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RESEARCH ARTICLE

A comparative study of cardiac autonomic function tests in hypothyroid patients and euthyroid subjects

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ABSTRACT

Background: Thyroid hormone has very deep effects on the heart and can cause sympathovagal imbalance. Sympathovagal imbalance can lead to cardiac autonomic neuropathy (CAN) in hypothyroid patients. **Aims and Objectives:** The study aimed to assess the CAN in hypothyroidism and compare CAN in hypothyroid patients and euthyroid subjects. **Materials and Methods:** Fifty hypothyroid patients and 50 euthyroid subjects were selected for the study after satisfying the inclusion and exclusion criteria. Autonomic function tests were performed as per Ewing's and Clarke criterion including three parasympathetic (deep breathing test, 30:15 ratio, and Valsalva ratio [VR]) and two (sustained handgrip and postural hypotension test) sympathetic tests. **Results:** On comparing the mean of the test between euthyroid and hypothyroid patient, VR in parasympathetic and both sympathetic tests were statistically significant. **Conclusion:** There is an increased prevalence of CAN in hypothyroidism in comparison to the controls.

KEY WORDS: Cardiac Autonomic Neuropathy; Deep Breathing Test; Valsalva Ratio; Sustained Handgrip; Postural Hypotension Test

INTRODUCTION

In hypothyroidism, as the thyroid hormone is not produced in enough amount by the thyroid gland, can cause central neuropathy and autonomic dysfunction.[1] The autonomic nervous system regulates and modulates predominant cardiovascular activity through its sympathetic and parasympathetic divisions.

In this study, we are assessing autonomic neuropathy in hypothyroid patients as thyroid hormone also affects the cardiovascular system.[2] Cardiac autonomic function tests (AFTs) were done for diagnosis of autonomic neuropathy.

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MATERIALS AND METHODS

This case–control study was carried out in the Department of Physiology in collaboration with the Department of Medicine and Department of Biochemistry, Gandhi Medical College and associate Hamidia Hospital, Bhopal, after approved by the ethical committee of the institution approval no. 3809-11/MC/IEC/2018. From all the participants, informed consent was taken before enrolling them in the study. In this study, 50 hypothyroid patients and 50 euthyroid subjects were taken.

Inclusion Criteria

- The study included hypothyroid patients within the age group above 20 years.

Exclusion Criteria

The following patients were excluded from the study.

- Diabetes, hypertension, multiple sclerosis, and any other demyelinating disease which may lead to neuropathy
- Patient with prior history of head injury, cerebrovascular accident, and epilepsy
- The patient suffering from cardiovascular illness or cardiac autonomic neuronal dysfunction
- History of smoking, alcoholism, and chronic drug intake.

All the information about the procedure of test and plausible adverse effect were provided to the patients in detail as (handouts of the test to be performed) before performing the test.

Data Collection Protocol

All those patients who satisfied the inclusion and exclusion criterion and gave written consent were included in the study. Anthropometric measurements weight, height, and body mass index were recorded. A detailed history was taken from hypothyroid patients and euthyroid subjects. It included personal details, history of presenting complaints, history, family history, and dietary history. General examination was performed and recorded in pro forma. Detailed clinical and neurological examination was done on the patients to rule out other causes of demyelinating or neurological disorder.

Relevant information was collected from the study groups with the help of detailed questionnaire covering all signs and symptoms related to hypothyroidism and autonomic disturbances.

Baseline Parameters

The baseline parameters of subjects recorded were blood pressure (BP) and heart rate (HR) which were taken as control or baseline values. In every test, these parameters were taken.

AFTs

Ewing's and Clarke were given the five different AFTs.[3] AFTs are used to evaluate autonomic nervous system. Depending on the involvement of sympathetic as well as parasympathetic divisions, these tests are divided into two categories.

Tests for Parasympathetic Functions

HR response to deep breathing

The HR change during respiration is assessed by this test. The subject was asked to take deep breathing at the rate of 6 breaths per minute (allowing 5 s each for inspiration and expiration). Continuous electrocardiogram (ECG) (Lead II) was taken for six cycles after taking a baseline recording. The longest and shortest R-R intervals were recorded which gets further converted into beats per minute.

Normal: The difference of 15 beats/min or more, borderline: 11–14 beats/min, abnormal: ≤10 beats/min.

HR changes during Valsalva maneuver

A baseline ECG (lead II) recorded, then instructed to the subject exhale forcefully into a mercury sphygmomanometer with the help of mouthpiece and maintained the pressure of 40 mmHg for 15 s. After taking the baseline ECG, the continuous ECG recording was taken throughout and for 30 s after the Valsalva maneuver.

The result of the Valsalva ratio (VR) is the ratio of the longest R-R interval after the ending of maneuver to the shortest R-R interval during the maneuver.

Reference values: VR
Normal: ≥1.21, borderline: =1.11–1.20, abnormal: ≤1.10

HR response to standing

The patient was lying gently in the supine position baseline BP and HR was taken. Then, the patient was instructed to stand without any support. Then, continuous ECG (lead II) of the patient was recorded for 1–3 min after standing. The 30:15 ratio is the ratio of the longest R-R interval at beat 30 and shortest R-R interval at beat15 while standing.

Reference values –
Normal: ≥1.04, borderline: 1.01–1.03, abnormal: ≤1.

Sympathetic Tests

Handgrip dynamometry/grip test (HGT)

Apparatus used in this test was handgrip dynamometer (manufactured by INCO). In this test, the patient was requested to sit comfortably. Then, baseline BP was recorded then asked the patient to maintain the handgrip with the dominant hand at 30% of maximum force for 4–5 min. BP during handgrip was recorded on the opposite hand.

Difference between these two diastolic pressure was calculated. Reference values: Increased diastolic BP (DBP): >16 mmHg – normal, increased DBP: 11–15 mmHg – borderline, and increased DBP: <10 mmHg – abnormal.

BP response from lying to standing

BP was taken after giving rest preferably for 10 min and then serially recorded for 1–5 min after standing. First recorded within 30 s of standing up, then at the 1st, 2nd, 3rd, and 5th min. Fall of at least 20 mm of Hg systolic BP or 10 mm of Hg DBP on assuming erect posture will be considered as orthostatic hypotension. Reference values: Fall in systolic BP (SBP) ≤10 mm Hg – normal, fall in SBP ≤11–20 mmHg – borderline, and fall in SBP ≤20 mmHg – abnormal.

Statistical Analysis

SPSS software, version 16 was used for data analysis. Result expressed as mean ± SD. The results of various parameters between the two groups were compared by Student's *t*-test.

RESULTS

Observations made in the present study are presented in Tables 1-3.

DISCUSSION

Cardiovascular AFT was used to assess autonomic neuropathy. The difference in the mean value of different parameters between hypothyroidism and euthyroid subjects was analyzed and the following results were obtained.

On comparing the difference of mean of serum level of T3, T4, and thyroid-stimulating hormone (TSH) between control and hypothyroid patients by Student's t-test, no statistically significant difference was observed in serum T3 levels. However, serum T4 and TSH levels were statistically significant. The parasympathetic activity was assessed by HR alteration to deep breathing (E/I ratio), 30:15 ratio, and VR in controls and hypothyroid patients. On comparing the statistical difference of means of changes in HR during deep breathing test (DBT) and statistical deference of mean of 30:15 ratio in the study group by t-test, no statistically significant difference was found. On comparing of changes HR during Valsalva maneuver, VR between the study groups controls and hypothyroid patients statistically significant difference was observed in the study group. In sustained HGT, BP changes were obtained for the evaluation of the sympathetic activity. The difference between the mean of the rise in DBP during sustained handgrip was significantly reduced in hypothyroid patients as compared to euthyroid subjects. The BP changes from supine to standing position were also recorded for sympathetic evaluation. The observation showed that the difference between SBP during supine and standing position in hypothyroid patients was statistically significant as compared to euthyroid subjects.

Sahin *et al*.,[4] Karthik *et al*.,[5] and Syamsunder *et al*.[6] also found that T4 and TSH values were statistically significant and support the present study. Our study result consistent with the result of Mahajan *et al*.[7] they found that E/I ratio and 30:15 ratio were not statistically significant between control and subclinical hypothyroid. The finding of our study also consistent with the result of Bhat *et al*.[8] they also found 30:15 ratio statistically insignificant between control and hypothyroid patient. In the present study, it is quite possible that in hypothyroid patients in the resting condition, sympathetic activity is more on the heart which is mainly responsible for compensation for the lower intrinsic HR in hypothyroidism so the variability of HR in hypothyroid patients during DBT and supine to standing was not statistically significant from euthyroid subjects. Mahajan *et al*.[7] and Bhat *et al*.[8] found that *P*-value was statistically insignificant in comparison of VR in the study group. Their result stands in contradiction to the observation of the present study. Klein and Ojamaa and Polikar *et al*.[9-11] also postulated that there is a reduction in catecholamine responses to heart in hypothyroid patients; therefore, the contractility property of the heart is severely affected. During straining period of Valsalva maneuver, HR increased and BP decreased, but in the hypothyroid patient, the rise in HR during strain and decrease in HR during the relaxation period is decreased. In the present study, reduced sympathoexcitation of sinus node as well as reduced responsiveness of the heart to circulating catecholamines may well depress the sympathetic reactivity to a stressor stimulus leading to altered VR in hypothyroid patients. Lakshmi *et al*.[12] observed that in the study of the effect of thyroxine therapy in hypothyroid patients, in sustained HGT, the diastolic BP changes were statistically significant and they also found that improvement in DBP changes after treatment as compared to pre-treatment. This observation is similar to the present study. In our study during sustained handgrip, we found that the rise in DBP was significantly lesser in hypothyroid patients as compared to control. This lesser rise of DBP proposed that sympathetic reactivity reduced in hypothyroid patients to the stressor

Table 1: Age and sex distribution in the study groups

Age groups (years)	Hypothyroidism *n*=50			Control *n*=50		
	Total	Male	Female	Total	Male	Female
20–30	25	0	25	26	3	23
31–40	17	0	17	12	4	8
41–50	8	1	7	12	3	9
Total	50	1	49	50	10	40

Table 2: Biochemical tests

Thyroid profile	Cases *n*=50	Control *n*=50	*t*	*P*	Remark
T3 (ng/ml)	1.76±0.94	1.91±0.42	1.03	0.30	NS
T4 (µg/dl)	7.71±3.04	9.67±2.146	3.72	0.0003	S
TSH (µlU/ml)	15.82±10.81	3.14±1.38	8.22	0.0001	S

P≤0.05=significant. TSH: Thyroid-stimulating hormone

Table 3: Various cardiac AFTs

Variables	Cases *n*=50	Control *n*=50	*t*	*P*	Remark
E/I	1.41±0.164	1.44±0.15	0.96	0.33	NS
30:15	1.22±0.133	1.25±0.12	1.18	0.239	NS
VR	1.41±0.28	1.61±0.22	3.97	≤0.0001	S
DBP	18.84±3.10	14.32±3.38	6.96	≤0.0001	S
Mean systolic changes	6.92±4.68	4.36±2.57	3.39	0.001	S

S=Significance, NS=Non-significance. DBP: Diastolic blood pressure, VR: Valsalva ratio, AFTs: Autonomic function tests

situation, which may be the possible reason for the finding of the present study. Postural hypotension can be supported by a previous study by Christensen[13] as they postulated that in hypothyroid patients, the cardiac output is decreased which causes a decrease in BP which is responsible for a compensatory increase in the release of noradrenaline. In the context of our study, in hypothyroid patients, the increased influence of the sympathetic activity of the heart leads to a far greater fall of systolic BP in comparison to the controls. Despite the clinical impact of low adrenergic response due to decrease of adrenergic receptors on the heart, it appears to confirm on adaptation to cardiovascular responsiveness. Thyroid hormones deficiency may cause decreased cardiac output, impaired cardiac contractility, electrical abnormalities in heart, and increased resistance in the systemic vascular system.[14-16] The clinical sign and symptom in hypothyroid patient proposed reduced adrenergic response at the level of the heart. In hypothyroid patients, there is an increased level of catecholamines and their urinary metabolites are also found.[2,17,18] In hypothyroid patients, decrease catecholamines responses to the heart, the cardiac contractility, and its functional reserve are severely compromised.[15-17] In the present study, it is found that in hypothyroid patients, there is sympathovagal imbalance due to this imbalance, the cardiac autonomic functions of hypothyroid patients are affected. In our study, the parasympathetic, that is, VR was affected the most, whereas both sympathetic were also affected. Hence, it becomes imperative that assessment of AFT should be evaluated in hypothyroid patients.

Strength of the present study is well characterized study subjects, and standardized techniques and procedure were used to measures various parameters of the study. Increasing the sample size could have given more precise results for assessing autonomic dysfunction.

CONCLUSION

The present study concludes that there is an increased prevalence of cardiac autonomic dysfunction in hypothyroid patients. Both sympathetic and parasympathetic autonomic functions were altered in hypothyroid patients in comparison to the control group. Therefore, it can be assumed that hypothyroid patients apart from clinical evaluation shall also be assessed regularly for the presence of dysautonomia. Early detection of autonomic neuropathy dysautonomia and their treatment can improve the overall prognosis of hypothyroid patients and also may aid to improve the quality of life of hypothyroid patients.

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