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Original Research Article

Association of Thyroid Function Test and Heart Rate in Hypothyroid Patient Before and After Treatment

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Abstract:

Background: In terms of prevalence, hypothyroidism is second only to diabetes mellitus among endocrine disorders. The cardiovascular system is one of the key organs that hypothyroidism targets, and this system is extremely sensitive to even minute variations from normal levels. A decrease in cardiac contractility, a reduction in cardiac output, and an increase in peripheral vascular resistance are all examples of the cardiovascular manifestation of hypothyroidism. It has also been noted that administering L-thyroxine medication to these individuals will be useful in preventing the issues mentioned above.

Aims and Objectives: Association of Thyroid function test and Heart Rate in Hypothyroid patient before and after treatment.

Materials and Methods: Thirty newly diagnosed female hypothyroid patients with high serum TSH and age-matched healthy controls were studied. Heart rate variability analysis was performed before L-thyroxine therapy and after 3 months. Heart rate variability was examined after achieving euthyroid levels with serum TSH.

Results: Hypothyroid females had autonomic imbalance with increased sympathetic activity and decreased parasympathetic activity before treatment, as shown by very highly significant ($p<0.000$) changes in frequency domain Heart rate variability. After treatment with L-thyroxine the changes were comparable with normal to normal individuals. The elevated serum TSH levels were also shows highly significant ($p<0.001$) after treatment.

Conclusion: This study suggests that L Thyroxine replacement medication would help avoid hypothyroidism's cardiovascular consequences including autonomic instability. Heart rate variability can check hypothyroidism patients for CVS problems and frequent follow-up following therapy because they are non-invasive.

Keywords: Hypothyroidism, L-Thyroxine, HRV, Thyroid Function test.

Introduction

Nowadays, thyroid diseases are prevalent endocrine illnesses. As per the results of a large scale survey conducted across India in 2021, about 7.3 percent of the respondents suffered from thyroid related problems. [1] Women have 8–10 times more thyroid disorders than males. Hypothyroid disorders may need more attention since they are more common than hyperthyroidism, more common in women than men, and increase with age. [2]

Action of Thyroid Hormone on Cardiovascular System

Thyroid hormone has several cardiovascular consequences. They include improved cardiac contractility, output, systemic vascular resistance, and electrophysiological and pro-angiogenic effects. Genomic and non-genomic (extra nuclear) pathways have been postulated. [3]

Genomic activities occur when triiodothyronine (T3) reaches the nucleus and binds to particular nuclear receptors (TR alpha and TR beta). The T3 receptor complex subsequently attaches to thyroid-hormone response elements (TREs) in target gene promoters and changes their expression. Genomic actions. Protein kinase C (PKC), mitogen activated protein kinases (MAPKs) 6, 7, and Akt8 may activate signalling pathways to regulate membrane ion channels or pumps in faster non-genomic activities. [3]

Peripheral resistance decreases because of cutaneous vasodilation, and this increases levels of renal Na+ and water absorption, expanding blood volume.

Cardiac output is increased by the direct action of thyroid hormones, as well as that of catecholamines, on the heart, so that pulse pressure and cardiac rate are increased and circulation time

is shortened. T3 is not formed from T4 in cardiac myocytes, but circulating T3 enters myocytes, combines with its receptors, and enters the nucleus, where the complex promotes the expression of some genes and inhibits the expression of others. Those that are enhanced include the genes for α-myosin heavy chain, sarcoplasmic reticulum Ca2+ ATPase, β-adrenergic receptors, G-proteins, Na, K ATPase, and certain K+ channels. Those that are inhibited include the genes for β-myosin heavy chain, phospholamban, two types of adenylyl cyclase, TRs, and NCX, the Na+–Ca2+ exchanger. The net result is increased heart rate and force of contraction. The two myosin heavy chain (MHC) isoforms, α-MHC and β-MHC, produced by the heart are encoded by two highly homologous genes located on the short arm of chromosome 17. Each myosin molecule consists of two heavy chains and two pairs of light chains. The myosin containing βMHC has less ATPase activity than the myosin containing α-MHC. α-MHC predominates in the atria in adults, and its level is increased by treatment with thyroid hormone. This increases the speed of cardiac contraction. Conversely, expression of the α-MHC gene is depressed and that of the β-MHC gene is enhanced in hypothyroidism. [4]

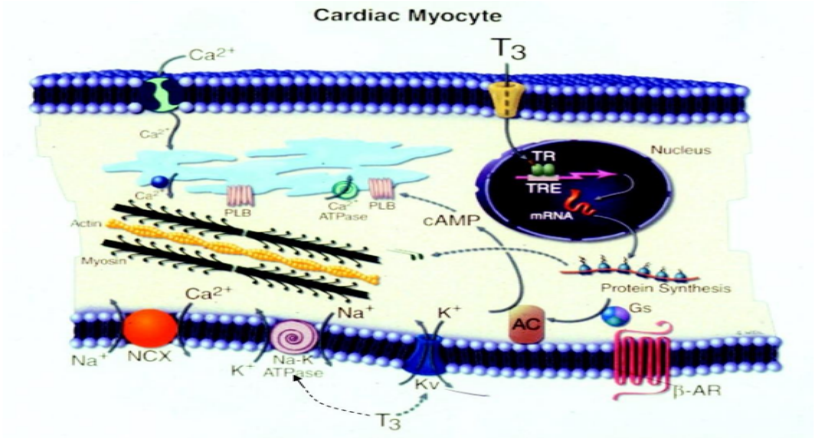


Figure 1: Mechanism of action of thyroid hormone on cardiac myocyte.AC indicates adenylyl cyclase; -AR, adrenergic receptor; Gs, guaninenucleotide binding protein; Kv, voltage-gated potassium channels; NCX, sodium calcium exchanger; and PLB, phospholamban.

It is well known that decreased thyroid hormone activity can cause cardiovascular abnormalities like bradycardia, decreased cardiac output, diastolic dysfunction, mild diastolic hypertension, increased peripheral vascular resistance, dilated cardiomyopathy, and increased coronary atherosclerosis due to impaired sympatho-vagal balance of the heart.

Nowadays, life-threatening heart illnesses are more concerning. The people are becoming more health conscious and willing to undertake necessary tests to detect illnesses early. [5]

Heart rate variation:

Heart rate variability is the variance of heartbeats. Albrecht Von Haller noted in the 18th century that the resting heartbeat is irregular even in healthy people.

Heart rate variability is the spontaneous change of the RR interval in milliseconds between beats. The sinoatrial node's intrinsic automaticity and the autonomic nervous system modulate heart rate and rhythm. Resting vagal or parasympathetic tone prevails. Therefore in our study, the sympathovagal balance was assessed by doing the Resting heart rate variability analysis in the newly diagnosed hypothyroid female individuals and compared with normal controls before and after treatment with L-thyroxine.

Aims and objectives: To evaluate Resting Heart rate variability in normal and hypothyroid (female) patients before and after therapy.

Materials and Methods:

This study was conducted in the Department of Biochemistry, Kurnool Medical College, Kurnool after obtaining the ethical committee clearance.

The study was conducted in the period of Jan 2023 to Nov 2023.

The study group consists of 30 female subjects who were newly diagnosed hypothyroid individuals in the age group 20-35 years.

The control group includes of 30 age matched, euthyroid females for comparison with the cases.

The subjects were informed about the study details, procedures and their acceptance to participate in the study was obtained as written consent from them.

Inclusion Criteria

Newly diagnosed hypothyroid females with estimated (serum TSH levels above 10mIU-100mIU/ml with both normal and decreased serum T_3, T_4 levels) in the age group of 20-35 years are included in this study as cases. For the purpose of statistical analysis, the study subjects are considered as following groups**:**

Group A: Normal control

Group B_{BT}: Hypothyroid (newly diagnosed cases, before starting treatment)

Group B_{AT}: Hypothyroid (after treatment with L-thyroxine for minimum 3months and who have attained euthyroid status with therapy)

Exclusion Criteria

Pregnant females, subjects taking oral contraceptives or drugs affecting heart rate, subjects with anemia (Hb less than 10gm/dl), hypertension, diabetes mellitus, underlying known respiratory, cardiac, renal, hepatic, neoplastic conditions, and other concurrent medical illness are excluded from the study**.**

Materials:

- Niviqure ambulatory digital ECG recorder (INCO)
- Sphygmomanometer
- Stethoscope

Estimation of serum T_3, T_4, TSH levels:

Serum analysis of T_3, T_4, TSH levels were done in Biochemistry Laboratory at GGH Kurnool. The T_3, T_4, TSH levels are measured using ELISA method. As a parameter for statistical analysis the serum TSH levels only taken.

Methodology

The subjects were asked to fill a proforma to assess the general status and clinical symptoms suggestive of hypothyroidism.

After getting an informed and written consent from the subjects, general and systemic examination were carried out and height in meters and weight in kilograms were also measured. Body mass index (BMI) was calculated using the formula weight/height in m^2. The short term Resting HRV analysis for 5 minutes was recorded in the subjects.

Short term HRV analysis

As per the recommendations of the Task force of the European Society of Cardiology and the North-American Society of Pacing and Electrophysiology in 1996, the short term HRV recording was done for 5 minutes. Pretest instructions were given to the subjects as below:

The subjects were advised to have a good sleep at night before the examination day.

No heavy activity 24 hours prior to recording.

Advised to avoid tea, coffee like drinks on the day of testing Mobile phones must be switched off.

The subjects were asked to empty the bladder before the test the subjects should be relaxed, comfortable and free from recent acute illness, and without significant anxiety.

The test should be performed in a quiet room with lighting sub duded; temperature controlled and sound proofed, well electrified room. The subject was made to rest quietly in supine position in a cool and calm environment, for a minimum period of twenty minutes. Electrodes were placed in the respective positions after cleaning the site with spirit cotton and connecting the channels to transducer for ECG with computer the HRV was recorded. The rest period was increased to 30 minutes and then ECG was acquired by continuous ECG recording for five minutes (320 seconds) which is needed for short term HRV analysis. After screening for the artefact and editing it, the results were fed to HRV analysis software.

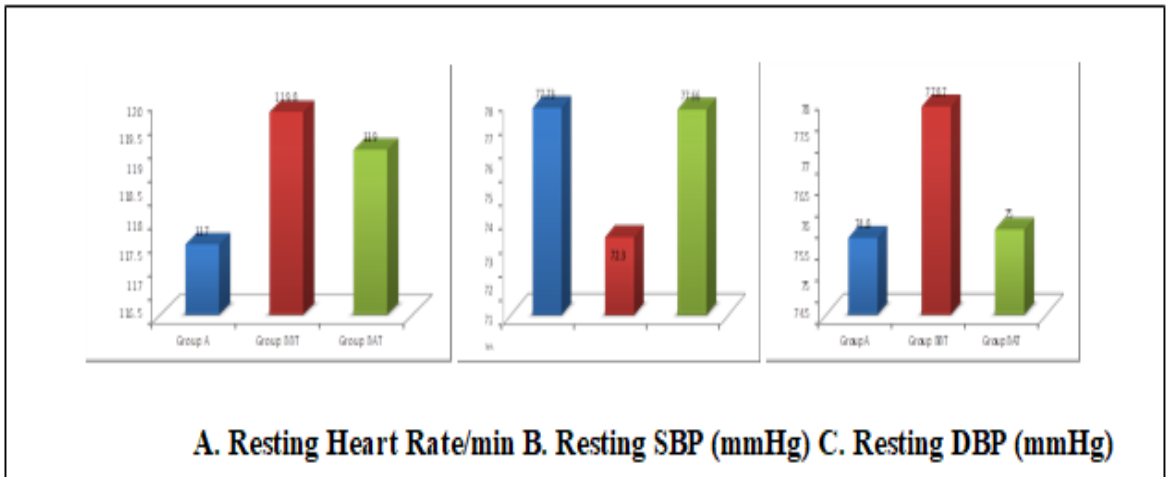
By using the same methodology, the above said estimation of serum TSH, Short term HRV analysis, Echocardiographic measurements were done in the normal controls. Then the study group (newly diagnosed hypothyroid) were started on L-thyroxine therapy for 3 months at a dose of minimum 12.5µg-100µg once daily according to the serum TSH estimation.

After 3 months of therapy serum TSH levels are estimated and after attaining normal euthyroid levels, the short term Resting Heart rate variability analysis were repeated. The results were analyzed for both the controls and study group before and after therapy.

Statistical analyses of the data were done using paired and unpaired t tests.

The statistical analysis of the data obtained from conducting the Heart Rate Variability analysis and Echocardiographic study in normal and hypothyroid female individuals before therapy and after attaining euthyroid status with L thyroxine were done using the Statistical Package for the Social Sciences (SPSS) software version 21

Results:

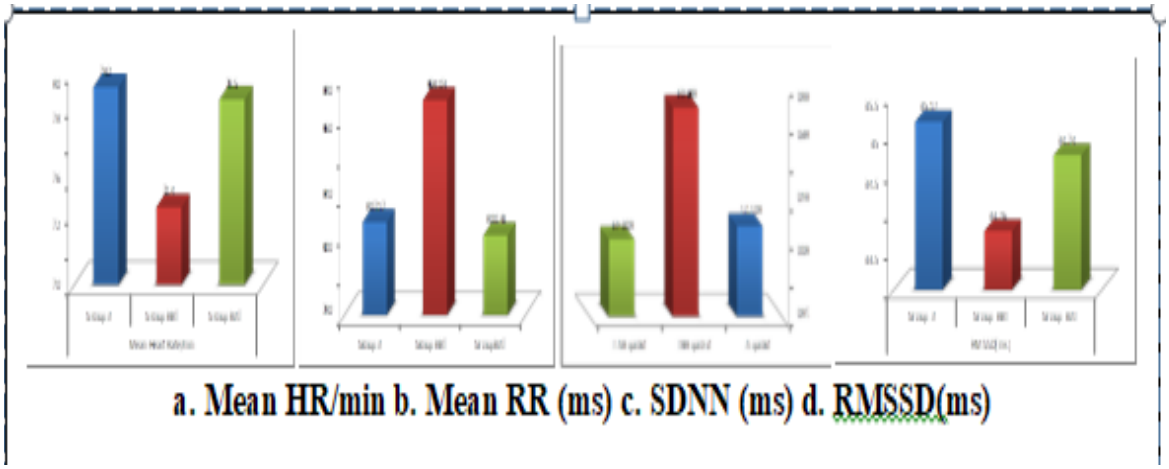


Graph 1: Comparison of resting parameters among study groups

Table 1: Comparison of Serum TSH in mIU/ml, among study groups

Study groups	N	Mean ± SD	P value
Group A	30	3.54 ± 1.32	
Group B_{BT}	30	30.32 ± 13.46	0.0001***
Group B_{BT}	30	30.32 ± 13.46	
Group B_{AT}	30	4.18 ± 1.02	0.0001***

***- very highly significant. TABLE-1 shows the comparison of serum TSH levels among study groups. The mean value of serum TSH levels between normal and hypothyroid individuals before treatment was very highly significant. And the mean value of serum TSH levels among hypothyroid individuals before and after L-thyroxine therapy was also very highly significant.



Graph 2: Comparison of HRV parameters- Time domain measures among study groups

Discussion

Hypothyroidism increases cardiovascular morbidity and death. It impacts heart anatomy, function, and hemodynamics (Hills LD, Lange RA, Winniford MD, Page RL et al)[6]. Hypothyroidism causes heart rate, peripheral resistance, cardiac output, myocardial contractility, and autonomic dysfunction.

Heart Rate Variability Analysis used to assess cardiac autonomic function in newly diagnosed hypothyroid females and the effects of L thyroxine. Our study comprised 30 newly diagnosed hypothyroid females with serum TSH levels over 10mIU/ml and 30 age-matched normal controls. Following HRV hypothyroid patients received L thyroxine for three months and had their serum TSH levels tested. HRV was examined after euthyroid blood TSH levels (0.5-5.5mIU/ml). L-thyroxine treatment compared all parameters. Hypothyroid patients had considerably lower Resting HR before therapy than controls. Hypothyroidism increases sympathetic and decreases vagal modulation. (Cacciatori et al.) [7]. the hypothyroid group had a considerably lower mean HR. Sympathetic overactivity may cause this.

Hypothyroid patients' mean Resting HR increased significantly following L-thyroxine medication. Before and after therapy, normal and hypothyroid patients had similar resting systolic blood pressures. (S. Karthick et al, G.K. Pal et al) [8], discovered this. Thyroid hormone replacement can help. Thyroxine reduces SBP and DBP.

In our study the serum TSH levels among the study groups were estimated by the ELISA method. (S. Karthick et al, G.K. Pal et al) [8,9] discovered that hypothyroid patients had higher mean serum TSH levels than normal adults. L-thyroxine treatment reduced blood TSH levels to statistically significant levels, as shown by Vijayalakshmi et al., N. Vaney, and S. V. Madhu [10]. Resting HRV.

HRV analysis may examine ANS function non-invasively. Altered resting HRV increases cardiac event risk. The research groups' resting heart rate variability was analysed using HRV analysis software version1.1.

Time-domain measures:

The Task force74 analysed mean RR, mean HR, SDNN, and RMSSD. Hypothyroid patients had lower HRV. Lower HRV suggests higher sympathetic or parasympathetic tone. Hypothyroid patients had a considerably lower mean HR than normal controls before therapy, but L thyroxine improved it. Hypothyroid patients had higher mean RR intervals before therapy than normal controls. The hypothyroid's mean RR indicates relative bradycardia interval negatively affects heart rate. (Galetta F et al, Franzoni F) [11] Found similar results. L-thyroxine also slightly increased mean RR intervals (Inukai et al and Kahaly) [12,13]. Hypothyroid people had lower SDNN and RMSSD than normal controls in our research. S. Karthick et al.8 found this. L-thyroxine increased SDNN and RMSSD somewhat. Our findings were consistent with (Galetta F, Franzoni F, Fallahi P et al) [11], who found that hypothyroid people had considerably lower resting time domain measurements and statistically improved following L-thyroxine replacement. Hypothyroid patients with low SDNN and RMSSD values had diminished vagal activity.

Frequency-Domain Measures:

Study groups differed in frequency domain characteristics. Hypothyroid patients had greater sympathetic tone LF values than normal controls. Hypothyroid patients had lower HF values in normalised units (nu), an indication of parasympathetic tone, before therapy than normal controls. This matched (Vittorio Cacciatori et al) [7]. Our data imply that hypothyroidism has reduced parasympathetic activity, which is consistent with (Hoshi 14. HF power is tightly under vagal activity. HF power rose following therapy, indicating greater sympathetic to vagal nerve transit to the heart in hypothyroid patients.

Hypothyroid patients with sympathovagal balance had a high LF/HF ratio before therapy. This was congruent with (Galetta F, Franzoni F, Fallahi P, Tocchini L et al, [11] who found reduced HF, increased LF amplitude, and increased LF/HF ratio in untreated hypothyroid people and dramatically improved HF amplitude and comparable LF/HF ratios after L thyroxine replacement therapy.

These findings are similar with recent research (Gupta et al, Mavai, Peixotode Mirinda,Syam sundar Celik et al) [15,16,17,18,19] that found hypothyroid people had considerably greater LF/HF ratios than controls. Matia Ahmed, Noorzahan Begum et al. [20] observed similar results in hypothyroid patients compared to controls and treated patients.

Hypothyroidism decreases vagal modulation and increases sympathetic. Hypothyroidism causes low HR. Desensitization and reduced heart chronotropic (adrenergic stimulation) notwithstanding sympathetic overactivity cause this. Hypothyroidism also causes peripheral resistance, diastolic blood pressure, peripheral vasoconstriction, and cold intolerance. Reduced catecholamine binding to cardiac myocyte beta and alpha receptors causes cardio-vascular consequences and hypothyroidism alterations (Galetta et al.

Overall HRV power reveals RR interval variability and cardiac autonomic nervous and hormonal activities on the heart (Task force). Our investigation showed lower total power before hypothyroid therapy compared to the normal control group, which was similar with (Caccitori, Galetta et al, Sahin Turan et al [9]). In their studies, L thyroxine improved overall power.

Conclusion

Resting Heart rate variability analysis assessed newly diagnosed hypothyroid females' cardiovascular autonomic nervous system activity and heart function before therapy. L-thyroxine replacement treatment continues for 3 months. After euthyroid condition, individuals were reevaluated and compared.

This study found an autonomic imbalance by decreasing SDNN, RMSSD, and increasing LF power (nu) in hypothyroid patients before therapy. Hypothyroid patients had a higher LF/HF ratio before therapy, indicating sympathetic autonomic nervous system dominance. Hypothyroid people also have lower overall power.L-thyroxine replacement treatment improved all these parameters.

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