

Association of Sympathovagal Imbalance with Cardiovascular Risks in Overt Hypothyroidism

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Abstract

Background: Cardiovascular morbidities have been reported in hypothyroidism. **Aims:** The objective of this study is to investigate the link of sympathovagal imbalance (SVI) to cardiovascular risks (CVRs) and the plausible mechanisms of CVR in hypothyroidism. **Materials and Methods:** Age-matched 104 females (50 controls, 54 hypothyroids) were recruited and their body mass index (BMI), cardiovascular parameters, autonomic function tests by spectral analysis of heart rate variability (HRV), heart rate response to standing, deep breathing and blood pressure response to isometric handgrip were studied. Thyroid profile, lipid profile, immunological and inflammatory markers were estimated and their association with low-frequency to the high-frequency ratio (LF-HF) of HRV, the marker of SVI was assessed by multivariate regression. **Results:** Increased diastolic pressure, decreased HRV, increased LF-HF, dyslipidemia and increased high-sensitive C-reactive protein (hsCRP) were observed in hypothyroid patients and all these parameters had significant correlation with LF-HF. BMI had no significant association with LF-HF. Atherogenic index (β 1.144, $P = 0.001$) and hsCRP (β 0.578, $P = 0.009$) had independent contribution to LF-HF. LF-HF could significantly predict hypertension status (odds ratio 2.05, confidence interval 1.110-5.352, $P = 0.008$) in hypothyroid subjects. **Conclusions:** SVI due to sympathetic activation and vagal withdrawal occurs in hypothyroidism. Dyslipidemia and low-grade inflammation, but not obesity contribute to SVI and SVI contributes to cardiovascular risks.

Keywords: Autonomic imbalance, Body mass index, Cardiovascular risks, Dyslipidemia, High-sensitive C-reactive protein, Hypothyroidism, Sympathovagal imbalance

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Introduction

Hypothyroidism is among the common endocrine diseases accounting for 2-15% of diseases in the general population.^[1] In India, hypothyroidism is the second most metabolic disorder, next to diabetes mellitus.^[2] Hypothyroidism in general is a prominent hypometabolic state and sympathetic activities are anticipated to be less in this condition as sympathetic activation is a common manifestation of hypermetabolic state such

as hyperthyroidism.^[3,4] However, sympathovagal imbalance (SVI) due to increased sympathetic activity has been reported in hypothyroidism.^[5,6] In addition, one report indicates that autonomic neuropathy in hypothyroidism is due to increased vagal tone that partly subsides with thyroxine therapy.^[7] We have recently reported that SVI in hypothyroidism in females is due to sympathetic activation and vagal withdrawal.^[8] Increased parasympathetic tone is beneficial for cardiac health and poor vagal tone is associated with increased cardiovascular morbidities.^[9] Though cardiovascular morbidities are not uncommon in hypothyroidism,^[10-13] the pathophysiologic mechanisms of cardiovascular dysfunctions in hypothyroidism has not yet been fully elucidated.

Chronic SVI,^[14,15] inflammation,^[16,17] obesity^[18] and hyperlipidemia^[19] are reported to be associated with cardiovascular risks (CVRs). Though obesity is a common

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clinical feature of hypothyroidism^[20] and obesity has been reported to induce autonomic imbalance,^[21] until date no study has assessed the link of obesity to SVI in hypothyroidism. There is a report of increased CVRs in hypothyroidism^[22] and recently one report has suggested that insulin resistance and increased plasma level of insulin, C-peptide and lipoproteins in hypothyroid patients increases their risk for cardiovascular diseases.^[23] Though hyperlipidemia is a biochemical hallmark of hypothyroidism^[20] and there are reports of inflammation in subclinical hypothyroidism,^[24] to best of our knowledge no study has been conducted to date to assess the contribution of hyperlipidemia and inflammation to SVI in the causation of cardiovascular morbidities in hypothyroidism. Therefore, in the present study we have assessed the magnitude of SVI in hypothyroidism and its plausible link to the CVRs in this condition. In addition to the classical autonomic function tests (CAFTs) to assess sympathovagal balance,^[25] recently power spectral analysis of heart rate variability (HRV) has been documented as a sensitive measure of sympathovagal balance.^[26] Therefore, in the present study we have used HRV analysis to assess SVI in hypothyroidism. As hypothyroidism is more common in females compared with males with the male-female ratio 1:6-8,^[20] in the present study we have assessed the contribution of obesity, dyslipidemia and inflammation to SVI in female 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, 104 female subjects (50 euthyroid subjects and 54 hypothyroid patients) were recruited from the endocrinology clinic of JIPMER Hospital. Written informed consent was obtained from all the participants prior to initiation of the study. Subjects of study groups were freshly diagnosed untreated female hypothyroid patients.

Inclusion criteria

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

Exclusion criteria

Patients, who were already on treatment for 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 at about 8 am without breakfast. Height and weight were measured to calculate body mass index (BMI). Following 10 min of supine rest in polygraph laboratory (room temperature maintained at 25°C), the following recordings were done.

Recording of baseline heart rate (HR), blood pressure (BP) and HRV

Baseline HR and 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 the recording of short-term HRV, the procedure as described earlier^[8] and recommendation of the task force on HRV was followed.^[27] For the purpose, electrocardiography (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. (BIOPAC Inc., Goleta, CA, USA). Ectopics and artefacts were removed from the recorded ECG. HRV analysis was performed 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 low-frequency to high-frequency power (LF-HF ratio) and time domain indices such as mean of the peak of R to R wave of ECG (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 functions tests

Three CAFTs were performed following the standard procedures.^[25]

Lying to standing test

In this test, HR and BP response to standing was assessed. The BP and ECG were recorded in the supine position. The subject was instructed 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) until 5th min. 30:15 ratio (ratio

of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing) was calculated.

Deep breathing test

The subject in sitting posture, the HR and respiration monitoring was done from ECG recording and stethographic respiratory tracings recorded 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 minute. 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 min and 2nd min of contraction. $\Delta\text{DBP}_{\text{IHG}}$ (maximum rise in diastolic blood pressure above baseline) was noted.

Measurement of biochemical parameters

A total 5 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 3 (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) were assayed by chemiluminiscence method using the kits of Siemens Healthcare Diagnostics Inc., USA. Lipid profile (total cholesterol, triglycerides, high density lipoprotein [HDL], low density lipoprotein [LDL] and very low density lipoprotein [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 (IgE) 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 the enzyme immunoassay method using ELISA kit (dbc Diagnostics Biochem Canada Inc., Canada).

Statistical analysis

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 \pm 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 non-parametric 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 logistic regression was performed for the prediction of BP (normotension) status in control subjects and hypertension status in hypothyroid patients by LF-HF ratio. *P* values are lesser than 0.05 were considered to be statistically significant.

Results

There was no significant difference in age of control and hypothyroid subjects [Table 1]. BMI of hypothyroids was significantly more compared with that of controls

Table 1: Age, BMI, basal CV, HRV and CAFT parameters of control and hypothyroid subjects

Parameters	Controls (<i>n</i> =50)	Hypothyroids (<i>n</i> =54)	<i>P</i> value
Age, BMI and CV parameters			
Age (years)	25.48 \pm 5.61	27.20 \pm 4.67	0.091
BMI (kg/m ²)	20.83 \pm 2.95	26.53 \pm 3.52	0.000
BHR (min ⁻¹)	75.60 \pm 5.60	71.29 \pm 6.55	0.005
SBP (mmHg)	108.56 \pm 8.37	109.44 \pm 9.80	0.624
DBP (mmHg)	71.78 \pm 5.12	78.64 \pm 7.25	0.000
MAP (mmHg)	83.88 \pm 6.74	88.96 \pm 7.25	0.004
HRV parameters			
TP (ms ²)	918.02 \pm 329.14	374.94 \pm 125.09	0.000
LFnu	35.27 \pm 15.88	57.68 \pm 20.10	0.000
HFnu	64.36 \pm 21.60	42.18 \pm 15.72	0.000
LF-HF ratio	0.53 \pm 0.24	1.18 \pm 0.32	0.000
Mean RR (s)	0.793 \pm 0.11	0.841 \pm 0.12	0.036
RMSSD (ms)	55.99 \pm 18.36	42.47 \pm 12.30	0.000
SDNN (ms)	44.72 \pm 12.76	26.50 \pm 5.45	0.000
NN50	59.46 \pm 14.30	42.42 \pm 11.54	0.000
pNN50	29.12 \pm 5.61	20.12 \pm 4.81	0.000
CAFT parameters			
30:15 ratio	1.21 \pm 0.16	1.44 \pm 0.10	0.000
E:I ratio	1.42 \pm 0.13	1.12 \pm 0.14	0.000
$\Delta\text{DBP}_{\text{IHG}}$	22.40 \pm 5.70	30.30 \pm 6.10	0.000

Data presented are mean \pm SD; *P*<0.05 were considered statistically significant. RR: Peak of R to R wave of ECG; SD: Standard deviation; BMI: Body mass index; CV: Cardiovascular; BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HRV: Heart rate variability; MAP: Mean arterial pressure; TP: Total power; LFnu: Normalized low-frequency power; HFnu: Normalized high-frequency power; CAFT: Conventional autonomic function test; RMSSD: The square root of the mean of squares of the differences between adjacent NN intervals; SDNN: Standard deviation of normal to normal interval; NN50: The number of interval differences of successive NN intervals greater than 50; pNN50: The proportion derived by dividing NN50 by the total number of NN intervals; 30:15 ratio: The ratio of maximum RR interval at 30th beat to minimum RR interval at 15th beat following standing; E:I ratio: The ratio of average RR interval during expiration to that of during inspiration in six cycles of deep breathing; $\Delta\text{DBP}_{\text{IHG}}$: The maximum rise in DBP above baseline following 30% of maximum voluntary contraction by isometric handgrip method; LF-HF ratio: ratio of low-frequency power to high-frequency power of heart rate variability

($P = 0.000$). The basal heart rate of hypothyroid patients was significantly less ($P = 0.005$) compared with that of euthyroid subjects. Though, there was no significant difference in systolic blood pressure (SBP), the diastolic blood pressure (DBP) ($P = 0.000$) and mean arterial pressure (MAP) ($P = 0.004$) were significantly more in hypothyroid patients compared with the control subjects [Table 1].

TP of HRV spectrum, HFnu were reduced significantly ($P = 0.000$) and LFnu and LF-HF ratio were increased significantly ($P = 0.000$) in hypothyroid group [Table 1]. The time domain indices of HRV (mean RR, RMSSD, SDNN, NN50, pNN50) were significantly decreased ($P = 0.000$) in hypothyroid group compared with the control group. The 30:15 ratio and $\Delta\text{DBP}_{\text{IHG}}$ were significantly increased ($P = 0.000$) and E:I ratio was significantly decreased ($P = 0.000$) in hypothyroids compared to that of euthyroids [Table 1].

There was a significant decrease ($P = 0.000$) in fT3 and fT4 and increase in TSH ($P = 0.000$) in hypothyroid group compared to the euthyroid group [Table 2]. Total cholesterol, triglyceride, LDL, VLDL were increased ($P = 0.000$) and HDL ($P = 0.000$) was decreased in hypothyroid patients. All the lipid risk factors were significantly high ($P = 0.000$) in hypothyroid subjects. Levels of anti-TPO Ab, anti-TG antibody and hsCRP

were increased ($P = 0.000$) and the level of IgE was not significantly altered in hypothyroid group compared to the control group [Table 2].

LF-HF ratio was not significantly correlated with any of the parameter except fT3 ($P = 0.026$) in the control group [Table 3]. In hypothyroid group, there was a significant correlation of LF-HF ratio with all cardiovascular parameters, thyroid and lipid profile parameters, lipid risk factors and inflammatory and immunological markers except BMI, SBP and IgE [Table 3]. Multiple regression analysis revealed independent contribution of MAP (β 0.298, $P = 0.020$), hsCRP (β 0.578, $P = 0.009$), atherogenic index (AI) (β 1.144, $P = 0.001$) to LH-HF ratio [Table 4]. Bivariate logistic regression [Table 5] showed significant prediction of LF-HF to hypertension status (odds ratio [OR] 2.05, confidence interval [CI] 1.110-5.352, $P = 0.008$) in hypothyroid subjects, but the prediction was not significant in control subjects (OR 0.54, CI 0.37-2.115, $P = 0.170$).

Discussion

In the present study, significant increase in LF-HF ratio in female hypothyroid patients compared to their age-matched controls [Table 1] indicates the presence of considerable SVI in these patients, as LH-HF ratio is a sensitive marker of sympathovagal balance.^[26,27]

Table 2: Thyroid profile, lipid profile, lipid risk factors, immunological and inflammatory markers of control and hypothyroid subjects

Parameters	Controls (n=50)	Hypothyroids (n=54)	P value
Thyroid profile			
Free-T3 (pg/mL)	2.95±0.91	1.500±0.50	0.000
Free-T4 (ng/dL)	1.340±0.55	0.620±0.28	0.000
TSH (μIU/mL)	3.75±1.28	97.63±55.82	0.000
Lipid profile			
TC (mg/dL)	161.44±14.87	279.72±44.12	0.000
TG (mg/dL)	70.34±16.08	125.07±23.25	0.000
LDL-cholesterol (mg/dL)	94.95±15.19	216.22±45.10	0.000
VLDL-cholesterol (mg/dL)	15.00±2.99	25.13±4.41	0.000
HDL-cholesterol (mg/dL)	51.48±7.83	38.37±5.71	0.000
Lipid risk factors			
TC/HDL	3.190±0.50	7.60±2.19	0.000
TG/HDL	1.380±0.34	3.40±1.05	0.000
LDL/HDL	1.900±0.46	5.91±1.99	0.000
AI	0.120±0.11	0.500±0.14	0.000
Immunological parameters			
Anti-TPO Ab (IU/mL)	133.75±31.16	423.94±77.15	0.000
Anti-TG Ab (IU/mL)	2.000±0.62	77.45±51.33	0.000
IgE (IU/mL)	213.56±42.08	211.05±40.37	0.757
Inflammatory marker			
hsCRP (ng/mL)	584.83±205.53	1057.30±239.65	0.000

Data presented are mean±SD; $P < 0.05$ were considered statistically significant. AI=Log10 (TG/HDL); TSH: thyroid stimulating hormone; Anti-TPO Ab: Anti-thyroperoxidase antibody; Anti-TG Ab: Anti-thyroglobulin antibody; IgE: Immunoglobulin E; hsCRP: high-sensitive C-reactive protein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein; TC: Total cholesterol; TG: Triglycerides; AI: Atherogenic index; SD: Standard deviation

Increase in LF-HF ratio indicates increased sympathetic activity.^[26] This was further supported by increase in LFnu ($P = 0.000$) in hypothyroid group, as increased LFnu is an index of increased cardiac sympathetic drive.^[26,27] In hypothyroid subjects, significant decrease in HFnu ($P = 0.000$) indicates decreased parasympathetic tone in these patients, as HFnu represents vagal drive to the

heart.^[26,27] This was supported by a significant reduction in TP of HRV in hypothyroid group, as TP in general indicates the vagal modulation of cardiac function.^[26,27] Moreover, all time-domain indices (mean RR, RMSSD, SDNN, NN50, pNN50) were significantly less in hypothyroid subjects [Table 1] further indicating the decreased vagal tone in these subjects, as time-domain indices of HRV represent cardiac parasympathetic drive. Thus, it is evident from the present study that SVI in hypothyroid patients is due to the concomitant increase in sympathetic activity and decrease in vagal activity, that corroborates with our earlier report^[8] and the report of Cacciatori *et al.*^[28] Further, there was increased autonomic reactivity in these patients as evident from changes in CAFT parameters [Table 1]. HR response to standing (30:15 ratio) and deep breathing (E:I ratio) are parasympathetic function tests and BP response to isometric handgrip ($\Delta\text{DBP}_{\text{IHG}}$) is sympathetic function test.^[17] Significantly high 30:15 ratio and decreased E:I ratio in hypothyroid subjects reflects lower vagal reactivity in hypothyroids.^[25] A heightened diastolic pressure response to isometric handgrip ($\Delta\text{DBP}_{\text{IHG}}$) in these subjects reflects increased sympathetic reactivity, as increase in DBP in handgrip test depends primarily on the vascular resistance that reflects sympathetic response.^[25] Thus, findings of the present study substantiate that the SVI in hypothyroidism is due to increased sympathetic activity and reactivity, along with decreased parasympathetic activity and reactivity.

Though LF-HF ratio, the marker of sympathovagal balance,^[26,27] was correlated with T3, T4 and TSH in hypothyroid subjects [Table 3], multivariate regression did not show independent contribution of these parameters to LF-HF [Table 4]. Therefore, alteration in SVI in hypothyroidism does not appear to be directly linked to the level of thyroid hormones and TSH. Though SVI is linked to the plasma level of thyroid hormones and TSH in hyperthyroidism (state of thyroid excess),^[29]

Table 3: Correlation of LH-HF with various parameters of control and hypothyroid subjects

Parameters	Controls ($n=50$)		Hypothyroids ($n=54$)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
BMI	-0.025	0.861	0.181	0.189
BHR	0.018	0.900	-0.746	0.000
SBP	0.230	0.108	0.108	0.438
DBP	-0.082	0.571	0.832	0.000
MAP	0.066	0.648	0.825	0.000
Free-T3	0.315	0.026	-0.283	0.038
Free-T4	0.247	0.084	-0.864	0.000
TSH	-0.168	0.244	0.312	0.022
TC	0.094	0.517	0.841	0.000
TG	0.002	0.990	0.841	0.000
HDL	0.141	0.330	-0.821	0.000
LDL	0.023	0.872	0.844	0.000
VLDL	0.007	0.963	0.852	0.000
TC/HDL	-0.083	0.568	0.860	0.000
TG/HDL	-0.080	0.579	0.870	0.000
LDL/HDL	-0.073	0.615	0.858	0.000
AI	-0.086	0.552	0.841	0.000
Anti-TPO Ab	0.130	0.369	0.852	0.000
Anti-TG Ab	-0.013	0.927	0.190	0.028
hsCRP	-0.200	0.165	0.784	0.000

$P < 0.05$ were considered statistically significant. BMI: Body mass index; BHR: Basal heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; 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; LH-HF: Low frequency-high-frequency

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

Independent variables	Standardized regression coefficient beta	95% CI		<i>P</i> values
		Lower bound	Upper bound	
MAP	0.298	0.004	0.023	0.020
hsCRP	0.578	0.283	3.214	0.009
Atherogenic index	1.144	0.329	2.236	0.001
Anti-TPO Ab	0.344	-0.002	0.005	0.435
Anti-TG Ab	-0.077	-0.001	0.000	0.260
Free T3	-0.092	-0.031	0.014	0.286
Free T4	-0.110	-0.115	0.100	0.276
TSH	0.211	0.000	0.001	0.077

$P < 0.05$ were considered statistically significant. MAP: Mean arterial pressure; hsCRP: high-sensitive C-reactive protein; Anti-TPO Ab: Anti-thyroperoxidase antibody; Anti-TG Ab: Anti-thyroglobulin antibody; TSH: thyroid stimulating hormone; CI: confidence interval; LF-HF ratio: ratio of low-frequency power to high-frequency power of heart rate variability

Table 5: Bivariate logistic regression analysis of BP status or hypertension status (as dependent variable) with LF-HF ratio (as independent variable) in the control group and hypothyroid group after adjusting for age and BMI

Control group		Hypothyroid group	
OR (95% CI)	P value	OR (95% CI)	P value
0.54 (0.37-2.115)	0.170	2.05 (1.110-5.352)	0.008

P<0.05 considered as significant. OR: odds ratio; LF-HF ratio: ratio of low-frequency power to high-frequency power of heart rate variability; CI: confidence interval; BMI: Body mass index; BP: Blood pressure

findings of the present study does not illustrate the association of autonomic imbalance with thyroid profile in hypothyroidism (thyroid deficiency state).

One may suggest that significantly high BMI in hypothyroid subjects [Table 1] could be a major contributor to SVI in this dysfunction, as increased adiposity has been reported to cause vagal inhibition and sympathetic overactivity.^[30,31] However, obesity in hypothyroidism is not primarily due to excess adiposity as increase in bodyweight in thyroid deficiency state is mostly due to accumulation of water and mucopolysaccharides in subcutaneous tissues.^[32] Moreover, there was no significant correlation of LF-HF ratio with BMI in hypothyroid patients [Table 3]. Therefore, contribution of increased BMI to SVI in hypothyroidism appears to be negligible.

Though the exact cause of SVI in hypothyroidism cannot be fully ascertained from the present study, it appears that SVI is linked to the degree of hyperlipidemia. Not only there was significant dyslipidemia (hypercholesterolemia, triglyceridemia, high LDL-hypercholesterolemia, high VLDL-hypercholesterolemia and low HDL-cholesterolemia) and increased lipid risk factors [Table 2] in hypothyroid subjects compared to the control subjects, but also all these factors were significantly correlated with LF-HF ratio [Table 3]. Moreover, the AI had significant independent contribution to LF-HF ratio [Table 4]. From among the lipid risk factors assessed in the present study, we selected AI for the regression model, as AI has recently been reported to be the better indicator of CV risk.^[33] Other lipid risk factors were excluded from the same regression model to avoid multicollinearity. Hyperlipidemia is very common in hypothyroidism^[32] and hypercholesterolemia has been reported to be associated with increased sympathetic activity.^[34,35] Thus, from findings of the present study it appears that chronic and profound hyperlipidemia could be a major contributor to SVI in hypothyroidism.

There is a report of low-grade immunological inflammation in thyroid deficient subjects.^[24] In the

present study hsCRP, anti-TPO Ab and anti-TG Ab were more in hypothyroid subjects compared to that of control subjects. The hsCRP was significantly correlated with LF-HF and had significant independent contribution to LF-HF ratio. It has been reported that CRP influences cardio-respiratory health through alteration in autonomic functions.^[36] Therefore, low-grade inflammation might play a significant role in the genesis of SVI in hypothyroidism. However, anti-TPO and anti-TG antibodies had no significant contribution to LF-HF ratio [Table 5]. Therefore, it is unlikely that immunological markers contribute to the genesis of SVI in hypothyroidism.

There are reports of increased CVRs in conditions of SVI,^[14,15] inflammation^[16,17] and hyperlipidemia.^[9] As such there are reports of increased CVRs in subclinical and overt hypothyroidism.^[10-13] In the present study, SVI was associated with dyslipidemia, increased lipid risk factors and low-grade inflammation. A report has suggested that lipid risk factors and CRP are better markers of cardiovascular dysfunctions in females compared to the other predictors of adverse cardiovascular events such as apolipoproteins.^[37] Moreover, the reduction in HRV *per se* has been reported as an important CVR.^[38,39] In the present study, magnitude of HRV (TP of HRV) was grossly reduced in hypothyroid subjects predisposing them to CVR [Table 2]. Furthermore, DBP and MAP had significant link to LF-HF ratio (SVI) in hypothyroid subjects [Tables 3 and 4]. Recently we have reported the close association of SVI with increased vascular tone and hypertension status that increases CVRs in prehypertensives.^[40] In the present study, LF-HF ratio had significant prediction for hypertension status in hypothyroid subject [Table 5]. Therefore, we presume that SVI in hypothyroidism contributes to CVRs in hypothyroidism.

In the present study, CVRs observed in hypothyroid patients are hypertension, decreased HRV, dyslipidemia and low-grade inflammation that are associated with SVI. It appears that dyslipidemia and inflammation contribute to the SVI, which contributes to the hypertension status. Thus, considerable SVI, sustained hyperlipidemia and chronic low-grade inflammation in hypothyroid patients predispose them to increased risk of cardiovascular morbidity and mortality. As such hypothyroidism is a chronic disorder that takes months and years to achieve euthyroidism even after judicious treatment, especially in developing countries like India where patients' compliance is poor. Therefore, further research warrants the assessment of the efficacy of hypolipidemic and anti-inflammatory therapy on alleviation of SVI in hypothyroidism. Hypothyroid subjects should also be encouraged to adapt non-pharmacological 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.^[41,42] Limitation of the present study is that we have not assessed cardiac dysfunctions by radio-imaging techniques and their possible correlation with SVI in hypothyroid subjects.

Conclusions

In this study, HRV was found to be grossly reduced in hypothyroid patients predisposing them to cardiovascular morbidities. SVI in hypothyroid subjects was due to the concomitant increased sympathetic and decreased vagal activities, which was contributed by dyslipidemia and low-grade inflammation. SVI is linked to hypertension status in these patients. As chronic SVI, hypertension, hyperlipidemia and inflammation are known CVR factors, further research should be conducted to assess if improvement in sympathovagal homeostasis can improve the cardiovascular health in hypothyroid subjects.

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