Original Article

Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients

Aarti S. Mahajan, Ram Lal[1], Dinesh K. Dhanwal[2], Ajay K. Jain, Veena Chowdhury[3]

Departments of Physiology, [2]Medicine, and [3]Radiology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, [1]Department of Medicine, Government Medical College, Haldwani, Uttarakhand, India

ABSTRACT

Background: Autonomic dysfunction may contribute to cardiovascular morbidity in subclinical hypothyroid patients. It is controversial whether the abnormality exists in sympathetic or the parasympathetic function. It is also not known whether the severity of autonomic dysfunction is related to the degree of thyroid deficiency. **Design of Study:** Prospective case control. **Materials and Methods:** Autonomic functions based on heart rate (HR) and blood pressure (BP) responses to various maneuvers were evaluated and scored in twenty two subclinical hypothyroid patients, 30-50 years and compared with twenty hypothyroid patients. Biochemical estimation of TSH, fT_3, fT_4, TPO antibody was done. **Result:** Sympathetic function abnormalities were seen in 82% subclinical hypothyroid patients and 85%hypothyroid patients when one test was abnormal. Parasympathetic dysfunction was also recorded in eight patients in both groups. When two abnormal tests were used as the selection criteria sympathetic function abnormality was observed in about 41% subclinical hypothyroid and 65% hypothyroid patients. There were no intergroup differences in autonomic functions, score and TPO levels. The TSH levels were not related to type or degree of autonomic dysfunction. Systolic BP in both groups and diastolic BP in hypothyroid patients were higher with lower thyroxine levels but the patients were normotensive. **Conclusion:** Autonomic dysfunction of comparable degree was seen in subclinical hypothyroid and hypothyroid patients. Sympathetic function abnormality was more common although decreased parasympathetic function reactivity was also present. These abnormalities were unrelated to TSH levels.

Key words: Autonomic dysfunction cardiovascular morbidity, hypertension, subclinical hypothyroidism

Introduction

The thyroid hormone influences the autonomic nervous system.[1] Previous studies have shown sympathovagal imbalance with sympathetic withdrawal and decreased vagal modulation in hypothyroid patients.[2,3] In contrast other studies have shown that thyroid hormone deficiency is associated with increased sympathetic influence on the cardiovascular autonomic system.[4,5]

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.111642

There is scarcity in scientific documentation about autonomic function in subclinical hypothyroidism. Kahaly *et al*, reported a hypofunctional parasympathetic system by analyzing time and frequency domains of heart rate variability (HRV).[6] A similar response was observed by authors who studied the heart rate response to exercise and recovery.[7] Galetta *et al* showed an increase in sympathetic tone with a decrease in HRV suggesting a decrease in vagal tone.[8] However Sahin *et al* suggested that in subclinical hypothyroid patients with TSH more than 10 mIU/L there was decrease in sympathetic tone and increase in parasympathetic activity.[9] Thus the limited reports on subclinical hypothyroidism are themselves contradictory. These studies have compared subclinical hypothyroid patients with euthyroid controls and not hypothyroid patients. Many studies have reported improvement in autonomic function abnormalities following thyroxine treatment.[4,6,8] This study was therefore undertaken to evaluate autonomic functions in subclinical hypothyroid

Corresponding Author: Dr. Aarti Sood Mahajan, Department of Physiology, Maulana Azad Medical College, New Delhi, India.
E-mail: aartis_mahajan@yahoo.co.in

patients, compare them with hypothyroid patients. In addition we used standard cardiovascular reflex tests based on change in HR and BP during various maneuvers and scored them in order to ascertain the severity of cardiac autonomic dysfunction and assessed their relationship to the thyroxine and TSH level.

Material and Methods

The pilot study was carried out in the departments of Physiology, Medicine and Radiology, Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, in the year 2010-2011. Twenty two subclinical hypothyroid female patients, 30-50 years and for comparison, 20 age matched female hypothyroid patients were recruited in the medical outpatient department. The patients were selected on the basis of clinical features suggestive of decreased thyroid function,[10] and laboratory findings of a normal free T_3 and T_4 levels and TSH more than 5 mIU/L, on two occasions six months apart suggesting subclinical hypothyroidism. The hypothyroid patients had decreased free T_3 and T_4 levels. Patients with diagnosed hypertension, ischemic or valvular cardiac disease, heart failure, previous vascular surgery, pulmonary hypertension, respiratory, hepatic, renal, neurological disease, psychological morbidity, malignancy, history of radiotherapy, taking iodide drugs, lithium carbonate, sulphonyl urea, amiodarone, smokers, postmenopausal and pregnant women were excluded from the study.

The study protocol was approved by the institutional ethical committee and informed consent was taken. The details of patient's history and investigations including basal electrocardiography (ECG) and colour Doppler of thyroid gland, lipid profile and blood sugar estimation were recorded in a proforma. Height and weight were measured and body mass index (BMI) was computed.

Autonomic function testing

Standardized procedure was adopted for autonomic testing.[11] The battery of tests done were, standing to lying ratio (SL ratio), immediate heart rate response to standing (30:15 ratio), valsalva ratio, heart rate variations with respiration (EI ratio), hand grip test(HGT) and cold pressor test(CPT). One or more abnormal test was considered an indication of autonomic dysfunction.[12,13] In order to make the evaluation more objective, five of these tests (valsalva ratio, 30:15 and EI ratio to evaluate parasympathetic function, hand grip and cold pressor response for sympathetic function) were scored. They were scored 0, for normal, 0.5 if borderline and 1 for abnormal response, as has been standardized in our lab and previously done by other authors.[14,15] The sum of the scores were calculated and graded, zero was no damage, more than zero to three was mild damage, more than three to six was moderate damage and more than six indicated severe damage to the ANS.[16] They were further evaluated to see if they had sympathetic, parasympathetic dysfunction or both.

All measurements of heart rate were done using a continuous ECG recording (lead II) and blood pressure (BP) was recorded using appropriate zero error mercury sphygmomanometer by auscultatory method. Baseline BP was taken after five minutes rest, as the average of two consistent readings one minute apart. All patients were asked to come in the immediate post menstrual phase of their cycle for autonomic function testing to alleviate any changes related to the cycle.

Protocol for testing autonomic functions

Patients were instructed to come after a light meal and to refrain from any caffeinated drinks on the day of testing. All testing of autonomic functions was done in the forenoon, after they were familiarized with the testing procedure.

Statistical analysis

The outcome of the study was the mean and standard deviation of the record of age, weight, height, computed BMI, biochemical investigations, changes in HR and BP following autonomic function testing and their scoring. Both intragroup and intergroup analysis was done. Chi square test was done to compare age group of two groups. Independent sample test like Levene's test for equality of means and t test was done for age, weight, height, BMI, resting heart rate (RHR), resting systolic and diastolic BP(RSBP, RDBP), blood sugar and lipid profile and autonomic functions. Mann Whitney, Wilcoxan test was done and two tailed significance calculated for, fT_3, fT_4, TSH, TPO antibody, and autonomic score. Pearson's correlation was done for various parameters.

Results

The clinical and biochemical profile of the two groups is shown in Table 1. The fT_3, fT_4, TSH values were different, with lower thyroxine and higher TSH in hypothyroid patients. Both total cholesterol and triglycerides, although within the normal reference range, were higher in subclinical hypothyroid patients. Also the TPO values, although higher in hypothyroid patients, were not significantly different between the groups.

The comparison of RHR, RSBP, RDBP, autonomic function assessment and autonomic function score is shown in Table 2. There was no significant difference between the groups. However on the basis of individual autonomic

Table 1: Demographic and metabolic characteristics of study groups

Parameter	Subclinical Hypothyroid (*n* = 22)	Hypothyroid (*n* = 20)	*P value*
Age (years)	36.95±6.04	35.05±5.45	0.292
Height (cm)	158.91±5.44	155.70±4.52	0.045
Weight (Kg)	61.45±4.13	59.00±8.12	0.218
B.M.I (Kg/m^2)	24.38±2.01	24.28±3.05	0.898
fT_3 (pg/ml)	1.88±0.74	0.95±0.55	0.000
fT_4 (ng/dL)	1.08±0.31	0.57±0.32	0.000
T.S.H (mIU/L)	8.18±1.31	40.23±22.67	0.000
TPO (IU/ml)	89.71±48.16	117.39±52.68	0.072
FBG (mg/dL)	81.91±6.89	80.50±5.88	0.482
PPBG (mg/dL)	154.27±17.17	127.00±19.88	0.000
Total.C (mg/dL)	162.68±25.07	147.45±12.05	0.018
TG (mg/dL)	101.64±22.96	70.95±15.29	0.000
HDL -C (mg/dL)	45.82±7.66	44.90±3.97	0.634
LDL -C (mg/dL)	40.82±9.87	40.05±10.37	0.807

All values are expressed as Mean ± Standard deviation. *P* values <0.05 are significant, *P* = 0.000 is corrected to three decimal places, fT3-free Tri-iodo thyroxine, fT4-free thyroxine, TSH: Thyroid stimulating hormone, FBG: Fasting plasma glucose, PPBG: Post Prandial plasma glucose, C: Cholesterol, TG: Triglyceride, LDL: Low density lipoprotein, HDL: High density lipoprotein

Table 2: Autonomic functions in subclinical hypothyroid and hypothyroid patients

Parameter	Subclinical Hypothyroid (*n* = 22)	Hypothyroid (*n* = 20)	*P value*
RHR (beats/min)	77.00 ± 4.81	76.70 ± 4.60	0.838
RSBP (mmHg)	119.27 ± 5.37	118.00 ± 4.72	0.421
RDBP (mmHg)	79.00 ± 3.99	78.00 ± 3.67	0.404
S:L	1.13 ± 0.09	1.07 ± 0.12	0.105
30:15	1.16 ± 0.18	1.12 ± 0.13	0.354
VAL	1.32 ± 0.20	1.39 ± 0.22	0.263
E:I	1.31 ± 0.13	1.44 ± 0.29	0.068
HSCFR (mmHg)	18.27 ± 3.62	15.90 ± 4.75	0.074
HDCFR (mmHg)	11.82 ± 3.26	11.50 ± 5.46	0.818
CSCFR (mmHg)	15.00 ± 4.35	11.80 ± 5.91	0.051
CDCFR (mmHg)	10.36 ± 3.58	8.30 ± 5.40	0.149
SCORE(5)	1.79 ± 1.08	2.03 ± 1.14	0.329

All values are expressed as Mean ± Standard deviation. P values <0.05 are significant, RHR: Resting heart rate, RSBP: Resting systolic BP, RDBP: Resting diastolic BP, S:L: Standing to lying ratio, 30:15: Immediate heart rate response to standing, VAL: Valsalva ratio, E:I: heart rate variations with respiration, HSCFR: Hand grip test systolic BP change from resting, HDCFR: Hand grip test diastolic BP change from resting, CSCFR: Cold pressor test. systolic BP change from resting, CDCFR: Cold pressor test. diastolic BP change from resting, SCORE (5): autonomic scoring using 5 tests

function test and scoring analysis it was found that 95.45% (21) of subclinical hypothyroid patients and 85% (17) of hypothyroid patients had autonomic dysfunction. In subclinical hypothyroid patients 59% (13) had sympathetic dysfunction, 13.63% (3) had parasympathetic function abnormality, while 22.72% (5) had both. Similarly, 45% (9) hypothyroid patients had sympathetic dysfunction alone and 40% (8) had both abnormalities. The autonomic score was less than three in both groups. When two test abnormalities was used as a selection criteria, then 50% (11) subclinical hypothyroid and 75% (15) hypothyroid patients had autonomic dysfunction. In subclinical hypothyroid patients TSH>10 mIU/L. was observed in two patients only, one case with sympathetic dysfunction and a case of parasympathetic dysfunction.

The correlation analysis showed that in subclinical hypothyroid patients the systolic BP had a significant positive correlation with age (r = 0.528, $P = 0.012$) and a negative correlation with fT_4 levels (r = –0.459, $P = 0.032$). In hypothyroid patients the fT_3 levels negatively correlated with the resting systolic and diastolic blood pressure (r = –0.454, $P = 0.042$; r = –0.581, $P = 0.007$ respectively). There was no correlation between TSH levels and autonomic functions and score in both groups.

Discussion

This study found both subclinical hypothyroid and hypothyroid patients to have autonomic dysfunction with the sympathetic reactivity being affected in most cases. Sahin *et al*[9] found no difference in the time and frequency domains of HRV compared to controls in those subclinical hypothyroid patients who had TSH levels less than ten but there was a decrease in sympathetic tone if TSH levels were greater than ten. These patients with high TSH are probably a high risk group likely to proceed to hypothyroidism. Our patients had impaired sympathetic functions although the average TSH level was lower. Galetta *et al* had reported an increase in LF/HF frequency in heart rate variability reflecting higher sympathetic activity in subclinical hypothyroid patients. They also found that the TSH values correlated with LF/HF ratio.[8] These findings are in variance to our observations in this study but the authors had also suggested that the lower HF component of the HRV reflected a decrease in vagal tone. Similarly we also found parasympathetic dysfunction in eight patients. Other studies in subclinical hypothyroid patients have also reported a hypofunctional parasympathetic system based on analysis of the heart rate recovery and RR variations in ECG.[6,7] Inukai *et al*, referred to a group of patients as masked hypothyroid (normal T_3, T_4 and high TSH), and found no change in parasympathetic function. This was in comparison to a decrease in parasympathetic activity in hypothyroid patients.[17]

This controversial trend continues to be observed in hypothyroid patients also. Galetta *et al*,[3] had found a decrease in sympathovagal balance characterized by decreased cardiovascular sympathetic and vagal modulation in hypothyroid patients. However an increase in sympathetic and decrease in parasympathetic activity have also been suggested.[18] Some authors have even reported that the

decrease in parasympathetic activity normalizes following restoration to euthyroid stage.[6,19,20] Reviewing many studies Heemestra *et al*, postulated that heterogeneity in the study population, cause and duration of disease may be responsible for the varied response observed in all these cases.[2]

Cacciatore *et al*,[4] found that thyroid deficiency is associated with increased sympathetic influence on the heart but commented that hypothyroid and controls did not differ in the reflex responses as evaluated by traditional autonomic function tests. They suggested that power spectral analysis was more sensitive than these tests. However we have used some of the traditional tests and found autonomic dysfunction in both subclinical and hypothyroid patients but no major intergroup differences. Moreover autonomic scoring could be done by these methods. To the best of our current knowledge this may be the first study to report autonomic dysfunction score in subclinical hypothyroid patients. As mild autonomic dysfunction[16] was seen in both groups, we can extrapolate our observations to suggest that autonomic abnormalities can begin early, even in the subclinical stage of hypothyroidism and are comparable in severity to that seen in hypothyroid patients.

The mechanisms suggested for autonomic disturbances in thyroid disorders include a high level of plasma adrenaline with a decreased receptor or post receptor sensitization,[21,22] a decreased chronotropic response to β adrenergic stimulation or adrenergic sensitivity,[23] increase in thyrotropin releasing hormone (TRH) which directly influences the sympathetic outflow, direct effect of thyroid hormone on the heart.[24] Metabolic effects of decreased thyroid hormone, may also lead to increased protein deposition in extracellular space, resulting in water accumulation in myocardial wall, fibrosis in ventricular wall, all leading to increased regional inhomogeneity of ventricular repolarization. Also adverse effects on circulating lipids, vascular smooth muscle cell swelling and impaired endothelial function have been suggested.[2,6]

Autonomic dysfunction has been linked to prehypertension, to family history of hypertension and may lead to development of hypertension.[25,26] We did not find any hypertension, in subclinical hypothyroid patients, but systolic BP was higher in older patients and in those with a lower fT_4. In hypothyroid patients both SBP and DBP was higher in patients with lower fT_3 levels. In Galetta *et al*'s study, patients had higher systolic BP,[8] and were prehypertensive.[27] In another study subclinical hypothyroid patients had a higher diastolic blood pressure when compared to euthyroid controls.[28] However Walsh *et al*, reported that subclinical hypothyroidism was not associated with hypertension.[29]

In conclusion we report that in this study, both subclinical and hypothyroid patients had autonomic dysfunction but were normotensive. Sympathetic function abnormality was more prominent although selective parasympathetic dysfunction was also seen. Apparently there was no relationship between the autonomic function score and TSH or TPO levels. We propose that larger studies investigating autonomic functions and their reversibility with treatment should be undertaken in subclinical hypothyroid patients. Autonomic dysfunction could be a risk factor for cardiovascular morbidity and its correction following therapy, one criterion that favors treatment in these patients.

References

1. Foley CM, McAllister RM, Hasser EM. Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. Am J Physiol Heart Circ Physiol 2001;280:2061-8.
2. Heemstra KA, Burggraaf J, vander Klaauw AA, Romijn JA, Smit JW, Corssmit EP. Short term overt hypothyroidism induces sympathovagal imbalance in thyroidectomized differentiated thyroid carcinoma patients. Clin Endocrinol 2010;72:417-21.
3. Galetta F, Franzoni F, Fallani P, Tocchini L, Braccini L, Santoro G. Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. Eur J Endocrinol 2008;158:85-90.
4. Cacciatori V, Gemma ML, Bellavere F, Castello R, De Gregori ME, Zoppini G, *et al*. Power spectral analysis of heart rate in hypothyroidism. Eur J Endocrinol 2000;143:327-33.
5. Ahmed M, Begum N, Ferdousi S, Begum S, Ali T. Power spectral analysis of heart rate variability in hypothyroidism. J Bangladesh Soc Physiol 2010;5:53-9.
6. Kahaly GJ. Cardiovascular and atherogenic aspect of subclinical hypothyroidism. Thyroid 2000;10:665-79.
7. Akcakoyun M, Emiroglu Y, Pala S, Kargin R, Guler GB, Esen O. Heart rate recovery and chronotropic incompetence in patients of subclinical hypothyroidism. Pacing Clin Electrophysiol 2010;33:2-5.
8. Galetta F, Franzoni F, Fallani P, Rossi M, Carpi A, Rubello D, *et al*. Heart rate variability and QT dispersion in patients with subclinical hypothyroidism. Biomed Pharmacother 2006;60:425-30.
9. Sahin I, Turan N, Kosar F, Taskapan C, Gunen H. Evaluation of autonomic activity in patients with subclinical hypothyroidism. J Endocrinol Invest 2005;28:209-13.
10. Jayakumar RV. Clinical approach to thyroid disease. J API 2011;59(Special issue):11-3.
11. Mourya M, Mahajan AS, Singh NP, Jain AK. Effect of slow and fast breathing exercises on autonomic functions in patients with essential hypertension. J Altern Complement Med 2009;15:711-7.
12. Kempler P, Tesfaye S, Chaturvedi N, Stevens LK, Webb DJ, Eaton S, *et al*. Autonomic neuropathy is associated with increased cardiovascular risk factors: The EURODIAB IDDM complication study. Diabet Med 2002;19:900-9.
13. Walsh D, Nelson KA. Autonomic nervous system dysfunction in advanced cancer. Support Care cancer 2002;10:523-8.
14. Ohno T, Toyama T, Hoshizaki H, Okamoto E, Naito S, Nogami A, *et al*. Evaluation of cardiac sympathetic nervous function by ^{123}I-Metaiodobenzylguanidine scintigraphy in insulin treated non-insulin dependent diabetics with hypoglycemia unawareness. Intern Med 1996;35:94-9.

15. Smith SA. Reduced sinus arrhythmia in diabetic autonomic neuropathy: Diagnostic value of age related normal range. BMJ 1982;285:1599-601.
16. Carvalho MJ, vanden Meiracker AH, Boomsma F, Lima M, Freitas J, Veld AJ, *et al*. Diurnal Blood pressure variations in progressive autonomic failure (Scientific contributions). Hypertension 2000;35:892-7.
17. Inukai T, Kobayashi I, Kobayashi T, Ishu A, Yamaguchi Y, *et al*. Parasympathetic nervous system in hypothyroidism determined by RR interval variation on electrocardiogram. J Intern Med 1990;228:431-4.
18. Kartik S, Pal GK, Nanda N, Hamide A, Bobby Z, Amudharaj D, *et al*. Sympathovagal imbalance in thyroid dysfunction in females: Correlation with thyroid profile, heart rate and blood pressure. Indian J Physiol Pharmacol 2009;53:243-52.
19. Laxmi V, Vaney N, Madhu SV. Effect of thyroxine therapy on autonomic status in hypothyroid patients. Indian J Physiol Pharmacol 2009;53:219-26.
20. Osman F, Gammage MD, Franklyn JA. Thyroid disease and its treatment: Short term and long term cardiovascular consequences. Curr Opin Pharmacol 2001;1:626-31.
21. Manhem P, Bramnert M, Hallengren B, Lecerof H, Werner R. Increased arterial and venous plasma noradrenaline levels in patients with primary hypothyroidism during hypothyroid as compared to euthyroid state. J Endocrinol Invest 1992;15:763-5.
22. Bilezikian JP, Loeb JN. The influence of hyperthyroidism and hypothyroidism on a and b adrenergic receptor system and adrenergic responsiveness. Endocrine Rev 1983;4:378-85.
23. Polikar R, Kennedy B, Maisel A, Ziegler M, Smith J, Dittrich H, *et al*. Decreased adrenergic sensitivity in patients with hypothyroidism. J Am Coll Cardiol 1990;15:94-8.
24. Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation 1993;87:1435-41.
25. Wu JS, Lu FH, Yang YC, Lin TS, Chen JJ, Wu CH, *et al*. Epidemiological study on the effect of prehypertension and family history of hypertension in cardiac autonomic failure. J Am Coll Cardiol 2008;51:1896-901.
26. LiaoD, Caj J, Barnes RW, Tyroler HA, Rautaharju P, Holmes H, *et al*. Association of cardiac autonomic function and the development of hypertension: the ARIC study. Am J Hypertens 1996;9:1147-56.
27. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, *et al*. Seventh report of joint national committee on prevention, detection evaluation and treatment of high blood pressure. Hypertension 2003;42:1206-52.
28. Luboshitzky R, Aviv A, Herer P, Lavie L. Risk factors for cardiovascular disease in women with subclinical hypothyroidism. Thyroid 2002;12:421-5.
29. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, *et al*. Subclinical thyroid function and blood pressure: a community-based study. Clin Endocrinol 2006;65:486-91.

Cite this article as: Mahajan AS, Lal R, Dhanwal DK, Jain AK, Chowdhury V. Evaluation of autonomic functions in subclinical hypothyroid and hypothyroid patients. Indian J Endocr Metab 2013;17:460-4.

Source of Support: Nil, **Conflict of Interest:** None declared.