefore, this index seems to be the most susceptible to variations in thyroid hormone levels. Furthermore, in the groups of patients with Subclinical Hypothyroidism treated with replacement LT4 therapy, SVR was significantly reduced, which confirms a direct vasodilation effect of thyroid hormone[25].

Evidence of early mild thyroid failure is a relatively common finding in women with subfertility, although it is rarely an explanation for being unable to conceive. Meta-analyses of observational data indicate that pregnant women with subclinical hypothyroidism have an increased risk of adverse pregnancy outcome[26]. Subclinical hypothyroidism increases the odds of pregnancy complications, including preeclampsia, placental abruption, preterm birth and neonatal mortality[27]. While there is evidence to suggest that subclinical hypothyroidism in early pregnancy may also be associated with impaired intellectual and psychomotor development[27-30] and that this impairment may be prevented with levothyroxine treatment, this is not supported by a recent randomized control trial[31]. Doppler-echocardiography represents a simple and reliable method for the evaluation of morphology and function in patients with SCH. An additional advantage is its easy repeatability and, therefore, it could be used to serially evaluate the adequacy and efficacy of LT4 dose. To support this concept, Biondi *et al* demonstrated in the subgroup of patients treated with substitutive doses of LT4, the ECHO-Doppler evaluation performed after 6 months demonstrated an improvement of cardiac function.

Based on the data available, it appears that low dose LT4 replacement with periodic evaluation of TSH should be considered in patients with mild hypothyroidism in presence of associated cardiovascular risk factors in the attempt to reverse these negative prognostic factors and improve the cardiovascular outcomes. Furthermore, larger randomized trials are necessary to evaluate the potential benefit of LT4 therapy.

CONCLUSION

To conclude, this study strongly supports the concept that subclinical hypothyroidism is a mild form of thyroid failure, associated with initial signs of cardiovascular hypothyroidism. Subclinical hypothyroidism is associated with altered lipid profile and diastolic dysfunction contributing to cardiovascular morbidity and mortality. Hence, timely levothyroxine replacement therapy could help to prevent cardiovascular hemodynamic involvement or the progression of atherosclerosis in these patients.

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