

THE PRESENCE OF THYROID DYSFUNCTION IN NEWLY DETECTED METABOLIC SYNDROME PATIENTS

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ABSTRACT

BACKGROUND

The metabolic syndrome is also known as syndrome X, the insulin resistance syndrome and the deadly quartet. The constellation of metabolic abnormalities includes insulin resistance, glucose intolerance, central obesity, dyslipidaemia and hypertension, as well documented risk factors for cardiovascular disease. When grouped together, they are associated with increased risk of cardiovascular disease. The concept of metabolic syndrome exists at least 80 years. That was first described in the 1920s by Kellin, a Swedish physician as the clustering of hypertension, hyperglycaemia and gout. An overt hypothyroidism is associated with all the parameters of metabolic syndrome, except increase in fasting blood glucose.

The objectives of this study is to study the prevalence of thyroid dysfunction in the newly detected Metabolic Syndrome patients and to find out the correlation between the thyroid dysfunction and metabolic syndrome parameters.

MATERIALS AND METHODS

This is a cross-sectional study and it was conducted at Institute of Diabetology, Madras Medical College and Government General Hospital for a period of 8 months.

RESULTS

Total number of participants in this study was 60 in number. In this study group, 33 (60%) were females and 27 (40%) were males. On analysis of 60 people for the thyroid dysfunction, 8 were positive which represents 16.7% in percentage. Prevalence of hypothyroidism is 15.0% (overt hypothyroidism 3.3% and subclinical hypothyroidism 11.7%) in metabolic syndrome patients. Only one study subject among the metabolic syndrome found to have subclinical hyperthyroidism (1.7%). There were no overt hyperthyroidism patients in our study. Correlation coefficient values between FT4, TSH and metabolic parameters are not significant in our study.

CONCLUSION

One sixth of metabolic syndrome patients or every sixth metabolic syndrome had hypothyroidism either overt or subclinical. Exclude the presence of Thyroid dysfunction, while managing metabolic syndrome patients.

KEYWORDS

MS - Metabolic Syndrome, WC - Waist Circumference, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, FBS - Fasting Blood Sugar, TC - Total Cholesterol, HDL-C - High Density Lipoprotein Cholesterol, TGL - Triglycerides, LDL-C - Low Density Lipoprotein Cholesterol, FT4 - Free Thyroxine 4, TSH - Thyroid Stimulating Hormone.

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BACKGROUND

Metabolic Syndrome (MS) is a cluster of metabolic abnormalities wherein people are obese and have hypertension, high triglyceride level, low high density lipoprotein and abnormal fasting glucose levels.^(1,2) People

with metabolic syndrome are at high risk for developing cardiovascular disease.⁽³⁾ Insulin resistance is supposed to be the central pathophysiological phenomenon underlying the clustering.⁽⁴⁾

Thyroid disease is associated with atherosclerotic cardiovascular disease.⁽⁵⁻⁸⁾ This association may be in part be explained by thyroid hormone's regulation of lipid metabolism and its effect on blood pressure. Thyroid hormones have ubiquitous effects and influence the function of most organs. This hormone appears to serve as a general pacemaker accelerating metabolic process and may be associated with metabolic syndrome.⁽⁹⁾

Both metabolic syndrome and thyroid dysfunction are associated with increased risk of atherosclerotic heart disease. Little is known about the relationship between metabolic syndrome and thyroid dysfunction. Only a few small studies have been performed.^(10,11) In a cross-sectional

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study in 220 metabolic syndrome patients, it was found that subclinical hypothyroidism was prevalent in 16.4% of metabolic syndrome patients.⁽¹⁰⁾ In another study, it was found that metabolic syndrome was prevalent in thyroid dysfunction patients.⁽¹¹⁾ There is no information available in literature regarding this association in this part of the country. Therefore, the association of thyroid dysfunction with metabolic syndrome was evaluated in this study.

Although, Reaven GM already highlighted the concepts of insulin resistance and metabolic syndrome in 1988, it was not until 1998 before the first attempt for an internationally accepted definition was put forward.⁽¹²⁾ Since then several expert groups have formulated and adapted definitions.⁽¹³⁻¹⁷⁾ In an attempt to achieve some agreement on definition and to provide a tool for clinicians and researchers, a WHO consultation proposed a set of criteria. Subsequently, the National Cholesterol Education Program's Adult Treatment Panel (NCEP: ATP III) and the European Group for the Study of Insulin Resistance (EGIR) have formulated definitions. These definitions agree on essential components - glucose intolerance, obesity, hypertension and dyslipidaemia - but do differ in the detail and criteria.

IDF 2005⁽¹⁷⁾ Criteria for MS

For a person to be defined as having the metabolic syndrome they must have:

Central Obesity - waist circumference \geq 94 cm for European men and \geq 80 cm for European women.

For South Asians - Waist circumference \geq 90 for men and \geq 80 for women.⁽¹⁸⁾

Plus any two of the following four Factors

1. Raised TG level \geq 150 mg/dL or any specific treatment.
2. Reduced HDL cholesterol $<$ 40 mg/dL in males and $<$ 50 mg/dL in females.
3. Raised blood pressure \geq 130/85 mmHg or medication.
4. Raised fasting glucose \geq 100 mg/dL or previously diagnosed type 2 diabetes.

A major issue for the IDF consensus consultation was the fact that criteria used for obesity in Asian and other populations could be different from those used in the west. This issue was supported by International Obesity Task Force.⁽¹⁹⁾ They noted that in urban Asians, the body mass index range of 23 - 24 has an equivalent risk of type 2 diabetes, hypertension and dyslipidaemia as a body mass index of 25 - 29.9 in white people.

Thyroid Function and the Metabolic Syndrome

It is well documented that hypothyroidism is associated with all the parameters of metabolic syndrome, except increase in fasting blood glucose.

Obesity

The obesity (increase in waist circumference) is the important symptom and sign of hypothyroidism. More than 60% of hypothyroid patients have obesity (increase in waist circumference).⁽²⁰⁾ There is decrease in basal metabolic rate and energy metabolism in hypothyroidism.

Hypertension

In hypothyroidism, the haemodynamic alterations cause narrowing of pulse pressure, prolongation of circulation time and decrease in blood flow to the tissues. Systemic vascular resistance is increased in hypothyroidism and results in hypertension.⁽²¹⁾ Rotterdam study⁽⁶⁾ suggested that there was a two-fold increase in risk of atherosclerosis in hypothyroid patients.

Lipid Profile

Both the synthesis and degradation of lipid are depressed in hypothyroidism, the latter especially so, the net effect being one of the lipid accumulation, especially of low-density lipoprotein cholesterol and triglycerides.⁽²²⁾ The increase in serum cholesterol in hypothyroidism is accompanied by increased levels of serum phospholipids, serum triglycerides, and the low density lipoprotein cholesterol. The activity of cholesterol ester transfer protein is decreased in hypothyroidism, thus high density lipoprotein cholesterol level reduced in hypothyroidism.⁽²³⁾

Previous Related Studies

On population based study found that even in euthyroid state, thyroid hormone assay is associated with components of the metabolic syndrome.⁽²⁴⁾ In this population based study, there was a negative correlation between thyroid hormone levels (free T4 and free T3) and metabolic syndrome components, Apo B and insulin resistance levels in people with euthyroid state. Free T4 was very significantly related to four of five metabolic syndrome components - waist circumference, fasting glucose, high density cholesterol and triglycerides and insulin resistance level, which assessed by the Homeostasis Model Assessment (HOMA) model, i.e. low normal free T4 was associated with higher triglycerides, lower high density lipoprotein cholesterol, increased fasting glucose and higher waist circumference. Free T3 levels correlated well with systolic blood pressure, triglycerides and Apo-B levels. In insulin resistance individuals are more susceptible to the association of TSH with higher low density lipoprotein cholesterol and lower high density lipoprotein cholesterol.⁽²⁵⁾ The morbid obese subjects have higher level of T3, T4 and TSH, probably of the reset of their central thyrostat at higher levels.⁽²⁶⁾

In a study done by Uzunulu et al, at Japan, they have analysed the prevalence of sub-clinical hypothyroidism among 220 metabolic syndrome patients. They found that sub-clinical hypothyroidism was 16.4% prevalent in metabolic syndrome patients.⁽¹⁰⁾ One sixth of metabolic syndrome patients had sub-clinical hypothyroidism and more prevalent in female gender.

In a study from Nepal, done by Chandra L et al, found that the metabolic syndrome prevalent in 21.1% of thyroid dysfunction patients.⁽¹¹⁾ They have assessed the association of metabolic syndrome and its components with thyroid dysfunction in 100 female patients. This study found that the prevalence of overall metabolic syndrome was 32%, more in euthyroid group (21/48) than hyperthyroid group (5/24) and hypothyroid group (6/28).⁽¹¹⁾

MATERIALS AND METHODS

Setting

The study was conducted on the outpatients attending the Institute of Internal Medicine and Institute of Diabetology, Madras Medical College and Government General Hospital, Chennai. Institutional Ethical Committee approved the study.

Study Design

Single Center, non-randomised cross-sectional study.

Sample Size

In the study period of 8 months among the patients attending the Institute of Diabetology, after applying inclusion and exclusion criteria 60 patients were included in this study.

Selection of Study Subjects

The patients who fulfilled the criteria for metabolic syndrome by IDF were taken into the study. For a person to be defined as having the metabolic syndrome they must have:

1. Central obesity - waist circumference ≥ 90 cm for men and ≥ 80 cm for women.

Plus any two of the following Four Factors

2. Raised TG level ≥ 150 mgs/dL or any specific treatment.
3. Reduced HDL cholesterol < 40 mg/dL in males and < 50 mg/dL in females.
4. Raised blood pressure $\geq 130/85$ mmHg or medication.
5. Raised fasting glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes.

Inclusion Criteria

Metabolic syndrome patients not on any medications - newly detected metabolic syndrome patients.

Exclusion Criteria

1. Known Hypothyroid/Sub-clinical Hypothyroid.
2. Taking medications for DM/SHT/Thyroid Disorder.
3. Taking steroids.
4. Severely ill patients.
5. Pregnant women.
6. Individuals below 18 yrs.

Consent

All participants gave written informed consent.

Methodology

Detailed history of medication and anthropometric measurements like height, weight and waist circumference were noted in a semi-structured proforma. Blood pressure was recorded in right upper limb in sitting posture. After eight hours of fasting, blood drawn for fasting blood sugar, lipid profile and thyroid assay in a single sitting.

The fasting blood sugar was done by enzymatic colorimetric method using semi autoanalyser. The high-density lipoprotein cholesterol and triglycerides were done enzymatically on XL-300 ERBA fully automated clinical chemistry analyser. The thyroid hormone assay (TSH and FT4) were done by Chemiluminescence Immunoassay (CLIA) using ADVIA Centaur equipment.

Definitions

As per the joint statement from the American Association of Clinical Endocrinologists, the American Thyroid Association and The Endocrine Society.⁽²⁷⁾

Euthyroidism is defined as

TSH - 0.4 mU/L to 4.5 mU/L
FT4 - 0.70 ng/dL to 1.80 ng/dL

Sub-Clinical Hypothyroidism

TSH - 4.51 mU/L to 10.0 mU/L
FT4 - 0.70 ng/dL to 1.80 ng/dL

Hypothyroidism

TSH - > 10.0 mU/L
FT4 - < 0.70 ng/dL

Sub-Clinical Hyperthyroidism

TSH - 0.1 mU/L to 0.4 mU/L
FT4 - 0.70 ng/dL to 1.80 ng/dL

Hyperthyroidism

TSH - < 0.1 mU/L
FT4 - > 1.80 ng/dL

Statistical Analysis

SPSS 12 and Excel were used for data analysis.

RESULTS

Population Characteristics

Among the 60 patients included in our study, 27 patients were men accounting for 45% of the total cases. The remaining 33 patients were (55%) women.

According to the age, patients between 30 and 39 years of age were 15 in number (25%). Majority of the patients were in the age group between 40 and 49 years - 28 patients (47% of study population) were in this group; 11 patients (18%) were between the age of 50 and 59 years; 6 patients (10%) were above the age of 60. Population characteristics are shown in Table 1.

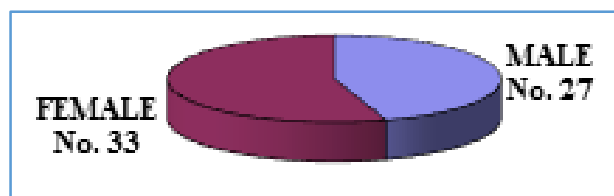


Figure 1. Sex Wise Population Characteristics

| Age | Total No. | Percentage | Male | Female |
|---------|-----------|------------|------|--------|
| 30 - 39 | 15 | 25% | 6 | 9 |
| 40 - 49 | 28 | 47% | 14 | 14 |
| 50 - 59 | 11 | 18% | 1 | 10 |
| 60 - 69 | 6 | 10% | 6 | 0 |

Table 1. Population Characteristics

According to the metabolic syndrome parameters, in the included 60 members in the study 19 fulfilled three among five metabolic syndrome parameters criteria. Another 19 members fulfilled four metabolic syndrome parameters criteria and the rest of 22 members fulfilled all the metabolic syndrome criteria.

Thyroid Function Test Results

The TSH in this study was ranging from 0.17 mU/L to 150 mU/L and free T4 levels ranging from 0.16 ng/dL to 1.68 ng/dL. Patients were grouped into four groups according to the definitions based on TSH and FT4 levels and further statistical analysis was done based on these groups.

According to our definitions, 50 patients found to be euthyroid and two patients were hypothyroid. Seven patients had sub-clinical hypothyroidism and one patient had sub-clinical hyperthyroidism. There were no overt hyperthyroid patients in our study.

| Group | No. | % | Male | Female |
|---------------------------|-----|--------|------|--------|
| Euthyroid | 50 | 83.33% | 26 | 24 |
| Hypothyroid | 2 | 3.33% | 1 | 1 |
| Sub-clinical Hypothyroid | 7 | 11.67% | 0 | 7 |
| Sub-clinical Hyperthyroid | 1 | 1.67% | 0 | 1 |
| Hyperthyroidism | 0 | 0 | 0 | 0 |

Table 2. Thyroid Dysfunction

The thyroid dysfunction is 16.7% prevalent in metabolic syndrome patients. Among the thyroid dysfunction, sub-clinical hypothyroidism is highly prevalent - 11.7%. The hypothyroidism is 3.3% prevalent in metabolic syndrome patients (one patient had TSH levels of more than 150 mU/L) and sub-clinical hyperthyroidism is 1.7% prevalent. There were no overt hyperthyroidism patients in our study.

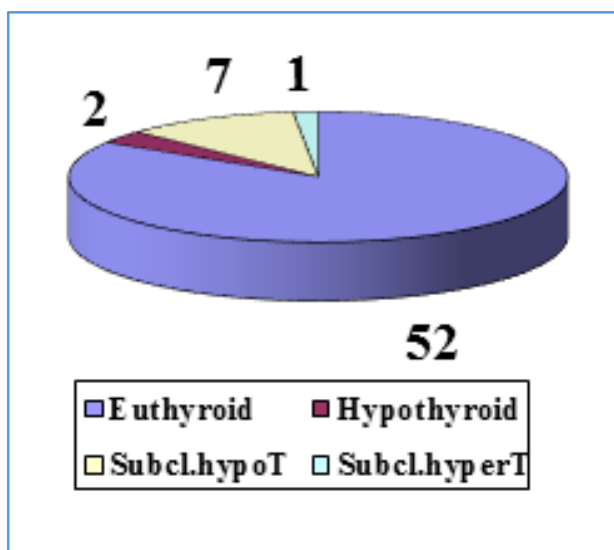


Figure 2. Thyroid Dysfunction

According to the age patient's age between 30 and 39 years were 15 in number, among them one patient had frank hypothyroidism and one patient had sub-clinical hypothyroidism. In the 40 - 49 age group, 4 patients had sub-clinical hypothyroidism and one patient had sub-clinical hyperthyroidism. In the 50 - 59 years' age group, one patient had frank hypothyroidism and two patients had sub-clinical hypothyroidism. In the above at the age of 60, all 6 patients were normal.

| Age | Total No. | Euthyroid | Hypo-Thyroid | Sub-Clinical Hypo-thyroid | Sub-Clinical Hyper-thyroid |
|---------|-----------|-----------|--------------|---------------------------|----------------------------|
| 30 - 39 | 15 | 13 | 1 | 1 | 0 |
| 40 - 49 | 28 | 23 | 0 | 4 | 1 |
| 50 - 59 | 11 | 8 | 1 | 2 | 0 |
| 60 - 69 | 6 | 6 | 0 | 0 | 0 |

Table 3. Age Wise Thyroid Dysfunction

Based on the metabolic syndrome criteria, of those patients who fulfilled three of the five risk factors three had thyroid dysfunction; of the patients who had four risk factors, two had thyroid dysfunction; of the patients who had all five risk factors, five had thyroid dysfunction.

| MS Criteria Fulfilled | Total No. | Euthyroid | Hypo-Thyroid | Sub-Clinical Hypo-thyroid | Sub-Clinical Hyper-thyroid |
|-----------------------|-----------|-----------|--------------|---------------------------|----------------------------|
| 3 | 19 | 16 | 1 | 2 | 0 |
| 4 | 19 | 17 | 0 | 1 | 1 |
| 5 | 22 | 17 | 1 | 4 | 0 |

Table 4. Metabolic Syndrome Parameters Wise Thyroid Dysfunction

(P valve = 0.36 not significant)

As there were a considerable number of patients only in both euthyroid group (50) and sub-clinical hypothyroid group (7), both groups were analysed statistically using student t-test. But these analyses were not statistically significant, as they were very small no. of individuals in both sub-groups and variants are very high in both sub-groups. Correlation between the FT4, TSH and metabolic parameters were also analysed.

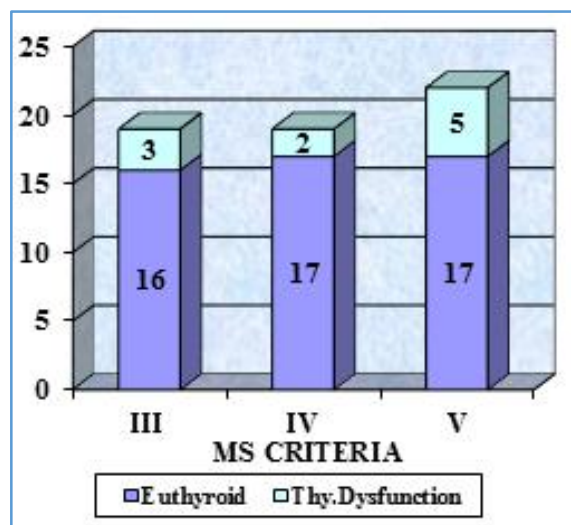


Figure 3. Metabolic Syndrome Parameters Wise Thyroid Dysfunction

| MS Parameters | Euthyroid | | Sub-Clinical Hypothyroidism | | P Value |
|---------------|-----------|--------|-----------------------------|-------|---------|
| | Mean | SD | Mean | SD | |
| WC | 97.16 | 6.98 | 98.57 | 8.32 | 0.626 |
| SBP | 139.88 | 14.14 | 140.29 | 14.40 | 0.944 |
| DBP | 89.52 | 7.28 | 88.29 | 9.20 | 0.689 |
| FBS | 158.28 | 51.04 | 141.43 | 37.82 | 0.405 |
| HDL | 43.46 | 6.25 | 43.43 | 4.58 | 0.990 |
| TGL | 234.20 | 170.18 | 185.57 | 93.75 | 0.434 |

Table 5. Distribution of Thyroid Dysfunction

(P valve > 0.05 not significant at 5% level)

As there were small no. of patients with very high variants, statistically significant results were not found.

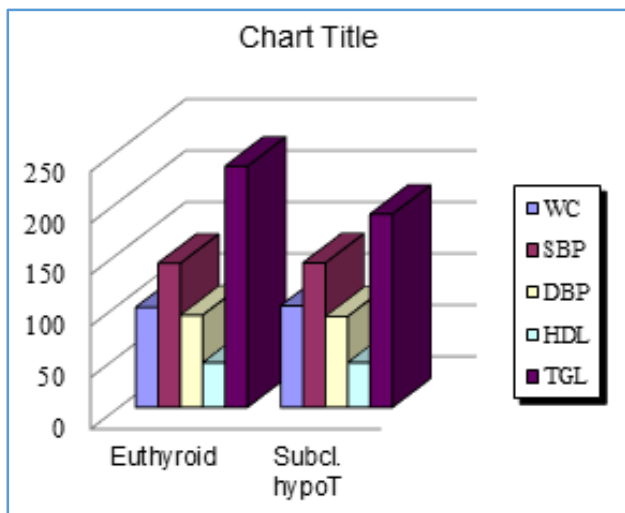


Figure 4. Distribution of Thyroid Dysfunction

| MS | FT4 | P Value | TSH | P Value |
|-----|-------|---------|--------|---------|
| WC | 0.243 | 0.08 | -0.029 | 0.839 |
| SBP | 0.078 | 0.59 | 0.076 | 0.60 |
| DBP | 0.125 | 0.38 | -0.416 | 0.77 |
| FBS | 0.175 | 0.22 | -0.095 | 0.59 |
| HDL | 0.067 | 0.64 | -0.108 | 0.45 |
| TGL | 0.056 | 0.69 | -0.066 | 0.30 |

Table 6. Correlation between FT4, TSH and Metabolic Syndrome Parameters in Euthyroid Patients

(P value > 0.05 not significant at 5% level)

| MS | FT4 | P Value | TSH | P Value |
|-----|--------|---------|--------|---------|
| WC | 0.650 | 0.11 | -0.577 | 0.17 |
| SBP | 0.514 | 0.23 | -0.511 | 0.24 |
| DBP | -0.049 | 0.91 | 0.060 | 0.89 |
| FBS | 0.741 | 0.05 | -0.576 | 0.17 |
| HDL | 0.460 | 0.29 | -0.249 | 0.58 |
| TGL | -0.104 | 0.82 | -0.134 | 0.77 |

Table 7. Correlation between FT4, TSH and Metabolic Syndrome Parameters in Sub-Clinical Hypothyroid Patients

(P value > 0.05 not significant at 5% level)

Correlation coefficient values between FT4, TSH and metabolic parameters are not significant in our study, because of limited number of study subjects and variants are high.

CONCLUSION

In our study population, we found that presence of thyroid dysfunction in 16.7% of newly detected metabolic syndrome patients. Prevalence of hypothyroidism is 15.0% (overt hypothyroidism 3.3% and sub-clinical hypothyroidism 11.7%) in newly detected metabolic syndrome study patients, which is higher than that of thyroid dysfunction in general population. One-sixth of metabolic syndrome patients or every sixth metabolic syndrome had hypothyroidism, either overt or subclinical. Herewith, we recommend routine screening of thyroid dysfunction in all newly detected thyroid dysfunction patients and exclude the presence of thyroid

dysfunction, while managing existing metabolic syndrome patients.

DISCUSSION

The metabolic syndrome is a cluster of metabolic abnormalities wherein people are obese and have hypertension, high triglyceride level, low high density lipoprotein cholesterol and abnormal fasting glucose levels.⁽⁴⁾ People with metabolic syndrome are at high risk for developing cardiovascular disease and type 2 diabetes. Hypothyroidism is associated with lipid abnormalities like high triglycerides and low high density lipoproteins, weight gain, glucose intolerance and hypertension. Thus, hypothyroidism mimics the parameters of metabolic syndrome.

In this study, thyroid dysfunction prevalence is 16.7% among metabolic syndrome patients. Hypothyroidism is 15% prevalent in metabolic syndrome patients (overt hypothyroidism 3.3% and sub-clinical hypothyroidism 11.7%). The prevalence of thyroid dysfunction and hypothyroidism in metabolic syndrome patients are higher than the prevalence in normal population, which is 5.9% for thyroid dysfunction and 4.6% for hypothyroidism (0.3% overt and 4.3% sub-clinical hypothyroidism).⁽²⁸⁾ This study is consistent with study done by Uzunulu et al, as 16.4% of metabolic syndrome patients had hypothyroidism in Japan.⁽¹⁰⁾ In this study, prevalence of sub-clinical hyperthyroidism is 1.7% and there is no overt or clinical hyperthyroidism.

In this study, one-sixth of metabolic syndrome patients or every sixth patient with metabolic syndrome has hypothyroidism. In these hypothyroidism patients, treatment with levothyroxine replacement reverses the symptoms and signs of hypothyroidism, thereby those factors which mimic metabolic syndrome.

It is well known and proven that by treating with levothyroxine replacement in all overt or clinical hypothyroid patients, we can reduce all the metabolic parameters and cardiovascular risk. There is some controversy in treating sub-clinical hypothyroidism patients.^(29,30,31)

Management of patients' sub-clinical hypothyroidism remain controversial, because the body of scientific evidence available to guide clinical decision is limited. The risk of progression from subclinical hypothyroidism to overt hypothyroid is 2% - 5% per year.⁽³²⁾ A meta-analysis report shows that levothyroxine therapy in individuals with sub-clinical hypothyroidism lowers mean serum total and low density cholesterol concentration significantly and the reduction in serum cholesterol may be larger in individuals with higher pre-treatment cholesterol levels.⁽³³⁾ Another double-blind placebo-controlled trial (Basal Thyroid Study) shows that an important risk reduction of cardiovascular mortality of 9% - 31% possible by improvement in low density lipoprotein cholesterol in sub-clinical hypothyroidism patients treated with levothyroxine therapy.^(34,35) Surks et al recommends treating sub-clinical hypothyroidism associated with type 2 diabetes and hypertension in his scientific review. As the metabolic syndrome patients have hyperlipidaemia, diabetes, hypertension and increased cardiovascular risk, it looks logical to treat metabolic syndrome patients having sub-clinical hypothyroidism by levothyroxine replacement therapy. While there appears to be no adverse effects of

initiating levothyroxine treatment in this setting, inadvertent overtreatment occurs in 14% - 21% of levothyroxine treated patients⁽³⁶⁾ carrying potential risks of osteoporosis and atrial fibrillation when serum TSH falls below 0.1 mU/L. These patients need frequent thyroid function tests to avoid this complication. Latest evidences suggest that Metformin induces a reduction in TSH levels, both in overt and in subclinical hypothyroidism.⁽³⁷⁾ Since Metformin is the treatment of choice for Metabolic syndrome and as the evidences suggest Metformin may reduce the TSH level, Metformin is the preferred drug for newly detected metabolic syndrome patients with subclinical hypothyroidism.

This study shows that the prevalence of thyroid dysfunction in metabolic syndrome patients is higher than in normal subjects. One sixth of metabolic syndrome patients or every sixth metabolic syndrome had hypothyroidism either overt or subclinical. This finding indicates a need for investigating the presence of Thyroid dysfunction during managing metabolic syndrome patients. As shown in previous evidences, managing these hypothyroid in metabolic syndrome patients are rewarding by improvement in the metabolic parameters and reducing cardiovascular risk.

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