International Journal of Multidisciplinary Research and Development

Volume: 2, Issue: 8, 515-523
Aug 2015
www.allsubjectjournal.com
e-ISSN: 2349-4182
p-ISSN: 2349-5979
Impact Factor: 3.762

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Original Article - Study of Cardiovascular Manifestations in Patients of Hypothyroidism with Special Reference to TMT (Tread Mill Test)

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Abstract
Aims And Objectives--To study TMT changes in patients of hypothyroidism, to study clinical manifestations, thyroid hormone level and duration of hypothyroidism with TMT changes. To study lipid profile, body mass index in patients of hypothyroidism with TMT changes**.**
Material And Methods - The present study was conducted in Department of Medicine, J A group of hospital, G.R. Medical College, Gwalior (M.P.).The present study is a cross sectional study, conducted over a period between September 2011 to November 2012 on the patients of hypothyroidism without history of coronary artery disease. Total of 100 patients were included in the study.
Results- In present study 20% were males and 80% were females, maximum cases 36% were in 51-60 yrs of age group. Most common symptoms was lethargy followed by facial puffiness. 39% of patients were overweight and 10% was obese. In 84% cases there were normal resting ECG and 16% cases had abnormal ECG. Most common abnormalities were bradycardia 10%, low voltage complex 7%, RBBB 7%, ST-T changes (nonspecific) 5% and VPC's 4%. In 100 of patients, TMT was positive in 12% of cases and negative in 88% of cases. Out of 12 TMT positive patients, serum TSH value >10μiU/ml was present in 11 (91%) of patients and only 1 (8.3%) had serum TSH values <10μiU/ml. The characteristics of patients with TMT positive and negative group compared and it was seen the group varied significantly ($p<0.05$) with respect to their average BMI, average Free T4, average total cholesterol, average LDL, average triglyceride and average diastolic blood pressure. Majority of TMT positive patients (58.3%) had normal resting ECG and 41.7% TMT positive patients had abnormal resting ECG but in this study we found that if resting ECG was showing nonspecific ST-T changes chances of TMT positive in increased. In present study hypothyroidism was significantly associated with TMT positivity and was more common in overt hypothyroidism than subclinical hypothyroidism.
Conclusion- In this study, it was concluded that TMT was significantly positive in patients of hypothyroidism. However chances of TMT positivity increase when resting ECG especially had nonspecific ST-T changes and VPC's. The prevalence of TMT positive in hypothyroidism is likely when patients had dyslipidemia, high BMI (overweight or obese) diastolic hypertension, FT4 level deficiency.

Keywords: hypothyroidism, cardiovascular manifestations, trade mill test

1. Introduction
The most common functional disorder of the thyroid gland is hypothyroidism. It is a clinical state due to the decreased secretion of thyroid hormones or more rarely, from their impaired activity at tissue level. It is the most common pathological hormone deficiency. Pathology of the thyroid gland (Primary hypothyroidism) accounts for 99% of cases of thyroid gland failure and rest 1% result from disorder of the pituitary gland or hypothalamus (central hypothyroidism). Overt hypothyroidism refers to cases in which the serum thyroid stimulating hormone (TSH) concentration is elevated and serum T4 (free thyroxine) is below the reference range, while subclinical hypothyroidism is defined as an elevated serum TSH value, associated with a serum free T4 within the reference range. Incidence of hypothyroidism is higher among women and elderly and its incidence varied depending upon population in study. Thyroid hormones have a profound effect on a number of metabolic process in virtually all tissues and hence virtually every tissues in the body is affected to a greater or lesser extent by thyroid hormone deficiency, the heart being particularly sensitivity to its effect. The clinical features dependent on patient age, rate at which hypothyroidism develops. As thyroid hormones are universal determinants of organ function, there may be a multiplicity of symptoms. Hypothyroidism is associated with increased cardiovascular mortality and morbidity the dysfunction range from diastolic and systolic dysfunction to overt failure and coronary artery disease. The cardiovascular risk in hypothyroid patients is related to an increased risk of functional cardiovascular abnormalities.

The pattern of cardiovascular abnormalities is similar in subclinical and overt hypothyroidism suggesting that a lesser degree of thyroid hormone deficiency may also the cardiovascular system. It is important to reveal clinical or subclinical thyroid disease in time for the manifestation of cardiovascular system. Hypothyroidism is treated by hormone replacement therapy; which is simple, affordable and effective. So that present study was planned to find out the early asymptomatic coronary artery disease in patients of overt or subclinical hypothyroidism by doing treadmill test (TMT) so that they can be detected and treat as early as possible.

Aims and objective-To study TMT changes in patients of hypothyroidism, To study clinical manifestations, thyroid hormone level and duration of hypothyroidism with TMT changes, To study lipid profile, body mass index in patients of hypothyroidism with TMT changes.

Material & Methods -The present study was conducted in Department of Medicine, J A group of hospital, G.R. Medical College, Gwalior (M.P.).Study Design-The present study is a cross sectional study, conducted over a period between September 2011 to November 2012 on the patients of hypothyroidism without history of coronary artery disease. Source of data-The patients of hypothyroidism attending JAH Group of hospital, Gwalior, M.P. were enrolled in the present study. Sample Size-Total of 100 patients were included in the study.

Selection Criteria-Inclusion criteria:-1-Cases diagnosed as hypothyroid by estimation of FT3, FT4 & TSH and having signs and symptoms of hypothyroidism.

	FT4	TSH
Overt hypothyroidism	< 0.8 ng/dl (free) < 5.4 µg/dl (total)	> 4.25 µIU/ml (total)
Subclinical hypothyroidism	0.8-1.7 ng/dl (free) 5.4-11.7 µg/dl (total)	> 4.25 µIU/ml (total)
Normal	0.8-1.7 ng/dl (free) 5.4-11.7 µg/dl (total)	0.34-4.25 µIU/ml (total)

Source: Harrison 18th Edition, Principle of Internal Medicine, pg. 3595) 2-Patients with hypothyroidism age between 20-60 yrs.

Exclusion criteria: -Patients with known primary cardiac disease (e.g. CAD, valvular heart disease, cardiomyopathy), Patients with chronic pulmonary disease, severe anemia, DM or any other endocrinal disorder that can alter cardiac functions. Patients taking medicines that could alter cardiac function like amiodarone, β-blocker, CCB, etc., Patients having contraindication of TMT. Patient older than 60 yrs.

Method and Data Collection-All the hypothyroid patients attending JAH Groups of Hospital, Gwalior, (M.P.) were screened for eligibility. Informed consent was taken from the eligible patients and enrolled in the present study. The patients were interviewed and underwent thorough physical examination. Their Data comprising of name, age, sex, personal, occupational and proper history was recorded on the proforma. All patients were evaluated on the basis of clinical, haematological, ECG and TMT study.Resting ECG was done in all patients in lead I, II, III, aV_L, aV_R, aV_F and V_1 to V_6. Tread Mill Test (TMT) was performed in all patients irrespective of ECG changes.

History and Examination-A detailed history was elicited from all patients with emphasis on symptomatology and duration of hypothyroidism. Body mass index (BMI) was calculated according to Quetelet's formula and subjects were accordingly categorized.

Type	BMI (Kg/m2)
Underweight	<18.5
Healthy weight	18.5-24.9
Overweight	25-29.9
Obese class I	30- 34.9
Obese Class II	35-39.9
O bese Class III	>40

Source: Adapted from National Institutes of Health, National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. U.S. Department of Health and Human Services, Public Health Service, 1998.)

Hypertension according to JNC[01] 7 Classification:

Category	SBP (mmHg)	DBP (mmHg)
Normal	<120	<80
Pre-hypertension	120-139	80-89
Hypertension stage 1	140-159	90-99
Hypertension stage 2	>160	>100

Lipid profile according to ATP III guideline.[02]

Investigations-All patients were subjected to the following investigation at the time of inclusion into the study. Routine hemogram, Random blood sugar, Thyroid hormone profile, Lipid profile (total cholesterol, triglycerides, LDL, HDL), Blood urea and serum creatinine, Urine routine and microscopic examination. Resting Electrocardiogram, Tread mill testing.

Technique of treadmill test-The patient was instructed not to eat or drink caffeinated beverages three hours prior to testing and to wear comfortable shoes and loose fitting clothes. A brief physical examination was performed prior to the test and a written informed consent was taken. A standard 12 lead electrocardiogram was taken following which a torso ECG was obtained in the supine position and in the sitting or standing position. Blood pressure was recorded in both positions and the patient was instructed on how to perform the test. Standard multistage maximal exercise test was done on a motorised treadmill according to Bruce protocol. The heart rate, blood pressure and electrocardiograms were recorded at the end of each stage of exercise, immediately before and after stopping the exercise and for each minute for at least 5 to 10 minutes in the recovery phase. Exercise test was terminated in all patients following the achievement of target heart rate or an abnormal ischemic response. This was defined as development of 0. 10 mV (1 mm) of J point depression measured from the PQ junction, with a relatively flat ST segment slope (<lmV/sec), depressed > 0.10 mV 60 to 80 msec after the J point in three consecutive beats with a stable baseline. Exercise test was also terminated if patient developed dyspnoea, fatigue or chest pain.

Statistical analysis-Data was analysed using Microsoft excel, the software statistics calculator, described data was analysed using student's t test and chi-square test. Two tailed P value <0.05 was considered significant.

Observations -The present study was carried out in department of medicine, J.A. Group of Hospitals, G.R. Medical College, Gwalior (M.P.) over a period between Sept., 2011 to Nov., 2012 on the 100 cases of hypothyroidism. After applying inclusion and exclusion criteria written in materials and methods. The following observations were drawn as follows:

Table 1: Age and Sex wise distribution of study population (n=100)

Age group (in yrs)	Male (n=20)	Female (n=80)	Total (n=100)
21-30	1 (5%)	13 (16.25%)	14 (14%)
31-40	3 (15%)	20 (25%)	23 (23%)
41-50	9 (45%)	18 (22.5%)	27 (27%)
51-60	7 (35%)	29 (36.25%)	36 (36%)
Total	20	80	100
Mean $\pm$ SD	45.7 $\pm$ 9.05	43.48 $\pm$ 12.38	43.93 $\pm$ 11.78

Maximum number of patients 36% found in age group of 51-60 years followed by 27% in age group of 41-50 years. Mean age of all patients is 43.93 $\pm$ 11.78 (SD). Out of 100 cases there were 20 males and 80 females with male female ratio is 1:4.

Table 2: Distribution of study population according to duration of hypothyroidism (n=100)

Duration	Male (n=20)	Female (n=80)	Total (n=100)
Newly detected	5 (25%)	20 (25%)	25 (%)
$\leq$ 1 yr	9 (45%)	38 (47.5%)	47 (%)
> 1 yr	6 (30%)	22 (27.5%)	28 (%)
Total	20	80	100 (%)

Hypothyroidism being a disease of insidious onset the duration of illness can be determine approximately.

A. Newly detected patients - Are those patients which are diagnosed recently and have not taken any thyroid drugs.
B. $\leq$ 1 year - Patient has been diagnosed with in 1 year period and are on thyroid drugs.
C. >1 year - Patients whose are diagnosed case of hypothyroidism and are on thyroid drugs for more than 1 year period.

Maximum (47%) hypothyroid patients were of < 1 yr duration. 25% of patients are newly detected cases of hypothyroidism. 28% of patients are of > 1 yr duration.

Table 3: Symptomatology of study population (n=100)

Symptomatology	Male (n=20)	Female (n=80)	Total (n=100)
Weakness/lethargy	19 (95%)	72 (90%)	91(%)
Facial puffiness	18 (90%)	63 (78.75%)	81 (%)
Decreased Appetite	15 (75%)	58 (72.5%)	73 (%)
Skin changes	14 (70%)	52 (65%)	66 (%)
Cold intolerance	10 (50%)	49 (61.25%)	59 (%)
Constipation	13 (65%)	46 (57.5%)	59 (%)
Weight gain	10 (50%)	48 (60%)	58 (%)
Hoarseness of voice	4 (20%)	21 (26.25%)	25 (%)
Menstrual abnormality	-	12 (18.75%)	12 (%)

In present study, most common symptom was weakness and lethargy 91% followed by facial puffiness 85%, decreased appetite 75%, skin changes 66%, Cold intolerance 59%, constipation 59%, weight gain 50%, hoarseness of voice 25% and mental abnormality 12% (oligomenorrhoea were more common than menorrhegia) This descending order of symptoms were similar in both male and female.

Table 4: Cardiovascular symptoms in study population (n=100)

Cardiovascular symptoms	Male (n=20)	Female (n=80)	Total (n=100)
Breathlessness	1(5%)	7(8.7%)	8(%)
Effort intolerance	4(20%)	5(6.2%)	9(%)
Palpitation	1(5%)	1(1.2%)	2(%)

Most common cardiovascular symptom was breathlessness present in 8% of patients. Least common symptom was palpitation only in 2% cases.

Table 5: Sign on general physical examination of study population (n=100)

Signs	Male (n=20)	Female (n=80)	Total (n=100)
Skin changes	14 (70%)	52 (63.75%)	66(%)
Edema	10 (50%)	44 (55%)	54(%)
Goiter	0	3 (3.7%)	3(%)
DAR (decreased angle reflex)	4 (20%)	15 (18.75%)	19(%)
Pulse (<60/min)	1 (5%)	9 (11.25%)	10(%)
SBP ($\geq$140)	1 (5%)	7 (8.75 %)	8(%)
DBP ($\geq$ 90)	5 (25%)	16 (20%)	21(%)

In present study, most common signs was skin changes 66% followed by edema 54%, DAJ 19%, DBP HTN 21%, SBP HTN 9%, bradycardia 10%.

Table 6: Body Mass Index of the study population (n=100)

BMI (kg/m^2)	Male (n=20)	Female (n=80)	Total (n=100)
18.5-24.9 (Normal)	9 (45%)	42 (52.5%)	51 (%)
25-29.9 (Over weight)	10 (50%)	29 (36.5%)	39 (%)
$\geq$ 30 (Obese)	1(5%)	9 (11.25%)	10(%)

51% patients were in normal BMI range, 39% were over weight, and 10% were obese patients. This shows that the prevalence of high BMI (overweight or obese) is approximately in every 2nd patients of hypothyroidism.

Table 7: Blood lipid profile of the study population (n=100)

Lipid profile	Male (n=20)	Female (n=80)	Total (n=100)
Inc. TC (> 240 mg/dl)	10 (50%)	25 (31.25%)	35(%)
Inc. TG ($\geq$ 150 mg/dl)	9 (45%)	23 (28.7%)	32 (%)
Inc. LDL (> 160 mg/dl)	5(25%)	24 (30%)	29 (%)
Dec. HDL (<40 mg/dl)	5 (25%)	15(18.75%)	20 (%)

Out of 100 patients, increase total cholesterol was present in 35%, increased triglyceride in 32%, increased LDL in 29% and decreased HDL in 20%. This shows that hypothyroidism is commonly associated with dyslipidemia and it is more common in overt than subclinical hypothyroidism.

Table 8: Distribution of study population on basis of TSH value (n=100)

TSH value (µIu/ml)	Male (n=20)	Female (n=80)	Total (n=100)
4.25-10	8 (40%)	43 (53.75%)	52 (%)
11-50	2 (10%)	19 (26.25%)	21 (%)
>50-100	4 (20%)	6 (7.5%)	10 (%)
> 100	6 (30%)	12 (15%)	18 (%)

52% of patients had serum TSH value in between 4.25-10 μIU/ml. 21% of patients in between 11-50, 10% in between 51-100 and 18% of patients had serum TSH > 10 μIU/dl. This shows that there is higher prevalence of patients of sublinical hypothyroidism than overt hypothyroidism.

84% of patients had normal ECG and 16% of patients had abnormal ECG. Out of these, bradycardia in 10%, low voltage complex of in 7%, RBBB 7%, non specific ST-T changes 5%, QTc interval increase in 4%, VPCs in 4%. This table shows most patients had normal resting ECG.

Table 9: Resting ECG features of study population (n=100)

ECG finding	Male (n=20)	Female (n=80)	Total (n=100)
1. Normal	16(80%)	68(80%)	84(%)
2. Abnormal	4(20%)	12(15%)	16(%)
(A) Bradycardia (<60/min)	1(5%)	9(11.25%)	10(%)
(B)Low voltage complex	1(5%)	6(7.5%)	7(%)
(C) RBBB	1(5%)	6(7.5%)	7(%)
(D) ST-T segment changes (Non-specific)	1(5%)	4(5%)	5(%)
(E) QTc interval increase	1(5%)	3(3.7%)	4(%)
(F) VPCs	1(5%)	3(3.7%)	4(%)
(G) 1º heart block	0	2(2.5%)	2(%)

Table 10: TMT results in study population (n=100)

Sex	TMT positive	TMT negative	P value	Inference
Male (n=20)	4 (20%)	16 (80%)	<0.05	S
Female (n=80)	8 (10%)	72 (90%)	<0.05	S
Total (100)	12	88	-	-

p value 0.05 (S)

TMT was positive in 12% of cases and negative in 88% of cases. Out of 12 positive cases, 4 were males (20%) and 8 were females (10%).In both male and female, there is statistically significant difference between TMT positive and TMT negative patients of hypothyroidism.

Table 11: Correlation of TMT results with age and sex wise distribution (n=100)

Age group (in yrs)	TMT positive (n=12)			TMT negative (n=88)			P value	Inference
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
21-30 (n=14)	0	0	0	1 (6.25%)	13 (18.05%)	14 (15.90%)	-	-
31-40 (n=23)	1 (25%)	1 (12.5%)	2 (16.66%)	2 (12.5%)	19 (26.38%)	21 (23.16%)	0.59	NS
41-50 (n=27)	1 (25%)	3 (37.5%)	4 (33.33%)	8 (50%)	15 (20.83%)	23 (26.86%)	0.84	NS
51-60 (n=36)	2 (50%)	4 (50%)	6 (50%)	5 (31.25%)	25 (36.72%)	30 (34.09%)	0.78	NS

p value <0.05 (S)

Out of 12 TMT positive patients, 2 (16.66%) were in age group of 31-40 years, 4 (33.33%) were in age group of 41-50 years, 6(50%) were in age group of 51-60 years. Maximum positive cases (83.33%) had age in between 41-60 years of age. This is no statistical significant difference for any age group in patients study in between TMT possible and TMT negative patients of hypothyroidism.

Table 12: Correlation of TMT results with duration of hypothyroid patients (n=100)

Duration)	TMT positive (n=12)			TMT negative (n=88)			P value	Inference
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
Newly detected (n=25)	2 (50%)	2 (25%)	4 (33.33%)	3 (18.7%)	18 (25%)	21 (23.86%)	0.33	NS
≤ yr (n=47)	1 (25%)	3 (37.5%)	4 (33.33%)	8 (50%)	35 (48.7%)	43 (48.86%)	0.72	NS
> 1 yr (n=28)	1 (25%)	3 (37.5%)	4 (33.33%)	5 (31.25%)	19 (26.3%)	24 (27.27%)	0.63	NS
Total	4	8	12	16	72	88	-	-

p value <0.05 (S)

Out of all 12 TMT cases, 4 each patient were newly detected, ≤ 1 year duration and in > 1 year. This shows that all TMT positive cases were equally distributed duration wise. There was no statistical significance difference for any duration of hypothyroidism in TMT positive and TMT negative patients of hypothyroidism. It means even in longer duration of hypothyroidism, there is less chances of TMT positivity when hypothyroidism is well controlled or treated. It does not like that longer duration of hypothyroidism would have more TMT positive.

Table 13: Correlation of TMT results with symptomatology of patients in study population (n=100)

Symptom-atology	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
Weakness/ lethargy	4 (100%)	8 (100%)	12 (100%)	15 (93.7%)	64 (88.8%)	79 (89.7%)	> 0.05	NS
Facial puffiness	3 (75%)	8 (100%)	11 (91.6%)	15 (93.7%)	55 (76.38%)	70 (9.50%)	> 0.05	NS

Skin changes	3 (75%)	7 (87.5%)	10 (83.3%)	11 (68.75%)	43 (62.5%)	54 (63.3%)	> 0.05	NS
Cold intolerance	3 (75%)	4 (50%)	7 (58.3%)	7 (48.75%)	45 (62.5%)	45 (51.13%)	> 0.05	NS
Decreased Appetite	3 (75%)	6 (75%)	9 (75%)	12 (75%)	52 (72.22%)	64 (72.72%)	> 0.05	NS
Weight gain	3 (75%)	7 (87.5%)	10 (83.3%)	7 (62.5%)	41 (56.9%)	48 (54.54%)	> 0.05	NS
Constipation	3 (75%)	5 (62.5%)	8 (66.6%)	10 (62.5%)	40 (55.56%)	50 (56.31%)	> 0.05	NS
Hoarseness of voice	1 (25%)	3 (37.5%)	4 (53.3%)	3 (18.75%)	18 (25%)	21 (23.86%)	> 0.05	NS
Menstrual abnormality	0	2 (25%)	2 (16.6%)	0	10 (13.8%)	10 (11.36%)	> 0.05	NS

p value <0.05 (S)

In both TMT positive and TMT negative patients of hypothyroidism symptom were distributed in similar frequency and there was no statistical significance difference in between TMT positive and TMT negative patients for any symptoms.

Table 14: Correlation of TMT results with cardiovascular symptoms in study population (n=100)

Cardiovascular symptoms	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
Breathlessness	0	2 (25%)	2 (16.67%)	1 (6.25%)	5 (6.25%)	6 (6.8%)	> 0.05	NS
Effort intolerance	1 (25%)	1 (12.5%)	2 (16.67%)	3 (18.75%)	4 (5.55%)	7 (7.99%)	> 0.05	NS
Palpitation	1 (25%)	0	1 (8.33%)	0	1 (1.38%)	1 (1.13%)	> 0.05	NS

p value <0.05 (S)

For any cardiovascular symptoms, there was no statistically significant difference between TMT positive and TMT negative patients

Table 15: Correlation of TMT results with signs on general physical examination of study population (n=100)

Signs	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
Edema	3 (75%)	5 (62.5%)	8 (66.6%)	7 (43.75%)	39 (54.16%)	46 (52.27%)	0.85	NS
Skin changes	3 (75%)	7 (87.5%)	10 (87.5%)	11 (62.5%)	45 (68.75%)	56 (62.5%)	0.92	NS
Goiter	0	0	0	0	3 (4.16%)	3 (3.40%)	0.47	NS
DAR	2 (50%)	2 (25%)	3 (25%)	2 (18.75%)	13 (18.67%)	16 (18.18%)	0.09	NS
Pulse (<60/min)	0	1 (12.5%)	1 (8.33%)	1 (8.33%)	8 (11.11%)	8 (10.27%)	0.67	NS
SBP (≥140)	0	1 (12.5%)	1 (8.33%)	1 (8.33%)	6 (8.33%)	7 (7.95%)	0.96	NS
DBP (≥ 90)	2 (50%)	3 (37.5%)	5 (41.66%)	3 (8.75%)	13 (18.05%)	16 (18.88%)	0.02	S

p value < 0.05 (S)

For all signs on general examination, there was only statistical significant difference, for DBP ≥ 90 in between TMT positive and TMT negative group of hypothyroidism and not for any other sign.

Table 16: Correlation of TMT results with BMI in study population (n=100)

BMI (kg/m^2)	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
18.5-24.9 (Normal)	0	0	0	79 (56.25%)	42 (58.33%)	51 (57.79%)	-	-
25-29.9 (Over weight)	3 (75%)	5 (62.5%)	8 (66.66%)	7 (43.75%)	24 (33.33%)	31 (35.22%)	0.03	S
≥ 30 (Obese)	1 (25%)	3 (37.5%)	4 (33.33%)	0	6 (8.33%)	6 (6.8%)	0.005	S

P value <0.05 (S)

This table shows that 66.66% of TMT positive patients were overweight and 33.33% of TMT positive patients were obese. No cases of TMT positive in normal BMI range. There is statistical significance difference for overweight and obese individual in TMT positive and TMT negative patients of hypothyroid.

Table 17: Correlation of TMT results with thyroid hormone level in study population (n=100)

TSH value (μIU/ml)	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
4.25-10 (n=51)	0	1 (12.5%)	1 (8.33%)	8 (50%)	42 (58.55%)	50 (56.81%)	0.34	NS
10-50 (n=21)	1 (25%)	4 (50%)	5 (41.6%)	1 (6.25%)	15 (20.83%)	16 (18.98%)	0.96	NS
50-100 (n=10)	2 (50%)	1 (2.5%)	3 (25%)	2 (12.5%)	5 (6.94%)	7 (7.95%)	0.67	NS
> 100 (n=18)	1 (25%)	2 (25%)	3 (25%)	5 (31.25%)	10 (13.88%)	15 (17.04%)	0.50	NS

P value <0.05 (S)

Out of 12 TMT positive cases, 11 patients had serum TSH value above > 10 μIU/ml, only 1 patient was in between TSH range of 4.25-100 μIU/ml.Highest cases (41.6%) found in TSH range of 10-50 μIU/ml. There was no statistically significant difference in any range of TSH between TMT positive and TMT negative cases.

Table 18: Correlation of TMT results with lipid profile in study population

Lipid profile	TMT positive (n=12)			TMT negative (n=88)			p value	Infer-ence
	Male (n=4)	Female (n=8)	Total (n=12)	Male (n=16)	Female (n=72)	Total (n=88)		
Inc. TC (> 240 mg/dl)	3 (75%)	8 (100%)	11 (91.6%)	7 (43.75%)	17 (23.61%)	24 (27.27%)	0.001	S
Inc. TG (≥ 150 mg/dl)	3 (75%)	6 (75%)	9 (75%)	6 (37.5%)	17 (23.61%)	23 (26.13%)	0.010	S
Dec. HDL (<40 mg/dl)	1 (25%)	3 (37.5%)	4 (25%)	4 (25%)	12 (16.67%)	16 (18.18%)	0.57	NS
Inc. LDL (> 160 mg/dl)	3 (75%)	5 (62.5%)	8 (66.6%)	2 (12.5%)	9 (12.5%)	21 (23.86%)	0.005	S

p < 0.05(S)

Out of 12 TMT positive cases, 11 (91.6%), 9(75%), 4 (25%) and 8(66.6%) had increase total cholesterol, increase triglyceride, decreased HDL and increase LDL. This shows that most of cases were having deranged lipid profile. There was statistically significant difference for increase total cholesterol, increase triglyceride, increase LDL but no statistically significant difference for decreased HDL in TMT positive and TMT negative patients of hypothyroidism.

Table 19: Correlation of TMT positive with resting ECG changes

Resting ECG changes	TMT positive		
	M (04)	F (08)	Total (12)
Normal (n=84)	2(50%)	5(62.5%)	7(58.3%)
ST-T changes with VPC's (n=02)	0	2 (25%)	2 (16.6%)
ST-T changes without VPC's (n=03)	1(25%)	1(12.5%)	2 (16.6%)
RBBB (n=07)	1 (25%)	0	1(8.3%)

Out of 12 TMT positive patients, 7 cases (58.3%) were having normal resting ECG, while 16.6% (2cases) had nonspecific ST-T changes with VPC's and (16.6%) had ST-T changes without VPC's and only 1 case (8.3%) had RBBB.

Table 20: TMT changes in normal resting ECG study population

ECG changes after TMT	M (16)	F (68)	Total (84)
ST-T segment depression	2	3	7 (8.3%)
Ventricular ectopic	1	2	3 (3.5%)

This table shows that 8.3% of patients who had normal resting ECG develop ST- segment depression >1mm and 3.5% patients developed ventricular ectopic during treadmill test

Table 21: Correlation of characteristics of hypothyroidism with respective to TMT positive and TMT negative patients

Parameters	TMT	Mean	SD	P value	Inference
Avg. age (yrs)	Positive	48.5	7.3174	0.1531	NS
	Negative	43.306	12.1668		
Avg. duration of hypothyroidism(mths)	Positive	17.41	17.25	0.2847	NS
	Negative	11.90	16.5681		
Pulse rate	Positive	66.66	6.98	0.799	NS
	Negative	80.85	191.04		
SBP	Positive	126.83	7.50	0.147	NS
	Negative	122.29	10.38		
DBP	Positive	88.83	7.35	0.0089	S
	Negative	80.04	11.05		
Avg. BMI (kg/m^2)	Positive	29.10	2.022	0.0001	S
	Negative	24.89	2.80		
Avg. Total cholesterol (mg%)	Positive	275.66	20.04	0.0001	S
	Negative	210.28	46.47		
Avg. Triglyceride (mg%)	Positive	169.85	24.186	0.0001	S
	Negative	123.625	35.47		
Avg. LDL (mg%)	Positive	163.08	61.9117	0.002	S
	Negative	119.972	30.9931		
Avg. HDL (mg%)	Positive	44.83	10.35	0.2677	NS
	Negative	48.97	12.27		
Avg. TSH	Positive	51.63	42.97	0.2225	NS
	Negative	34.39	45.96		
FT4	Positive	0.54	0.335	0.0127	S
	Negative	0.84	0.39		

In present study, there was statistically significant difference was seen between TMT positive and TMT negative cases in hypothyroidism patients for diastolic blood pressure, average BMI, average total cholesterol, average LDL, average triglyceride and average serum free FT4 but no significant difference for average serum TSH, average age of the patients, average duration of hypothyroidism, average pulse rate, average systolic blood pressure and average HDL.

Discussion-The present study was planned to study cardiovascular manifestations and to detect asymptomatic coronary heart disease in patients of hypothyroidism by doing TMT (Tread Mill Test) before CAD becomes symptomatic because restoration of Euthyroidism may revert cardiovascular manifestations and even CAD. So timely treatment is advisable in an attempt to avoid all cardiovascular events.

Epidemiology -The present study found that as age increases the prevalence of hypothyroidism increase. and the maximum cases found in age group of 51-60 years (36%). It was comparable with results of Watanakunakorn *et al.* [3] and Wright-Rasco *et al.* [4] and in both studies maximum incidence was in 6th decade.

Sex distribution -In present study, female preponderance found in all age group and all range of serum TSH. The male female ratio was 1:4 and it was comparable with other studies like Khurram *et al.* [5] (2003) and Vanheals *et al.* [6] and in them male female ratio was 1:4 and 1:4 respectively.

Clinical features-Symptomatology -In both male and female most common symptom was weakness and lethargy (91%), facial puffiness (81%), decrease appetite (73%), skin changes (66%), Cold intolerance (59%), constipation (59%), weight gain (58%), hoarseness of voice (25%) and menstrual abnormality was (12%) in which oligomenorrhoea were most common followed by menorrhogia. All the symptoms were fairly comparable with other studies like Watanakunakorn [3] (1965) in which most common symptom were general weakness and facial puffiness (67%).Khurram *et al.* (2003) [5] also compared the symptoms and signs of 394 patients and the most common symptoms was also lethargy (67.9%).

Cardiovascular symptoms-Cardiovascular symptoms were also fairly comparable with results of other studies like Watanakunakorn *et al.* [3] in which breathlessness, palpitation and effort intolerance had similar incidence.

Sign-In our study, in both male and female the most common sign were in same descending order and with overall frequency were coarse skin changes (66%), edema in 54%, DAJ (19%), goiter (3%), results were comparable with Samantha *et al.* [82], they also found common presenting sign were edema (56%) then delayed jerk (53.3%), dry coarse skin (40%). In our study frequency of DAJ were not comparable with frequency of DAJ mentioned in Samatha *et al.* [7]

Pulse rate-In our study, bradycardia (< 60/min) found in 10% of overall patients. Present study was comparable with incidence of bradycardia (8%) reported by Wayne [8] and (14.3%) by Anil Kumar *et al.* 14.

Blood pressure-Hypothyroidism is common cause of secondary hypertension. In our study the incidence of hypertension was 21% and it was fairly comparable with results of Kelin I (1990) [9] and Watanakunakorn *et al.* (1965) [3], in which incidence of hypertension was 21% and 18% respectively.

Hypothyoridism and Asymptomatic Coronary Artery Disease-Hypothyroidism is a common clinical problem which plays a key role in clinical course of CAD. In overt hypothyroidism and some cases of subclinical hypothyroidism, important association have been identified among hypercholesterolemia, hypertension and certain newer risk factors for atherosclerosis. There is no difference in opinion that overt hypothyroidism associated with coronary artery disease but association of CAD with subclinical

hypothyroidism remain controversial. Following observations: Among 100 patients, TMT was positive in 12% cases and was negative in 88% cases. Out of these, there were 4 (20%) male and 8 (10%) were female. In our study, it was statistically significant both for male and female. The prevalence of asymptomatic CAD in hypothyroidism was found to be 12%. Few studies has been done studying CAD in hypothyroidism patient. The prevalence of ischemic heart disease reported in various studies the incidence of ischemic heart disease in hypothyroidism reported by E.J. Weyne (1960) [8], Watanakunakorn *et al.* (1965) [3] and Mohammad Alzaidi (2011) [10] was 16%, 11.75% and 23.3% respectively. However, there previous studied symptomatic ischemic heart disease. First case control study by Vanhaest *et al.* [6] found a greater prevalence in severity of coronary atherosclerosis in hypothyroid group compared to euthyroidism. A hospital based study [11] in both male and female with TSH value (>4.0 MU/L) had higher prevalence of CAD than age matched control although this was statistically significant only for women. Rotterdam study [12], in a cross sectional analysis, higher prevalence of CAD found in elderly hypothyroid female, with odds ratio (2.3:95% CR, 1.3-4.2).So supported with other studies, there is high prevalence of CAD in hypothyroidism.

Hypothyroidism, Dyslipidemia and Cad-In present study, increased total cholesterol (35%), increased Triglyceride (32%), increased LDL in 29% and decreased HDL in 20% of patients. It clearly shows there is thyroid hormone deficiency that causes dyslipidemia in hypothyroidism, it is more common in overt hypothyroidism than subclinical hypothyroidism. The average mean of lipid profile was higher in present study and it fairly comparable with average mean of lipid profile in studies of S.K. Rajan (2003) [13] and Anil Gupta *et al.* (1996) [14]. There was statistically significant difference for average total cholesterol, average LDL and average triglyceride in between TMT positive and TMT negative but not for average HDL. It is accepted that hypothyroidism accelerates development of CAD by its impairment on lipid metabolism (Jung *et al*., 2003 and Rizos *et al.* 2011) [15, 16]. Hyperlipidemia is more often in patients with serum concentration of thyrotropin more than 10 mIU/L (Biondi & Klein) [17]. As supported with other studies dyslipidemia was very common in hypothyroidism and highly prevalent in TMT positive patients with hypothyroidism. However, decrease HDL which is common risk factor for CAD is not significant in case TMT positive and TMT negative patients.

Hypothyroidism, hypertension and CAD-In present study, we found avg. SBP±SD in TMT positive and TMT negative case 126.83±7.50 and 122.29±10.38. There was no statistical significance difference of avg. SBP in TMT positive and TMT negative (p= 0.147).There was also no statistical significance difference for SBP hypertension (> 140) in TMT positive and TMT negative patients (p=0.96).Avg. DBP±SD in TMT positive and TMT negative were 88.83±7.35 and 80.04±11.05 and there was statistical significance for avg. DBP in TMT positive and TMT negative group (p=0.0089) (S). There was statistically significance difference for DBP hypertension $\geq$ 90 in TMT positive and TMT negative p=0.02 (S).It was comparable with other studies, hypertension is more common in hypothyroid population, its prevalence reaches 20-40% (Klein and Ojamaa 1995 [18]; Streeten *et al.* 1988) [19]. Hypertension is frequent symptom of hypothyroidism and independent risk factor for CAD. Thyroid hypofunction is associated with predominantly diastolic hypertension as a result of increase systemic vascular resistance and common cause of CAD in hypothyroid population (Biondy and Kelin 2004 [7], Kanbery *et al.* [20], & Obuabic *et al.* 2002) [21].

Hypothyroidism, obesity and CAD -In this study 39% patients were overweight (BMI $\geq$ 25kg/m^2) and 10% patients were obese ($\geq$30 kg/m^2). In this study, average BMI with S.D. for TMT positive and TMT negative case were 29.10±2.02 and 24.89±2.80. There was statistical significance difference (p=0.001) for avg. BMI in between TMT positive and TMT negative groups of patients. Out of 12 TMT positive patient, 4 (33.33%) were obese and 8 (66.66%) were overweight. So it was clearly shown all TMT positive patient in our study associated with higher BMI ($\geq$25 kg/m^2). Obesity is independent risk factor for CAD given in standard textbooks like Harrison's Principles of Internal Medicine, page no. 1987, 18th Edition. Hypothyroidism is associated with low basal metabolic rate and higher BMI (obesity or overweight) (Khurram *et al.* 2003) [5]. Hypothyroidism and obesity coexist in varying degree of severity. Overt hypothyroidism leads to increased body weight, increasing mucin deposits in skin and other organs.

Serum TSH and CAD: In present study, out of 12 TMT positive cases, 1 case (8.33%) found in between serum TSH in range 4.25-10μiU/ml, 5 (41.6%), 3(25%), 3(25%) were found in between TSH range of 10-50, 50-100 & >100μiU/ml respectively. The overage TSH value for TMT positive and negative were 51.63±42.97, 34.39±49.96 respectively. There was no statistical significant difference for average TSH in TMT positive and TMT negative patients. There was also no statistically significance difference in any range of TSH between TMT positive and TMT negative patients of hypothyroidism. A study Ventaka M Alla (2011) [22] who studied 138 patients, of hypothyroidism with coronary artery disease. They divide the HT patients with CAD into two groups. TSH was normal in 108 patients (78%) (on drugs and well controlled) and TSH was higher in 30 patients (22%). This study showed that TSH level does not influence the presenting feature and inhospital outcomes in hypothyroid patients with CAD. However, there was higher prevalence of TMT positivity in patients of serum TSH $\geq$10μiU/ml in our study. It's because of common association of dyslipidemia with serum TSH value. Higher the TSH value, more would be dyslipidemia. A study [23] shows that subclinical hypothyroidism is associated with increased risk of CAD in those with higher TSH levels, particularly level with >10μiU/ml.

Serum T4: In our study average FT4 in TMT positive and TMT negative patients are 0.54±0.335 and 0.84±0.39. There was statistically significant difference in between TMT positive and TMT negative patients of FT4 (p = 0.027). It means that higher the thyroid hormone deficiency, there is higher prevalence of TMT positivity in hypothyroidism. Its because of common association of overt hypothyroidism with other coronary risk factors like dyslipidemia and high BMI.

Duration and clinical manifestation of hypothyroidism with TMT changes -There was not any statistical significance difference for duration and clinical manifestation in patients of hypothyroidism with TMT positive and TMT negative patients.

Resting ECG changes and its correlation with positivity TMT changes -In present study, 84% of cases had normal resting ECG and 16% had abnormal resting ECG. Most frequent resting ECG abnormalities were bradycardia (10%), low voltage complex 7%, RBBB 7%, nonspecific ST-T changes 5%, VPCs 4%, increase QTc interval in 4%. These ECG changes were comparable with incidence reported by William F.C. *et al.* [24] and Tajiri J. *et al.* [25]. 7 (58.3%) out of 12 TMT positive cases had normal resting ECG and 2 (16.6%) cases had resting nonspecific ST-T changes with VPCs and 2(16.6%) had ST-T changes without VPCs developed TMT positivity. Out of 5 cases ST-T changes at rest, 4 (80%) cases developed TMT positivity and 4 cases of hypothyroidism had VPCs at resting ECG in which 2(50%) developed TMT positivity. It clearly shows that TMT positivity can develop in both normal resting and abnormal resting ECG. However chances of TMT positivity is increased a patients already had ST-T changes and VPCs.

Conclusion-In this study, it was concluded that TMT was significantly positive in patients of hypothyroidism. It can be positive in patients either with normal resting ECG or abnormal resting ECG. However chances of TMT positivity increase when resting ECG especially had nonspecific ST-T changes and VPC's. There were no statistical significance difference for duration of hypothyroidism, average TSH values and clinical manifestation of hypothyroidism in TMT positive and TMT negative patients. There is statistical significance for average FT4, average T. cholesterol, average Triglyceride, average LDL, average BMI in patients of TMT positive and TMT negative in hypothyroidism. Serum FT4 level was significantly lower in patients of hypothyroidism with TMT positivity as compare to TMT negativitiy. The prevalence of TMT positive in hypothyroidism is likely when patients had dyslipidemia, high BMI (overweight or obese) diastolic hypertension, FT4 level deficiency.

Acknowledgement-None
Source of fund – None
Ethical approval-Yes
Conflicts of Authors –None

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