Original Article

Association of stress and primary hypothyroidism

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Abstract

Background: Hypothyroidism is the result of impaired production and secretion of thyroid hormones. The cardiovascular system is affected by fluctuations in thyroid hormone levels. Stressful events or stressors can affect the hypothalamic-pituitary-thyroid (HPT) axis and psychological and physiological responses. Stress increases thyroid hormone levels while decreasing TSH levels, which exacerbates autoimmune thyroid disease. **Aim:** To evaluate the relationship between stress and primary hypothyroidism. **Methods:** A total of 77 newly diagnosed hypothyroid patients (TSH >5.0 mIU/L) and 77 healthy adults (TSH 0.5–5.0 mIU/L) were enrolled. During a brief general physical examination, the following values were measured: height, weight, blood pressure, pulse, and pulse rate. A brief systemic examination of the cardiovascular system and lungs was also performed to rule out systemic diseases. Heart rate variability (HRV) processing and analysis were performed using Pro LabChart (PowerLab 8Pro) data analysis software from AD Instrument. **Results:** Mean Avg. RR was significantly higher, RM SSD and pRR50 were significantly lower in cases than in controls. Mean HF was significantly lower and LF/HF (frequency range) was significantly higher in cases than in controls. Mean PSS was significantly higher in cases (25.82 ± 2.83) than in controls (22.47 ± 2.10). The majority of cases (54.5%) had a high stress level. The TSH level showed a highly significant correlation with the LF/HF ratio and with the PSS score. **Conclusion:** The mean Avg. RR and HF were significantly higher, RM SSD and pRR50 and LF/HF (frequency range) were significantly lower in hypothyroid patients.

Keywords: Cardiovascular system, hypothyroidism, stress, T3, T4, TSH

Introduction

Endocrine disorders affect a large proportion of the world's population. The prevalence of abnormal thyroid disease has increased significantly. About 42 million Indians have thyroid problems today.[1] In India, the prevalence of hypothyroidism is about 11%.[2] Primary care physicians often deal with patients who present with symptoms that may be associated with hypothyroidism or stress. Because of this overlap, it can be difficult to distinguish between the two conditions based on symptoms alone. To correctly diagnose primary hypothyroidism, primary care physicians must perform a comprehensive examination that includes a medical history, physical examination, and necessary laboratory tests. Hypothyroidism is the result of impaired production and secretion of thyroid hormones.

Hypothyroidism is the result of impaired production and secretion of thyroid hormones. Thyroid hormones are important for overall body energy metabolism and neuroendocrine function.[3] Thyroid dysfunction can manifest as hyperthyroidism or hypothyroidism. Thyroid hormones affect cardiac systolic and diastolic function, peripheral vascular resistance, and arrhythmogenesis.[4]

The cardiovascular system is affected by fluctuations in thyroid hormone levels. Left ventricular hypertrophy, cardiac arrhythmias,

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Received: 22-05-2023 **Revised:** 10-12-2023
Accepted: 22-12-2023 **Published:** 04-04-2024

Access this article online
Quick Response Code:
Website: http://journals.lww.com/JFMPC
DOI: 10.4103/jfmpc.jfmpc_845_23

How to cite this article: Singh M, Narayan J, Thakur R, Bhattacharya S, Sonkar SK, Ali W. Association of stress and primary hypothyroidism. J Family Med Prim Care 2024;13:1073-8.

diastolic dysfunction, and increased systolic function have been associated with both overt and subclinical hyperthyroidism.[5-7] In addition, (subclinical) hyperthyroidism causes sympathovagal imbalance characterized by increased sympathetic activity and decreased vagal tone.[8-11] In contrast, hypothyroidism is characterized by bradycardia, decreased cardiac output, diastolic cardiac dysfunction, mild diastolic hypertension, and increased peripheral cardiovascular resistance.[8,12,13] Similar cardiovascular abnormalities to those seen in chronic hypothyroidism, e.g. bradycardia, diastolic dysfunction, decreased systolic function on exertion, and increased systemic vascular resistance, also occur in acute short-term hypothyroidism.[14]

The hypothalamic–pituitary–adrenal axis, which is also responsible for maintaining homeostasis, is affected by stress, which is defined as the body's ad hoc response to any demand.[3] Stressful events or stressors can affect the hypothalamic–pituitary–thyroid (HPT) axis as well as psychological and physiological responses. In healthy individuals without thyroid disease, TSH and free thyroxine (T4) levels decrease during hunger and depression and increase during cold, psychosis, and obesity.[4] In contrast, TSH levels may increase during depressive episodes, and high TSH levels complicate the treatment of depression.[15,16] Therefore, individual TSH levels may vary even in the presence of identical stressors. In addition, stress increases thyroid hormone levels while decreasing TSH levels, which exacerbates autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.[6] In autoimmune thyroid diseases, it can be difficult to understand how the HPT axis responds, even if the stressor is the same. There is strong evidence that hypothyroidism often affects mental health. Psychological well-being and quality of life can be affected by the physical symptoms. In this study, we aim to evaluate the association of stress and primary hypothyroidism.

Material and Methods

Newly diagnosed patients with hypothyroidism were included in the case–control study after obtaining approval from the ethical committee of King George's Medical University (Ref. Code—IV PGTSC—IIA/P18). Written informed consent was obtained from each patient and recorded on the form provided by the research department. Of the 144 patients, a total of 77 newly diagnosed hypothyroid patients (TSH >5.0 mIU/L) were included as cases, and 77 healthy adults (TSH 0.5–5.0 mIU/L) were included in the study on the basis of well-defined inclusion and exclusion criteria. Newly diagnosed hypothyroid patients aged 18–45 years were included in this study. Pregnant women, patients with other endocrine disorders, cardiovascular diseases, and patients with psychiatric disorders were excluded from the study. The sample size was calculated based on a previous study, reporting that the prevalence of hypothyroidism in the general population in India is 11% (3.7 to 22.5%) [Bagcchi, 2014], with a confidence level of 95% and a margin of error that is usually 0.07.

A brief general physical examination was performed, during which the following parameters were measured: blood pressure, pulse, height, and weight. To rule out systemic diseases, a brief systemic examination of the respiratory and cardiovascular systems was also performed.

Pro LabChart (PowerLab 8Pro) data analysis software from AD Instrument was used for heart rate variability (HRV) processing and analysis. HRV was recorded with one lead II ECG in an upright sitting position for five minutes (short-term HRV). A nine-channel recorder was used to record the electrocardiographic waveforms. Five leads were used for ECG recording. Two negative electrodes (red and white) are placed in the right arm, one positive electrode (brown) in the left arm, one electrode (black) in the left leg, and one ground electrode (green) in the right leg. After recording the ECG, we select the HRV module and select the whole channel and no ectopic beats in the setting. The ECG signal was continuously amplified, digitized, and stored in the computer for offline analysis. Only cycles in which beats had normal morphological characteristics were used for analysis. Intervals between ectopic beats, between normal and ectopic beats, and intervals that were inaccurately measured because of artifacts were excluded from the analysis. The ECG recording in the computer confirmed that no ectopic beats or murmurs were present, and the RR interval was calculated and fed into the software for analysis (time domain and frequency domain).

For HRV (heart rate variability) analysis, both linear and nonlinear methods were used Frequency domain analysis was performed using the nonlinear fast Fourier transform (FFT) method. The power spectral density analyzes the information of the total power distribution as a function of frequency. The components of total power (frequency range 0.00–0.4 Hz) include: very low frequency (VLF, frequency range < 0.04 Hz), low frequency (LF, frequency range 0.04–0.15 Hz), and high frequency (HF, frequency range 0.15–0.4 Hz).

Measurements of the power components are usually made in absolute power values (ms^2), but LF and HF are also expressed in normalized units (n.u.), which represent the relative value of each power component with respect to the total power (TP) minus the VLF component. This shows the balanced and controlled behavior of the two branches of the autonomic nervous system in an individual, i.e., LF (nu) = LF/TP − VLF HF (nu) = HF/TP − VLF.

The time domain method determines the heart rate at any given time or the intervals between successive normal QRS complexes in a continuous ECG recording. Statistical time domain variables include standard deviation of RR interval (SDRR), root mean squared differences of successive RR intervals (RMSSD), proportion obtained by dividing RR50 by a total number of RR intervals (pRR50), RMSSD and pRR50 in time domain method are correlated with HF band in frequency domain method. Nonlinear parameters include: SD1 (ms)-Poincaré plot standard deviation perpendicular to the identity line. SD2 (ms)-Poincaré plot standard deviation along the identity line was observed.

All subjects (cases and controls) were given a Perceived Stress Scale questionnaire (PSS-14) and asked to complete the responses. The score on the perceived stress scale was used to assess the level of perceived stress in the study participants. The scores were calculated by reversing the responses (0 = 4, 1 = 3, 2 = 3, 3 = 1, and 4 = 0) for seven positively stated items (items 4, 5, 6, 7, 8, 9, 10, and 13) and summed.

Chemiluminescence microparticle immunoassay (CMIA) was used for the quantitative determination of thyroid-stimulating hormone (TSH), thyroxine (total T4), and triiodothyronine (total T3) in serum.

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 21.0. The values were represented in Number (%) and Mean ± SD. The Chi-square test was used to compare the categorical variables and the independent t test was used to compare discrete variables between groups. Statistical significance was set at $P < 0.05$

Results

The mean age and sex were comparable between the case and control groups. Mean weight (kg), height (cm), and BMI (kg/m^2) were 68.17 ± 5.54, 162.01 ± 4.82, and 25.97 ± 1.77 in cases and 61.86 ± 5.11, 161.97 ± 5.78, and 23.56 ± 1.25 in controls, respectively. Mean weight (kg) and BMI (kg/m^2) were significantly higher in cases than in controls.

Mean systolic BP (mm Hg), diastolic BP (mm Hg), and heart rate (bpm) were 124.52 ± 7.19, 80.92 ± 3.95, and 67.69 ± 4.16 in cases and 125.25 ± 6.62, 81.09 ± 3.22, and 79.84 ± 4.53 in controls. Mean heart rate (bpm) was significantly lower in cases than in controls [Table 1].

Mean T3 (ng/ml), T4 (μg/dl), and TSH (mIU/ml) values were 1.02 ± 0.26, 4.61 ± 2.38, and 13.64 ± 3.93 in cases and 1.48 ± 0.81, 7.34 ± 1.31, and 1.81 ± 0.90 in controls. Mean T3 (ng/ml) was significantly decreased and T4 (μg/dl) and TSH (mIU/ml) were significantly increased in cases compared with controls [Table 2].

Heart rate variability parameters of cases and controls are shown in Table 2. The mean Avg. RR, SD RR, RM SSD, and pRR50 (time domain) were 737.24 ± 114.41, 50.50 ± 18.32, 37.36 ± 21.19, and 6.51 ± 6.71 in cases and 685.34 ± 96.51, 54.65 ± 24.78, 52.69 ± 34.05, and 11.99 ± 10.70 in controls, respectively. Mean Avg. RR was significantly higher and RM SSD and pRR50 were significantly lower in cases than in controls. Mean HF was significantly lower and LF/HF (frequency range) was significantly higher in cases compared with controls. The mean VLF and LF were comparable [Table 3].

The mean PSS score was significantly higher in cases (25.82 ± 2.83) than in controls (22.47 ± 2.10). Using the PSS score, all subjects participating in the study were evaluated for their stress level. Subjects with a PSS score of 14–26 were classified as moderately stressed, while subjects with a PSS score of 27–40 were classified as severely stressed. The majority of cases (54.5%) had high-stress levels, while the vast majority of control subjects had moderate stress levels (98.7%). Based on stress level, the frequency of high perceived stress was significantly higher among cases than controls [Table 4].

The TSH level showed a highly significant correlation with the LF/HF ratio and with the PSS score. The significance level between the TSH level and LF/HF ratio was high ($r = 0.781$), whereas that between the TSH level and PSS score was moderate [Table 5].

Discussion

Primary care physicians play an important role in recognizing, treating, and determining the causes of primary hypothyroidism and stress. Understanding the possible interaction between these two elements is essential for comprehensive and efficient patient care.

In this study, the age ranged between 20 and 44 years and the mean age was 33.40 ± 5.33 years in cases and 32.81 ± 4.91 in controls. Total 66 (85.7%) were females and the rest 11 (14.3%) were males in cases. Moreover, hypothyroidism was more common in females. This finding is in accordance with the previous data available to us which indicates that females are

Table 1: Baseline characteristics of the patients

	Cases (n=77)		Controls (n=77)		't'/ Chi-Sq.	P
	Mean/n	±SD/%	Mean/n	±SD/%		
Age	33.40	5.33	32.81	4.91	−0.71	0.476
Gender (n,%)						
Female	66	85.7	66	85.7	0.00	1.000
Male	11	14.3	11	14.3		
Weight (kg)	68.17	5.54	61.86	5.11	7.351	<0.001
Height (cms)	162.01	4.82	161.97	5.78	0.045	0.964
BMI (kg/m^2)	25.97	1.77	23.56	1.25	9.750	<0.001
Systolic BP (mm Hg)	124.52	7.19	125.25	6.62	−0.653	0.515
Diastolic BP (mm Hg)	80.92	3.95	81.09	3.22	−0.291	0.772
Heart rate (bpm)	67.69	4.16	79.84	4.53	17.356	<0.001

more prone to develop thyroid dysfunction. Previous studies have shown that women (10:1) are more frequently affected by hyperthyroidism than men.[17] The prevalence of hyperthyroidism in women ranges from 0.54 to 2.0%.[17,18] Due in part to the autoimmune nature of many thyroid problems, women are more commonly affected by thyroid disease than men.[19] Both premenopausal and postmenopausal women frequently suffer from hypothyroidism and thyroid nodules.

In our study, body weight and BMI were significantly higher in hypothyroid patients compared with control subjects (euthyroid). Obesity was significantly associated with a higher risk of hypothyroidism, including overt and subclinical hypothyroidism, and was associated with at least a 1.86-fold increase in the development of hypothyroidism. An increased risk of overt (OR: 3.21, 95% CI: 2.12–4.86, *P* 0.001) and subclinical (OR: 1.70, 95% CI: 1.42–2.03, *P* 0.001) hypothyroidism was found in obese individuals.[20] Numerous other studies have associated excessive body weight with either increased TSH levels or reduced FT3 and FT4 levels.[21-24]

Only 27.3% of cases were within the range of normal BMI, 68.8% were overweight and 3.9% were obese, while 87.0% of controls had normal BMI and the remaining 13.0% were overweight and none were obese.[25] The proportion of overweight and obese cases was significantly higher than controls (68.8% vs. 13.0% and 3.9% vs. 0.0%, respectively). This may indicate that physicians should pay close attention to altered thyroid function in individuals with higher BMI. Data from previous studies suggest that more than just an elevated serum TSH level may be needed to detect subclinical hypothyroidism in adults with severe obesity. To confirm the diagnosis of autoimmune thyroid insufficiency in these patients, it seems appropriate to determine the levels of thyroid autoantibodies and thyroid hormones in circulating plasma.[24]

Table 2: Comparison of thyroid function parameters between cases and controls

Parameter	Case (*n*=77)		Controls (*n*=77)		Student "*t*" test	
	Mean	±SD	Mean	±SD	*t*	*P*
T3 (ng/ml)	1.02	0.26	1.48	0.81	4.817	0.067
T4 (μg/dl)	4.61	2.38	7.34	1.31	8.794	<0.001
TSH (mIU/ml)	13.64	3.93	1.81	0.90	25.732	<0.001

In our study, the mean systolic BP (mm Hg) and diastolic BP (mm Hg) were not significantly different between hypothyroid patients and controls, whereas the heart rate (bpm) was significantly lower in cases than in controls. As mentioned in the previous study, heart rate was an increase in sympathetic level and decreased level of vagal modulation in hypothyroid patients.[22] The mean heart rate was significantly lower in the hypothyroid group. Therefore, this can explain the relative bradycardia seen in hypothyroidism. The mean systolic blood pressure was no significant difference between the case and control groups.[25] Another study reported that diastolic blood pressure was a slight rise in hypothyroid patients.[26] The decrease in thyroid hormone may cause the elevation of blood pressure levels and also trigger of sympathetic/adrenal system.[27] In this study, we could not find any significant changes in blood pressure which may be due to a small sample size.

Heart rate variability (HRV) is a noninvasive, simple tool to assess the sympathovagal balance. Altered HRV has been associated with an increased risk of cardiovascular disease. HRV has been measured under two domains, i.e. time domain measures and frequency domain measures. In the time domain, the variables used for analysis were Avg. RR, SDRR, and RMSSD as mentioned by the Task Force.[28] SDRR signifies the standard deviation of the beat-to-beat interval of normal sinus beats (SDRR). The measurable unit for SDRR is ms. Both parasympathetic and sympathetic components of the autonomic nervous system contribute to SDRR. In this study, no significant difference was seen in the mean value of SDRR among the case and control groups.

In our study, the mean Avg. RR of controls (737.24) was significantly higher than the mean Avg. RR of cases (685.34). The mean RR was measured in the case and control groups, showing an increased mean RR interval in the hypothyroid subjects compared with the controls. Since the average RR interval is inversely related to heart rate, this explains the relative bradycardia in hypothyroid patients. The results of our study are in agreement with the studies of Galetta *et al*.[29]

Table 3: Comparison of heart rate variability parameters between cases and controls

	Cases (*n*=77)		Controls (*n*=77)		*t*	*P*
	Mean	±SD	Mean	±SD		
SN HRV parameters (Time domain)						
Avg. RR	737.24	114.41	685.34	96.51	3.043	0.003
SD RR	50.50	18.32	54.65	24.78	−1.182	0.239
RM SSD	37.36	21.19	52.69	34.05	−3.355	0.001
pRR50	6.51	6.71	11.99	10.70	−3.808	<0.001
SN HRV parameters (Frequency domain)						
VLF	850.97	517.90	766.82	527.98	0.998	0.320
LF	863.70	604.36	747.73	628.93	1.167	0.245
HF	358.24	326.44	949.56	798.43	−6.015	<0.001
LF/HF	3.11	1.60	0.90	0.38	11.780	<0.001

Table 4: Between Group Comparison of PSS-14 Score

	Cases (n=77)		Controls (n=77)		t	P
	Mean	±SD	Mean	±SD		
PSS score	25.82	2.83	22.47	2.10	8.33	<0.001
Level of stress	**No.**	**%**	**No.**	**%**	**Chi-Sq.**	***P***
Mod stress (PSS 14–26)	42	54.5	76	98.7	41.91	<0.001
High perceived (PSS 27–40)	35	45.5	1	1.3		

Table 5: Correlation of TSH levels with LF/HF Ratio and PSS Score

	Correlation coefficient	P
LF/HF ratio	0.781	<0.001
PSS score	0.690	<0.001

In this study, the mean value of RMSSD was lower in hypothyroid patients (37.37 ± 21.19) ms compared with controls (52.69 ± 34.05) ms. It was found that RMSSD was statistically significantly lower in hypothyroid patients (P value—0.001). Similarly, the time domains were lower in hypothyroid patients and there were statistically significant improvements in these parameters after thyroxine replacement treatment.[25,29]

In this study, the mean pRR50 was significantly low in the case group (6.51 ± 6.71) ms compared with the control subjects (11.99 ± 10.70) ms. The avg. RR, SDRR, RMSSD, and pRR50 are sensitive indicators of parasympathetic function. The high avg. RR and low values of SDRR, RMSSD, and pRR50 indicate decreased vagal activity in hypothyroid patients. The LF values, which are an indicator of sympathetic tone, were comparable in hypothyroid subjects (863.70 ± 604.36) ms^2 compared with controls (747.73 ± 628.93) ms^2.

The value HF is an indicator of parasympathetic tone. In this study, the mean value of HF was significantly lower in cases (358.24 ± 326.44) ms^2 and controls (949.56 ± 798.43) ms^2 in hypothyroid patients compared with controls (P value <0.001).

In this study, a significant increase in the LF/HF ratio (3.11 ± 1.60) was found in hypothyroid subjects, which may be due to sympathovagal imbalance. This is consistent with the findings of Galetta *et al.*[30] who observed decreased HF, increased LF amplitude, and increased LF/HF ratio in hypothyroid patients.

In our study, the mean value of HF was significantly higher in controls than in cases, and LF/HF was significantly higher in cases than in controls. There are important clinical consequences from the decreased vagal tone and increased sympathetic activity in hypothyroidism. A reduction in cardiac output due to desensitization of the catecholamine receptor leading to a compensatory increase in norepinephrine release, fatal arrhythmias,[31] coronary heart disease, and cardiovascular mortality[32] are all associated with hypothyroidism. Reduced systolic function, diastolic hypertension, an atherogenic profile, and sympathovagal imbalance contribute to these outcomes.[29]

In our study, the PSS score of hypothyroid cases was significantly higher than that of euthyroid cases (25.82 ± 2.83) compared with controls (22.47 ± 2.10). In addition, the majority of cases (54.5%) had a high-stress score, whereas the vast majority of controls had moderate stress (98.7%). This difference proved to be statistically significant. Regarding the positive association between PSS and TSH in subclinical hypothyroidism, the results of this study are comparable to those of the study by Chaudhuri *et al.*[33] The study showed that the patients had higher stress levels than the subjects in the control group.[34]

In addition, our study showed that hypothyroid patients had higher PSS levels. In this study, the TSH level showed a highly significant correlation with the LF/HF ratio as well as with the PSS score. In addition, the significance level between TSH and LF/HF ratio was strong (r = 0.781), while that between TSH and PSS scores was moderate.

This correlation indicates that with an increase in TSH levels, stress perception also increases. The opposite is observed with the values of HF, that is, when the value of HF decreases, the stress level increases. The increased values of the parameters LF and LF/HF ratio and the decreased values of HF indicate low heart rate variability. Decreased HRV indicates altered autonomic control of the heart, i.e., dominance of the sympathetic nervous system or decreased parasympathetic tone. This predisposes individuals to a higher risk of developing cardiovascular disease. Elevated stress levels in hypothyroid patients indicate poor psychological well-being in patients.

Conclusion

The HPT axis and the HPA axis are closely linked and function synchronously, so we can conclude that a change in thyroid hormone levels may affect the sympathovagal balance and ultimately lead to a disruption of ANS. A positive correlation was found between TSH and PSS. Measurement of resting HRV and PSS may be useful for screening stress, cardiovascular disease risk, and mental health in hypothyroid patients. Elevated PSS levels and low HRV should alert physicians to take appropriate action as soon as possible to reduce cardiovascular risk.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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