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Subclinical Hypothyroidism and the Effect of Autoimmunity on the Echocardiography Indices of Left Ventricular Function, Lipid Profile, and Inflammatory Markers

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ABSTRACT

Background: Subclinical hypothyroidism (Sch) is the most frequent thyroid disease. The relationship between overt hypothyroidism and cardiovascular diseases has been well documented, but conflicting data have remained regarding Sch.

Objectives: The present study aimed to assess the effect of Sch on increasing the risk of cardiovascular involvement considering the autoimmune subset.

Patients and Methods: This case-control study was conducted on thirty patients with Sch and 30 healthy controls. Serum levels of thyroperoxidase antibody (TPOab), lipids, hsCRP, homocysteine, and ferritin were measured. Besides, conventional echocardiographic study and tissue Doppler imaging (including strain rate indices) was done to evaluate Left Ventricular (LV) systolic function.

Results: The results showed a significant difference between the Sch patients and the controls regarding the serum level of triglyceride (117.43 ± 63.51 mg/dL vs. 86.86 ± 41.57, P = 0.031), echocardiographic parameters (longitudinal systolic strain rate [SRs: -1.006 ± 0.4 vs. -1.26 ± 0.16, P = 0.002; SRl: -1.43 ± 0.27 vs. -1.68 ± 0.29, P = 0.001]), and Sm of septal mitral annulus (6.90 ± 0.6 vs. 7.43 ± 0.8, P = 0.006)]. However, no significant difference was observed between the two groups regarding the serum levels of the inflammatory markers. Moreover, a significant correlation was found between TSH and Sm (r = -0.36, P = 0.005) and longitudinal systolic strain rate (SRs: r = 0.42, P < 0.001; SRl: r = 0.40, P = 0.001). Systolic strain rate was significantly lower in the TPOab positive patients (-0.99 ± 0.18 vs. -1.15 ± 0.25, P = 0.047).

Conclusions: The clear association between Sch and subclinical LV systolic dysfunction which was more evident in the subgroup of patients with circulating anti-thyroid antibodies would remind a greater emphasis for considering the subgroup of TPOab positive patients for directing toward hormone replacement.

►*Implication for health policy/practice/research/medical education:*
Uncertainty still remains in treatment of Sch patients. A clear association was found between Sch and subclinical LV systolic dysfunction, which was more evident in the subgroup of patients with circulating anti-thyroid antibodies. This would put greater emphasis on consideration of the subgroup of TPOab positive patients for directing toward hormone replacement.

1. Background

Subclinical hypothyroidism (Sch) is the most frequent thyroid disease (1), affecting 4 - 20% of the general population. The cardiovascular system is a major target of the thyroid hormone (2). This hormone can also indirectly affect the cardiovascular system via atherogenic changes found in thyroid disorders. The relationship between overt hypothyroidism and the risk of cardiovascular diseases has been well documented (3, 4). Diastolic hypertension due to increased Systemic Vascular Resistance (SVR), increased arterial stiffness, endothelial dysfunction, altered coagulability, and increased levels of C-Reactive

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Protein (CRP) may further contribute to the increased cardiovascular risk associated with overt hypothyroidism (2). However, controversy still remains on the relationship between Sch and increased risk of cardiovascular diseases. The same controversy surrounds thyroid autoimmunity.

2. Objectives

Considering these conflicting data, the present study aims to assess the correlation between autoimmune Sch and serum markers of inflammation and echocardiographic indices of Left Ventricular (LV) function.

3. Patients and Methods

This case-control study was performed on thirty consecutive patients with Sch and thirty healthy controls from 2012 to 2013. The exclusion criteria of the study were having a history of diabetes mellitus, cardiovascular diseases, and smoking, Body Mass Index (BMI) ≥ 30 kg/m^2, ischemic electrocardiographic changes, and thyroid test abnormalities previously treated with thyroxin. Sch was defined as an elevated serum level of thyrotropin (4.5 < TSH < 10 mu/L) and normal free T4 (FT4). TSH was repeated after at least one month to confirm the diagnosis. Thyroid examination was also performed. Besides, a questionnaire regarding the symptoms (dyspnea, weight gain, constipation, dry skin, hair loss, hoarseness, edema, paresthesia, myalgia, menstruation irregularity, and galactorrhea) was filled out for each participant. BMI, blood pressure, and serum levels of fasting blood sugar, TSH, FT4, thyroperoxidase antibody (TPOab), lipid profile, hsCRP, homocysteine, ferritin, and hematocrite were also measured. For this purpose, blood samples were taken from the participants at 8 AM after a 12-hour fasting. BMI was calculated as body weight (in kg) divided by body height squared (in meters). In addition, TPOab serum level was measured and the values ≥ 16 IU/mL were considered as positive. The healthy controls were selected on the basis of normal thyroid tests (TSH, FT4, TPOab) and examination. It should be mentioned that both groups were matched regarding age and sex.

3.1. Echocardiographic Study

Echocardiography was done for all the subjects using a Vivid 7 dimensional ultrasound scanner (GE Vingmed, Horten, Norway) with a 4-MHz transducer. LV Ejection Fraction (LVEF) was calculated by biplane Simpson's method. Additionally, the LV mass was determined using the following formula proposed by Devereux et al. (5):

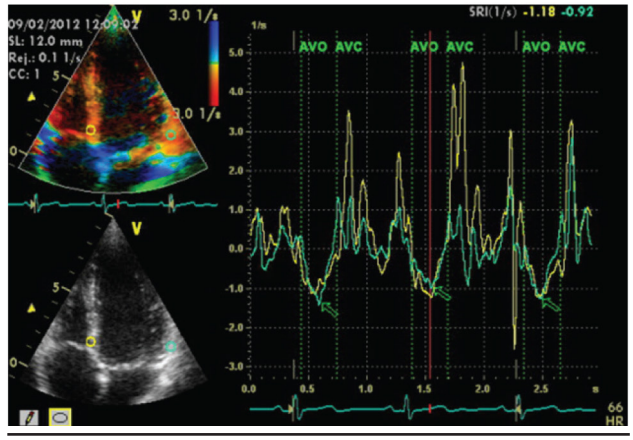
0.8 x {1.04 × [(septal thickness + LV internal diameter + Posterior wall thickness) ^{3} - (LV internal diameter) ^{3}]} + 0.6 gram

LV diastolic function was also assessed using mitral inflow pattern and diastolic velocity (Em) of mitral annulus at the septal side and was presented as normal versus dysfunctional state (grades 1-3) (6).

Moreover, tissue Doppler echocardiography was used to measure the peak systolic velocity of the mitral annulus (Sm) at septal side. Strain rate imaging (tissue Doppler - derived) was done to assess the rate of longitudinal deformation at basal segments of the septal and lateral walls. The area of interest was placed in the center of the imaging field parallel to the sector angle. Gain was minimized to allow clear tissue signal with minimal background noise. The frame rate was set at 100/sec. Sample volume (5 mm in diameter) was placed in the center of the basal segments. The timing of the aortic valve opening and closure was determined from the pulsed-wave Doppler of the LV outflow tract and was superimposed on the LV segments' related strain rate wave forms. The time interval between opening and closing of the aortic valve was used for precise determination of the systolic phase (Figure 1). Three consecutive cycles were stored and strain rate analysis was done in an offline basis (7).

Only peak systolic strain rate (SRs and SRl) in the basal segments of the LV septum and lateral wall were measured in this study. The echocardiograms were performed and interpreted blind to the patients' thyroid status.

Figure 1A. Measurements of Longitudinal Strain Rate



A, Strain Rate Curves (Yellow and Green) with Arrows Denoting the Peak Systolic Strain Rate in the Basal Segment of the Lateral Wall in Three Consecutive Beats

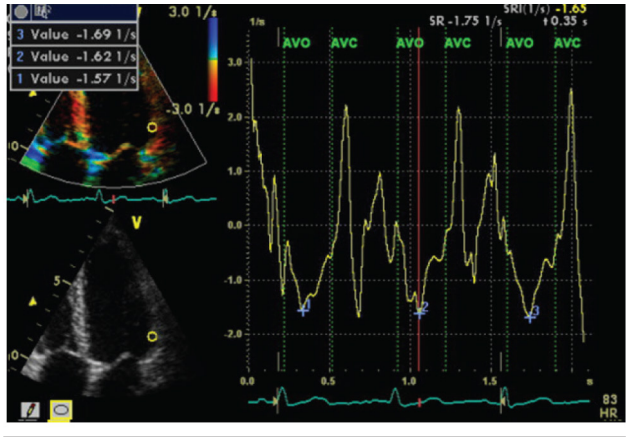


Figure 1B. B, The Peak Systolic Values Have Been Shown in the Left-Upper Box

3.2. Statistical Analysis

All the statistical analyses were performed using the SPSS statistical software (Statistical Package for Social Sciences, version 11.0). Continuous variables were presented as means ± Standard Deviation (SD). T-test and chi-square test were used for analysis of quantitative and qualitative variables, respectively. Normal distribution of the quantitative data was checked using Kolmogorov–Smirnov test (hsCRP, Strain rate, Sm, and inter-ventricular septum diameter were found to have non-normal distribution). In case

the data were not normally distributed, non-parametric tests were used for comparison. Moreover, Pearson's and Spearmen's correlation coefficients were used to assess the relationship between the continuous variables (Pearson's test for normally distributed data and Spearman's test for others). Level of significance was set at 0.05.

4. Results

There was a predominance of women found to have Sch in the endocrinology clinic. Both groups (thirty each) included 29 females. The results revealed no significant difference between the two groups' mean age (31.73 ± 6.18 years in the patients vs. 31.76 ± 6.15 years in the controls, P = 0.983). Free thyroxin was significantly lower in the Sch group (11.12 ± 2.66 vs. 13.48 ± 22.99, P = 0.002). However, no significant difference was observed between the two groups regarding BMI. The questioned symptoms have been shown in Figure 2, with fatigue being the most common complaint. In addition, menstruation irregularity was more frequently seen as oligomenorrhea rather than polymenorrhea.

The thyroid gland was precisely examined in all the Sch patients. According to the results, it was impalpable, palpable, and with diffuse goiter in 20%, 66.6%, and 13.4% of the patients, respectively.

Systolic and diastolic blood pressures were higher in the Sch group, but the difference was not statistically significant (109.33 ± 11.19 vs. 102.33 ± 19.77, P = 0.174 and 70.17 ± 9.69 vs. 68.67 ± 8.9, P = 0.540, respectively) (Table 1).

In comparison to the control group, the patients with Sch showed a significantly higher mean of triglyceride (117.43 ± 63.51 vs. 86.86 ± 41.57, P = 0.031) and total cholesterol/HDL-C ratio (3.73 ± 0.92 vs. 3.29 ± 0.67, P = 0.041) (Table 2). Although the serum concentrations of total cholesterol, LDL-C, and LDL-C/HDL-C ratio were higher in the patients, the differences were not statstically significant.

The results demonstrated no significant difference between the patients and the controls concerning the serum levels of hsCRP (1.35 ± 1.91 vs. 1.34 ± 1.97, P = 0.976), ferritin (45.42 ± 51.57 vs. 48.03 ± 36.63, P = 0.816), and homocysteine (11.75 ± 3.07 vs. 11.99 ± 6.10, P = 0.325) (Table 3).

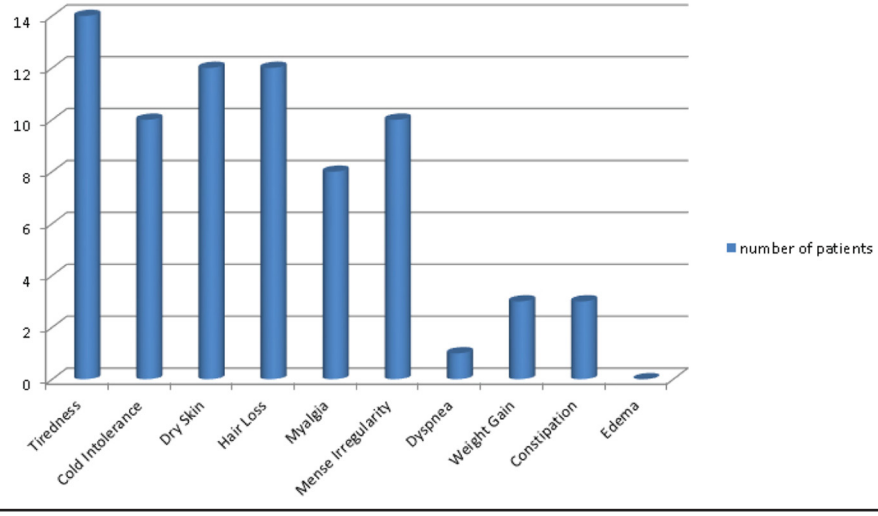


Figure 2. The Frequency of the Symptoms in the Sch Patients (the Values Have Been Presented as the Number of Patients Having Each Symptom)

Table 1. Demographic Features, Systemic Blood Pressure, and Hormonal Variables in Sch and Control Groups

Variables	Sch Group (N = 30)	Control Group (N = 30)	P value
Sex (F : M)	29 : 1	29 : 1	1.000
Age (years) [a]	31.73 ± 6.18	31.76 ± 6.15	0.983
BMI (Kg/m²) [a]	22.98 ± 3.69	23.27 ± 2.73	0.731
Systolic BP (mmHg)	11.19 ± 109.33	19.77 ± 102.33	0.174
Diastolic BP(mmHg)	9.69 ± 70.17	8.95 ± 68.67	0.540
FT4 (Pmol/L) [a]	11.12 ± 2.66	13.48 ± 2.99	0.002
TSH (Mu/L) [a]	7.2 ± 1.86	2.11 ± 1.15	< 0.001

Abbreviations: NS, Not significant

[a] Body mass index; all the results have been presented as mean ± SD

Table 2. The Differences between the Sch and Control Groups Regarding Atherosclerosis Factors

Variables	Sch Group (N = 30)	Control Group (N = 30)	P value (t test)
Total cholesterol (mmol/L)	36.41 ± 189.96	33.28 ± 175.76	0.120
Triglyceride (mmol/L)	117.43 ± 63.51	86.86 ± 41.57	0.031
LDL-C (mmol/L)	27.72 ± 111.73	21.77 ± 101.50	0.117
HDL-C (mmol/L)	10.90 ± 51.50	14 ± 54.10	0.426
Total Cholesterol / HDLc	3.73 ± 0.92	3.29 ± 0.67	0.041
LDLc/HDLc	2.24 ± 0.7	1.93 ± 0.53	0.062

Abbreviations: CHD risk, total cholesterol to HDLc ratio; AF, LDLc/HDLc

Table 3. Serum Levels of Inflammatory Markers in the Two Groups

Variables	Sch group (N = 30)	Control group (N = 30)	P value
HsCRP	1.35 ± 1.91	1.34 ± 1.97	0.976
Homocysteine (mmol/L)	11.75 ± 3.07	6.1 ± 11.99	0.325
Ferritin (Ng/mL)	45.42 ± 51.57	48.03 ± 36.63	0.819

All the results have been presented as mean ± SD

Table 4. The Differences between the Two Groups Regarding Echocardiographic Parameters

Variables	Sch group (n = 30)	Control group (n = 30)	P value
IVSd (cm)	0.7 ± 0.1	0.7 ± 0.09	0.507
LV mass (gr)	87.24 ± 18.77	92.53 ± 20.59	0.302
EF (%)	59.93 ± 3.86	61.26 ± 3.68	0.177
ESV (cc)	33.96 ± 6.77	33.04 ± 5.37	0.721
EDV	84.36 ± 13.62	86.46 ± 12.51	0.536
Sm (cm/sec)	6.9 ± 0.61	7.43 ± 0.82	0.006
Em (cm/sec)	11.23 ± 1.85	11.63 ± 2.24	0.453
E/Em	7.05 ± 1.35	7.36 ± 1.7	0.439
SRs (s^{-1})	-1.006 ± 0.40	-1.266 ± 0.17	0.002
SRl (s^{-1})	-1.436 ± 0.27	-1.683 ± 0.29	0.001

Abbreviations: IVSd, thickness of interventricular septum at end diastole; ESV, end systolic volume; SRs, Longitudinal systolic strain rate in basal segment of inferoseptum; SRl, longitudinal systolic stain rate in the basal segment of lateral wall; Sm, peak systolic velocity in the septal side of mitral annulus

4.1. Echocardiographic Parameters

LV diastolic function was normal in all the healthy controls, except for two (aged 44 and 45 years) who had mild diastolic dysfunction (grade 1). In the Sch patients, on the other hand, five cases had abnormal diastolic function (mild, grade1). No significant difference was found between the two groups regarding diastolic function (P = 0.425). The two groups were also similar with respect to E velocity of mitral inflow (P = 0.453) and E/Em ratio (P = 0.439), as indices of diastolic function. Also, the results of independent samples T-test indicated no significant difference between the two group regarding LV mass (92.5 ± 20.6 vs. 87.2 ± 18.7, P = 0.3).

However, longitudinal systolic strain rate in the inferoseptal base and lateral wall of the left ventricle (SRs: -1.006 ± 0.4 vs. -1.26 ± 0.16, P = 0.002; SRl: -1.43 ± 0.27 vs. -1.68 ± 0.29, P = 0.001) and Sm of the septal mitral annulus (6.90 ± 0.6 vs. 7.43 ± 0.8, P = 0.006) were significantly lower in the Sch patients compared to the matched controls (Table 4).

The results revealed no significant correlation between hsCRP and systolic strain rate (r = 0.64, P = 0.76), Sm (r = -0.18, P = 0.16), and Em (r = 0.06, P = 0.62).

However, a significant correlation was observed between TSH and Sm (r = -0.36, P = 0.005), Em (r = -0.25, P = 0.03), and longitudinal systolic strain rate (SRs: r = 0.42, P < 0.001; SRl: r = 0.40, P = 0.001). Furthermore, systolic strain rate was significantly lower in the TPOab positive patients (-0.99 ± 0.18 vs. -1.15 ± 0.25, P = 0.047). The relationship between TPOab and systolic longitudinal strain rate has been illustrated in Figure 3, indicating a marginally significant correlation (r = 0.19, P = 0.049) (2-tailed).

Thyroperoxidase antibody (TPOab): Serum levels of TPOab have been presented in Table 1. Accordingly, positive TPOab was more prevalent among the Sch patients compared to the control group (60 % vs. 6%, P = 0.001). Besides, it was significantly correlated to the FT4 levels (r = -0.37, P = 0.04) and TSH (r = 0.49, P = 0.005).

The serum levels of TSH (7.77 ± 1.84 vs. 6.33 ± 1.56, P = 0.03) were higher in the TPOab positive patients compared to the negative ones. Nevertheless, no significant difference was found between the two groups with regard to lipids, hsCRP, ferritin, and hematocrite levels.

Table 4. The Differences between the Two Groups Regarding Echocardiographic Parameters

Variables	Sch group (n = 30)	Control group (n = 30)	P value
IVSd (cm)	0.7 ± 0.1	0.7 ± 0.09	0.507
LV mass (gr)	87.24 ± 18.77	92.53 ± 20.59	0.302
EF (%)	59.93 ± 3.86	61.26 ± 3.68	0.177
ESV (cc)	33.96 ± 6.77	33.04 ± 5.37	0.721
EDV	84.36 ± 13.62	86.46 ± 12.51	0.536
Sm (cm/sec)	6.9 ± 0.61	7.43 ± 0.82	0.006
Em (cm/sec)	11.23 ± 1.85	11.63 ± 2.24	0.453
E/Em	7.05 ± 1.35	7.36 ± 1.7	0.439
SRs (s^{-1})	-1.006 ± 0.40	-1.266 ± 0.17	0.002
SRl (s^{-1})	-1.436 ± 0.27	-1.683 ± 0.29	0.001

Abbreviations: IVSd, thickness of interventricular septum at end diastole; ESV, end systolic volume; SRs, Longitudinal systolic strain rate in basal segment of inferoseptum; SRl, longitudinal systolic stain rate in the basal segment of lateral wall; Sm, peak systolic velocity in the septal side of mitral annulus

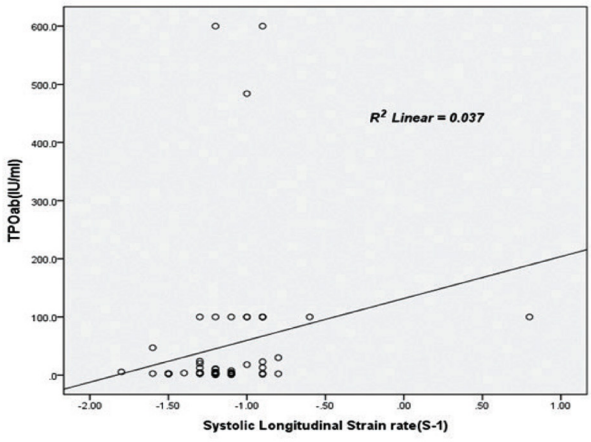


Figure 3. The Relationship between Serum Levels of TPOAb and Strain Rate Values

5. Discussion

5.1. Lipid Profile

There are conflicting results concerning the pattern of lipid abnormalities in Sch. In Wickham's survey, Sch was not related to hyperlipidemia. That population-based cohort study was the first large-scale examination on the relationship between thyroid status and cardiovascular outcomes. No evidence was found suggesting that autoimmune thyroid disease, identified 20 years ago, was associated with an increased risk of ischemic heart disease (8).

In the NHANES III, the mean cholesterol levels were higher in the Sch patients than in the euthyroid controls (9). Rotterdam study also showed lower total cholesterol levels in the females with Sch compared to the euthyroid ones. Similar results were obtained in Nagasaki study (10).

In New Mexico Elder Health Survey, no differences were found between the patients with serum TSH levels below 4.6 mIU/liter and those with serum TSH levels between 4.7 and 10 mIU/liter regarding TC, HDL-C, and triglycerides. Nevertheless, the levels of LDL-C and HDL-C were higher among the females with serum TSH > 10 mIU/liter in comparison to the euthyroid ones (11).

In a Danish study, Sch was associated with higher concentrations of triglycerides and CRP (12). In the present study, the mean triglyceride and total cholesterol/HDLc levels were significantly higher among the patients compared to the controls. Total and LDL cholesterol levels were also higher, but not significantly different.

Arguably, LDL cholesterol remains to be the major player in atherogenesis. Although it is apparent that hypertriglyceridemia is more closely linked to constellation of abnormalities which constitute the metabolic syndrome, the exact atherogenic properties of triglycerides have been hard to explain perhaps due to the greater biologic variance than cholesterol. On the other hand, it has been proposed that the elevated levels do not necessarily indicate increased atherogenicity (13). This is in contrast to some other studies, showing the contributory role of hypertriglyceridemia and coronary diseases (14, 15).

Benfante et al. disclosed that triglyceride level in below-60-year-old individuals, but not in older populations, was an independent predictor of coronary heart diseases (15). A meta-analysis on the same subject also revealed that only 1 mmol/L increase in triglycerides increased the risk of cardiovascular diseases by 76% (14).

5.2. Echocardiographic Variables

Echocardiographic parameters (SRs, SRl, Sm) were significantly lower in the Sch patients compared to the matched controls. All the patients had normal global systolic function determined by conventional echocardiography (normal LVEF and absence of regional wall motion abnormality). This was in favor of the presence of subtle abnormalities which could be detected by Doppler imaging or deformation indices (16).

Di Bello et al. showed Sch to be associated with changes in video densitometric myocardial structure which could represent an early sign of myocardial damage in hypothyroidism (17). Alterations in resting LV diastolic dysfunction in Sch have also been reported previously (18).

In the present study, Em velocity decreased in the Sch patients compared to the matched controls, but the difference was not statistically significant. Also, no significant difference was found between the two groups regarding diastolic function (normal versus graded diastolic dysfunction). Yet, it was noticed that younger patients (aged 27, 37, or 38 years) were enrolled with grade 1 diastolic dysfunction. Therefore, future studies with larger sample sizes are recommended to evaluate the changes in LV diastolic function. Several other studies have been performed regarding the changes in LV function in Sch with tissue Doppler imaging, showing a great importance in this context (19).

Impairment of both systolic and diastolic function (20) versus only diastolic function has been proposed so far (21). Echocardiographic evidence of predominant systolic dysfunction was found in the present study.

5.3. Inflammatory Markers

The current study results indicated no significant difference between the Sch patients and the controls with regard to the serum level of inflammatory markers (hsCRP, Ferritin, and homocysteine). The atherogenicity, if present, does not seem to be mediated by inflammatory markers. Inflammation has an evolving role in atherosclerosis, but we did not find remarkable differences in the level of serum markers or correlations with echocardiographic indices of systolic function. It should be mentioned that this was the first study on the correlation between serum levels of inflammatory markers and echocardiographic indices. There were some supportive evidences for cardiovascular involvement in the Sch patients in this study (the significantly lower free thyroxin level in the Sch group, the correlation between FT4 and atherogenic factor, and the relationship between TSH and systolic parameters of LV function). Low FT4 might adversely affect the cardiovascular system and has been proposed as a risk factor for atherosclerosis, even when in the reference range (22). Up to now, some mechanisms have been proposed for anti-atherosclerosis effects of thyroid hormones (e.g., regulation of endothelial function and vascular homeostasis, production of vasodilator molecules, and inhibition of angiotensinogen II receptor expression) (23). Yet, arguments and uncertainty still remain

in treatment of Sch patients. Elevated level of thyrotropin, antithyroid antibodies, total cholesterol, or LDL, pregnancy, hypothyroidism symptoms, and goiter have all been proposed as indications for hormone therapy. The risk of conversion to overt hypothyroidism is high in the presence of increased TSH alone or TPOab alone (2.6% per year and 2.1% per year, respectively). The annual risk was estimate to increase to 4.3% in the presence of elevated TSH and TPOab (8).

In our study, LV dysfunction was more evident in the subgroup of patients with circulating anti-thyroid antibodies. This emphasizes consideration of the subgroup of TPOab positive patients for directing toward hormone replacement. For preventing or at least slowing down the process of ventricular dysfunction in Sch, we suggest thyroid replacement therapy for such patients with a greater degree of confidence than ever before.

5.4. Study Limitations

-The changes in LV diastolic function or LDL cholesterol should be assessed in a larger sample size.

-Patient follow-up is crucial to evaluate the incidence of cardiovascular events, which was not included in this study. The prognostic implication of such subtle ventricular function abnormalities should be determined by long-term monitoring of the patients.

-Measurement of strain rate by tissue Doppler imaging could raise some errors if the cursor was not aligning with the wall of interest.

5.5. Conclusion

This study emphasized hypertriglyceridemia as the most prominent lipid disorder in Sch patients. The study results indicated a clear association between Sch and subclinical LV systolic dysfunction, which was more evident in the subgroup of patients with circulating anti-thyroid antibodies. This would put greater emphasis on considering the subgroup of TPOab positive patients for directing toward hormone replacement. However, this should be confirmed in further studies.

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Authors' Contribution

Zohreh Moossavi: Responsible for study design, referring the patients, writing discussion and conclusion sections, and revising the thesis and the article; Hoorak Poorzand: corresponding, study design, gathering the echocardiographic data, writing discussion and conclusion sections, revising the article, and finding the journals that best fitted the article; Foroogh Salehi: completing the questionnaires, entering the data in the statistical software, and writing the thesis.

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References

1. Sych Iu P, Kalatnikov V, Syrkin AL, Mel'nichenko GA. [Impairment of cardiovascular function in subclinical hypothyroidism]. *Klin Med (Mosk)*. 2003;**81**(11):4-9.
2. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;**29**(1):76-131.
3. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. *Curr Hypertens Rep*. 2003;**5**(6):513-20.
4. Vanhaelst L, Neve P, Chailly P, Bastenie PA. Coronary-artery disease in hypothyroidism. Observations in clinical myxoedema. *Lancet*. 1967;**2**(7520):800-2.
5. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I*, et al*. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;**57**(6):450-8.
6. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA*, et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009;**10**(2):165-93.
7. Gilman G, Khandheria BK, Hagen ME, Abraham TP, Seward JB, Belohlavek M. Strain rate and strain: a step-by-step approach to image and data acquisition. *J Am Soc Echocardiogr*. 2004;**17**(9):1011-20.
8. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F*, et al*. The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid*. 1996;**6**(3):155-60.
9. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med*. 2004;**2**(4):351-5.
10. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med*. 2000;**132**(4):270-8.
11. Lindeman RD, Schade DS, LaRue A, Romero LJ, Liang HC, Baumgartner RN*, et al*. Subclinical hypothyroidism in a biethnic, urban community. *J Am Geriatr Soc*. 1999;**47**(6):703-9.
12. Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J. Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf)*. 2004;**61**(2):232-8.
13. Ballantyne CM, Grundy SM, Oberman A, Kreisberg RA, Havel RJ, Frost PH*, et al*. Hyperlipidemia: diagnostic and therapeutic perspectives. *J Clin Endocrinol Metab*. 2000;**85**(6):2089-112.
14. Austin MA. Epidemiology of hypertriglyceridemia and cardiovascular disease. *Am J Cardiol*. 1999;**83**(9B):13F-6F.
15. Benfante RJ, Reed DM, MacLean CJ, Yano K. Risk factors in middle age that predict early and late onset of coronary heart disease. *J Clin Epidemiol*. 1989;**42**(2):95-104.
16. Weidemann F, Strotmann JM. Detection of subclinical LV dysfunction by tissue Doppler imaging. *Eur Heart J*. 2006;**27**(15):1771-2.
17. Di Bello V, Monzani F, Giorgi D, Bertini A, Caraccio N, Valenti G*, et al*. Ultrasonic myocardial textural analysis in subclinical hypothyroidism. *J Am Soc Echocardiogr*. 2000;**13**(9):832-40.
18. Akcakoyun M, Kaya H, Kargin R, Pala S, Emiroglu Y, Esen O*, et al*. Abnormal left ventricular longitudinal functional reserve assessed by exercise pulsed wave tissue Doppler imaging in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab*. 2009;**94**(8):2979-83.
19. Ozturk S, Alcelik A, Ozyasar M, Dikbas O, Ayhan S, Ozlu F*, et al*. Evaluation of left ventricular systolic asynchrony in patients with subclinical hypothyroidism. *Cardiol J*. 2012;**19**(4):374-80.
20. Oner FA, Yurdakul S, Oner E, Arslantas MK, Usta M, Erguney M. Evaluation of ventricular functions using tissue Doppler echocardiography in patients with subclinical hypothyroidism. *Turk Kardiyol Dern Ars*. 2011;**39**(2):129-36.
21. Chen X, Zhang N, Zhang WL, Shi JP. [Meta-analysis on the association between subclinical hypothyroidism and the left ventricular functions under Doppler echocardiography]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2011;**32**(12):1269-74.
22. Valentina VN, Marijan B, Chedo D, Branka K. Subclinical hypothyroidism and risk to carotid atherosclerosis. *Arq Bras Endocrinol Metabol*. 2011;**55**(7):475-80.
23. Klein I, Ojamaa K. Thyroid hormone: targeting the vascular smooth muscle cell. *Circ Res*. 2001;**88**(3):260-1.