Original Article

Dyslipidemia and low-grade inflammation are associated with sympathovagal imbalance and cardiovascular risks in subclinical and overt hypothyroidism

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Abstract

Background and Aim: Hypothyroidism in both its subclinical and overt form has been reported to be associated with cardiovascular (CV) morbidities. Dyslipidemia, inflammation, and sympathovagal imbalance (SVI) contribute to CV risks. The present study has assessed role of dyslipidemia and inflammation in the genesis of SVI and hypertension status in subclinical hypothyroidism (SCH) and overt hypothyroidism (OH).

Methods: Age-matched 209 females (70 euthyroids, 67 subclinical hypothyroids, and 72 overt hypothyroids) were recruited for this study. Body mass index (BMI), CV parameters, and autonomic function tests (AFT) like spectral analysis of heart rate variability (HRV), heart rate (HR) response to standing, HR response to deep breathing, and blood pressure (BP) response to isometric handgrip were assessed. Thyroid profile, lipid profile, and immunological and inflammatory markers were estimated. The independent association of the ratio of low-frequency to high-frequency (LF-HF ratio) power of HRV and the marker of SVI with various parameters were determined by multiple regression analysis. The prediction of hypertension status by LF-HF ratio was assessed by logistic regression.

Results: CV and AFT parameters, lipid profile, and inflammatory marker were altered and correlated with LF-HF ratio in both SCH and OH groups. Mean arterial pressure, atherogenic index, and high-sensitive C-reactive protein had independent contribution to LF-HF ratio in both the groups. The prediction of hypertension status by LF-HF ratio was more significant in OH groups (odds ratio (OR) 2.15, CI 0.126-5.867, and $P = 0.002$) compared to SCH group (OR 1.90, CI 1.108-4.352, and $P = 0.009$).

Conclusion: SVI due to sympathetic activation and vagal withdrawal occurs in SCH that progressively increases from SCH to OH. Dyslipidemia and low-grade inflammation are associated with SVI and CV risks in hypothyroidism.

Key words: Autonomic imbalance, cardiovascular risks, dyslipidemia, hypothyroidism, inflammation, subclinical hypothyroidism, sympathovagal imbalance

Received: 10th October, 2013; ***Revised:*** 24th December, 2013; ***Accepted:*** 8th January, 2014

INTRODUCTION

Decreased function of the thyroid gland is one of the common endocrine disorders of India, where prevalence of overt hypothyroidism (OH) is 10.95% and subclinical hypothyroidism (SCH) is 8.02%.[1] OH is defined as a combination of high thyroid stimulating hormone (TSH) with low free thyroxine (fT4), while SCH is defined as a combination of high TSH with normal fT4 levels.[2] Dyslipidemia and increased inflammatory markers are associated with OH[3,4] and SCH.[5-7] Increased plasma levels of C-peptide and lipoproteins are reported to increase the risk for cardiovascular (CV) diseases in hypothyroid patients.[3,4] Hyperlipidemia, low-grade inflammation and oxidative stress have been reported to increase CV risks in SCH.[5,6]

Access this article online	
Quick Response Code:	Website: www.ijcep.org
	DOI: 10.4103/2348-8093.129726

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Conventional autonomic function tests (CAFT) and power spectral analysis of heart rate variability (HRV) are useful tools to measure cardiac autonomic activity and sympathovagal balance.[8-10] OH is associated with decreased sympathovagal modulation of heart rate (HR).[11] Though hypothyroidism is a hypometabolic state, sympathovagal imbalance (SVI) due to increased sympathetic activity and decreased parasympathetic activity has been reported in OH.[3,12,13] The cardiac autonomic activity is also altered in SCH.[14] Hyperlipidemia and inflammation have been reported to cause SVI,[15,16] and SVI has been observed to be associated with increased CV risks.[8,17] Recently, we have reported SVI in the form of sympathetic overactivity and vagal inhibition, which is linked to hypertension status in hypothyroidism patients.[3] However, till date the pathophysiology of SVI in SCH has not been adequately studied. Moreover, the cause and progression of SVI from the state of SCH to OH and its link to increased CV risks in these conditions have not been elucidated. Therefore, in the present study we have assessed the association of dyslipidemia, inflammatory markers with SVI, hypertension status, and CV risks in subclinical and overt hypothyroid patients.

MATERIALS AND METHODS

The present study was conducted in the Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India. After obtaining approval of the project plan from research and ethics committees of JIPMER, 209 female subjects (70 euthyroid, 67 subclinical hypothyroid, and 72 overt hypothyroid patients) were recruited from the Endocrinology Clinic of JIPMER Hospital. Euthyroidism was defined as a serum TSH level of 0.35-5.50 μIU/mL with normal fT4 concentration (0.89-1.76 ng/dL). OH was defined as a serum fT4 concentrations <0.89 ng/dL with serum TSH level >5.50 μIU/mL. SCH was defined as a serum TSH level of >5.50 μIU/mL with normal fT4 concentrations. Written informed consent was obtained from all the participants prior to initiation of the study. Subjects of study groups were freshly diagnosed untreated female subclinical and overt hypothyroid patients.

Inclusion criteria

Female patients freshly diagnosed as subclinical hypothyroids and overt hypothyroids, before initiation of the treatment were included for the study. Control group had age-matched healthy euthyroid females.

Exclusion criteria

Patients, who were already on treatment for SCH or hypothyroidism, known cases of diabetes mellitus, hypertension, heart diseases, autonomic failure, or endocrine disorders and those receiving chronic medications, were excluded from the study. Females receiving oral contraceptives, females in the perimenopausal age and who had attained menopause were also excluded from the study.

Brief procedure

The subjects reported to polygraph laboratory of physiology department at about 8 AM without breakfast. Height and weight were measured to calculate body mass index (BMI). After 10 min of supine rest in polygraph laboratory (room temperature maintained at 25°C), the following recordings were done.

Recording of baseline CV and HRV parameters

Baseline HR and blood pressure (BP) were recorded in the left arm after 10 min of rest in the supine position using automatic BP monitor (Omron Healthcare Co. Ltd, Kyoto, Japan). For recording of short-term HRV, the procedure as described earlier,[12] and recommendation of the Task Force on HRV was followed.[18] For the purpose, electrocardiogram (ECG) electrodes were connected and Lead II ECG was acquired at a rate of 250 samples/s during supine rest using BioHarness 2 data acquisition system (BIOPAC Inc, Goleta, CA, USA). The data was transferred from BioHarness to a windows-based PC with AcqKnowledge software version 4.1.0. Ectopics and artefacts were removed from the recorded ECG tachogram [Figure 1]. HRV analysis was done using the HRV analysis software version 1.1 (Bio-signal Analysis group, Kuopio, Finland). Frequency domain indices such as total power (TP), low-frequency power expressed in normalized unit (LFnu), high-frequency power expressed in normalized unit (HFnu), ratio of LF to HF power (LF-HF ratio), and time domain indices (TDI) such as mean RR, square root of the mean squared differences of successive normal to normal intervals (RMSSD), standard deviation of normal to normal interval (SDNN), the number of interval differences of successive NN intervals greater than 50 ms (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) were recorded.

Other autonomic function tests

Three CAFTs were performed following the standard procedures:[9]

Lying to standing test

In this test, HR and BP response to standing was assessed. The BP and ECG were recorded in supine position. The subject was instructed to stand up in 3 s. The ECG was continuously recorded during the procedure. The BP was recorded every 40 s by automatic BP monitor (Omron, SEM-1, Kyoto, Japan) till 5th min. 30:15 ratio (ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing) was calculated.

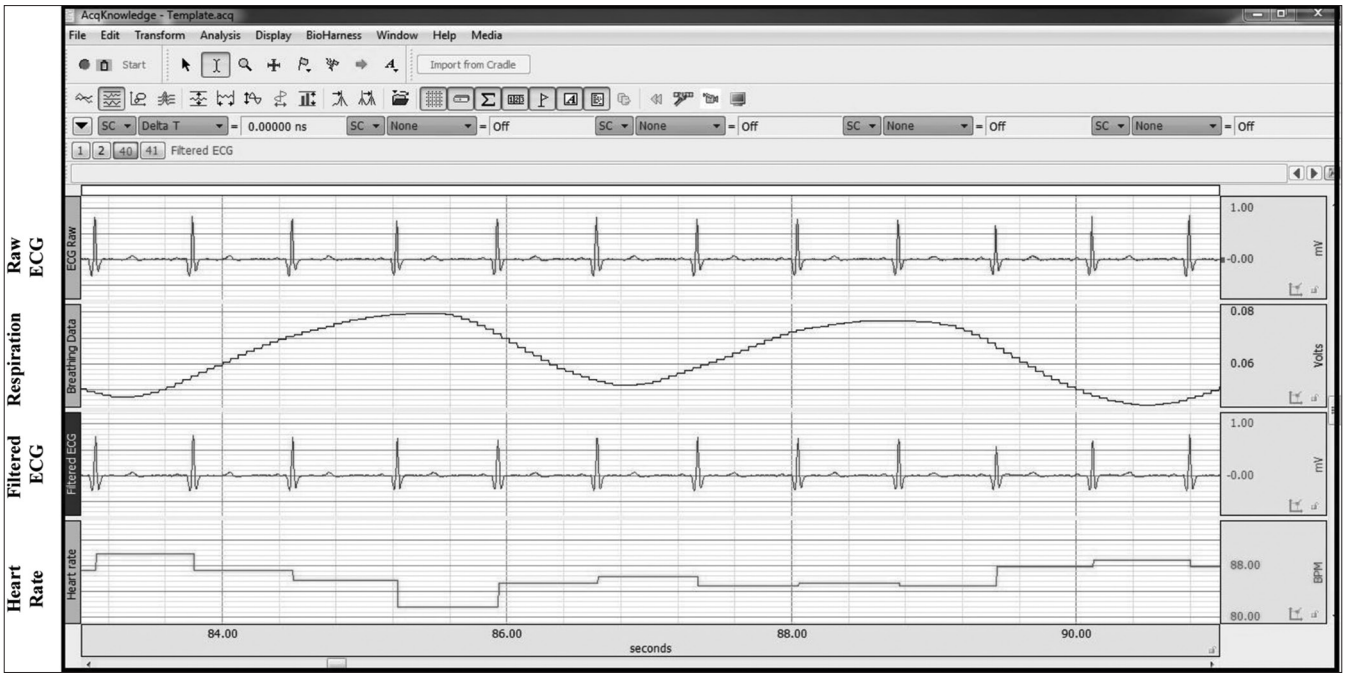

Figure 1: Tachogram of HRV recording by AcqKnowledge software version 4.1.0

Deep breathing test

The subject in sitting posture, the HR, and respiration monitoring was done from ECG recording and stethographic respiratory tracings recorded respectively, on the multichannel polygraph (Nihon-Kohden, Tokyo, Japan). A baseline recording of ECG and respiration was taken for 30 s. The subject was asked to take slow and deep inspiration followed by slow and deep expiration such that each breathing cycle lasted for 10 s, consisting of six breathing cycles per min. E:I ratio (ratio of average RR interval during expiration to average RR interval during inspiration in six cycles of deep breathing) was calculated from ECG tracing.

Isometric handgrip test

The baseline BP was recorded. The subject was asked to press handgrip dynamometer at 30% of maximum voluntary contraction for 2 min. The BP was recorded at 1st and 2nd min of contraction. ΔDBP_{IHG} (maximum rise in diastolic BP above baseline) was noted.

Measurement of biochemical parameters

Five ml of fasting blood sample was collected. The serum was separated from the blood samples of all the subjects for estimation of biochemical parameters. Free triiodothyronine (fT3), fT4, and TSH were assayed by chemiluminiscence method using the kits from Siemens Healthcare Diagnostics Inc, USA. Lipid profile (total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoproteins (VLDL)) were assessed using fully automated analyzer (AU400, Olympus, USA). Anti-thyroperoxidase antibody (anti-TPO Ab), anti-thyroglobulin antibody (anti-TG Ab) and immunoglobulin E (Ig E) were estimated by indirect immunoenzymatic colorimetric method using enzyme-linked immunosorbent assay (ELISA) kits (Dia Metra, Segrate, Italy). The high-sensitive C-reactive protein (hsCRP) was estimated by using ELISA kits (dbc Diagnostics Biochem Canada Inc, Canada).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 19 (SPSS Software Inc, Chicago, IL, USA) and GraphPad InStat softwares (GraphPad Software Inc, San Diego, CA, USA) were used for statistical analysis. All the data were presented as mean ± SD. Normality of data was tested by Kolmogorov Smirnov test. For parametric data, the level of significance between the groups was tested by Student's unpaired '*t*' test and for nonparametric data, the Welch's corrected *t* test was used. The association between LF-HF and various parameters was assessed by Pearson's correlation analysis. The independent contribution of various factors to LF-HF ratio was assessed by multiple regression analysis. Bivariate logisitc regression was performed for the prediction of BP status in control subjects and hypertension status in subclinical and overt hypothyroid patients by LF-HF ratio. The *P* values less than 0.05 was considered statistically significant.

RESULTS

There was no significant difference in age of control, subclinical and overt hypothyroid patients [Table 1].

BMI of subclinical and overt hypothyroid patients were significantly more compared to that of controls ($P < 0.001$). The basal HR (BHR) was significantly less ($P < 0.05$) only in overt hypothyroid patients compared to controls. The DBP ($P < 0.001$) and mean arterial pressure (MAP) ($P < 0.001$) were significantly more in subclinical and overt hypothyroid patients compared to the controls [Table 1]. BMI ($P < 0.001$), DBP ($P < 0.001$), and MAP ($P < 0.05$) were significantly more in overt hypothyroid patients compared to that of subclinical hypothyroid patients.

There was significant reduction in TP ($P < 0.001$) and HFnu ($P < 0.01$) and significant increase in LFnu ($P < 0.01$) and LF-HF ratio ($P < 0.001$) in subclinical hypothyroid patients compared to the controls [Table 1]. TP and HFnu reduced significantly ($P < 0.001$) and LFnu and LF-HF ratio increased significantly ($P < 0.001$) in overt hypothyroid patients compared to the controls [Table 1 and Figure 2]. Also, TP and HFnu were significantly ($P < 0.001$) less and LFnu and LF-HF ratio were significantly ($P < 0.001$) more in overt hypothyroid patients compared to subclinical hypothyroid patients [Table 1]. The TDI of HRV (RMSSD, SDNN, NN50, and pNN50) were significantly decreased ($P < 0.001$) in overt hypothyroid patients compared to the control group. In subclinical hypothyroid patients compared to controls, there was significant reduction in SDNN, pNN50 ($P < 0.001$) and in RMSSD and NN50 ($P < 0.05$). All TDI except RMSSD decreased significantly ($P < 0.01$) in overt hypothyroid patients compared to subclinical hypothyroid patients. The 30:15 ratio and ΔDBP_{IHG} were significantly increased ($P < 0.001$) and E:I ratio was significantly decreased ($P < 0.001$) in subclinical and overt hypothyroid patients compared to controls and in OH patients compared to subclinical hypothyroid patients [Table 1].

There was a significant decrease ($P < 0.01$) in fT4 and increase in TSH ($P < 0.05$) in subclinical hypothyroid patients compared to control group [Table 2]. There was a significant decrease ($P < 0.001$) in fT3 and fT4 and increase in TSH ($P < 0.001$) in overt hypothyroid patients compared to control group and subclinical hypothyroid patients [Table 2]. TC, TG, LDL, and VLDL were increased ($P < 0.001$) and HDL ($P < 0.001$) was decreased in subclinical and overt hypothyroid patients compared to control group and in overt hypothyroid patients compared to subclinical hypothyroid patients. All the lipid risk factors were significantly high ($P < 0.001$) in subclinical and overt hypothyroid patients compared to controls and in overt hypothyroid patients compared to subclinical hypothyroid patients. Levels of anti-TPO antibody, anti-TG antibody and hsCRP were increased ($P < 0.001$) in subclinical and overt hypothyroid patients and in overt hypothyroid patients compared to SCH patients [Table 2].

Table 1: Age, BMI, basal cardiovascular, HRV and CAFT parameters of control group, SCH group and OH group

Parameters	Control group (*n*=70)	SCH group (*n*=67)	OH group (*n*=72)	*P* value
General parameters				
Age (years)	25.90±6.56	26.54±5.20	27.15±6.08	0.4624
BMI (kg/m^2)	21.20±3.33	23.79±3.65***	26.80±4.10***,###	<0.0001
BHR (per min)	75.80±8.10	75.04±6.85	72.51±6.00*	<0.0153
SBP (mmHg)	108.24±9.34	110.68±10.52	109.70±8.35	<0.3131
DBP (mmHg)	70.92±7.06	77.80±7.83***	82.88±8.16***,###	<0.0001
MAP (mmHg)	83.32±7.12	88.75±8.17***	92.10±8.32***,#	<0.0001
HRV indices				
TP (ms^2)	934.75±318.75	725.56±170.48***	390.52±115.20***,###	<0.0001
LFnu	35.80±14.30	45.75±13.28*	57.78±22.76***,###	<0.0001
HFnu	64.14±21.65	54.22±15.20**	42.10±15.63***,###	<0.0001
LF-HF ratio	0.52±0.25	0.90±0.40***	1.20±0.46***,###	<0.0001
RMSSD (ms)	57.17±21.42	48.08±17.56*	42.98±15.94***	<0.0001
SDNN (ms)	46.80±15.35	35.37±14.20***	27.44±8.96***,##	<0.0001
NN50	59.87±18.75	51.06±20.23*	41.87±15.56***,##	<0.0001
pNN50	30.56±10.65	24.63±8.14***	20.18±5.98***,##	<0.0001
CAFT parameters				
30:15 ratio	1.21±0.17	1.32±0.14***	1.45±0.16***,###	<0.0001
E:I ratio	1.45±0.15	1.34±0.13***	1.14±0.15***,###	<0.0001
ΔDBP_{IHG}	20.46±4.14	26.66±5.50***	31.53±6.15***,###	<0.0001

Data presented are mean±SD. SD: Standard deviation, BMI: Body mass index, BHR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, SCH: Subclinical hypothyroidism, TP: Total power, LFnu: Normalized low-frequency power, HFnu: Normalized high-frequency power, RMSSD: Square root of the mean of the sum of the squares of the differences between adjacent NN intervals, SDNN: Standard deviation of normal to normal interval, NN50: Number of interval differences of successive NN intervals greater than 50, pNN50: Proportion derived by dividing NN50 by the total number of NN intervals, 30:15 ratio: Ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing, E:I ratio: Ratio of average RR interval during expiration to that of during inspiration in six cycles of deep breathing, ΔDBP_{IHG}: The maximum rise in DBP above baseline following 30% of maximum voluntary contraction by isometric handgrip method. *Comparison with control group: *($P<0.05$); **($P<0.01$); ***($P<0.001$), #Comparison with SCH group: #($P<0.05$); ##($P<0.01$); ###($P<0.001$), OH: Overt-hypothyroidism

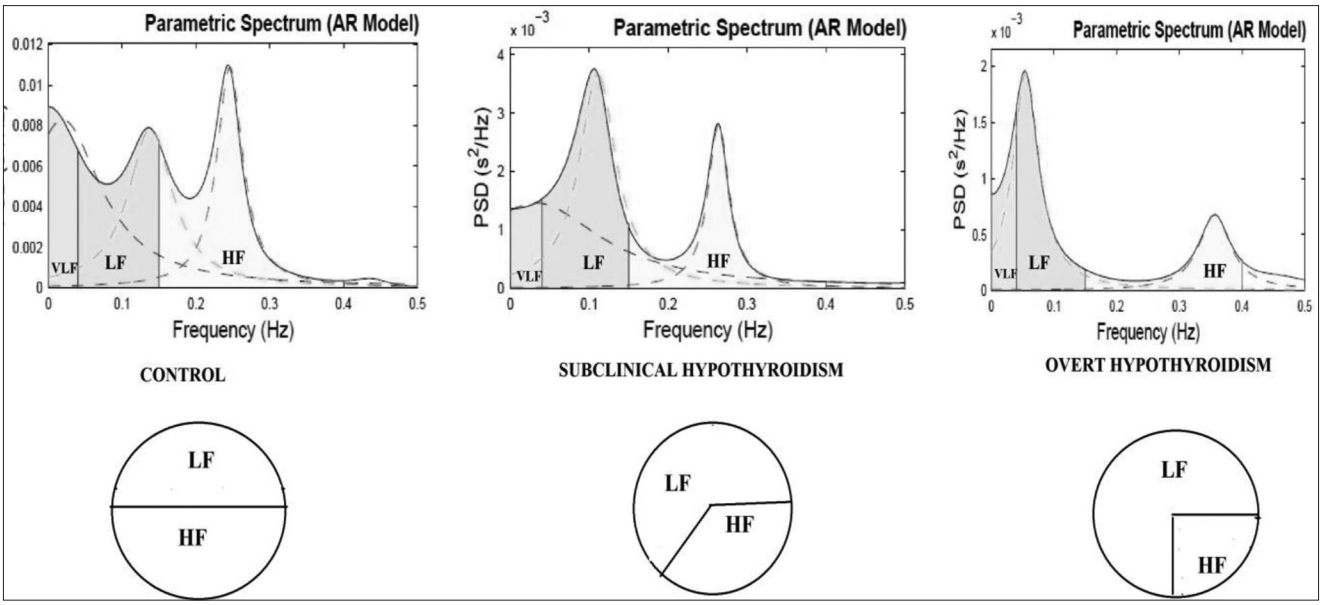

Figure 2: This picture depicts the power spectral analysis (Auto Regression model) of heart rate variability of one sample subject each from control, subclinical and overt hypothyroid groups. The LF power and HF power were almost 50:50 in control subject; LF power was more than HF power in subclinical hypothyroid subject; LF power was maximum and HF power was minimum in overt hypothyroid subject

Table 2: Biochemical parameters of control, SCH, and OH subjects

Parameters	Control group (*n*=70)	SCH group (*n*=67)	OH group (*n*=72)	*P* value
Thyroid profile				
fT3 (pg/mL)	2.93±0.85	2.65±0.82	1.54±0.55***,###	<0.0001
fT4 (ng/dL)	1.38±0.50	1.15±0.48**	0.601±0.27***,###	<0.0001
TSH (IU/mL)	1.98±0.64	12.85±2.30*	98.86±42.15***,###	<0.0001
Lipid profile (mg/dL)				
Total cholesterol	162.85±18.10	197.56±32.87***	271.59±42.69***,###	<0.0001
Triglycerides	78.25±16.22	110.36±24.62***	128.26±25.70***,###	<0.0001
LDL-cholesterol	95.45±17.27	132.80±27.52***	178.28±35.90***,###	<0.0001
VLDL-cholesterol	15.65±3.16	20.06±4.55***	26.92±5.78***,###	<0.0001
HDL-cholesterol	50.38±7.42	43.74±6.26***	38.26±5.34***,###	<0.0001
Lipid risk factors				
TC/HDL	3.24±0.54	4.53±1.22***	7.11±2.15***,###	<0.0001
TG/HDL	1.55±0.36	2.51±1.08***	3.36±1.12***,###	<0.0001
LDL/HDL	1.90±0.44	3.10±1.12***	4.65±1.78***,###	<0.0001
AI	0.18±0.08	0.39±0.12***	0.52±0.14***,###	<0.0001
Immunological parameters				
Anti-TPO Ab (IU/mL)	33.50±7.64	286.25±54.57***	420.94±70.15***,###	<0.0001
Anti-Tg Ab (µg/dL)	2.17±0.82	61.74±30.12***	78.45±46.33***,##	<0.0001
Inflammatory marker				
hsCRP (ng/mL)	512.96±192.15	760.20±212.36***	1045.19±230.58***,###	<0.0001

Data presented are mean±SD. SD: Standard deviation, fT_3: Free triiodothyronine, fT_4: Free thyroxine, TSH: Thyroid stimulating hormone, TC: Total cholesterol, TG: Triglycerides, HDL: High density lipoproteins, LDL: Low density lipoproteins, VLDL: Very low density lipoproteins, AI: Atherogenic index, anti-TPO Ab: Anti-thyroperoxidase antibody, anti-Tg Ab: Anti-thyroglobulin antibody, hsCRP: High-sensitive C-reactive protein, SCH: Subclinical hypothyroidism, OH: Overt-hypothyroidism. *Comparison with control group, *(P<0.05), **(P<0.01), ***(*P*<0.001). #Comparison with SCH group: #(*P*<0.05), ##(*P*<0.01), ###(*P*<0.001)

LF-HF ratio was not significantly correlated with any of the parameter in control group and with BMI in any of the groups [Table 3]. In subclinical and overt hypothyroid patients, there was a significant correlation of LF-HF ratio with BHR, MAP, TSH, lipid profile parameters, lipid risk factors, and inflammatory and immunological markers except Anti-Tg Ab [Table 3]. Multiple regression analysis revealed independent contribution of MAP (β 0.878, $P = 0.000$ in SCH and β 0.510, $P = 0.011$ in OH), atherogenic index (AI) (β 0.786, $P = 0.002$ in SCH and β 1.152, $P = 0.000$ in OH) and hsCRP (β 0.568, $P = 0.012$ in SCH and β 0.625, $P = 0.005$ in OH) to LH-HF ratio [Table 4]. Bivariate logistic regression [Table 5] showed significant prediction of LF-HF to hypertension status in SCH (odds ratio (OR) 1.90, CI 1.108-4.352, $P = 0.009$) and OH (OR 2.15, CI 0.126-5.867, $P = 0.002$) patients.

Table 3: Correlation of LH-HF ratio with various parameters of control, SCH and OH subjects

Parameters	Controls group		SCH group		OH group	
	r	*P*	*r*	*P*	*r*	*P*
BMI	−0.038	0.625	0.156	0.194	0.189	0.168
BHR	0.142	0.224	−0.285	0.023	−0.540	0.000
MAP	0.090	0.434	0.525	0.000	0.735	0.000
TSH	−0.160	0.216	0.302	0.015	0.317	0.009
TC	0.096	0.425	0.524	0.000	0.748	0.000
TG	0.012	0.806	0.515	0.000	0.754	0.000
LDL	0.030	0.635	0.834	0.000	0.804	0.000
VLDL	0.010	0.945	0.560	0.000	0.815	0.000
HDL	0.125	0.272	−0.268	0.045	−0.716	0.000
TC/HDL	−0.075	0.542	0.718	0.000	0.832	0.000
TG/HDL	−0.082	0.515	0.592	0.000	0.856	0.000
LDL/HDL	−0.088	0.487	0.687	0.000	0.824	0.000
AI	−0.090	0.480	0.605	0.000	0.794	0.000
Anti-TPO Ab	0.110	0.258	0.387	0.002	0.755	0.000
Anti-Tg Ab	−0.025	0.733	0.234	0.088	0.255	0.064
hsCRP	−0.210	0.114	0.612	0.000	0.725	0.000

P<0.05 was considered statistically significant. LF-HF ratio: Ratio of low-frequency power to high-frequency power of heart rate variability, BMI: Body mass index, BHR: Basal heart rate, MAP: Mean arterial pressure, TSH: Thyroid stimulating hormone, TC: Total cholesterol, TG: Triglycerides, HDL: High density lipoproteins, LDL: Low density lipoproteins, VLDL: Very low density lipoproteins, AI: Atherogenic index, anti-TPO Ab: Anti-thyroperoxidase antibody, anti-Tg Ab: Anti-thyroglobulin antibody, hsCRP: High-sensitive C-reactive protein, SCH: Subclinical hypothyroidism, OH: Overt-hypothyroidism

Table 4: Multiple regression analysis of LF-HF ratio (as dependent variable) with various other associated factors (as independent variables) in SCH and OH group

Independent Variables	SCH group		OH group	
	Standardized *β* (95% CI)	*P* value	Standardized *β* (95% CI)	*P* value
MAP	0.878 (0.003-0.075)	0.000	0.510 (0.003-0.025)	0.011
AI	0.786 (1.892-3.085)	0.002	1.152 (0.315-2.356)	0.000
hsCRP	0.568 (0.215-1.289)	0.012	0.625 (0.278-3.012)	0.005
Anti-TPO Ab	0.090 (0.000-0.002)	0.417	0.098 (−0.005-0.007)	0.324
TSH	0.211 (0.000-0.003)	0.090	0.232 (0.000-0.001)	0.065

P<0.05 was considered statistically significant. LF-HF ratio: Ratio of low-frequency power to high-frequency power of heart rate variability, MAP: Mean arterial pressure, AI: Atherogenic index, hsCRP: High-sensitive C-reactive protein, anti-TPO Ab: Anti-thyroperoxidase antibody, TSH: Thyroid stimulating hormone, CI: Confidence interval, SCH: Subclinical hypothyroidism, OH: Overt-hypothyroidism

DISCUSSION

In the present study, LH-HF ratio, a sensitive indicator of SVI,[18,19] was significantly increased in subclinical and overt hypothyroid patients compared to controls and the increase in LF-HF ratio was more significant in overt hypothyroid group. As increase in LF-HF ratio indicates increased sympathetic drive to the heart,[18,19] it is evident that cardiac sympathetic drive was more in both subclinical and overt hypothyroid patients, which was more accentuated in overt hypothyroids. Further, LFnu that primarily reflects sympathetic modulation of heart,[18] was significantly increased in subclinical and overt hypothyroid patients, especially more prominent in overt hypothyroid group [Table 1]. In addition, DBP was significantly increased in subclinical and overt hypothyroid patients compared to controls, which indicates increased sympathetic activity in these patients as DBP is the reflection of sympathetic vasoconstrictor tone.[9] The HRV parameters like TP, HFnu, and all TDI (RMSSD, SDNN, NN50, and pNN50) represent parasympathetic drive to the heart.[18] In hypothyroid patients, all these parameters were significantly decreased indicating reduced parasympathetic activity. In addition, these parasympathetic indices were more prominently reduced in overt hypothyroid patients compared to subclinical hypothyroid patients. Thus, there was increased sympathetic and decreased parasympathetic activity leading to SVI in these patients, which was more intense in overt hypothyroid patients. This indicates that the autonomic imbalance could be proportionate with the degree of thyroid hormone deficiency. HRV analysis has been used as a marker for the progression of CV disease in several high-risk populations,[20] and also as a predictor of sudden cardiac death.[21]

Table 5: Bivariate logistic regression for assessment of link of hypertension status (as dependent variable) with LF-HF ratio (as independent variable) in SCH group and OH group after adjusting for age and BMI

SCH group		OH group	
OR (95% CI)	*P* value	OR (95% CI)	*P* value
1.90 (1.108-4.352)	0.009	2.15 (0.126-5.867)	0.002

P<oo.05 considered significant. OR: Odds ratio, LF-HF ratio: Ratio of low-frequency power to high-frequency power of heart rate variability, CI: Confidence interval, SCH: Subclinical hypothyroidism, OH: Overt hypothyroidism

Among CAFT parameters, increase in 30:15 ratio (HR response to standing) and decrease in E:I ratio (deep breathing) indicate lower parasympathetic reactivity and increase in BP response to isometric handgrip (ΔDBP_{IHG}) indicates higher sympathetic reactivity.[19] There was decreased vagal and increased sympathetic reactivity in subclinical and overt hypothyroid patients [Table 1], and the changes were more significant in overt hypothyroid patients. Thus, findings of the present study suggest that the SVI in subclinical and overt hypothyroid patients is due to decreased parasympathetic activity and reactivity, along with increased sympathetic activity and reactivity. However, the degree of SVI was more in overt hypothyroids compared to subclinical hypothyroid patients.

There was significant dyslipidemia (hypercholesterolemia, triglyceridemia, high LDL-hypercholesterolemia, high VLDL-hypercholesterolemia, and low HDL-cholesterolemia) and increased lipid risk factors [Table 2] in subclinical and overt hypothyroid patients compared to the controls, and the degree of dyslipidemia was more marked in overt hypothyroid group compared to the subclinical hypothyroid group. All lipid parameters were significantly correlated with LF-HF ratio [Table 3]. However, the degree of correlation was more in overt hypothyroid patients compared to subclinical hypothyroid patients. Besides AI, which is a better indicator of CV risk, had significant independent contribution to LF-HF ratio [Table 4], and its contribution was more in overt hypothyroid patients compared to subclinical hypothyroid patients. As dyslipidemia significantly impairs endothelial dysfunction and increases sympathetic drive,[15] the rising dyslipidemia contributes significantly to SVI in a gradual manner from subclinical to overt hypothyroid condition.

Low-grade inflammation and altered immunological status have been reported in both SCH and OH.[3,7] In the present study hsCRP, anti-TPO Ab, and anti-TG Ab were significantly increased in subclinical and overt hypothyroid patients compared to controls and in overt hypothyroid patients compared to subclinical hypothyroid patients. The LF-HF ratio was significantly correlated with hsCRP and anti-TPO Ab in subclinical and overt hypothyroid patients with the significance being more for overt hypothyroid patients [Table 3]. However, only hsCRP had significant independent contribution to LF-HF ratio and the contribution was more in overt hypothyroid patients compared to subclinical hypothyroid patients [Table 5]. Therefore, alteration in SVI in SCH and OH appears to be directly linked to the level of hsCRP. It has been reported that CRP is an independent predictor for carotid artery intima-media thickness progression in asymptomatic younger adults.[22] Therefore, gradually elevated hsCRP from subclinical to overt hypothyroid condition plays a role in progression of SVI and adds to the CV risk.

Dyslipidemia, inflammation,[7,15] and SVI[17] are known CV risk factors, which are increased in SCH[23] and OH.[3,4] In the present study, SVI was associated with dyslipidemia and inflammation, and the risk factors were observed to be increasingly more with decrease in thyroid function. Furthermore, increased MAP was significantly associated with LF-HF ratio (SVI) in subclinical and overt hypothyroid patients [Table 4]. Recently, we have reported the association of SVI with hypertension status that increases CV risks in hypothyroid patients.[3] In the present study, LF-HF ratio had significant prediction for hypertension status in both subclinical and overt hypothyroid patients, which was more prominent in OH [Table 5]. Therefore, the findings of the present study demonstrate that considerable SVI, sustained hyperlipidemia, and chronic low-grade inflammation in both subclinical and overt hypothyroid patients predispose them to increased risk of CV morbidity and mortality, and SVI could be the physiological basis of CV risks in these patients.

In the present study, LF-HF ratio had more independent contribution to MAP in subclinical compared to overt hypothyroids [Table 4], indicating that SVI profoundly contribute to rise in BP in SCH. As such, usually SCH is clinically less symptomatic, and these abnormalities may remain undetected for several years during which these patients could be susceptible to greater CV risks. SCH has been reported to be associated with impaired left ventricular diastolic function, mild systolic dysfunction and enhanced risk for atherosclerosis and myocardial infarction.[24] Further, subclinical hypothyroid patients have an increased risk for all-cause mortality and CV disease death.[25,26] Also, SCH may progress to OH in approximately 2-5% cases annually.[27] As AI and hsCRP had independent association with SVI, further research should evaluate the cause-effect relationship among these factors, and should also assess if hypolipidemic and anti-inflammatory therapy can improve sympathovagal balance in SCH and OH. Moreover, subclinical and overt hypothyroid patients should also be encouraged to adapt nonpharmacological therapies such as pranayamic breathing exercises and yoga, as reports from our laboratory and others have documented reduction of sympathetic activity and improvement of vagal activity following practice of such life style modification programs.[28,29]

Limitations of the study

In the present study we have not assessed cardiac dysfunctions directly by radioimaging techniques and their possible correlation with SVI in subclinical and overt hypothyroid patients.

CONCLUSION

In this study, HRV was found to be grossly reduced in subclinical and overt hypothyroid patients predisposing them to CV morbidities, which was more intense in overt hypothyroids. SVI in SCH was due to the concomitant increased sympathetic and decreased vagal activities, which was proportionately accentuated in OH. SVI was associated with dyslipidemia and low-grade inflammation. SVI was linked to hypertension status in these patients. As chronic SVI, hypertension, hyperlipidemia, and inflammation are known CV risk factors, further research should be conducted to assess if improvement in cardiometabolic functions and attainment of sympathovagal homeostasis can improve the CV health in subclinical and overt hypothyroid patients.

ACKNOWLEDGMENTS

We acknowledge the intramural financial assistance from JIPMER as Intramural PhD Research Grant for supporting this study.

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How to cite this article: Syamsunder AN, Pal P, Kamalanathan CS, Parija SC, Pal GK, Jayakrishnan G, *et al*. Dyslipidemia and low-grade inflammation are associated with sympathovagal imbalance and cardiovascular risks in subclinical and overt hypothyroidism. Int J Clin Exp Physiol 2014;1:26-33.

Source of Support: JIPMER as Intramural PhD Research Grant, **Conflict of Interest:** Nil.