National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Correlation of body fat percentage with the occurrence of subclinical cardiac autonomic neuropathy in hypothyroidism

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Received: April 05, 2020; **Accepted:** April 28, 2020

ABSTRACT

Background: The incidence of cardiac-related mortality is increasing in hypothyroid. **Aims and Objective:** The objectives of the study were to assess the incidence of cardiac autonomic neuropathy (CAN) in hypothyroid and its correlation with body fat levels. **Materials and Methods:** Thirty diagnosed hypothyroid in the age group of 25–50 of both genders were involved (n = 30). Age- and sex-matched euthyroid were controls (n = 30). CAN was evaluated in terms of the presence of resting tachycardia, loss of sinus arrhythmia by calculating deep breath difference, and heart rate response to Valsalva maneuver by calculating Valsalva ratio recorded by electrocardiogram in the lead II. Body fat was measured using skin calipers at four sites using Durnin and Womersley equation. The correlation was assessed using Pearson's matrix. **Results:** The study shows in hypothyroid among 30 (n = 30), 27% (n = 8) were having borderline CAN. Among euthyroid 13% (n = 4) and 10% (n = 3) were having borderline and definitive CAN. The study shows a negative correlation exists between body fat percentage and deep breathing difference and Valsalva ratio. ($r = –0.20$ $P = 0.289$, $r = –0.19$ $P = 0.30$). **Conclusion:** The incidence of subclinical CAN is more in hypothyroid than euthyroid which shows a negative correlation with body fat level.

KEY WORDS: Cardiac Autonomic Neuropathy; Deep Breathing Difference; Hypothyroidism; Resting Tachycardia; Valsalva Ratio

INTRODUCTION

Thyroid gland secretes thyroid hormone, which maintains metabolic activities of almost all cell in body, have a role in all organs in body and necessary for proper growth and development in adults.[1] The decreased secretion of thyroid hormone leading to hypothyroidism, which can be primary due to reduced secretion of thyroid hormones (T3 and/or T4) or secondary due to reduced secretion of thyrotropin-releasing hormone or thyroid-stimulating hormone (TSH). Primary hypothyroidism can be clinical where there is reduced FT4 (Free T4) and TSH is increased or subclinical where T4 is normal with increased TSH.[2] An epidemiological study done in 2013 shows the overall prevalence of hypothyroidism about 10.95% with statistically significant prevalence seen in females when compared to males and also in older when compared to the younger population.[3] In females, hypothyroidism leads to infertility due to hyperprolactinemia, sex hormone imbalance, and luteal phase defects.[4] Studies showed that thyroid dysfunction patient shows various

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 0.5455/njppp.2020.10.04102202028042020	

psychiatric disorder such as schizophrenic spectrum disorder, mood disorder, and bipolar disorder.[5] Hypothyroidism has various effects on cardiovascular system affecting heart rate, vascular resistance, contractility, and blood pressure.[6] Hypothyroidism leads to increased peripheral vascular resistance resulting in elevated diastolic blood pressure and mean arterial pressure which in turn leads to an increase afterload on heart. It also inactivates the rennin angiotensin system leading to reduce preload which results in decreased cardiac output, this ultimately results in narrow pulse pressure.[6,7] Along with diastolic hypertension because of impaired ventricular relaxation resulting to heart failure with pericardial effusion leading to increased cardiac mortality in hypothyroid.[8,9] Autonomic dysfunction in terms of altered sympathovagal balance also adds up to cardiovascular mortality in hypothyroid.[10] Cardiac autonomic neuropathy (CAN) which develops due to lesion in cardiac autonomic nerves either sympathetic or parasympathetic can lead to various manifestations such as resting tachycardia, exercise intolerance, orthostatic hypotension, coronary vessels ischemia, and silent myocardial infarction.[11] Development of CAN is multifactorial such as age, diabetes mellitus, poor glycemic control, systolic blood pressure, and lipid levels, associated diabetic complications such as diabetic nephropathy and diabetic neuropathy, smoking. There are various diagnostic tests available to diagnose CAN such as autonomic reflex tests, ECG recording, heart rate variability, baroreflex sensitivity, and catecholamine assessment.[10] Cardiovascular autonomic reflex tests (CART) are still considered the golden standard method for diagnosis of CAN.[12] There is a scarcity of research regarding of CAN in hypothyroidism, research has shown only altered cardiac autonomic functions but not much work on the prevalence of CAN in hypothyroid. Hence, the aim of our study is to see the occurrence of CAN in hypothyroid using CART and check for its association with body fat percentage. Ours is the first study to see for the correlation of body fat levels with the development of CAN in hypothyroid.

MATERIALS AND METHODS

This is a cross-sectional, case–control analytical study conducted in the Department of Physiology and Department of General Medicine, SDM Medical College and Hospital between July and October 2019. Institutional ethical clearance was taken before the beginning of the study (Ref: SDMIEC: 0182:2019 Dated 03/06/2019). Those who diagnosed as subclinical hypothyroid (TSH >5.5 μIU/ml, free T3: 2.3–4.2 pg/ml, and free T4: 0.89–1.76 ng/dl by chemiluminescence immunoassay) and clinically established hypothyroid were included in the study. All our clinical hypothyroid were on treatment. Subjects with euthyroid levels (TSH 0.35–5.50 μIU/ml, free T3: 2.3–4.2 pg/ml, and free T4: 0.89–1.76 ng/dl) taken as controls. All the participants were explained about the procedure and written consent taken.

Sample Size

As this study was done under ICMR, STS project, keeping in mind study duration (August–September 2019) and the incidence of hypothyroidism in our hospital, the sample size was decided as 30. The study includes 30 (n = 30) subclinical and clinical hypothyroid as cases and 30 (n = 30) euthyroid as controls. All the participants were in the age group of 25–50 years of both the genders. Cases were selected from the medicine OPD's and age- and sex-matched controls were selected from the general population.

Exclusion Criteria

Subjects with hyperthyroidism, those who have a cardiac abnormality, history of diabetes mellitus, and history of hypertension excluded from the study.

Study Design

Three CART were done on each subject to rule out CAN.[10]

a. Resting tachycardia
b. Loss of sinus arrhythmia (deep breathing difference)
c. Heart rate response to Valsalva maneuver (Valsalva ratio).

If any two of them are positive, the presence of CAN is confirmed.[13]

Instrument – ECG instrument with a paper speed of 25 mm/s used for all the above tests (BPL, Cardiart 6208 View. BPL Limited, Bannerghatta Road, Bengaluru).

Procedure

a. Resting tachycardia: Subjects were made to lie down in the supine position for 10 min. At the end of 10 min heart rate was calculated using ECG Lead II. Heart rate >100 beats per minute (BPM) was considered abnormal
b. Loss of sinus arrhythmia (deep breathing difference): In these subjects were made to take deep breaths at a rate of 6 breaths for 1 min. One cycle of deep inspiration and expiration was done at 10 s. A continuous ECG was recorded for six breaths for 1 min. We marked with pen onset of each deep inspiration and expiration. Then, using ECG, maximum heart rate during deep inspiration, and minimum heart rate during deep expiration were calculated. Deep breathing difference calculated as the difference between the maximum and minimum heart rate during deep breathing. The normal response is a difference of 15 BPM or more, while 10–15 beats and <10 BPM taken as borderline and definitive CAN, respectively[10]
c. Heart rate response to Valsalva maneuver (Valsalva ratio): In these subjects were asked to sit and blow into a mouthpiece connected to a mercury monometer and keep the pressure until 40 mmHg for 15 s. After 15 s blowing will be stopped.

A continuous ECG recorded during blowing for 15 s and also 15 s after the stoppage. Maximum R-R interval during the release of pressure and minimum R-R interval during strain was noted. Valsalva ratio calculated as the ratio of the longest R-R interval (during bradycardia)/to the shortest R-R interval (during tachycardia). Normal Valsalva ratio is 1.2 or more; values of 1–1.2 taken as borderline and values less or equal to 1 taken as evidence of CAN.[10]

Estimation of Body Fat Percentage

Body fat percentage calculated using the Siri equation which requires body density for its calculation and body density obtained by skinfold thickness which is measured using skinfold caliper. However, here we measured the body fat % directly from the skinfold thickness by the help of table (that directly give body fat % from the skinfold thickness by caliper in both male and females) as given in Durnin and Womersley in their article. We measured the skinfold thickness from four common places in both males and females at biceps, triceps, subscapular, and supra-iliac.[14]

Statistical Analysis

Statistical analysis done using SPSS software version 20. Intergroup analyses of variables done by *t*-test. Pearson's correlation used to test the correlation of body fat percentage on the incidence of CAN in hypothyroid. Values expressed as mean ± standard deviation. $P < 0.05$ considered as statistically significant and <0.01 as highly significant.

RESULTS

Above is a cross-sectional, case–control study done to assess the occurrence of CAN in hypothyroidism. Table 1 explains the descriptive characteristics of the participants. The mean age of hypothyroid was 36.06 ± 8.87 years, whereas of euthyroid was of 34.33 ± 8.73 years. There is a statistically significant increase in TSH in hypothyroid when compared to euthyroid ($P = 0.000$). Of 30 hypothyroid, 22 were of subclinical hypothyroidism and eight were having clinically established hypothyroidism. Table 2 shows a body mass index (BMI), body fat, and lean body mass between hypothyroid and euthyroid. There is an increase in BMI, body fat %, and lean body mass in hypothyroid compared to euthyroid which is not statistically significant. Table 3 shows autonomic function tests between hypothyroidism and euthyroidism. There is a significant reduction in resting heart rate in hypothyroid ($P = 0.03$). The deep breathing difference value is reduced in euthyroid, whereas a significant reduction of Valsalva ratio seen in hypothyroid ($P = 0.03$).

Table 4 shows the occurrence of CAN in hypothyroidism based on three autonomic function tests. According to values with deep breathing differences, there were eight who were having borderline CAN and two had definitive CAN. Based on values of Valsalva ratio, 18 were having borderline CAN. Table 5 summarizes all three autonomic function tests that show among 30 hypothyroid, 8 (27%) had borderline CAN and none of them had definitive CAN. Among euthyroid of

Table 1: The descriptive characteristics of hypothyroid (*n*=30) and euthyroid (*n*=30)

Parameter	Hypothyroidism (*n*=30)	Euthyroidism (*n*=30)	*t*-value	*P*-value
Age (years)	36.06±8.87	34.33±8.73	–0.762	0.939
Gender	Male *n*=09 (30%) Female *n*=21 (*n*=70%)	Male *n*=11 (*n*=37%) Female *n*=19 (*n*=63%)		
TSH (µIU/ml)	13.52±2.34	2.62±1.09	–4.458	0.000**
Subclinical hypothyroid Clinical hypothyroid	*n*=22 (73%) *n*=08(27%)	-		

Values are expressed as mean±standard deviation, $P<0.05$ *Considered as significant

Table 2: BMI, body fat percentage, and lean body mass between hypothyroid (*n*=30) and euthyroid (*n*=30)

Parameter	Hypothyroidism (*n*=30)	Euthyroidism (*n*=30)	*t*-value	*P*-value
BMI (kg/mt^2)	27.18±5.92	24.21±6.19	–1.898	0.849
Body fat %	32.84±5.65	30.57±3.51	–1.867	0.067
LBM (kg)	42.92±8.33	41.13±13.81	–0.607	0.093

Values are expressed as mean±standard deviation, $P<0.05$ considered as significant. BMI: Body mass index, LBM: Lean body mass

Table 3: Cardiac autonomic function tests between hypothyroid (*n*=30) and euthyroid (*n*=30)

Parameter	Hypothyroidism (*n*=30)	Euthyroidism (*n*=30)	*t*-value	*P*-value
RHR (beats/min)	72.46±12.38	85.26±14.48	2.22	0.03*
DBD (beats/min)	19.60±6.86	16.96±6.79	–1.493	0.418
Valsalva ratio	1.22±0.17	1.35±0.25	2.22	0.030*

Values are expressed as mean±standard deviation, $P<0.05$ considered as significant. RHR: Resting heart rate, DBD: Deep breathing difference

Table 4: Incidence of cardiac autonomic neuropathy in euthyroid and hypothyroid based on parameters to assess cardiac autonomic neuropathy (*n*=60)

Thyroid status	RHR (beats/min)		R-R variation with deep breathing (deep breathing difference)			Valsalva ratio		
	Normal (<100 BPM)	Resting tachycardia (>100 BPM)	Normal (>15)	Borderline (10–15)	Definitive (<10)	Normal (>1.2)	Borderline (1–1.2)	Definitive (<1)
Euthyroid (*n*=30)	*n*=22 (73%)	*n*=8 (27%)	*n*=17 (57%)	*n*=10 (33%)	*n*=03 (10%)	*n*=26 (87%)	*n*=4 (13%)	-
Hypothyroid (*n*=30)	*n*=30 (100%)	*n*=0 (0%)	*n*=20 (67%)	*n*=8 (27%)	*n*=2 (6%)	*n*=12 (40%)	*n*=18 (60%)	-

Values expressed as percentages present in parenthesis. RHR: Resting heart rate, BPM: Beats per minute

Table 5: Scores of the tests used to assess CAN in euthyroid and hypothyroid (*n*=60)

Scoring of three parameters results to assess CAN	Normal	Borderline CAN	Definitive CAN
Euthyroid	23 euthyroid all the 3 tests normal (77%)	4 euthyroid shows any two test as abnormal with values toward borderline CAN (13%)	3 euthyroid shows any two test as abnormal with values toward definitive CAN (10%)
Hypothyroid	22 hypothyroid all the 3 tests normal (73%)	8 hypothyroid shows any two test as abnormal with values toward borderline CAN (27%)	No hypothyroid shows any two test as abnormal with values toward definitive CAN (0%)

Table 6: Correlation of body fat levels with cardiac autonomic functions in hypothyroid (*n*=30)

Body fat %	Resting heart rate (beats/min)	Deep breathing difference (beats/min)	Valsalva ratio
	r=–0.397 *P*=0.234	r=–0.200 *P*=0.289	r=–0.196 *P*=0.300

r=–Negative correlation, r=+positive correlation. *P*<0.05 *Considered significant

30, 4 (13%) had borderline CAN and 3 (10%) had definitive CAN, respectively. Table 6 explains the correlation of body fat levels with various autonomic function tests. There exists a negative correlation between body fat levels with resting heart rate, deep breathing difference, and Valsalva ratio.

DISCUSSION

The above case-control analytical study done to observe the occurrence of CAN among hypothyroid and its correlation with body fat levels. The results of our study demonstrate that the incidence of hypothyroidism is common among females (70%) when compared to males (30%). Our study shows that body mass index, body fat levels, and lean body mass are higher in hypothyroidism when compared to euthyroid even though it is not statistically significant. Cardiac autonomic reflex function tests in hypothyroidism: Our study shows that resting heart rate is lower in hypothyroid when compared to euthyroid. Our study shows that deep breathing difference demonstrating sinus arrhythmia is more in hypothyroid when compared to euthyroid, whereas Valsalva ratio is significantly reduced in hypothyroid when compared to euthyroid (P = 0.030*). Even deep breathing difference and Valsalva ratio demonstrate parasympathetic function, in our study, we could see only Valsalva ratio is altered in hypothyroid when compared to the other two tests. Our study demonstrates a negative correlation between body fat levels with all three cardiac autonomic function tests. CAN in hypothyroidism: As mentioned in the methodology, based on values obtained in three cardiac autonomic function tests that are resting tachycardia, deep breathing difference, and Valsalva ratio, we could see that of 30 hypothyroid, there were no hypothyroid who had definitive CAN. However, there were 8 (27%) hypothyroid that was having borderline CAN who had any two tests positive with values toward borderline CAN (DBD = 10–15, VR= 1–1.2).

Our results are similar to a comprehensive literature review done by Bauer *et al*., which shows that the prevalence of hypothyroidism is common among women when compared to men and also the incidence increases with age, saying postmenopausal women are more prone around 20% to develop subclinical hypothyroidism.[15] The study shows hypothyroidism associated with decreased thermogenesis, reduced metabolism with altered glucose, and fat metabolism leads to obesity and overweight. The study says even subclinical hypothyroidism also associated with overweight saying slight variation in thyroid levels increases the incidence of obesity.[16] Research shows that hypothyroidism leads to impaired cardiac muscle relaxation, reduced resting heart rate, reduced cardiac output, and increases vascular resistance leading to heart failure.[6] As persistent tachycardia is one of the signs for the development of CAN, we could not find resting tachycardia in hypothyroid. This might demonstrate that vagal tone is not much altered in hypothyroid. Cacciatori *et al*. also assessed cardiac autonomic function in hypothyroid compared to euthyroid. They have

used frequency domain analysis of heart rate variability to measure autonomic function using high frequency (demonstrates parasympathetic function) and low frequency (demonstrates sympathetic function). Results of the study show that elevated sympathetic (elevated low frequency) and reduced parasympathetic tone (reduced high frequency) in newly diagnosed hypothyroid when compared to controls. However, other cardiovascular function tests such as deep breathing difference and Valsalva maneuver are not different from hypothyroid when compared to controls.[17] Aarti *et al*. done case–control prospective study to evaluate autonomic functions on subclinical hypothyroid. Battery of tests such as lying to standing ratio, Valsalva ratio, 30:15 ratio done to evaluate parasympathetic functions, cold pressor test, and handgrip tests done to assess sympathetic function. Based on scoring, 95% of subclinical hypothyroid and 85% of clinical hypothyroid had autonomic dysfunction. The study shows that sympathetic dysfunction was more common in hypothyroid even though reduced parasympathetic reactivity was present but to a lesser extent.[18] Kalra *et al*. also evaluated cardiac autonomic functions in hypothyroid using heart rate variability frequency domain analysis. Hypothyroid shows increased low-frequency domain, demonstrating elevated sympathetic activity and reduced Hf domain showing reduced parasympathetic activity when compared to euthyroid controls.[19] Debasish and Himel show that increased body weight alters autonomic function tests with sympathetic predominance.[20] Sheema and Malipatil also demonstrated altered heart rate variability in females, those having raised BMI in terms of increased low frequency, suggesting predominant sympathetic activity.[21] The study shows that CAN will be usually subclinical and it progresses to clinical CAN which can lead to coronary vessel ischemia, orthostatic hypotension, and silent myocardial infarction.[10] The postulated mechanism for altered autonomic balance in hypothyroid could be, thyroid hormone deficiency alters the function of the set of parvalbuminergic neurons present in hypothalamus, which reduces heart rate and blood pressure. The elevated level of TSH has a central effect that leads to sympathetic outflow.[22]

Limitations of Study

The lesser sample size is one of the limitations of our study as we had to finish the project within time boundaries. As our clinical established hypothyroid were on treatment, some of them having normal TSH levels, whereas subclinical hypothyroid is not with elevated TSH leading to some bias in our results.

Strength of Study

Our study shows hypothyroidism is one of the risk factors to develop CAN. The study can be further extended to see the association of TSH levels with the occurrence of CAN.

CONCLUSION

Our study concludes that both subclinical and clinical established hypothyroid are prone to develop CAN with body fat levels increase the risk of developing CAN.

ACKNOWLEDGMENT

We would like to extend our thanks to ICMR, STS 2018 project, Government of India, for accepting and funding our project.

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How to cite this article: Vijaykumar N, Khode V, Badiger S, Bennur N, Jadhav S, Gururaj H. Correlation of body fat percentage with the occurrence of subclinical cardiac autonomic neuropathy in hypothyroidism. Natl J Physiol Pharm Pharmacol 2020;10(07):568-573.

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