

EFFECT OF THYROXINE THERAPY ON AUTONOMIC STATUS IN HYPOTHYROID PATIENTS

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(Received on December 2, 2008)

Abstract : The aim of the present study was to evaluate the impact of hypothyroidism on the autonomic regulation of the cardiovascular system by analyzing sympathetic and parasympathetic influences on the heart and the effect of thyroxine replacement. Thirty newly diagnosed female hypothyroid patients with mean age 32.73 ± 9.98 years were recruited from the Thyroid Clinic, GTB Hospital, Delhi. Various Autonomic function tests to assess Basal heart rate variability, parasympathetic activity (E:I Ratio, 30:15 Ratio, Valsalva Ratio) and sympathetic activity (Postural Challenge test, Sustained handgrip test) were done before and after attainment of euthyroidism. There was significant increase in parasympathetic activity on achieving euthyroid state. The sympathetic activity too significantly improved after L-thyroxine supplementation. Lipid profile parameters significantly decreased after achieving euthyroid state. Our findings are consistent with previous reports that thyroxine therapy appears to restore the efferent vagal activity and alters the relative contribution of systems that maintain resting blood pressure and heart rate.

Key words : hypothyroidism autonomic function test L-thyroxine

INTRODUCTION

Thyroid hormones have prominent effects on the heart and the peripheral vascular system either directly or indirectly which may be due to changes at the autonomic nervous system level (1). Thyroid dysfunctions are associated with changes not only in cardiac or vascular function but are also believed to alter autonomic regulation of cardiovascular system (2).

The clinical features of hyperthyroidism and hypothyroidism are suggestive of sympathetic nervous system overactivity and hypoactivity respectively. Characteristic

features of hypothyroidism like bradycardia, decreased cardiac contractility, narrow pulse pressure, ptosis and low level of thermogenesis are suggestive of deficient adrenergic stimulation. Contrary to clinical picture thyroid hormone deficiency is associated with an increased sympathetic influence on the cardiovascular system. Studies have found overall depression of adrenergic responses at cardiac and peripheral level and an increased plasma noradrenaline concentration in hypothyroid state (3). The changes in sympathetic activity might represent an adaptation to altered adrenergic responsiveness at cardiac and peripheral level (4) that appears to be

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compensatory in nature and may be in response to the deficient peripheral responses to catecholamine, the thermal stress derived from the lack of the calorogenic effect of thyroid hormone, the reduction in cardiac output or from the lack of T_3 in critical regulatory centres of the central nervous system.

Thyroid hormone deficiency can lead to an increase in BP as well as activation of sympathetic/adrenal system. The sympathetic and adrenal activation in hypothyroidism, which is reversible with thyroid hormone treatment, contributes to the development of arterial hypertension (5).

Hypothyroidism is often accompanied by diastolic hypertension that, in conjunction with the dyslipidemia, may promote atherosclerosis (6). Overt hypothyroidism may result in accelerated atherosclerosis, coronary heart disease presumably because of the associated hypertension, hypercholesterolemia and hyperhomocysteinemia (7).

Some authors have observed hypofunctional abnormalities of cardiac parasympathetic nervous system associated with thyroid hormone deficiency (8, 9). Contrary to above findings Xing et al (10) reported that patients with hypothyroidism often have autonomic dysfunctions with a higher level of vagal tone.

Studies done in Indian population have assessed the autonomic status in thyroid dysfunction but very less data is available on the changes in autonomic functions after attainment of euthyroidism. In the present study we evaluated the autonomic functions and lipid profile in hypothyroid patients and observed the effect of treatment.

MATERIALS AND METHODS

The study was conducted on 30 newly diagnosed female hypothyroid patients (32.73 ± 9.98 years). The patients were recruited from the Thyroid Clinic, GTB hospital, Delhi. Diagnosis of hypothyroidism was done on the basis of general history, clinical examination and serum levels of fT_3 , fT_4 and TSH. The recordings for hypothyroid patients were taken before and three months after treatment with attainment of euthyroid state.

Patients suffering from other conditions known to affect autonomic function tests like diabetes mellitus, renal disease, psychiatric disease or cardiovascular disease were excluded from the study.

The study was approved by the Institute Ethical Committee and an informed written consent was taken from patients. All the patients were tested under similar laboratory conditions. They were allowed to get familiar with the experimental and environmental condition of the laboratory. The following parameters were studied in all the subjects.

- I. Autonomic function tests: Basal heart rate variability, E:I Ratio, 30:15 Ratio, Valsalva Ratio, Postural Challenge test, Sustained handgrip test.
- II. Biochemical parameters :
 1. Thyroid hormone profile – fT_3 , fT_4 , TSH.
 2. Lipid profile – Total cholesterol, Triglycerides, LDL-Cholesterol.

Autonomic function tests :

In the following tests, the ECG was

recorded from standard leads using the student physiograph machine (INCO), while the blood pressure was measured with a mercury sphygmomanometer.

Test for Autonomic Activity

(a) Basal Heart Rate Variability :

After making the subject lie down in the supine position for 5 minutes, lead II ECG was recorded for 1 minute. Each R-R interval was determined. The minimum and maximum R-R interval values were identified and converted into heart rate; the difference of the corresponding maximum and minimum value of heart rate was recorded as the heart rate variability in 1 minute.

Tests for Parasympathetic Reactivity

(b) Heart Rate Variation during deep breathing or the E:I Ratio :

The subject was asked to lie quietly supine for 1 minute with ECG leads (limb leads) applied and connected to the physiograph machine. After a verbal command the subject started to breathe deeply and continuously at a rate of 6 breaths per minutes (5 seconds inspiration and 5 second expiration). The result was expressed in terms of an average of 6 maximum R-R intervals during expiration to an average of 6 minimum R-R intervals during inspiration.

(c) 30:15 Ratio :

After making the subject lie supine for about 5 minutes, the subject was asked to stand up unaided and erect as quickly as possible. During this period lead II ECG was recorded and the point at the start of standing was marked on the ECG

record. The 30:15 ratio was calculated by taking the ratio of maximum R-R interval around the 30th beat to the minimum R-R interval around 15th beat after standing.

(d) Valsalva ratio :

Each subject was told to perform Valsalva manoeuvre for 15 seconds by blowing into a mouth piece attached to an aneroid manometer and maintain a pressure of 40 mm Hg for 15 sec. Three trials were performed at intervals of 5 minutes. A continuous ECG was recorded 1 minute before the manoeuvre (resting period), during manoeuvre (strain period, 15 sec.) and 60 seconds subsequent to strain period.

Valsalva ratio was taken as the maximum ratio of maximum R-R interval after the strain to that of shortest R-R interval during the strain.

$$\text{Valsalva Ratio} = \frac{\text{Maximum R-R interval after strain}}{\text{Shortest R-R interval during the strain}}$$

Shortest R-R interval during the strain
The maximum ratio of three trials was taken for the autonomic activity.

Tests for Sympathetic Reactivity

(e) Postural Challenge Test

Using sphygmomanometer two blood pressure recordings were taken in the supine position after a 5 minute rest and the average of the two readings was taken. The subject was then asked to stand up unaided and erect for 2 minutes at the end of which blood pressure was recorded again. The changes in systolic and diastolic blood pressure were calculated.

(f) Sustained Handgrip Test

The test was performed in the sitting position and the average of three basal blood pressure was taken. The maximum voluntary contraction was then determined with handgrip dynamometer using the dominant hand of the subject. Handgrip was then maintained at 30% of the subject's maximum capacity for 2–3 minutes. Blood pressure was recorded on the contra lateral arm every minute during contraction. The highest systolic and diastolic blood pressure during the handgrip exercise and the mean of the 3 blood pressure reading before the handgrip began were noted.

II. Biochemical parameters

1. Thyroid hormone Profile

Serum fT_3 , fT_4 , TSH

The estimation of fT_3 , fT_4 and TSH were done in the Endocrine & Metabolic laboratory of Guru Teg Bahadur Hospital. The quantitative determination of human thyroid stimulating hormone (hTSH) in serum was done using the Gamma Coat [1251] hTSH Immunoradiometric Assay (IRMA) Kit. Free Thyroxine (fT_4) levels was estimated using the Gamma Coat™ Free T4 (Direct-One-Step) Radioimmunoassay kit. Free Triiodothyronine (fT_3) level in serum was estimated using the Dia Sorin Free T3 RIA Kit.

2. Lipid Profile

Total Cholesterol

It was estimated using the cholesterol oxidase peroxidase (CHOD-POD) enzymatic end point method. Cholesterol was oxidized by cholesterol oxidase with

production of hydrogen peroxide. The hydrogen peroxide formed reacts with 4-aminoantipyrine to form quinoneimine. The absorbance of quinoneimine was read colorimetrically at 510 nm. The intensity of colour thus produced was directly proportional to total cholesterol concentration.

Triglycerides

Triglycerides were hydrolysed by lipoprotein lipase and the liberated glycerol was then phosphorylated with the help of glycerol kinase in presence of ATP to glycerol -3-phosphate which was then oxidized in presence of glycerol phosphate oxidase to dehydroxy acetone phosphate and hydrogen peroxide. Phenol and 4-aminoantipyrine then combined with hydrogen peroxide by oxidative condensation in presence of peroxidase to produce red coloured quinoneimine, which showed a maximum absorbance at 500 nm filter. The intensity of colour thus produced was directly proportional to triglyceride concentration.

LDL – Cholesterol

LDL – Cholesterol was estimated by formula: $LDL = Total\ Cholesterol - (HDL-C + VLDL-C)$.

Statistical analysis : The data was analyzed using SPSS-13 by paired t-test.

RESULTS

Table I shows the parasympathetic activity in hypothyroid patients before and after treatment. There was significant improvement in all the parasympathetic parameters in hypothyroid patients after treatment (BHRV, E:I Ratio, 30:15 Ratio, Valsalva Ratio).

TABLE I: Showing parasympathetic activity in hypothyroid patients before and after treatment (Mean±SD).

S.No.	Parameters	Pre treatment	Post treatment
1	BHRV (Beats/min)	11.27±2.98	20.10±5.12***
2	E:I Ratio	1.32±0.13	1.45±0.15**
3	30:15 Ratio	1.24±0.14	1.48±0.13***
4	Valsalva Ratio	1.42±0.19	1.61±0.23**

P<0.01; *P<0.001.

Table II shows the sympathetic activity in hypothyroid patients before and after treatment. During postural challenge test there was significant decrease in supine systolic and diastolic blood pressure showing improvement after treatment as compared to pretreatment. Postural fall in systolic BP was insignificant in pre and post treatment group. The change in diastolic BP after sustained hand grip test was significant in euthyroid state from that of hypothyroid state.

TABLE II: Showing values of basal BP (mm Hg), change during postural challenge test and sustained handgrip (HG) test (Sympathetic Activity) in hypothyroid patients before & after treatment (Mean±SD).

S.No.	Parameters	Pre treatment	Post treatment
1	Supine SBP	128.07±7.32	118.63±7.10***
2	Supine DBP	87.60±2.85	80.4±5.95***
3	Change SBP	7.80±2.64	8.50±2.47
4	Difference DBP	17.47±2.09	20.20±2.94***

***P<0.001.

Serum levels of fT₃ and fT₄ were significantly increased in euthyroid state as compared to their hypothyroid state, where as the TSH level significantly degraded on achieving euthyroid state as seen in Table III.

Total cholesterol level as well as the LDL-cholesterol level was borderline high, both of which significantly decreased once

TABLE III: Showing Thyroid hormone profile in hypothyroid patients before and after treatment (Mean±SD).

S.No.	Parameters	Pre treatment	Post treatment
1	fT ₃ (pg/ml)	1.24±0.77	3.21±1.06***
2	fT ₄ (ng/dl)	1.74±1.19	4.05±3.74**
3	TSH (µIU/ml)	37.26±28.31	1.83±1.39***

P<0.01; *P<0.001.

the hypothyroid subjects achieved the euthyroid state. The Triglyceride level was normal yet its level too significantly declined after the treatment (Table IV).

TABLE IV: Showing Lipid Profile in hypothyroid patients before and after treatment (Mean±SD).

S.No.	Parameters	Pre treatment	Post treatment
1	TC (mg/dl)	211.20±48.66	193.93±44.73*
2	TG (mg/dl)	116.00±63.64	89.87±32.19*
3	LDL (mg/dl)	132.97±47.86	113.80±26.14*

*P<0.05.

DISCUSSION

The autonomic nervous system (ANS), through its sympathetic and parasympathetic divisions regulates and modulates involuntary functions of the body. Dysautonomia is a condition which refers to a change in autonomic nervous system function that adversely affects a person's health (11). Thyroid hormones have prominent effects on the heart and the peripheral vascular system either directly or indirectly which may be due to changes at the autonomic nervous system level. They play an important role in the regulation of the function of sinoatrial node, the systolic and diastolic function of the myocardium and the peripheral resistance (12).

In the present study, we evaluated the ANS status in hypothyroid patients. The patients were reassessed after attainment of euthyroidism.

In our study, there was decrease in parasympathetic activity in hypothyroid patients which significantly increased on achieving euthyroid state. On the other hand even though the sympathetic activity was within normal limits during hypothyroidism but it significantly improved after supplementation of L-thyroxine. The thyroid hormone profile normalized after the treatment. All the parameters assessed in lipid profile too significantly decreased after achieving euthyroid state.

A previous study done in our department, found that there was decreased parasympathetic activity with increased T_3 and T_4 in hyperthyroid subjects, whereas the sympathetic activity remained unaffected both in hypothyroid & hyperthyroid subjects (13).

According to Conny MA, heart rate variability can be assessed in two ways: by calculation of indices based on statistical operations on R-R intervals (time domain analysis) or by spectral (frequency domain) analysis of an array of R-R intervals. Both methods require accurate timing of R waves. The analysis can be performed on short electrocardiogram (ECG) segments (lasting from 0.5 to 5 minutes) or on 24-hour ECG recordings (14). Beat-to-beat or short-term variability (STV) indices represent fast changes in heart rate.

In our study we have carried out the short-term variability indices for one minute to record the Time domain analysis of Heart rate variability. Our findings show decreased heart rate variability in hypothyroid patients. Decreased HRV is suggestive of a low parasympathetic (vagal) tone or increased sympathetic tone. BHRV, E:I Ratio, 30:15 Ratio and Valsalva Ratio showed a significant increase in euthyroid state when

compared to the hypothyroid state of the subjects. This suggests a decreased parasympathetic activity, but within normal range in hypothyroid patients which improved significantly after attaining euthyroidism.

Our findings are consistent with previous reports of Inukai et al and Kahaly. Inukai et al in 1990 observed a significant reduction in R-R interval variations in patients with primary severe hypothyroidism and concluded that in marked hypothyroidism there were hypofunctional abnormalities in the parasympathetic nervous system in association with a reduced levels of serum T_4 and T_3 (8). In a similar study, Kahaly in 2000 observed decreased HRV even in subclinical hypothyroidism with subtle changes in the levels of thyroid hormones. He also found that R-R variations were restored to normal level after treatment (9).

Inukai et al in 1998 observed on Power spectral analysis that the LF (low frequency)/HF (high frequency) ratio in hypothyroid patients with Hashimoto's thyroiditis was significantly lower than in healthy controls (15).

Contrary to the above studies, Xing et al 2001, found that time domain measurements of HRV in hypothyroid patients were much lower than those in control group. High frequency power was significantly higher but ratio of LF/HF power for hypothyroid patient was significantly lower than in controls and abnormal changes of HRV were improved after treatment (10).

In the present study the postural fall of systolic BP in postural challenge test and the rise in diastolic BP during sustained handgrip test were within normal limits during hypothyroid as well as euthyroid state. There was significant change in pre

and post treatment group thereby suggesting that thyroid hormone therapy alters sympathetic activity.

According to Matsukawa et al 1993, there was significant positive correlation of TSH and muscle sympathetic nerve activity which suggests an inverse relationship between thyroid function and sympathetic nerve activity (16). Momose in 1997 made a conclusion that cardiac sympathetic activity is increased in patients with hypothyroidism, in parallel with enhanced general sympathetic activity (17).

In 1997, Henley WN conducted experiments in unanaesthetized rats and made a conclusion that deranged autonomic control in hypothyroidism may be caused in part, by changes in central serotonergic activity (18).

Foley et al (19) studied the effect of thyroid status on arterial baroreflex function and autonomic contributions to arterial pressure and heart rate in conscious rats. Their results showed that thyroid status alters the balance of sympathetic to parasympathetic tone in the heart.

According to Guasti et al 2007, different local NE concentrations or post-receptor signaling may be present in patients with thyroid dysfunction. They said that the neurally mediated influences on the sinus node and the study of intracellular catecholamine production suggest a reduced sympathoexcitation in hypothyroidism compared with the treatment phase (20).

Recently, Galetta et al (21) too observed that hypothyroidism is associated with a decreased sympathovagal modulation of heart rate and with an increased inhomogeneity of ventricular recovery times. They stated that the diversity of techniques used to

monitor the sympathovagal imbalance may also be responsible for the contradictory results obtained. According to them L-T4 therapy appears to restore the vagal activity and reduces the sympathetic drive on the heart, thus supporting the view of an increased ratio of sympathetic to vagus nerve traffic to the heart in patients with clinical hypothyroidism.

According to Fommei et al (5) thyroid hormone deprivation promotes an increase in BP as well as activation of sympathetic/adrenal system. Elevated BP was seen to be reversible with thyroid hormone replacement therapy. In our study we also found significant decrease in resting SBP and DBP following thyroxine treatment. Hypothyroidism is often accompanied by diastolic hypertension that, in conjunction with the dyslipidemia, may promote atherosclerosis (6). Thyroid hormone is known to play a role in regulating the synthesis, metabolism and mobilization of lipids. Most lipid abnormalities in patients with overt hypothyroidism resolve with thyroid hormone replacement therapy (22). We also observed significant improvement in lipid profile after treatment.

On the basis of findings of present study we suggest that early diagnosis and treatment does have significant effect on cardiovascular autonomic activity, thyroid hormone profile and lipid profile of hypothyroid patients and can help in reducing the risk of atherosclerotic cardiovascular disease.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Mr. Manjhi for technical assistance and Dr. Abhinav Dixit and Dr. Anjana for their valuable comments during the work.

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