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Original Article

Evaluation of Autonomic Function in Polycystic Ovary Syndrome with Hypothyroidism

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ABSTRACT

Background and Aim: Polycystic ovary syndrome (PCOS) and thyroid disorders are commonest endocrine disorders; both of these disorders have profound effect on reproductive function in women's. An increase in ovarian volume and cystic changes in ovaries have been reported in hypothyroidism. Recent studies reveal that PCOS might be associated with cardiovascular autonomic dysfunction and the thyroid hormone also influences the autonomic nervous system. So the aim of the study was to first, evaluate and compare autonomic function in PCOS as well as in PCOS with hypothyroidism, second, correlation between thyroid stimulating hormone (TSH) and autonomic function tests (AFT) in both the groups and third, study also provided further exploration in autonomic function in PCOS in presence of hypothyroidism. **Methods:** Total 43 newly diagnosed not on medications subjects were recruited, these subjects were divided into group A PCOS (n=33) and group B PCOS with hypothyroidism (n=10). Anthropometric measurements were taken from all the participants and autonomic function tests for assessing parasympathetic function (such as heart rate response to immediate standing and standing to lying ratio) and sympathetic function (such as blood pressure response to immediate standing and mental arithmetic stress test) were employed, then measurements was taken according to the respective scoring procedures. **Results:** In our studied population PCOS as well as PCOS with hypothyroidism showed autonomic dysfunction but no significant difference was found between them. No correlation and significance was found between TSH and AFT in both the groups. **Conclusion:** Our study concluded that the presence of hypothyroidism did not further affect autonomic function in PCOS and TSH was unrelated to AFT.

Key words: Autonomic function test, Blood pressure, Heart rate recovery, Hypothyroidism, Polycystic ovary syndrome, Thyroid stimulating hormone.

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INTRODUCTION

Many studies have shown that hypothyroidism is more common in women with PCOS as compared to the general population. PCOS is characterized by clinical/biochemical hyperandrogenism (excess androgens that lead to acne, scalp hair loss, excessive facial and body hair, or hirsutism), insulin resistance, oligo/amenorrhea (infrequent or no menstruation), polycystic ovaries and infertility, or reduced fertility.[1,2] Number of morbidities associated with PCOS includes type 2 diabetes mellitus, insulin resistance with compensatory hyperinsulinemia, infertility, obstetrical complications, cardiovascular disease, and psychological implications.[3] The worldwide prevalence of PCOS ranges from 9 to 19.9%, depending on diagnostic criteria and population characteristics.[4] Thyroid hormones, thyroxine (T4) and triiodothyronine (T3) play an important role in growth and development and also regulate metabolic processes in adults.

In primary hypothyroidism, T3 and T4 levels are low and pituitary thyrotropin (TSH) levels are elevated, it can be overt, where circulating levels of free thyroxine (FT4) are below the lower limit of the reference range, or subclinical (sHT), where free T4 levels are within the reference range, but lower than they should be for that individual, with consequent mildly elevated circulating TSH levels. Overt hypothyroidism represents severe thyroid hormone deficiency disease which requires mandatory treatment as soon as it is diagnosed.[5] The prevalence of hypothyroidism in the developed world is about 4-5%. The prevalence of subclinical hypothyroidism in the developed world is about 4-15%.[6] The autonomic nervous system (ANS) is the part of the nervous system that is responsible for regulation and integration of internal organs' functioning. Together with the endocrine and immunological systems it determines the status of the internal environment of the organism and adjusts it to its current needs, thus enabling adaptation of the internal environment to changes in the external environment. Disturbances of the autonomic nervous system play a crucial role in the pathogenesis and clinical course of many diseases.[7]

Some of the commonly employed clinical tests for the early detection of autonomic dysfunctions are classified into parasympathetic and sympathetic

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function tests. Parasympathetic function test such as standing to lying ratio, immediate heart rate response to standing (30:15 R-R ratio), deep breathing etc., sympathetic function tests such as cold presser test, mental arithmetic stress test, handgrip test, blood pressure response to standing. The ANS and the thyroid gland are closely linked by their controlling center, the hypothalamus, and also by their effects on the cardiovascular system.[8]

The mechanisms suggested for autonomic disturbances in thyroid disorders include a high level of plasma adrenaline with a decreased receptor or post receptor sensitization[9,10] a decreased chronotropic response to β adrenergic stimulation or adrenergic sensitivity, increase in thyrotropin releasing hormone (TRH) which directly influences the sympathetic outflow, direct effect of thyroid hormone on the heart.[11]

Autonomic dysfunction have been documented in many studies done on PCOS patients and hypothyroidism due to serum testosterone and insulin resistance but none of the study further explored autonomic dysfunction in PCOS patients with presence of hypothyroidism. This study was therefore undertaken to evaluate autonomic function in PCOS patients with hypothyroidism and to find out correlation between TSH and AFT in both the groups of subjects.

MATERIALS AND METHODS

This study was carried out in HAHC hospital, Department of Obstetrics and Gynecology, Jamia Hamdard, New Delhi in the year 2019-2020. This study was non-experimental cross sectional causal comparative (ex post facto) study design. Total numbers of participants were 43. To avoid the effects of medications on testing only newly diagnosed not on medications subjects were selected, these subjects were divided into group A PCOS (n=33) and group B PCOS with hypothyroidism (n=10). Participants were selected by convenient method of sampling and a pool of participants were screened for the study based on inclusion and exclusion criteria. Female participants of age between 18-30 years and BMI 18 to 30 kg/m^2 were included. Patients with diagnosed diabetes mellitus and hypertension, with any recent surgical history like abdominothoracic surgery, spinal surgery, cardiac conditions and pulmonary condition like asthma, CHD, valve disease, those with any orthopedic condition which may hamper patient's testing like rheumatoid arthritis, genu valgum, genu varum etc., pregnancy, smokers and alcoholics were excluded from the study. All the participants performed all four test of autonomic function testing, electrocardiogram (ECG) machine (RMS-Vesta 301i electrocardiograph) was used for assessing parasympathetic and sympathetic function then the data was recorded and compared between both groups of participants. Biochemical estimation of TSH was done.

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 after they were familiarized with the testing procedure and after Informed consent was taken from the subjects.

Following four autonomic function tests were carried out:

1. **Heart rate response to immediate standing (30:15):** In the supine position, after a rest of 15 min, the ECG leads were positioned, and ECG recording was started, then the patient was asked to stand from the supine position without displacing the leads. 30:15 ratios was calculated by taking the ratio of longest R-R interval around beat 30, and shortest R-R interval around beat 15 after standing.
2. **Standing to lying ratio (S/L ratio):** In standing position, ECG was recorded for 20 beats, and then the patient was asked to lie down with the leads attached as fast as possible. The ECG recording continued for 60 more beats in the lying position. The point at which subject started to lie down was marked. S/L ratio was calculated as the longest R-R interval during 5 beats before lying down to shortest R-R interval 10 beats after lying down.
3. **Blood pressure response to standing:** In the supine position it was recorded and then the subject was asked to stand immediately motionless and blood pressure recording was noted after 30 s interval for 2 min. The difference between the readings of systolic blood pressure and diastolic blood pressure in lying and immediate standing were calculated.
4. **Mental arithmetic stress test:** This test was based on performing serial subtraction (usually 100 minus 7 or 1000 minus 13) which aims at activating sympathetic outflow. The subsequent increase in systolic blood pressure should exceed 10 mmHg.

Statistical Analysis of Data

Statistical data analysis was done with the help of SPSS (Statistical Package for Social Sciences) version 16 software for windows. All continuous data were summarized as mean and standard deviation (SD). Subjects of different groups were compared using independent *t* test which was done for age, weight, height, BMI, resting heart rate (RHR), resting systolic and diastolic BP (RSBP, RDBP) and other autonomic functions and Correlation between TSH and AFT was done using Pearson correlation. P value of < 0.05 was considered as statistically significant.

RESULTS

The demographic data analysis done between Group A and B was the mean age 22.394 ± 3.132; 26.100 ± 3.542, mean height 155.920 ± 7.002; 156.470 ± 6.849, mean weight 61.179 ± 14.161; 67.260 ± 6.527, mean BMI 25.200 ± 5.637; 27.510 ± 2.916, mean waist hip ratio 0.962 ± 0.402; 0.978 ± 0.233 as depicted in Table 1. P value of age 0.10 was significant but clinically it was not.

Comparison of HR Response between Group A and Group B

For immediate standing (30:15) it was 1.006 ± 0.065; 1.025 ± 0.077, and for standing to lying (S: L) it was 1.180 ± 0.178; 1.210 ± 0.161, respectively as described in Figure 1. P value of 0.4 and 0.6 for 30:15 and S:L was found not to be statistically significant between group A and B.

Comparison of BP Response between Group A and Group B

To immediate standing test at resting systolic (ISRSBP) in group A was 104.450 ± 11.150 and group B was 109.30 ± 4.620, resting diastolic (ISRDBP) in group A was 68.697 ± 7.796 and group B was 73.70 ± 9.081. At 30 sec systolic BP response (SYSBP30s) to immediate standing

Table 1: Demographic data such as age, height, weight, BMI and waist-hip ratio of group A and group B.

Demographic data	Group A Mean± SD	Group B Mean ± SD	T	P
Age	22.394 ± 3.132	26.100 ± 3.542	-2.975	.010
Height	155.920 ± 7.002	156.470 ± 6.849	-.217	.829
Weight	61.179 ± 14.161	67.260 ± 6.527	-1.891	.067
BMI	25.200 ± 5.637	27.510 ± 2.916	-1.239	.222
W:H	0.962 ± 0.402	0.978 ± 0.233	-.121	.905

P value <0.05 was considered statistically significant.

BMI: Body mass index; W:H: Waist-hip ratio.

in group A was 107.790 ± 9.915 group B was 110.80 ± 4.050, diastolic (DYSBP30s) in group A was 71.939 ± 8.463 and group B was 78.20 ± 9.295. At 120 sec systolic BP response (SYSBP120s) to immediate standing in group A was 110.390 ± 8.246 and group B was 109.70 ± 6.482, diastolic (DYSBP120s) in group A was 74.727 ± 8.910 and group B was 76.90 ± 12.041.

The mean values of blood pressure response to mental arithmetic stress test (MTRSYSBP) between group A and B at resting systolic was 108.910 ± 8.251; 108.40 ± 6.132, at resting diastolic (MTRDYDBP) was 73.758 ± 8.533; 75.30 ± 11.344. At 30 sec, systolic BP response (SYSBP30s) was 110.450 ± 9.131; 111.80 ± 6.426, and diastolic BP (DYSBP30s) was 76.485 ± 9.080; 76.90 ± 7.400. At 120 sec systolic BP (SYSBP120s) was 111.820 ± 9.098; 114.70 ± 6.093, diastolic BP (DYSBP120s) was 76.909 ± 8.935; 79.30 ± 6.668 respectively as described in Figure 2.

Correlation between TSH and AFT in Group A

Mean and Standard Deviation (SD) of TSH was 1.60±0.748. Negative coefficient correlation was found at 30:15 was -0.364 it indicates weak correlation, at S:l was -0.85 strong or large correlation, at ISR was -0.01 indicates weak correlation, at DYSBP30s was -0.11 indicates weak correlation, at SYSBP120 was -0.102 weak correlation, at MTRSYSBP was -0.164 indicates weak correlation, MT-SYSBP30s was -0.329 weak correlation, at MT-SYSBP120s was -0.237 indicates weak correlation.

Positive coefficient correlation was found at IS-RBPD was 0.084 indicates strong correlation, at DYSBP120s was 0.079 strong correlation, at MT-RDYDBP was 0.026 weak correlation, at MT-DYSBP30s was 0.026 weak correlation, at MT-DYSBP120s was 0.038 weak correlation as depicted in Table 2 and Figures 3-5.

TSH with each variable of AFT was found not to be statistically significant except at 30:15 with p value of 0.037.

Correlation between TSH and AFT in Group B

Mean and SD of TSH was 8.5±1.225. Negative coefficient correlation was found at 30:15 was -0.44 indicates moderate correlation, at ISR was -0.583 indicates moderate correlation, at IS-RBPD was -0.411 moderate correlation, at SYSBP30s was -0.30 weak correlation, at DYSBP30s, was -0.321 weak correlation, at SYSBP120 was -.173 weak correlation, at DYSBP120s was -0.39 weak correlation, at MTRSYSBP was -0.20 weak correlation, at MT-RDYDBP was -0.225 weak correlation, at MT-SYSBP30s was -0.69 moderate correlation, at MT-DYSBP30s was -0.44 moderate correlation, at MT-SYSBP120s was -0.677 moderate correlation, at MT-DYDBP120s was -0.626 as depicted in Table 3 and Figure 6.

Positive coefficient correlation was found at S:L with value of 0.132.

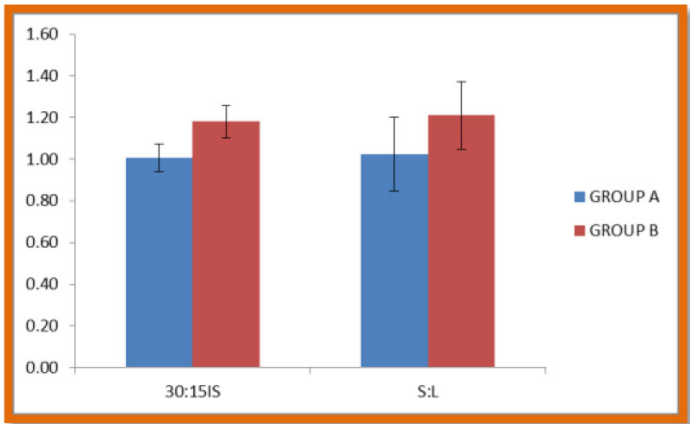

Figure 1: Comparison of heart rate response to immediate standing (30:15) and standing and lying (S:L) between group A and B.

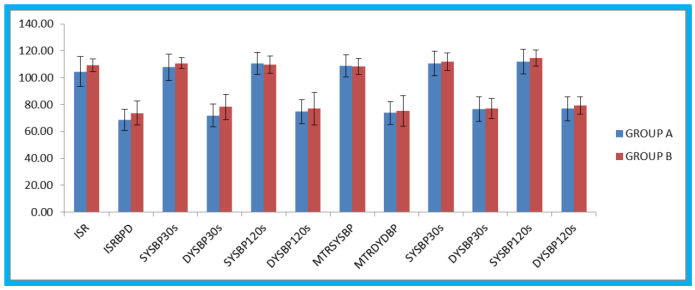

Figure 2: Comparison of BP response to immediate standing and mental arithmetic stress test at resting, at 30 sec interval and at 120 sec interval between group A and B.

Table 2: Correlation analysis between TSH and AFT in group A (PCOS).

Mean and SD 1.60+0.748		Immediate standing (30:15)	S:L	Immediate standing resting SBP	Immediate standing resting DBP	30sec SBP	30 sec DBP	120 sec SBP	120 sec DBP	Mental arithmetic resting SBP	Mental arithmetic resting DBP	30 sec SBP	30 sec DBP	120 sec SBP	120 sec DBP
TSH	Pearson Correlation	-0.364*	-0.085	-0.001	0.084	0.016	-0.011	-0.102	0.079	-0.164	0.079	-0.329	0.026	-0.237	0.038
	Sig. (2-tailed)	0.037	0.639	0.996	0.641	0.931	0.952	0.570	0.664	0.363	0.661	0.061	0.888	0.185	0.835

P value <0.05 was considered statistically significant.

Test variables used for parasympathetic function test are immediate standing (30:15),standing to lying ratio(S:L) and for sympathetic function test are immediate standing systolic and diastolic BP at rest, at 30 sec and at 120 sec and mental arithmetic function test systolic and diastolic BP at rest, at 30 sec and at 120 sec.

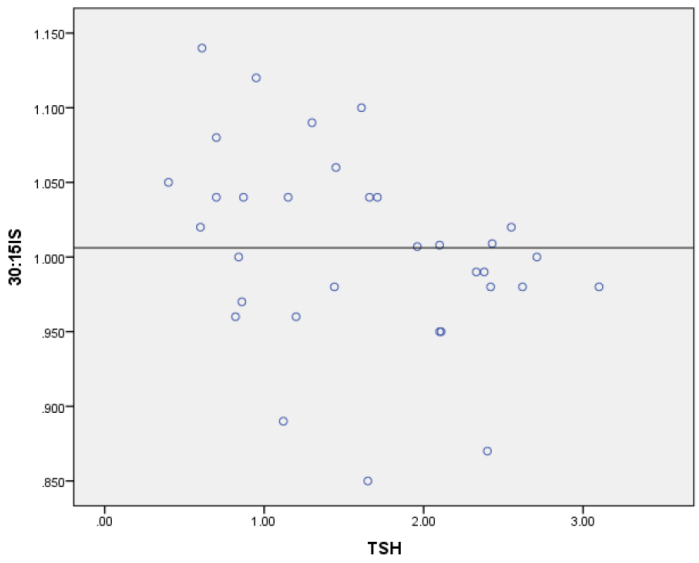

Figure 3: Correlation between TSH and immediate heart rate response (30:15) of AFT in group A.

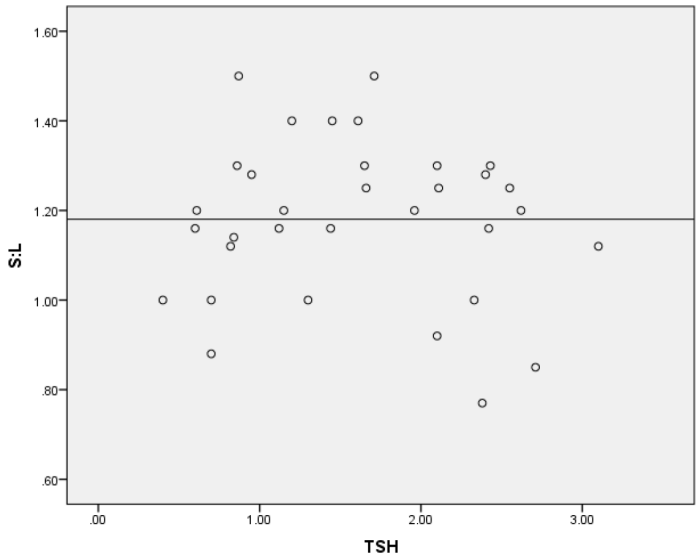

Figure 4: Correlation between TSH and standing to lying ratio (S:L) of AFT in group A.

TSH with variables of AFT was statistically significant at MT-SYS30s was 0.02 weak correlation, at MT-SYS120s was 0.032, weak correlation and with other variables of AFT it found not to be statistically significant.

DISCUSSION

Autonomic dysfunction was found in both PCOS and PCOS with hypothyroidism studied population but there was no significant difference found between them.

Significant alterations found in anthropometric parameters which included age, height, weight, BMI. It is known that anthropometric and hormonal abnormalities might contribute to the increased risk of cardiovascular diseases, fitness and partly contributed to the cardiovascular autonomic dysfunction in women with PCOS.[12,13]

A study done by Juan Gui, *et al.*[14] 8 studies with 243 PCOS and 211 controls, concluded that the PCOS might show cardiovascular autonomic dysfunction, with reduced total and parasympathetic cardiac modulation, and increased sympathetic activity.

Early diagnosis of autonomic dysfunction is very important. Short- or long-term electrocardiogram recordings can be easily performed in clinical routines and help early diagnosis. An improvement in cardiovascular prognosis of these patients might be achieved by early interventions such as aerobic exercise[15] or acupuncture[16] as these interventions

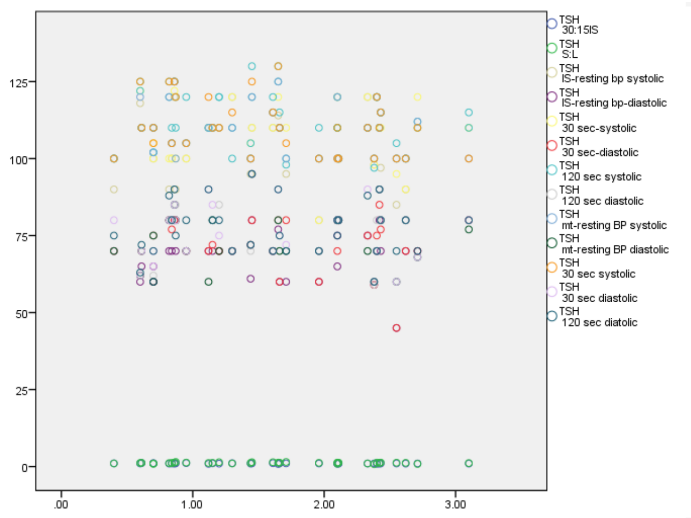

Figure 5: Correlation between TSH and variables of AFT (parasympathetic and sympathetic function test) in group A.

Table 3: Correlation between TSH and AFT in group B (PCOS with Hypothyroidism).

Mean and SD 8.5+1.225		Immediate standing (30:15)	S:L	Immediate standing resting SBP	Immediate standing resting DBP	30sec SBP	30 sec DBP	120 sec SBP	120 sec DBP	Mental arithmetic resting SBP	Mental arithmetic resting DBP	30 sec SBP	30 sec DBP	120 sec SBP	120 sec DBP
TSH	Pearson Correlation	-0.444	0.132	-0.583	-0.411	-0.30	-0.321	-0.173	-0.396	-0.206	-0.225	-0.693*	-0.440	-0.677*	-0.626
	Sig. (2-tailed)	0.199	0.716	0.077	0.238	0.39	0.366	0.632	0.257	0.567	0.532	0.026	0.203	0.032	0.053

P value <0.05 was considered statistically significant.

Test variables used for parasympathetic function test are immediate standing (30:15),standing to lying ratio(S:L) and for sympathetic function test are immediate standing systolic and diastolic BP at rest, at 30 sec and at 120 sec and mental arithmetic function test systolic and diastolic BP at rest, at 30 sec and at 120 sec.

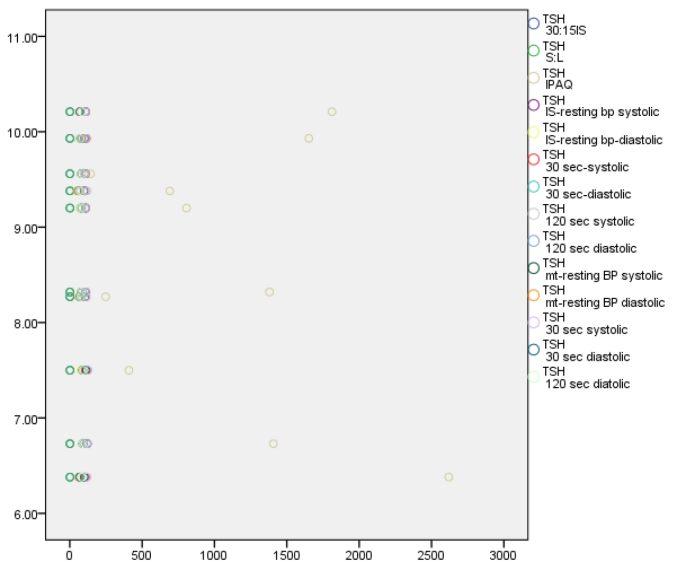

Figure 6: Correlation between TSH and AFT in group B.
Test variables used for parasympathetic function test are immediate standing (30:15), standing to lying ratio(S:L) and for sympathetic function test are immediate standing systolic and diastolic BP at rest, at 30 sec and at 120 sec and mental arithmetic function test systolic and diastolic BP at rest, at 30 sec and at 120 sec.

have been reported to improve cardiovascular autonomic functions in women with PCOS, with increased cardiovagal modulation and reduced sympathetic activity.

This study found out TSH values was not statistically significant with each variable test of AFT .In a study Aarti S *et al.*[5] reported sympathetic function abnormalities were seen in 82% subclinical hypothyroid patients and 85% hypothyroid patients. These abnormalities were unrelated to TSH levels and concluded there was no relationship between the autonomic function score and TSH or TPO levels.

The present study found positive correlation between TSH and AFT in one of the test variables in PCOS with hypothyroidism group at Standing to lying ratio one of the test of parasympathetic function and in PCOS group at immediate standing resting diastolic BP, diastolic BP at 120s, mental arithmetic test at resting diastolic BP, diastolic BP at 30s, diastolic BP at 120s.

A study done by Hoshi, *et al.*[8] concluded subjects with subclinical hypothyroidism presented higher sympathetic and lower vagal tonus at supine rest, with blunted sympathetic autonomic responses to active postural change and the sympathetic activity of heart rate dynamics is found to be a possible alternative, perhaps, a more sensitive method for cardiac autonomic assessment at rest and during physiological stress in this population.

A study included 31 patients with subclinical hypothyroidism and 28 healthy controls reported no difference in the time and frequency domains of HRV compared to healthy 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 and also correlated TSH and found positive relationship between TSH and root square of successive differences between adjacent R-R interval and reported SH may affect cardiac autonomic activity in correlation with TSH levels.

To our knowledge till present no study compared and evaluated autonomic function in newly diagnosed not on medications PCOS with hypothyroidism. Our study found dysfunctions in both sympathetic and parasympathetic components of the ANS in PCOS as wells as in PCOS with hypothyroidism it possibly could be due to physical inactivity or might be obesity contributed in dysfunction. Both sympathetic function abnormality and parasympathetic dysfunction was seen but there was no significant difference in sympathetic and parasympathetic activity when compared among them therefore the presence of hypothyroidism did not further affect autonomic function in PCOS. Our study also found no correlation between TSH and AFT in both PCOS and PCOS with hypothyroidism group.

Limitation of the Study

With the change in scenario due to COVID pandemic, time was very limited, could not able to include wide variety of patients with high BMI.

CONCLUSION

Autonomic function was affected in PCOS as well as in PCOS with hypothyroidism but no significant difference was found between them. Our study concluded that the presence of hypothyroidism in PCOS did not further affect autonomic function in PCOS.

An extension of this study may be done with more number of subjects as more number of sample sizes may be able give more generalized results. Equipment's with advanced technologies which will be more reliable for evaluation can be included in future research. Newly and previously diagnosed subjects can be included for further exploration. Hypothyroidism grades can be taken into consideration which was lacking in this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; **TSH:** Thyroid Stimulating Hormone; **AFT:** Autonomic Function Tests; **S/L Ratio:** Standing to Lying Ratio; **RHR:** Resting Heart Rate; **ISRSBP:** Immediate Standing Test at Resting Systolic Blood Pressure; **ISRDBP:** Immediate Standing Test at Resting Diastolic Blood Pressure; **SYSBP30s:** Systolic Blood Pressure at 30 sec; **DYSBP30s:** Diastolic Blood Pressure at 30 sec; **SYSBP120s:** Systolic Blood Pressure at 120 sec; **DYSBP120s:** Diastolic Blood Pressure at 120 sec; **MTRSYSBP:** Systolic Blood Pressure Response to Mental Arithmetic Stress Test; **MTRDYSBP:** Diastolic Blood Pressure Response to Mental Arithmetic Stress Test.

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