



AN ANALYTICAL CROSS SECTIONAL STUDY ON CARDIAC AUTONOMIC FUNCTIONS IN HYPO-THYROID PATIENTS

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ABSTRACT **Background:** Primary Hypothyroidism is a chronic endocrine disorder of thyroid gland with multifarious etiology having a prevalence of 5 to 15% in India.¹ The prevailing literature reports an increased risk of cardiovascular morbidity in hypothyroid patients and proposes derangements in the autonomic nervous system as an antecedent causative event. The present study was designed to explore these undermined autonomic nervous system derangements posing a risk of subsequent development of cardiovascular problems in hypothyroid patients.

Aim and Objective: The objective of the current study was to explore and compare the cardiovascular autonomic functions in hypothyroid patients with age and sex-matched healthy controls.

Materials and Methods: The present study was conducted in the Upgraded Department of Physiology, Sawai Man Singh Medical College and Attached Hospitals, Jaipur, enrolling 30 hypothyroid patients of both gender, recruited from the Department of Endocrinology and 30 age & gender-matched healthy controls recruited amongst the attendants and family members accompanying the hypothyroid patients. Prior approval and consent were obtained from the institutional ethics committee and research review board before commencement of the study. For assessing the autonomic functions, parasympathetic function tests namely E:I ratio, 30:15 ratio (lying to standing ratio), and Valsalva ratio were resorted to, whereas, tests like blood pressure (BP) response to standing and sustained handgrip were used for the assessment of sympathetic functions.

Results: When the subjects were tested for assessment of the sympathetic function, rise in diastolic BP during isometric handgrip exercise came out to be significantly lower in hypothyroid patients ($P < 0.05$) in comparison to controls. Similarly, the fall in systolic BP on immediate standing was higher in the hypothyroid group ($P < 0.05$). On assessing the subjects for parasympathetic functions, E: I ratio (Expiration: Inspiration), 30:15 ratio and Valsalva ratio were found to be significantly decreased ($P < 0.05$) in hypothyroid patients in comparison to healthy controls.

Conclusion: The deranged autonomic function tests in hypothyroid patients suggest an underlying cardiovascular autonomic dysfunction putting hypothyroid patients at a greater risk of cardiovascular diseases later in life. Due to these prognostic implications, the present study recommends regular and periodic assessment of autonomic functions in hypothyroid patients.

KEYWORDS : Hypothyroid, Sympathetic, Parasympathetic; Cardiovascular, Autonomic function test

INTRODUCTION

Thyroid dysfunctions are a common global health problem wherein hypothyroidism is present in 5–15% and hyperthyroidism is present in 0.3–0.6% of individuals in the general population^{2,3}. Also, for the last 30–40 years, the incidence of thyroid disorders has increased precipitously⁴.

For India, the burden of thyroid disorders including hypothyroidism, hyperthyroidism, goiter, etc is about 4.20 crore¹. Among the whole spectrum of thyroid disorders, hypothyroidism is more common in females in comparison to males.² The prevalence rates of hypothyroidism has been observed to be positively correlated with advancements in age and history of hypothyroidism in the family⁵.

Hypothyroidism, in general, is a hypo-metabolic state that is usually associated with diminished sympathovagal modulation of cardiac activities^{6,7}. Thyroid hormones target the cardiovascular system which is exquisitely sensitive to even the subtle variations in the circulating levels of thyroid hormones manifesting its effect on heartbeat, strength, and rate^{8,9}. The cardiovascular effects of hypothyroidism depend on the severity & duration of the disease and it ranges from minimal abnormalities to easily recognizable manifestations that are linked with variation in autonomic regulation of the cardiovascular system and in ventricular repolarization^{6,7}. Cardiovascular autonomic dysfunctions have also been linked to the occurrence of malignant ventricular arrhythmias and sudden cardiac death¹⁰.

The autonomic nervous system has a profound influence on cardiovascular regulations in health and diseases¹¹. There is a battery of autonomic function tests to assess the sympathovagal balance. The tests include resting heart rate, blood pressure response to standing & sustained handgrip, and heart rate change due to changes in posture.

Other tests are heart rate and blood pressure response to Valsalva manoeuvre, heart rate response to deep breathing & standing. Since it has been demonstrated in many previous studies that the autonomic function abnormalities improve after at least six months of thyroxine therapy¹², the sympathovagal imbalance, as proposed in thyroid dysfunctions, is nevertheless potentially muddled due to variations in the time course of the treatment¹³. The present study was therefore undertaken to evaluate the autonomic functions in hypothyroid patients who are yet to start treatment. In addition, cardiovascular reflex tests based on the change in HR and BP during conventional manoeuvres were performed, thereby assessing sympathovagal imbalance in hypothyroid subjects¹⁴.

The relationship between the sympathovagal balance and hypothyroidism is potentially complex and requires further exploration to gain insights into the understanding of the cardiovascular risk so that therapeutic targets can be developed and effective treatments employed. In the present study, a detailed evaluation of cardiovascular autonomic function in hypothyroid subjects was undertaken before restoration of euthyroid status by exogenous thyroxine replacement therapy. For this purpose, conventional cardiovascular autonomic tests were performed in newly diagnosed hypothyroid subjects who were yet to start thyroxine replacement therapy, and were compared with age and gender matched apparently healthy controls.

MATERIAL AND METHOD

The present study was a hospital-based cross-sectional type of observational study conducted on 30 hypothyroid patients in the age group of 30–40 years of both gender and 30 age and gender-matched healthy controls. Hypothyroid subjects were recruited from the Department of Endocrinology, Sawai Man Singh Medical College and

Attached Hospitals, Jaipur. Only newly diagnosed patients having TSH levels more than 5 mIU/L were selected. The age and gender-matched healthy controls were selected from the healthy attendants accompanying the patients. Prior approval and permission were taken from the institutional ethics committee and research review board. Written informed consent was obtained from all the subjects before commencing with any test procedure. Subjects having any chronic illness like hypertension, diabetes, cardiac, renal, liver diseases etc were excluded. Similarly, alcoholics, smokers and subjects on medications known to affect autonomic functions were also excluded from the study.

ANS Function Assessment All the subjects were instructed to refrain from caffeine and food for at least 4 hours prior to the commencement of test procedure. The subjects were asked to lie down on a couch in a silent room, with an ambient temperature of 25°C and autonomic function tests were carried out. Cardiovascular autonomic function evaluation was done according to Ewing's battery¹⁵ of tests using RMS CANWIN (cardiac autonomic neuropathy analyser) machine from 9 AM to 1 P.M. after ensuring a relaxation time of 15 min. Both sympathetic and parasympathetic autonomic function tests were carried out in the present study.

A. Parasympathetic reactivity tests

1. Heart Rate response to deep breathing (E/I ratio)
2. Lying to standing Ratio (30:15 ratio)
3. Valsalva maneuver.

B. Sympathetic reactivity tests

1. Blood pressure (BP) response to standing
2. Blood pressure response to isometric handgrip (IHG) exercise

STATISTICAL ANALYSIS:

Quantitative data were expressed as mean ± SD. Statistical analysis was done by using an unpaired *t*-test to compare the difference of means, by using Microsoft Excel 2007. Statistical significance was assigned at *p*<0.05.

Table 1: Baseline characteristics of the hypothyroid and control groups

Parameter	Group –A (Hypothyroid) (n=30) Mean ± SD	Group –B (Control) (n=30) Mean ± SD	Significance
	Age (Years)	35.77 ± 2.78	
BMI (kg/m ²)	20.93 ± 3.17	21.58 ± 3.28	^NS
T 3 (pg/ml)	3.14 ± 0.61	3.53 ± 0.584	*S
T 4 (ng/ml)	1.04 ± 0.29	1.79 ± 0.96	**HS
TSH (mIU/L)	31.56 ± 22.85	3.04 ± 1.23	**HS
Basal Heart Rate (per minute)	71.9 ± 8.044	80.06 ± 12.89	*S
Resting Systolic BP (mm Hg)	126.08 ± 17.47	120.8 ± 18.72	^NS
Resting Diastolic BP (mm Hg)	76.06 ± 8.29	76.33 ± 18.02	^NS

^NS-Not significant, *p* - Value > 0.05

*S-Significant, *p* - Value < 0.05

**HS-Highly Significant, *p* - Value < 0.001

Table 2: Autonomic function test in hypothyroid (cases) and control groups

AFT Variable	Group –A (Hypothyroid) (n=30) Mean ± SD	Group –B (Control) (n=30) Mean ± SD	Significance
30: 15 Ratio	1.02 ± 0.11	1.82 ± 0.39	*S
Valsalva ratio	1.11 ± 0.21	1.86 ± 0.73	**HS
Heart Rate Response to Deep Breathing (E: I Ratio)	1.13 ± 1.21	1.39 ± 0.49	*S
BP Response to Standing (Orthostatic fall of systolic BP in mmHg)	13.86 ± 3.67	7.06 ± 4.40	**HS

BP response to Isometric Handgrip Test (Diastolic BP Increased after sustained handgrip in mmHg)	7.4 ± 3.06	15.9 ± 11.31	**HS
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*S-Significant, *p* - Value < 0.05

**HS-Highly Significant, *p* - Value < 0.001

DISCUSSION

The study was undertaken in an effort to explore the extent of autonomic dysfunction in patients of hypothyroidism. Heart rate response to standing (30:15 ratio), heart rate response to deep breathing (Expiration/Inspiration ratio) and Valsalva ratio were resorted to as indicators of parasympathetic function whereas, blood pressure response to standing and blood pressure response to isometric handgrip tests provided the window for the assessment of sympathetic functions. Vagal tone is an important factor of the cardiovascular health of an individual as it influences the control of heart rate, cardiac output, and blood pressure. It has been already shown that persons with poor vagal tone show higher susceptibility towards cardiovascular diseases like myocardial infarction, heart failure, hypertension, etc¹⁶. The present study found significantly low 30:15 ratio and decreased E: I ratio in hypothyroid subjects reflecting a state of low parasympathetic reactivity in hypothyroidism implicating an unhealthy vagal tone (Table-2).

The present study also found a significant correlation between basal heart rate and hypothyroidism, indicating that the decrease in heart rate observed in hypothyroidism may be directly linked to the SVI (sympathovagal imbalance). However, Blood pressure in hypothyroid subjects was within the normal range and was not significantly different from healthy controls (Table-2).

The findings of the present study support the report published by Cacciatori et al¹⁷ proposing that sympathetic influence on the cardiovascular system is increased and vagal influence is decreased in hypothyroidism occurring due to derangement in normal and expected cardiovascular responses.

The results obtained in the present study not only indicate a withered parasympathetic reactivity but the sympathetic reactivity also demonstrated a hypoactive state. When assessment of the sympathetic functions was made, a failure of increment of diastolic blood pressure in response to isometric handgrip test was observed, reflecting decreased sympathetic reactivity in hypothyroid patients. Since an appropriate increase in diastolic blood pressure during isometric handgrip is an indicator of normal sympathetic response, the derangements reported in these domains suggest sympathovagal discordance.

Klein and Ojamaa and Polikar et al.^{18,19} also suggested that there is a decrease in catecholamine responses to the heart in hypothyroid patients affecting the contractility property of the heart hence indirectly implicating a possible role of abnormal sympathovagal balance. The results obtained in the present study are also in agreement with Fagius et al, who reported a higher level of sympathetic activity in hypothyroid subjects²⁰. The base line levels of the sympathetic activity were found to be higher in hypothyroid patients in the present study but it is the reactivity of the sympathetic system towards appropriately presented stressors in form of select sympathetic tests that have taken a beating. On the contrary, the results of the present study are not in accordance with the report of Xing H et al¹² who proposed that the sympathetic activity does not change much in hypothyroidism.

Strength of study:

Although there has been a plethora of studies directed towards exploration of autonomic dysfunctions in thyroid disorders, the present study has its merit on the fact that only newly diagnosed subjects suffering from hypothyroidism were taken as subjects. These subjects were not on thyroxine replacement therapy by the time test procedures were completed, hence the results proffered by the present study are free from being perplexed by the possible effect of concurrent thyroxine replacement on autonomic functions and ultimately masking the true effect. Therefore the present study extends its contribution towards providing a better understanding of the effect of hypothyroidism on autonomic functions and towards fulfilment of some research gaps.

Limitations of the study: The present study was based on cross sectional assessment of autonomic functions in hypothyroid patients prior to initiation of treatment and did not involved follow up assessment after initiation of thyroxine replacement that would have further reinforced the current proposal.

CONCLUSION

The findings of the present study indicate definite impairment of parasympathetic as well as the sympathetic nervous system in hypothyroid patients. The impaired status of autonomic functions puts hypothyroid patients at greater cardiovascular risk that warrants an early assessment of ANS functions in these patients for preventing overall morbidity and mortality.

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CONFLICTS OF INTEREST

None

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