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Original Article

Reversal of nocturnal non-dipping of blood pressure after Levothyroxine therapy in patients with subclinical hypothyroidism

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ABSTRACT

Aims: To study the loss of diurnal variation in blood pressure in normotensive patients with Subclinical/overt hypothyroidism and effect of Levothyroxine (L-T4) treatment.
Materials and methods: In this interventional study Eighty patients between 17- 50 years with newly detected OH and SCH (74 women and 6 men) and nine euthyroid subjects (all men) with blood pressure <140/90 were recruited. All patients underwent 24 h ambulatory blood pressure monitoring (ABPM) using ABPM machine before and after treatment with L-T4. Diurnal index (DI), Percent time elevation (PTE), Hyperbaric impact (HBI) were studied pre and post L-T4 treatment.
Results: Of the 89 subjects (22 SCH, 58 OH and 9 controls), 7 of the SCH and 30 of OH subjects reported back in follow up after L-T4 supplementation for evaluation. DI, HBI and PTE when compared at baseline between different groups (SCH- OH, SCH- control, OH- control) were insignificant. After L-T4 supplementation DI, HBI and PTE varied significantly with p value 0.007, 0.003 and 0.003 respectively between SCH- OH only. Post L-T4 analysis in SCH group was statistically insignificant (p-value 0.102) but a trend toward improvement in DI was noted (baseline and post treatment DI mean 7.00 and 13.00 respectively).
Conclusion: Loss of nocturnal dipping was found in patients with OH and SCH which was restored after L-T4 therapy only in patients with SCH and not with OH.
Treatment: of SCH patients with high cardiovascular risk may be beneficial in this setting and can be a new indication for LT4 therapy in SCH.

1. Introduction

Hypothyroidism is characterized by clinical features ranging from overt myxedematous state with multisystemic failure to an asymptomatic subclinical state characterized by mild elevation of serum thyrotrophin (TSH) level in presence of normal thyroxine and triiodothyronine [1–4].

Some of the studies have suggested that Hypothyroidism might promote atherosclerosis [5], stimulate myocardial fibroblasts and induce myocardial fibrosis [6,7]. All cardiovascular abnormalities present in overt hypothyroidism OH have also been reported in SCH, differing only in the degree of the alteration [8]. Diastolic blood pressure has been reported to be higher in women with Sub clinical hypothyroidism (SCH) than in the euthyroid controls [9]. In another study [10], even within the normal reference range of TSH, namely 0.50-3.5 mU/L, a linear positive association between TSH and systolic and diastolic blood pressure was noted, suggesting that the TSH concentration influenced cardiovascular condition on long-term basis.

The present study was designed to evaluate the effect of raised TSH on diurnal variation of blood pressure in normotensive patients with SCH and OH. The objective of this study was to find out diurnal variations in blood pressure in normotensive patients with either OH or SCH using of ABPM machine and to demonstrate the effect of treatment with LT4 on various ABPM parameters.

2. Materials and methods

Eighty patients with OH and SCH (74 women and 6 men) and nine euthyroid subjects (all men) were recruited from the outpatient clinic of the University hospital. Newly detected subjects of age between 17- 50 years with OH and SCH (TSH 4–10 μIU/ml) with Blood Pressure <140/90 measured on two occasions (one during 1st visit to the OPD and 2nd before enrollment in the study using mercury sphygmomanometer) were

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included in this study. Patients of age <17 or >50 years, with any disease or drug which might affect thyroid function and blood pressure and blood pressure ≥140/90 measured on any of the two occasions mentioned above were excluded. All participants gave their written informed consent for the study approved by the local Ethics Committee.

The euthyroid subjects had a negative history of thyroid diseases and normal evaluation of the thyroid gland on palpation and a serum measurement of TSH and T4 within the normal range. Fasting samples of venous blood were collected in the morning, from the antecubital vein of the participants. Serum TSH, T4 and anti thyroid peroxidase (anti TPO–Ab) were measured by chemiluminescent immunometric assay (DPC-Diagnostic Products Corporation/Immulite 1000 systems). Reference ranges for TSH and T4 were respectively 0.4–4.0 mUI/ml and 4.6–12 ug/dl. Levels of anti TPO-Ab > 35 UI/ml were considered positive. The intra-assay coefficients of variation were 4.5% –13.8%, 4.4- 7.5% and 4.3–5.6% for TSH, T4 and TPO-Ab, respectively. The coefficients of variation between assays were 8.0–17.9%, 4.8-9.0% and 7.8-10.5%, respectively. Serum total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides were measured by enzymatic methods and analysed by RX SUZUKA CH 8019,8032,8033,8067(RANDOX, UK) respectively. Inter assay coefficient of variation were 0.66%-2.0%, 0.89%- 1.43%, 0.72%- 0.88%, 0.69%- 3.29% respectively. Fasting plasma glucose was measured by Glucose Oxidase- Peroxidase method. Serum Creatinine was measured by calorimetric method (Randox RX SUZUKA CR 8022, UK). All cases underwent 24 h ABPM. ABPM machine using oscillometric blood pressure measurement method manufactured by Meditech ABPM 05 Serial no.2013/508406, Meditech Ltd., Budapest, Hungary was used. Subjects were allowed to perform their daily activity while remaining indoors and were asked to record the timings of sleep, any medication, postural change activity and any symptom. The measurements were carried out at 15 min intervals during the day and 30 min intervals at night. Diurnal index (DI), Percent time elevation (PTE), Hyperbaric impact (HBI) were noted from the recording of the ABPM machine. Subjects were classified as non dippers, normal dippers, extreme dippers, reverse dippers when DI was 0- 10%, 10–20%, >20% and <0% respectively [11]. All the patients with OH and SCH were treated with LT4 for 2–4 months to normalize the TSH levels.

3. Statistical analysis

Results were expressed as the mean ± SD and were compared between three groups using the Student *t*- test, for normally distributed data, and the Mann- Whitney test for non-parametric data. The SCH group was also evaluated according to serum TSH levels. The comparisons between the three groups (Euthyroidism *vs* SCH patients with serum TSH levels > 4.0-10.0 mUI/ml *vs* SCH patients with serum TSH >10.0mUI/ml) were performed by Kruskall Wallis or ANOVA test. The correlations between two continuous variables were assessed by Pearson's or Spearman's correlation, according to the distributions patterns (normal or not normal). The $\chi 2$ test or the Fisher exact test compared the proportions of qualitative variables in the two groups. A p value < 0.05 was considered statistically significant.

4. Results

A total of 89 subjects were included in this study after exclusion based on earlier fixed criteria. Of these, 22 subjects were having SCH, 58 OH and remaining 9 were healthy non hypertensive euthyroid controls. Seven of the SCH and thirty of OH subjects reported back in the follow up after LT4 supplementation for evaluation. The patients' demography and biochemical characteristics of the study groups were given in Tables 1 and 2.

When ABPM parameters were compared, DI at baseline between groups were insignificant (p value 0.410 for SCH- OH, 0.401 for SCH- control, 0.227 for OH- control), HBI comparison at baseline was insignificant (p value 0.073 for SCH- OH, 0.617 for SCH- control, 0.241 for OH- control), PTE at baseline also showed no significant variation (p value 0.061 for SCH- OH, 0.649 for SCH-control, 0.208 for OH- control). Significant variation was observed amongst the groups after LT4 supplementation. DI, HBI and PTE varied significantly with p value 0.007, 0.003 and 0.003 respectively for SCH- OH (Table 3).

Baseline and post LT4 comparison in SCH and OH group was done. No statistical significance was observed in SCH group (p value 0.102) but a trend toward improvement in DI was noted (Table 4). Post treatment value in OH group was significant for hormonal profile (T4 and TSH p value <0.001 and <0.0001 respectively) but the ABPM variables showed insignificant change (Table 4).

5. Discussion

Hypothyroidism is associated with decreased endothelium dependent vasodilatation. Endothelial dysfunction in patients with SCH may result from reduction in nitric oxide availability, with resultant impairment of flow-mediated vasodilatation [12,13].

In the present study, blood pressure variables recorded by ABPM in SCH, OH and control group was compared before and after LT4 supplementation. Small but significant reversal of diurnal index (DI) was observed after LT4 supplementation in patients with SCH, but it was statistically significant as compared to patients with OH. There was no change in other parameters like HBI and PTE after LT4 supplementation in both the SCH and OH group. Baseline DI, HBI and PTE was not different in all three groups. Reversal of diurnal index in SCH group from non dipper pattern to dipper may be attributed to the normalization of the autonomic and endothelial dysfunction. Autonomic dysfunction is almost always associated with a non-dipping BP profile and sometimes even with nocturnal Hypertension [14,15].

There were no significant changes in HBI and PTE after LT4 supplementation in SCH group, rather there was a trend towards progression of hypertension disease suggesting the influence of other factors on ABPM like hyperaldosteronism [16–18], and renal impairment [14,19] or initiation of early structural changes in vessel associated with hypothyroidism.

No significant change was observed in all the three variables i.e.; DI, HBI and PTE, in patients with OH which may be suggestive of established stiffened arterial wall with loss of elasticity [20]. This study did not show any correlation between T4 levels – SBP and TSH levels – SBP, which supports previous studies [21].

Earlier Ferreira et al. studied ABPM in subjects with SCH and compared with healthy euthyroid control and found no difference in blood pressure [22]. In other studies blood pressure measurement was done by either mercury or aneroid sphygmomanometer which was influenced by variability in examiners technique, white coat effect and inherent variations in BP instrument. Various other studies have been done suggesting an association between SCH

Table 1
Age and sex profile of subjects in different groups.

	SCH group	OH group	Control group	p value
Age in years (Mean + SD)	34.50 ± 8.51	33.07 ± 9.21	35.78 ± 7.87	0.622
Sex (Male/Female)	3/19	3/55	9/0	<0.001*

* ($\chi 2 = 50.21$; p = <0.001).

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