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THYROID DYSFUNCTION IN PATIENTS OF METABOLIC SYNDROME

General Medicine

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ABSTRACT

Background: The rising prevalence of cardio-metabolic risk factors like hypertension, diabetes, dyslipidemia and obesity significantly contributes to the rise in individuals with metabolic syndrome (MetS).1Interestingly, thyroid abnormalities like subclinical or overt hypothyroidism have been reported with a greater frequency in patients with MetS than general population.2Metabolic syndrome is clustering of various parameters which enhance the vulnerability of an individual to cardiovascular disorders. Previous studies suggested thatthyroid dysfunction, mainly hypothyroidism was prevalent among 35.2% of MetS patients.3.Alternatively, patients with thyroid dysfunction also found to have increased frequency of MetS. The consequences of untreated hypothyroidism can be additionally detrimental for cardiovascular health of anindividual who already has the MetS. Hence to assess the burden of thyroid dysfunction in patients of MetS, the present study was undertaken.

Methods: This cross-sectional observational study was conducted in tertiary hospital on 100 subjects with metabolic syndrome.

Results: Mean age of study subjects with MetS was 55.9±10.7 years. MetS was found in the age group of 51-60 yrs in most of the patients. We studied 54% males& 46% females.

We observed that 60% subjects were euthyroid and thyroid dysfunction was seen in remaining 40% subjects. Among these, 38% were hypothyroid and 2% were hyperthyroid. Further, subclinical and overt hypothyroidism was seen in 12% and 26% subjects respectively.

Mean WC in our subjects was 97.7±9.4 cm and it ranged from 62 to 139 cm. When defined by BMI, obesity was seen in 78% cases as per the criteria for South Asian population.

Among various components of MetS, dyslipidemia (96%) was most frequent and obesity (57%) was least common. The diabetes was newly detectedin33.6% and hypertension in 27.1% patients for first time. In MetS subjects, obesity was found to be significantly associated with hypothyroidism than euthyroidism (71.1% vs 48.3%, p=0.027). Similarly, hypertension showed significant association with hypothyroidism compared to euthyroid subjects (94.7% vs 78.3%, p=0.028). No significant association with diabetes (p=0.933) or dyslipidemia (p=0.129) was seen. Overall, distribution of various MetS components did not differ significantly in patients with subclinical and overt hypothyroidism.

In two subjects of hyperthyroidism, association with all components of MetS except obesity was seen.

Conclusion: The thyroid dysfunction in form of hypothyroidism is found to be common in subjects of MetS.It is evident that there is strong association of certain MetS components like obesity & hypertension with hypothyroidism. This necessitates that all patients with MetS should be screened for thyroid dysfunction so that the impact of various metabolic consequences of this dysfunction can be ameliorated by judicious treatment in time. It will improve the cardio-metabolic profile and therefore long term outcome of such patients.

KEYWORDS

Metabolic syndrome (MetS), thyroid dysfunction, dyslipidemia, Subclinical hypothyroidism (SCH),overt hypothyroidism

INTRODUCTION:

The rising prevalence of cardio-metabolic risk factors like hypertension, diabetes, dyslipidemia and obesity significantly contributes to the rise in individuals with metabolic syndrome.(MetS)[1] Metabolic syndrome is reported to be associated with increased incidence of subclinical hypothyroidism.[2] Interestingly, thyroid abnormalities have been reported with a greater frequency in patients with MetS than general population.

Literature Survey:

Thyroid dysfunction was noted in various Indian studies. A study from South India done in 54 MetS patients and 54 control population, reported that thyroid dysfunction was prevalent among 35.2% MetS patients. SCH was seen in 24.1% patients & overt hypothyroidism in 11.1%patients.[3]In defining obesity, waist circumference (WC) is advised. Comprising of various risk factors, individuals with MetS are at high risk of CV events.[4].Reavennoted that several risk factors like dyslipidemia, hypertension and hyperglycemia commonly cluster together which he called as **Syndrome X** and recognized it as a multiplex of risk factors for cardiovascular diseases[5]. Syndrome X has now been re-designated as metabolic syndrome **(MetS)** after WHO named it so in 1999.NCEP-ATP III definition is one of the commonly followed worldwide &incorporates any obesity, high blood pressure (BP), high triglyceride (TGs), low high-density lipoprotein cholesterol (HDL) and high fasting plasma glucose. (FPG).[6]MetS is a state of chronic low-grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome.[6]

Obesity is probably one of the forerunners of MetS. NCEP ATS III criteria for MetS includes waist circumference for obesity.[6]Itcan provide better estimate of intra-abdominal fat even in lean individuals compared to BMI.[7]Current estimates suggest that MetS affects 30–40% of people by age the 65yrs. Thyroid dysfunctions and the MetS are the two most common endocrine disorders with a substantial overlap and are associated with significant morbidity and mortality and thus impact substantially on health care.

A study on 100 patients with MetS found 37%subjects having SCH,12% withovert hypothyroidism and 2% with hyperthyroidism[8] Alternatively, patients with thyroid dysfunction also found to have increased frequency of MetS. A study from Algeria in 86 patients with thyroid dysfunction reported prevalence of MetS as 48.8%.Subjects with hypothyroidism (45.3%)& had significantly higher level of BMI, WC, TC, LDL-C, and higher prevalence of abdominal obesity (84.6%, $p < 0.01$) and) hypertension. (51.2%, $p < 0.01$)[9]

A higher prevalence of MetS is observed in individuals with TSH levels higher than normal as compared to those with normal TSH level.[10]These evidences clearly indicate the intricate relationship of MetS and thyroid dysfunction. Presence of undiagnosed thyroid dysfunction in patients with MetS can increase the obesity by promoting weight gain and increase in abdominal fat which further contributes to the insulin resistance. Also dyslipidemia & hypertension which are associated with hypothyroidism increase the risk of CVD. Seeing the relative lack of robust studies in Indian population assessing proportion of thyroid dysfunction in MetS and understanding the relationship of thyroid abnormalities with each component of MetS, we performed this study at a tertiary care center in central India.

Methodology
Aims: To determine frequency of thyroid dysfunction in patients with metabolic syndrome

Objective: To study association between MetS components with thyroid dysfunction categories& postulate the need of screening them for each other.

MATERIALS AND METHODS
Study Design: This was a cross-sectional, single center, hospital-based, observational study.

Study setting: This study was conducted on 100 patients of MetS from medicine in-patient and outpatients (OPD)of a tertiary care hospital in central India for one & half years.

Study Population: We evaluated patients with **Metabolic syndrome (MetS)**for thyroid dysfunction. MetS was diagnosed on the basis of National Cholesterol Education Program **(NCEP) ATP III criteria** as below.

Metabolic syndrome is present if three or more of the following **five criteria** are met (7)
1. Waist circumference (WC) ≥ 102 cm (40 inches; men) or 88 cm (35 inches; (women)
2. BP≥ 130/85 mmHg
3. Fasting TG ≥ 150 mg/dl
4. Fasting high-density lipoprotein cholesterol levels ≤ 40 mg/dl (men) or 50 mg/dl (women)
5. FBS ≥ 100 mg/dl

Inclusion Criteria:
- All female& male subjects above age 18 years.
- Patients who were diagnosed with MetS.

Exclusion Criteria:
- Patients with known primary thyroid disorder
- Patients with irradiation to thyroid gland or undergone thyroid surgery
- Patients receiving anti-thyroid medications or other drugs that can affect thyroid functions and lipid levels like statins, lithium, Amiodarone, oral contraceptive pills.
- Patients with liver, renal failure or heart failure
- Pregnant and lactating women

Ethical Approval
Institutional Ethics Committee (IEC) approval of study protocol & informed consent from the patients were obtained before beginning patient's enrolment in the study.

Statistical Analysis
The data captured was entered into Microsoft excel and analysed with same. Appropriate statistical tests were used for analyzing data.

Demographic and clinical data:
All patients' demographic data like age, sex, and clinical data like presenting symptoms, signs, blood pressure (BP), along with anthropometric data like height (cm), weight (kg) was obtained. Body mass index **BMI (kg/m 2**) was calculated using the standard formula. Classification of subjects was done based on cut off levels for South Asian population as shown in table. Waist circumference was determined at the level of waist. The following criteria were used while categorizing the study population.

Categories of BMI as per cut-off for South Asian population

Category	Cut-off
Underweight	<18.5
Normal	18.5-22.9
Overweight	23.0-27.4
Obese	≥27.5

The categorization of patients for thyroid abnormalities

Category	Thyroid levels
1.Euthyroidism	TSH 0.39 to 6.2
2.Hypothyroidism	TSH >6.2
Subclinical (SCH)	Without symptoms &normal T3,T4
Overt (OH)	With symptoms and abnormal T3,T4
3.Hyperthyroidism	TSH <0.039
Subclinical	Without symptoms &normal T3 T4
Overt	With symptoms and abnormal T3,T4

RESULTS:
The data was analyzed and results obtained are shown in the tables and figures as below,

The study shows that majority (63%) of the subjects were in the age group of 51 to 70 years and the mean age was 55.9±10.7 years.

There were 54 male and 46 female patients with M:F ratio of 1.17:1.

The mean FBS was 145.2±44.0 mg/dL. High FBS(>100 mg/dL) was one of the diagnostic criteria for metabolic syndrome. Mean levels of glycosylated hemoglobin was 8.9±1.7

Table 1: Frequency of components of metabolic syndrome in our subjects

MetS components	Frequency	Percentage
Dyslipidemia	96	96.0
Diabetes	90	90.0
Hypertension	85	85.0
Obesity	57	57.0

Table 1 shows that in MetS subjects, dyslipidemia (96%) was most commonfollowed by diabetes (90%) and hypertension (85%) and obesity (57%) wascommon

Table 2. Anthropometric parameters of subjects of metabolic syndrome

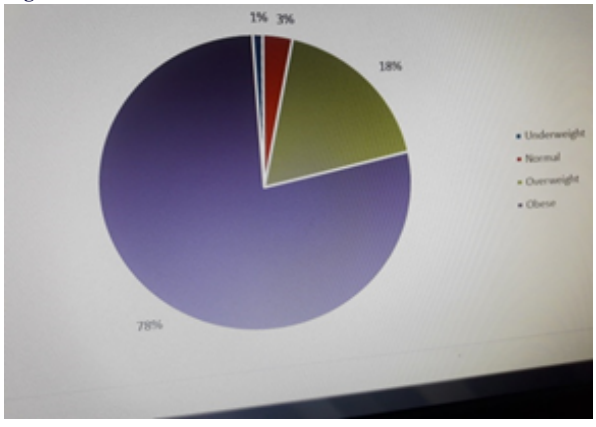
Anthropometric parameters	Mean±SD	Range
Weight (kg)	81.2±15.3	52 to 152
Body mass index (kg/m2)	31.3±5.2	18 to 51
Waist circumference (cm)	97.7±9.4	62 to 139

Table 2 shows mean WC was 97.7±9.4 and mean BMI was 31.3±5.2 kg/m2.

Table 3. Distribution of subjects as per BMI (South Asian Guidelines)

Category	Frequency	Percentage
Underweight (<18.5)	1	1.0
Normal (18.5-22.9)	3	3.0
Overweight (23.0-27.4)	18	18.0
Obese (≥27.5)	78	78.0

Figure No.1



The table 3 & Fig-1 shows that according to BMI criteria of obesity for South Asian population, 18% subjects were overweight and 78% were obese.

Table 4: Thyroid dysfunction in our subject

Thyroid Dysfunction	Frequency	Percentage
Euthyroidism	60	60.0
Total Hypothyroid	38	38.0
Subclinical Hypothyroidism	12	12.0
Overt Hypothyroidism	26	26.0
Hyperthyroidism	2	2.0

Figure:2

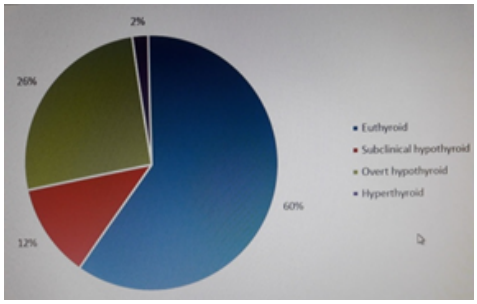


Table 4 and Fig-.2 shows that 60 % subjects with MetS were euthyroid and 38% subjects were hypothyroid. Further divided as overt hypothyroidism (26%) and subclinical hypothyroidism (12%). Hyperthyroidism was found only in 2% subjects.

It was seen that proportion of thyroid abnormality in males and females was 40.7% and 39.1% respectively. p value is insignificant.(0.199)

The study shows that in our study subjects, thyroid dysfunction was more common in age groups of 61 to 70 years followed by 51 to 60 years compared to younger age groups. The distribution of subjects was statistically non-significant (p=0.740).

Table 5: Association of obesity with hypothyroidism

Parameter	Euthyroid (n=60)	Hypothyroid (n=38)	P value
Obese	29 (48.3)	27 (71.1)	0.027
Non-obese	31 (51.7)	11 (28.9)	

Figure:3

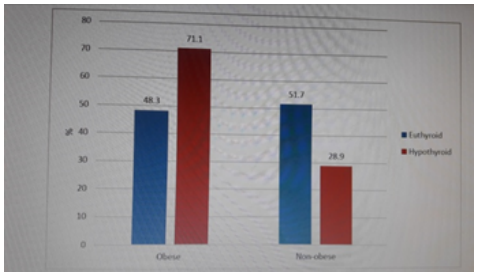


Table 5 & Fig.-3 shows that **significantly higher** proportion of subjects with hypothyroidism were obese than euthyroid subjects (71.1% vs 48.3%, **p=0.027**).

The study shows that proportion of dyslipidemia in hypothyroid and euthyroid subjects was nearly similar and statistically non-significant (92.1% vs 98.3%, p=0.129).

Similarly it was found out that proportion of diabetes in hypothyroid and euthyroid subjects was nearly similar and statistically non-significant (89.5% vs 90.0%, p=0.933).

Table 6: Association of hypertension with hypothyroidism

Parameter	Euthyroid (n=60)	Hypothyroid (n=38)	P value
Hypertension	47 (78.3)	36 (94.7)	0.028
No hypertension	13 (21.7)		

Figure: 4

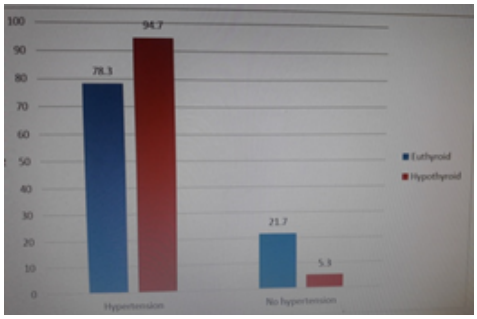


Table 6 and Fig. 4 shows that proportion of hypertension was **significantly higher** in hypothyroid than euthyroid subjects (94.7% vs 78.3%, **p=0.028).**

When we checked the **a**ssociation of MetS components with subclinical and overt hypothyroidism it was seen that among subjects with subclinical and overt hypothyroidism, proportions of MetS components like obesity (p=0.715),dyslipidemia (p=0.173), diabetes (p=0.402) and hypertension (p=0.565) did not differ significantly.

The TSH levels were correlated with various parameters of MetS,it was seen that there was **significant and positive correlation** of TSH levels with TGs (r2=0.201, p=0.045) and fasting blood glucose (r2=0.439, p<0.0001).

DISCUSSION:

In India and globally prevalence of metabolic risk factors like hypertension, DM & dyslipidemia is increasing. Along with obesity there is rise of population with metabolic syndrome**. Bandruska - Stankiewicz (2013)** summarized that thyroid dysfunction in patients of MetS.[11]**Gupta et al,** found significant association of thyroid dysfunction with high WC in MetS.[12] In India recent studies reported prevalence of MetS to be above 40%.[13,14,15] **Meng et al,(2015)** also reported higher incidence of thyroid dysfunction in MetS patients.[26]

1. Age-

Mean age of our study population is 55.9±10.7 yrs and most patients belonged to 51-70 yrs age group. **Gupta et al**,(2004)reported age wise prevalence of MetS in same age group.[12]**Prasad et al**,(2012) reported same age prevalence[13]

2. Sex-

We enrolled 46% females & 54% males in this study. However other studies reported more females with MetS. **Harikrishanan et al**,**(2018)**also reported similar finding with significantly higher females diagnosed as MetS. (28% vs 20%; p value <0.001)[10]

3. Frequency of MetS components-

We observed that dyslipidemia was most common (96%) followed by diabetes (90%),hypertension (85%) and obesity(57%) respectively. Gupta et al, reported dyslipidemia being most common similar to us. Other study from north India reported that most common abnormality was hyperglycemia (71.5%) followed by high TG (48.2%) & obesity.(47.6%)[12]

Prasad et al, observed that older age, female gender**,** obesity, hypercholestremia, middle to high socioeconomic status were contributors for increased risk of MetS.[13]

Bansal et al,(2017) studied total 350 patients to identify MetS prevalence and to evaluate risk factor for development of MetS. Their prevalence was found to be16.57% at older age group & with sedentary life style [14]

A study in Indian population by **Khan Y et al,(2018)** conducted nearly one and half decade earlier reported prevalence of MetS to be 31.6%. The rise in MetS is evident as recent studies from India reported prevalence of MetS to be above 40%.[15]

4. Obesity-

In our study obesity was seen in 57% by WC criteria &78% by BMI criteria as per south Asian population guidelines of WHO.WC is better measure of central obesity than BMI. Our finding of mean BMI was 31.3±5.2 kg/m2 and mean WC was of 97.7±9.4 cm. Thyroid dysfunction is significantly associated with high waist circumference in patients with MetS[12]**Gaywali et al,Chaudhary & Jani et al(2015,2016**) reported association of high WC in pts of MetS.[19,20]

5. Diabetes-

Many of our patients were newly diagnosed as diabetic at the time of screening for inclusion in the study. Mean levels of fasting (145.2±44.0 mg/dL), and post-prandial glucose (211.5±72.3 mg/dL) suggest uncontrolled hyperglycemia in the study group. In this regard, findings from **Khosravi et,al.(2017)**are important. They observed that patients of MetS with hyperglycemia had lower events of stroke (7.9%), ischemic heart disease (7.2%) and CVD mortality (4.8%) compared to patients of MetS with HTN (37.1%, 54.7% and 49% respectively) or MetS with hyperglycemia and HTN. (38.2%, 26.7% and 42.3%

respectively)[24]. Thus, control of individual components is essential in MetS.

6. **Hypertension-**
Most patients had HTN of 1to 5 years duration while 27.1% were newly diagnosed during screening. This shows that when there is presence of other components of MetS, the other component can be diagnosed during additional screening. As such MetS is a metabolic disorder wherein each component influences the other components.Mean levels of systolic and diastolic BP in our study were 153.9±24.3 and 91.8±13.5 respectively. This suggests that the BP was relatively uncontrolled in our study population. Khosarvi et al, observed that MetS patients with hypertension had more events of stroke, Ischemic heart disease & CVD mortality compared to MetS with diabetes.[24]Understanding the current levels of BP in MetS is important as it has been observed that HTN is strong predictor of CV outcomes.

7. Dyslipidemia-
Another important consideration in this regard is of TGs and HDL. The mean levels of these parameters in our study were 198.6±59.3 mg/dL and 35.5±6.5 mg/dL suggesting significant impairment in lipids. Other studies by **Meher et al,(2013)** also found the association of hypothyroidism & dyslipidemia.[18] **Gutch et al,(2017**)reported significantly high of LDL,VLDL &
TG in MetS compared to controls[23]A study from **Marotta et al,** (2010) reported that on multiple regression analysis, TG/HDL ratio was associated with coronary risk (r2 = 0.227) more closely than gender, blood pressure, waist-to-hip ratio, non-HDL cholesterol.[25].

8. Comorbidities:
Patients with MetS are at increased risk of developing cardiovascular disease (CVD).[29] We observed among our patients, 18% had CAD, 14% had stroke and 1% had peripheral arterial disease suggesting nearly one-third had existing CV disease.Development of obstructive sleep apnoea (OSA) has been reported in obese patients with
MetS.[30] We observed two cases of OSA.

9. Thyroid Dysfunction in MetS:
In our study we found that40% pts had thyroid dysfunction and 60% subjects were euthyroid. Hypothyroid status was seen in 38% of which 12% were found to have subclinical form & 2% were having hyperthyroidism.

Chang et al,(2017) reported that after controlling for risk factors, patients with MetS had
a 21% excess risk of developing subclinical hypothyroidism (adjusted hazard ratio(HR1.21; 95% CI 1.03–1.42).[2]

Thyroid hormones are metabolic hormones and affect weight, BP and lipid levels in individuals who suffer from thyroid dysfunction. In a similar study from **Meher et al,**subclinical hypothyroidism was detected in 22% and over thypothyroidism in 4% patients. Subclinical hypothyroidism was significantly associated with MetS group. (P = 0.032)[18]. Another study from **Gyawali et al**, assessed 358 previously diagnosed patients with MetS for thyroid function tests. The overall prevalence of thyroid disease in patients with MetS was nearly 32%. Prevalence of subclinical hypothyroidism was high (29.32%) than overt hypothyroidism in 2% and subclinical hyperthyroidism in 1%. [19]

This shows that nearly 30-40% patients with MetS have thyroid dysfunction mainly hypothyroidism than hyperthyroidism.

10. Thyroid dysfunction in two genders
We observed nearly equal distribution of different thyroid abnormalities in two genders (p=0.199). Overt hypothyroidism was slightly higher in females than males.(28.3% vs 24.1%) A study from **Lai et al**,(**2011**) reported that the prevalence of subclinical thyroid dysfunction was significantly higher among women as compared with men (9.9% vs. 6.3%, respectively; p<0.05)[17] Study from **Khatiwada et al.(2016**) reported that thyroid dysfunction was much common in females (39.7%) than males (26%) but not statistically significant (p=0.068). The relative risk of having thyroid dysfunction in females was 1.525 (CI: 0.983–2.368) as compared to males.[21]

11. Thyroid dysfunction in age groups
We observed that thyroid dysfunction was more common in older people aged beyond 50 years suggesting increasing prevalence by age of the patients. But, the difference in proportions was not significant (p=0.740). A study from **Chang et al,**.reported that beside factors like male, lower educational level, smoking, drinking, and physical inactivity, age ≥ 40 years significantly related to MetS.[9]A study from **Meng et al,**reported similar findin.[26]

12. Association of hypothyroidism with different components of MetS

A) Obesity
Though there was no significant correlation of WC with TSH levels, we observed that there was significantly higher prevalence of obesity in hypothyroid patients than euthyroid individuals (71.1% vs 48.3%, p=0.027)

In this regard, **Gyawali et al**, found that there was significant difference in WC with significantly higher levels in subclinical hypothyroidism compared to hyperthyroidism cases.[19]Another study from **Choudhary and Jani** reported that WC was significantly higher in patients with MetS (P<0.001)[20]**.** Study from **Khatiwada et al,** also reported significant differences (p=0.001) were observed in WC between patients with and without thyroid dysfunction**.**[21]These findings suggest there is increased risk of obesity in patients with hypothyroidism.

Along with increasing rates of obesity, there is rise in population with MetS. Association of various component of MetS with thyroid dysfunction has been established.

B) Hypertension
Though the correlation of TSH levels with systolic and diastolic BP was non-significant, we found that there was significantly higher proportion of patients with HTN in hypothyroid category compared to euthyroid patients (94.7% vs 78.3%, p=0.028). We found no difference in HTN prevalence in subclinical and overt hypothyroidism cases. Similarly, study from **Lai et al,** reported that the prevalence of hypertension was higher in the subclinical hypothyroid group than that in euthyroid group (42.86% vs. 33.2%, p<0.05).[17] A study from **Choudhary and Jani** reported that metabolic components including BP, WC FBS and TGs were significantly higher in patients with MetS (P<0.001), while HDL-C was significantly lower in study group (P<0.001) then control group.[20] This points thathypothyroidism is associated with components of MetS. A study from **Tehrani et al,(2011)**reported that TSH levels in subclinical hypothyroidism positively correlated diastolic BP even after adjustment for age, BMI and insulin resistance index[27].A study from **Haque et al.** reported that the systolic and diastolic BP levels were significantly higher in patients with hypothyroidism than euthyroidism (p<0.0001) in MetS cases.[28] This suggests association of high BP levels with thyroid dysfunction in MetS.

C) Diabetes
We observed significant positive correlation of FBS with TSH levels (r2=0.439, p<0.0001) but not with PLBS (r2=0.107, p=0.288). Overall, we found no association with presence or absence of diabetes with euthyroidism or hypothyroidism (p=0.933). A study from **Kannan et al,(2017)** reported no statistically significant difference in the prevalence of any single component of the metabolic syndrome though a uniform trend of increased prevalence among the hypothyroid group was reported. Subset analysis revealed a higher mean TSH among those with the metabolic syndrome as compared to those without, in both groups. Study showed that hypothyroid subjects are at about 2 to 5 fold increased risk for MetS independent of age, gender, smoking status & alcohol intake[22].**Choudhary and Jani** found that FBS was significantly higher in patients with MetS having hypothyroidism (P<0.001) suggesting hypothyroidism is associated with FBS levels in patients MetS**.**[20] The diabetes prevalence did not differ in patients with subclinical or overt hypothyroidism. Thus, it is important to know that individual component may vary in their association with thyroid dysfunction among MetS patients, overall thyroid abnormalities are more frequent in MetS than control population.[20]

D) Dyslipidemia-
We observed significant positive corelation of TSH levels with TGs.[8,18,23] It has been reported that low HDL is most common abnormality in Indian population hence did not differ between our euthyroid or hypothyroid patients.

Association of Hyperthyroidism with components of MetS

In two subjects of hyperthyroidism, all components of MetS were fulfilled except obesity. A study from **Lai et al,** reported that male subjects with subclinical hyperthyroidism had significantly lower BMI than females[17]**.** This is probably because of increased catabolic activity in hyperthyroidism.

SUMMARY:

Thyroid dysfunction in our study was seen in 40% subjects. Hypothyroidism was more common (38%) than hyperthyroidism (2%). Overall, subclinical and overt hypothyroidism was seen in 12% and 26% subjects with MetS respectively. Among MetS component, association of hypothyroidism with obesity and hypertension was significant but the association with dyslipidemia and diabetes was non-significant. A significant positive correlation of TSH levels with triglycerides and fasting blood glucose was seen. Thus, hypothyroidism in MetS is found to be of common occurrence. This necessitates that all patients with MetS should be screened for thyroid dysfunction.

There are no conflicts of interest.

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