

SUBCLINICAL HYPOTHYROIDISM IN METABOLIC SYNDROME AND ROLE OF CRP IN 50 ADULT PATIENTS

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ABSTRACT

BACKGROUND

Metabolic Syndrome (MetS) is generally characterised as a clustering of the abnormal levels of blood lipids (low HDL and high triglycerides), impaired fasting glucose, elevated blood pressure, and excess abdominal obesity.

The objectives of the study are-

To evaluate presence of Subclinical Hypothyroidism in the study population of the patients with metabolic syndrome.

To find out relation between Subclinical Hypothyroidism and different parameters of metabolic syndrome.

To evaluate whether patients of metabolic syndrome with raised hs-CRP have an increased risk of having hypothyroidism.

MATERIALS AND METHODS

A total of 50 adult patients who met with inclusion criteria were selected. Patients with metabolic syndrome (MetS) who fulfilled the NCEP-ATP III criteria: 3 out of 5 criteria positive. Patients with liver disorders, renal disorders, congestive cardiac failure, pregnant women, patients on oral contraceptive pills, statins and other medications that alter thyroid functions (e.g. lithium, amiodarone or γ -interferon) were excluded from the study.

RESULTS

A total of 50 patients of metabolic syndrome were enrolled. Out of which 36 were euthyroid, 3 were overt hypothyroid and 11 were subclinical hypothyroid. Out of 11 patients of subclinical hypothyroidism, 9 were female and 2 were male patients. Out of 28 females, 9 (32%) were SCH while out of 22 males, 2 (9%) were SCH. Out of 50 patients, 3 were overt hypothyroid. All 3 patients had BP >130/85, waist circumference was >88 cm and HDL of <50 mg/dL. In our study, prevalence of subclinical hypothyroidism was 22%, 6% were overt hypothyroid and 72% were euthyroid. In our study, amongst the components of metabolic syndrome, blood pressure >130/85, HDL <50 mg/dL and waist circumference criteria were more associated with females. While triglycerides >150 mg/dL and fasting blood glucose of >100 mg/dL were more associated with male patients.

CONCLUSION

Subclinical Hypothyroidism was present in 22% of study population and more so in females having metabolic syndrome (32%). Hence, it will be worthwhile to screen female metabolic syndrome patients for thyroid function abnormality. Abnormal blood pressure, triglycerides and HDL cholesterol levels were more associated with subclinical hypothyroidism. In our study, all patients of metabolic syndrome had raised hs-CRP levels. Hence, the role of raised hs-CRP with thyroid dysfunction could not be established.

KEYWORDS

MetS- Metabolic Syndrome, CRP - C-Reactive Protein.

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BACKGROUND

Metabolic syndrome (MetS) is generally characterised as a clustering of the abnormal levels of blood lipids (low HDL and high triglycerides), impaired fasting glucose, elevated blood pressure, and excess abdominal obesity.¹

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Insulin resistance is supposed to be the central pathophysiological phenomenon underlying this clustering.²

Obesity, insulin resistance, physical inactivity, advanced age and hormonal imbalance have been suggested as the underlying risk factors for the development of this syndrome.³

Metabolic syndrome (MetS) affects approximately one quarter of the population in developed countries. People with metabolic syndrome are at an increased risk of atherosclerotic cardiovascular disease and type 2 diabetes.⁴ The prevalence of cardiovascular disease is 2–3 times higher in individuals with metabolic syndrome than in age-matched controls.⁵ According to CURES 52 study, hypertension is prevalent in 20% of Chennai urban

population.⁶ Among these hypertensive patients, the prevalence of other components of metabolic syndrome was: diabetes in 31.8%, impaired glucose tolerance in 17.9%, hypercholesterolaemia in 38.8%, hypertriglyceridaemia in 38%, abdominal obesity in 64.3% and general obesity in 40%.⁶ The Jaipur Heart Watch Studies have reported that in urban Indian population, age-adjusted prevalence of metabolic syndrome was 18.4% in men, 30.9% in women, and 24.9% overall.⁷

As there is a strong correlation between rheumatoid arthritis and subclinical hypothyroidism^{8,9} because of autoimmunity as well as cytokines, which play a higher role in the inflammation, similarly in the metabolic syndrome because of insulin resistance, cytokines play an important role;^{10,11} also, cytokine mediated injury to thyroid follicle might lead to subclinical hypothyroidism in patients with metabolic syndrome.¹²

Several studies have reported that higher TSH (thyroid stimulating hormone) concentrations are associated with a higher likelihood for the occurrence of metabolic syndrome, especially in females.

Additionally, thyroid disease, especially overt hypothyroidism, is associated with atherosclerotic cardiovascular disease, hyperlipidaemia, low grade inflammation and hypercoagulability.¹³⁻¹⁵

Systemic inflammation measured by high sensitivity C reactive protein (hs-CRP) is a known risk factor for cardiovascular disease. Association between metabolic syndrome and hs-CRP has been clearly identified and a recent Japanese study has redefined metabolic syndrome with hs-CRP as a component in this definition.¹⁶

Our study is an effort to look for association between subclinical hypothyroidism and metabolic syndrome, to identify the factors that increase the risk of this association and also to find out whether metabolic syndrome patients with a raised hs-CRP have an increased risk of having hypothyroidism.

Objectives-

- I. To evaluate presence of subclinical hypothyroidism in the study population of the patients with metabolic syndrome.
- II. To find out relation between subclinical hypothyroidism and different parameters of metabolic syndrome.
- III. To evaluate whether patients of metabolic syndrome with raised hs-CRP have an increased risk of having hypothyroidism.

MATERIAL AND METHODS

The study was conducted in medical wards and OPD of SSG Hospital between the months of September 2011 and August 2012. The Sir Sayajirao General Hospital, Baroda, is a tertiary care hospital in central Gujarat with referral of patients from Baroda district as well as surrounding districts of Gujarat, Rajasthan and Madhya Pradesh.

Selection of Patients

A total of 50 adult patients were selected, who met with inclusion criteria.

Inclusion Criteria

Patients with metabolic syndrome (MetS) who fulfilled the NCEP-ATP III criteria (3 out of 5 criteria positive namely):

- 1) Blood pressure \geq 130/85 mmHg or on antihypertensive medications,
- 2) Fasting plasma glucose $>$ 100 mg/dL or on antidiabetic medications,
- 3) Fasting triglycerides $>$ 150 mg/dL,
- 4) HDL $<$ 40 mg/dL in males and $<$ 50 mg/dL in females,
- 5) Waist circumference $>$ 102 cm in men and 88 cm in women were included in the study group

Exclusion Criteria

Patients with

- Liver disorders,
- Renal disorders,
- Congestive cardiac failure,
- Pregnant women,
- Patients on oral contraceptive pills, statins and other medications that alter thyroid functions (e.g. lithium, amiodarone or γ -interferon) were excluded from the study.

Patients who are already diagnosed as having hyperthyroidism, subclinical hyperthyroidism and those under treatment for any thyroid related disorders were excluded from the study.

All candidates were explained about the purpose and nature of the study. Written and informed consent was taken.

Method

Clinical

Patients' personal data were enquired into. Following which a detailed clinical history was elicited to assess inclusion and exclusion criteria.

Past, family and personal history of patients asked in detail about, i.e. history of hypertension, type 2 diabetes mellitus, ischaemic heart disease, dyslipidaemia and thyroid dysfunction. Smoking and alcohol intake were inquired.

Anthropometric Measurements

Measurements were taken as per the WHO guidelines in the WHO Monica Project.

Height-

To measure the height patient was asked to remove his/her shoes and heavy outer garments and to stand with his/her back to the height rule. Back of the head, calves and heels would be touching the upright scale with feet together. The top of the external auditory meatus should be in level with the internal margin of the bony orbit. Position is aided by asking the patient to hold his head in a position that he/she can see a spot on the opposite wall.

Measurement was done with a metric scale to the closest 0.5 cm.

Weight

It was measured by a standardised weighing machine. Patient was asked to stand in the centre of the machine after removing shoes and heavy garments. The weight was measured and rounded off to the nearest 500 grams. Self-reported heights or weights were not acceptable.

Waist Circumference

It was recorded from midway between lower rib margin and iliac crest to the nearest 0.5 cm.

Hip Circumference

It was measured as maximum circumference of the buttocks round up to the nearest 0.5 cm. The waist and hip circumference were measured while the subjects were in light clothing with belt loosened and with pockets emptied.

Body Mass Index

It was calculated by dividing the weight in kilograms with square of the height expressed in metres. Obesity was defined and classified according to WHO.

Waist-Hip Ratio

It was calculated by dividing the waist circumference by the hip circumference. High waist-hip ratio was defined WHR > 0.95 in males and 0.85 in females.

Blood Pressure Measurements

Blood pressure was measured as per the recommendations of JNC VII.

Patients were also screened for skin changes like xanthoma, xanthelasma, acanthosis nigricans, striae. Thorough examination of the alimentary, cardiovascular and nervous system was done.

Biochemistry and Serology

Fasting blood samples were obtained (venous blood samples taken after overnight fast of a minimum of 8 hrs.); glucose, total cholesterol, HDL cholesterol and triglyceride levels were determined. LDL was calculated using Friedewald formula. Serum TSH and FT4 measurements were made using Roche Elecsys modular analytics E 170 using Electrochemiluminescence Immunoassay (ECLIA method). The analytical sensitivity of TSH was 0.005 μ IU/mL and for FT4 was 0.023 ng/dL.

Normal range for TSH was (0.27-4.2) μ IU/mL and for FT4 was (0.93-1.7) ng/dL.

A high serum TSH level (range between 4.2 μ IU/mL to 10 μ IU/mL) and a normal free thyroxine (FT4) level were required for the diagnosis of subclinical hypothyroidism (SCH).

Patients with high TSH (>10 μ IU/mL) and low FT4 levels (<0.93 ng/dL) were classified as being overt hypothyroid. Patients with normal TSH and FT4 were considered euthyroid.

A high sensitivity CRP (hs-CRP) was measured in each patient which detect concentrations down to 0.3 mg/L. These assays are necessary for cardiovascular risk stratification, which is based upon discrimination of CRP levels extending below 3 mg/L

- An electro cardiogram as well as a renal profile was obtained for each candidate.
- Data obtained were analysed statistically.
- Chi-square test was used to analyse the association between metabolic syndrome and hypothyroidism (overt and subclinical). Associations between patient characteristics (age, gender, smoking status, alcohol consumption, mean systolic blood pressure, mean diastolic blood pressure, waist circumference, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting blood sugar,) and hypothyroidism (overt and subclinical) in the study group were analysed using multiple logistic regression. P-value of <0.05 was considered statistically significant.

RESULTS AND DATA ANALYSIS

On completion of study of the clinical and investigative profile of the patients the analysis of the investigational data was done to derive results. Based on clinical opinion and correlating the clinical evidence with laboratory investigations (Thyroid function tests and hs-CRP), 50 patients of metabolic syndrome were divided into three groups; subclinical hypothyroid, euthyroid and overt hypothyroid.

1. Of total 50 patients taken for current study, the mean age was 47.5 ± 11.9 years. The study population consisted of 28 (56%) females and 22(44%) males. The mean BMI was 31.51 ± 5.21 kg/m². The mean systolic blood pressure was 139.04 ± 26.67 mmHg and the diastolic pressure was 88.32 ± 14.95 mmHg. Mean waist circumference was 102 ± 10.1 cm & mean waist-hip ratio was 0.97 ± 0.094 .

2. Age group distribution in study population.

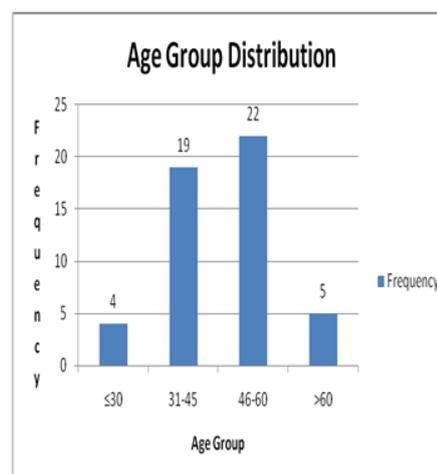


Figure 1. Age Group Distribution of Study Population

In our study, 19 patients were in age group of 31-45 years & 22 patients were in 46-60 years of age group. So, out of 50 patients, 41 were in the middle age group.

3. Age and gender wise distribution of study population.

TSH				
Gender	Euthyroid	Hypo Thyroid	Subclinical Hypothyroid	Total
Male	20	0	2	22
Female	16	3	9	28
Total	36	3	11	50

Table 1. Age and Gender Wise Distribution of Study Population

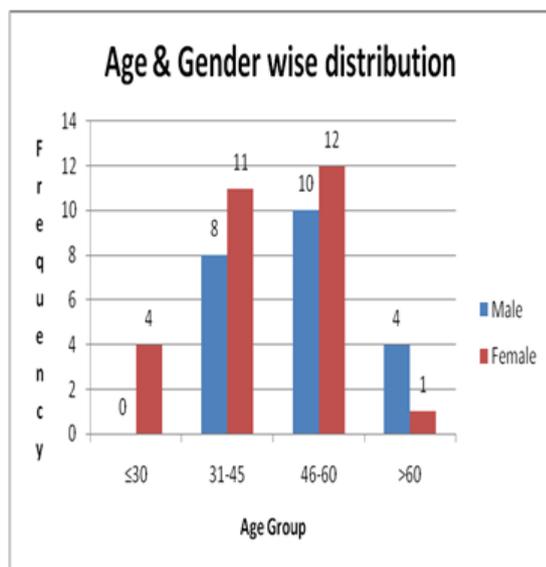


Figure 2. Age & Gender wise Distribution

4. Prevalence of subclinical hypothyroidism.

Total 50 patients of metabolic syndrome were enrolled. Out of which 36 were euthyroid, 3 were overt hypothyroid and 11 were subclinical hypothyroid. None of them had overt hyperthyroidism.

Euthyroid	36
Hypothyroid	3
Subclinical Hypothyroid	11
Total	50

Table 2. Prevalence of Subclinical Hypothyroidism

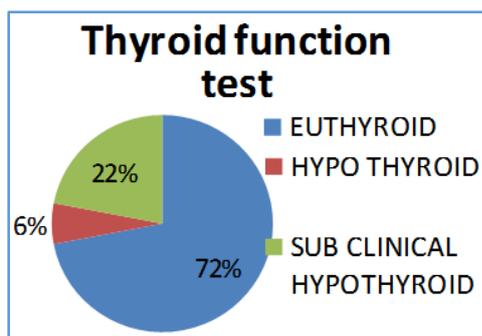


Figure 3. Prevalence of Subclinical Hypothyroidism in Study Population

In our study, prevalence of subclinical hypothyroidism was 22%, 6% were overt hypothyroid and 72% were euthyroid.

5. Thyroid functional status in metabolic syndrome with gender distribution.

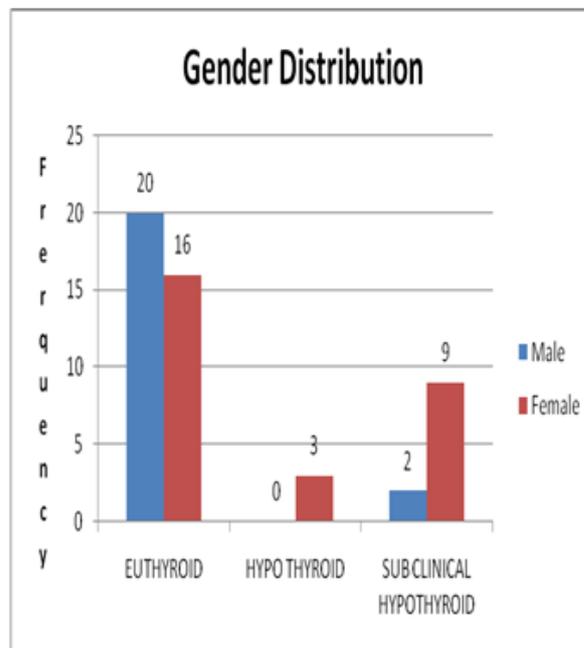


Figure 4. Thyroid Functional Status with Gender Distribution

Out of 11 patients of subclinical hypothyroidism, 9 were female and 2 were male patients.

Out of 28 females, 9(32%) were SCH while out of 22 males, 2(9%) were SCH.

6. In our study, out of 50 patients, 3 were overt hypothyroid. All 3 patients had BP >130/85, waist circumference was >88 cm and HDL of <50 mg/dL.

7. Blood pressure in study population.

BP (mm Hg)	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Total
<130/85	12	0	1	13
≥130/85	24	3	10	37
Total	36	3	11	50

Table 3. Blood Pressure in Study Population

In our study, out of 36 euthyroid patients 24 had BP >130/85 and 10 out of 11 SCH had BP >130/85mmHg.

8. Triglycerides in study population.

TG (mg/dL)	Euthyroid	Hypothyroid	Subclinical hypothyroid	Total
≤150	22	3	5	30
>150	14	0	6	20
Total	36	3	11	50

Table 4. Triglycerides in Study Population

In our study, out of 36 euthyroid patients, 14 had TG>150 mg/dL and 6 out of 11 SCH had TG>150 mg/dL.

9. Fasting blood glucose in study population.

FBG (mg/dL)	Euthyroid	Hypothyroid	Subclinical hypothyroid	Total
≤100	11	2	5	18
>100	25	1	6	32
Total	36	3	11	50

Table 5. Fasting Blood Glucose in Study Population

In our study, out of 36 euthyroid patients 25 had FBG>100 mg/dL & 6 out of 11 SCH had FBG>100 mg/dL.

10. HDL cholesterol in study population (Females).

HDL (mg/dL)	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Total
<50	15	3	8	26
≥50	1	0	1	2
Total	16	3	9	28

Table 6. HDL Cholesterol in Study Population (Females)

In our study, out of 16 euthyroid females, 15 had HDL <50 mg/dL and 8 out of 9 SCH had HDL <50 mg/dL.

11. HDL cholesterol in study population (Males).

HDL (mg/dL)	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Total
<40	8	0	1	9
≥40	12	0	1	13
Total	20	0	2	22

Table 7. HDL Cholesterol in Study Population (Males)

In our study, out of 20 euthyroid males, 8 had HDL <40 mg/dL & 1 patient of SCH had HDL <40 mg/dL.

12. Waist circumference in study population (Females).

WC (cm)	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Total
≤88	0	0	0	0
>88	16	3	9	28
Total	16	3	9	28

Table 8. Waist Circumference in Study Population (Females)

In our study, out of 16 euthyroid females all 16 had WC>88 cm & all 9 patients of SCH had WC >88cm.

13. Waist circumference in study population (Males).

WC (cm)	Euthyroid	Hypothyroid	Subclinical Hypothyroid	Total
≤102	2	0	2	4
>102	18	0	0	18
Total	20	0	2	22

Table 9. Waist Circumference in Study Population (Males)

In our study, out of 20 euthyroid males, 18 had WC>102 cm and out of 2 patients of SCH none had WC>102 cm.

14. Hs-CRP in study population.

Mean hs-CRP in patients of SCH was 6.29 ± 6.42 mg/L, while in euthyroid population it was 5.48 ± 6.07 mg/L (n=32 as, 4 patients were excluded). It was 5.71 ± 4.41 mg/L in overtly hypothyroid patients.

15. Gender wise distribution of components of metabolic syndrome is as follows.

Components of Metabolic Syndrome	Male (N=22)	Female (N=28)	Total (N=50)
Blood Pressure ≥130/85 mmHg	12	20	32
Triglycerides >150 mg/dL	13	7	20
HDL * (<50 or 40)	9	26	35
Waist Circumference **	18	28	46
Fasting Blood Glucose > 100 mg/dL	19	13	32

*HDL <40 in males, <50 in females

**Waist circumference of >102 in males, >88 in females

Table 10. Gender Wise Distribution of Components of Metabolic Syndrome

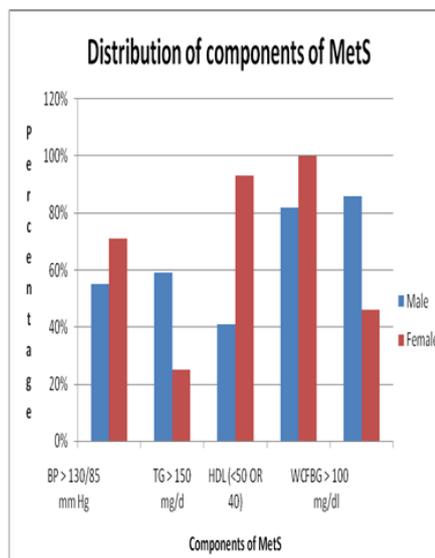


Figure 5. Gender Wise Distribution of Components of Metabolic Syndrome

In our study, amongst the components of metabolic syndrome, blood pressure >130/85, HDL <50 mg/dL & waist circumference criteria were more associated with females. While triglycerides >150 mg/dL and fasting blood glucose of >100 mg/dL were more associated with male patients.

Frequency distribution of components of metabolic syndrome

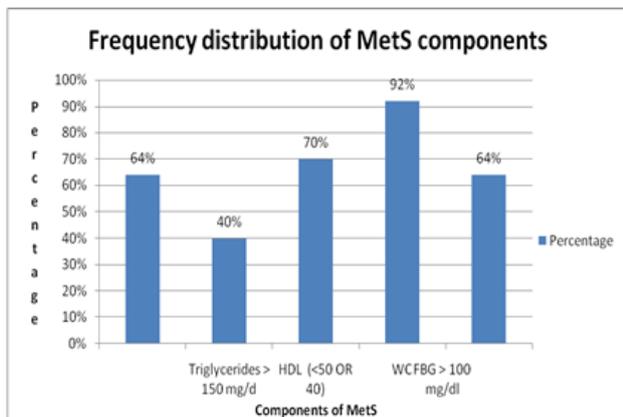


Figure 6. Frequency Distribution of MetS Components

16. Correlation of components of metabolic syndrome and thyroid function status as follows-

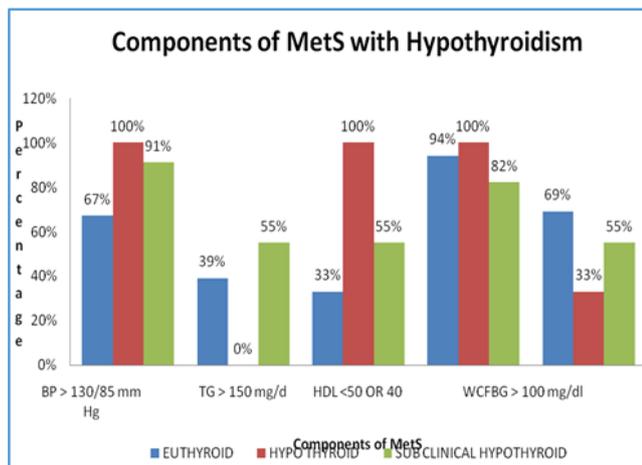


Figure 7. Correlation of Components of Metabolic Syndrome and Thyroid Function Status

Amongst the components of metabolic syndrome, blood pressure, triglycerides and HDL cholesterol levels were more associated with subclinical hypothyroidism.

DISCUSSION

Metabolic syndrome is a cluster of cardiometabolic risk factors and it is characterised by inflammation.

Epidemiological studies have shown that the metabolic syndrome occurs in a wide variety of ethnic groups including Asian Indians. The MetS is common in adult Asian Indians. 41% subjects aged more than 20 years had features of this syndrome. Its prevalence increased with age. A higher prevalence in women might be related to their higher rate of obesity.

As suggested by Stern, both cardiovascular diseases and diabetes showed common genetic and environmental antecedents, i.e., they spring from common soil. Therefore, early identification of the metabolic abnormality and appropriate intervention may be of primary importance in those populations who are having a high prevalence of these disorders. Inflammation, both acute and chronic, is an energy consuming phenomenon. To fuel the inflammatory state and sustain it, energy has to be continuously provided. Therefore, inflammatory cytokines such as TNF-alpha and various interleukins can affect insulin sensitivity locally at their site of production as well as in distant adipose tissues.

Similarly, adipokines can affect inflammation at different sites. TNF-alpha, interleukin-6, and platelets activator inhibitor are major pro-inflammatory adipokines; adiponectin has emerged as a major insulin sensitising and antifibrotic adipokine. Thus, inflammation begets insulin-resistance, and insulin-resistance perpetuates inflammation. Various studies have supported the notion of chronic inflammatory states producing insulin resistance and vice-versa. It is well established that obesity and insulin-resistance are directly related to chronic inflammation associated with atherosclerosis.

There is a strong association of rheumatoid arthritis with subclinical hypothyroidism. Cytokines depend upon the gene composition of an individual, site of adipose tissue, the type and degree of nutrients that are being consumed, hormonal factors from local areas as well as from distant organs, and site of inflammation. The activity of the insulin is modulated by both systemic counter regulatory hormones (e. g., growth hormone, thyroxin, and glucagon) as well as the above factors.

Cytokine-mediated injury to thyroid follicles could expose the enzymes on the apical border of follicles to TPO antibodies which may then bind to autoantigens and fix the complement leading to hypothyroidism. Various studies have reported the prevalence of subclinical hypothyroidism in metabolic syndromes varying from 16.4% to 26%.

The predominant functions of adipose tissue are either to store or to mobilise lipids. The degree to which each of these functions is performed depends upon the expression of an array of cytokines by adipose tissue. The adipocytokines are biologically active polypeptides that are produced either exclusively or substantially by adipocytes and act by the endocrine, paracrine, or autocrine mechanisms. Such adipokines may be broadly thought to be those that promote lipogenesis (insulin like cytokines) and those that promote lipid mobilisation (insulin-resistance promoting cytokines).

Our study revealed that the prevalence of thyroid dysfunction was more among the females with metabolic syndrome. Subclinical hypothyroidism was present in 22% of the cases and overt hypothyroidism was present in 6% of the patients. Among 22% of total cases of subclinical hypothyroidism, 82% were female and 18% were male. Uzunlulu et al also reported a high prevalence of subclinical hypothyroidism among the females with metabolic

syndrome in their series. In a study by R.V. Jayakumar et al, it was reported that 60 percent of the cases with metabolic syndrome had thyroid function abnormalities in their case series. In a study by BM Singh et al, they found a significant positive correlation between the TSH and insulin levels, as well as between the TSH and HOMA-IR (homeostasis model of assessment) levels in the female population suffering from both SCH and OH.

The Rotterdam study found a 10.8% prevalence of subclinical hypothyroidism among elderly women and the Fremantle Diabetes study found an 8.6% prevalence among women with type 2 diabetes.

In our study, out of 9 females of subclinical hypothyroidism, 7 were of more than 35 years of age. Our results were comparable with those of the abovementioned study. The incidence of thyroid dysfunction was more in patients having more than three components of the metabolic syndrome.

The HUNT study concluded that "Within the range of TSH that is considered clinically normal, increasing level of TSH was associated with less favourable lipid concentrations. The association with serum lipids was linear across the entire reference range of TSH".

With regard to other components of MetS, a low normal FT4 level was significantly associated with increased insulin resistance and SCH has been associated with fasting hyperinsulinaemia. Diastolic arterial pressure has been significantly associated with TSH levels and T4 resistance-index (freeT4. TSH product). Hence, in summary hypothyroidism is significantly associated with every individual component of metabolic syndrome.

The thyroid disease is much more prevalent in women than in men.

The prevalence of the thyroid disease in patients with diabetes is significantly higher than that in the general population.

This indicates a possible interplay between the thyroid status and insulin sensitivity. The main pathophysiological basis underlying the metabolic syndrome has been attributed to insulin resistance. Insulin resistance is a cardinal feature of type 2 diabetes mellitus and an increased risk of dyslipidaemia along with relatively frequently found mild thyroid dysfunction. Insulin resistance leads to an increased production of hepatic cholesterol and Very Low Density Lipoproteins (VLDL) and an increased HDL Cholesterol (HDL-C) clearance.

Bakker et al suggested that insulin resistance augments the deleterious effect of hypothyroidism on the lipid profile.

Subclinical Hypothyroidism (SCH) and Overt Hypothyroidism (OH) are established risk factors for insulin resistance, hyperlipidaemia, hypercoagulability and low grade inflammation.

Several studies have proved the association between insulin resistance and hypothyroidism for overt hypothyroidism, but the association between insulin resistance and subclinical hypothyroidism remains unclear. It is known that overt hypothyroidism leads to an increase

in the plasma cholesterol levels. The complex interplay between thyroid function and insulin resistance has been implicated in diabetic dyslipidaemia.

In a cross sectional study in 47 healthy euthyroid subjects, it was found that the concentrations of free Triiodothyronine (FT3) were associated with insulin production and hyperinsulinaemia.

The association between dyslipidaemia with thyroid hypofunction is well established. Over 90% of the overtly hypothyroid patients have hyperlipidaemia. The thyroid hormone is known to play a role in regulating the synthesis, metabolism, and the mobilisation of lipids.

In patients with overt hypothyroidism, there is an increase in serum total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, apolipoprotein B, lipoprotein (a) (Lp(a)) levels, and possibly, triglyceride levels. Normally, thyroid hormones increase the expression of the cell surface LDL receptors, thus leading to LDL clearance from the serum. In hypothyroidism, the depletion of the thyroid hormones leads to a reduced number of LDL receptors in the liver, thereby decreasing the biliary excretion of cholesterol, thus resulting in elevated serum LDL and VLDL levels. It also decreases the lipoprotein lipase activity and causes hypertriglyceridaemia.

Cardiovascular manifestations are frequent in thyroid dysfunction.

Overt hyperthyroidism induces a hyperdynamic cardiovascular state which is associated with an increased heart rate, enhanced left ventricular systolic and diastolic function and an increased prevalence of atrial fibrillation, whereas the opposite changes occur in overt hypothyroidism.

In our study, hs-CRP was found to be associated with subclinical hypothyroidism in patients with metabolic syndrome. Mean hs-CRP in patients of SCH was 6.29 ± 6.42 mg/L, while in euthyroid population it was 5.48 ± 6.07 mg/L. Previous published studies reflect a conflicting observation on the association between hs-CRP and hypothyroidism. Tuzcu et al and Christ-Crain et al have shown a clear association between hypothyroidism and a raised hs-CRP. In contrary, Pearce et al had shown that patients with Hashimoto's thyroiditis, short-term hypothyroidism and postpartum thyroiditis had similar hs-CRP as compared to their euthyroid controls and that hs-CRP levels may have only a limited role in the diagnosis of thyroid diseases. The study by Hueston et al also showed no difference in hs-CRP levels between patients with SCH and euthyroid individuals. The important difference between these studies and our study is that all our study patients had metabolic syndrome whereas the other studies did not address patients with metabolic syndrome.

With respect to the association between vascular disease and raised hs-CRP in hypothyroid patients, Nagasaki et al showed that hypothyroid patients with a raised hs-CRP have increased stiffness of the common carotid artery. Similarly, studies have shown hs-CRP to be an additional risk factor for cardiovascular disease in hypothyroid patients (130). The compounded

cardiovascular risk that patients with metabolic syndrome, hypothyroidism and systemic inflammation (raised hs-CRP) will suffer is yet to be determined. However, Framingham offspring study had shown that the combined cardiovascular risk in patients with metabolic syndrome and a raised hs-CRP were similar and not worse when compared to their individual risks.

Patients with subclinical hypothyroidism are at an enhanced risk for atherosclerosis and myocardial manifestations and thus, the thyroxine replacement in these patients has a beneficial effect on the low density lipoprotein cholesterol levels and the clinical symptoms of hypothyroidism. An improvement in the low density lipoprotein cholesterol levels in turn reduces the cardiovascular mortality by 9-31%.

Raising significant doubts about this estimated cardiovascular risk reduction, a recent review which analysed data from twelve trials conducted on levothyroxine replacement in subclinical hypothyroidism concluded that though thyroxine replacement improves some parameters in lipid profile and left ventricular function, this did not translate into improved survival and decreased cardiovascular morbidity. However, these trials did not address the issue of thyroxine replacement in patients with subclinical hypothyroidism in the setting of metabolic syndrome. Hence, further randomised trials have to be planned in this line to determine the efficacy of thyroxine replacement in this group of patients.

Data is again conflicting with respect to the effect of thyroxine replacement on hs-CRP levels in hypothyroid patients. In the study by Christ-Crain et al, thyroxine replacement did not alter hs-CRP levels, whereas Nagasaki et al observed a reduction of hs-CRP levels with thyroxine replacement and it predicted improvement of arterial thickness in their study cohort.

Since the prevalence of hypothyroidism (subclinical and overt) is more among females with metabolic syndrome as evident from our study, early detection and thyroxine replacement could reduce the significant cardiovascular risk in these patients. However, there is still a controversy whether the patients with subclinical hypothyroidism would be benefited from thyroxine replacement.

CONCLUSION

- Subclinical hypothyroidism was present in 22% of study population and more so in females having metabolic syndrome (32%). Hence, it will be worthwhile to screen female metabolic syndrome patients for thyroid function abnormality.
- Abnormal blood pressure, triglycerides and HDL cholesterol levels were more associated with subclinical hypothyroidism.

In our study, all patients of metabolic syndrome had raised hs-CRP levels. Hence, the role of raised hs-CRP with thyroid dysfunction could not be established.

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