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# Association of Metabolic Syndrome with Thyroid Dysfunction.

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**ABSTRACT**

The metabolic syndrome (MetSyn) is one of the major public health issues of this century, which is constellation of physical condition and metabolic abnormalities commonly associated with increased risk for development of Type 2 Diabetic Mellitus, cardiovascular disease and other medical condition.Obesity, insulin resistance, physical inactivity, advanced age and hormonal imbalance are suggested the risk factors of MetSyn. Thyroid hormone plays an important role in regulating energy homeostasis, glucose and lipid metabolism.We aimed to investigate the relationship between the thyroid dysfunction and components of the metabolic syndrome. One hundred eighty eight consecutive study subjects were enrolled in this study.Waist circumference and blood pressure were recorded using calibrated instruments. Fasting blood glucose, triglyceride, high-density lipoprotein (HDL) cholesterol and thyroid hormones were measured in fasting venous blood samples from all patients. Data were expressed in frequency, percentage, mean and standard deviation. Chi-square test, independent t test and Pearson's correlation were applied according the nature of data to test the significance at 95% confidence interval.Out of 188 study subjects, 49 (26.06%) were male and 139 (79.93%) female. About one third the study participant were diagnosed as Met Syn. Around two-third of the study subjects were euthyroid followed by 10.10 % hyperthyroid and 22.34 % hypothyroid.Systolic blood pressure and serum triglyceride were significantly different in Met Syn hypothyroid group as compared to the euthyroid Met Syn group as well as hyperthyroid Met Syn group. Free triiodothyronine and fT4 were significantly positively correlated with fasting glucose (r=0.236, p=0.001, r=0.159, p=0.03 respectively).Thyroid dysfunction were associated with an increased risk of Met Syn in the study population.

**Keywords:**Components of Metabolic Syndrome, NCEP ATP III, Metabolic syndrome, Thyroid dysfunction, Waist circumference

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## INTRODUCTION

The metabolic syndrome (Met Syn) is one of the major public health issues of this century. It is constellation of physical conditions and metabolic abnormalities commonly found in association with increased risk for development of type 2 diabetes mellitus (T2DM), cardiovascular disease and other medical conditions.[1] If current trend continues, the premature death and disabilities resulting from these conditions in both developed and developing countries will increase the financial burden on them. Several expert groups have attempted to define diagnostic criteria for the metabolic syndrome. The World Health Organization (WHO) developed a definition in 1998 stating that individual need to show evidence of insulin resistance and at least two of four factors should be present namely–hypertension, hyperlipidemia, obesity and microalbuminuria. In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment panel (ATP III) suggested another definition for the Met Syn, according to which as least three of five factors should be present for the diagnosis. The five factors/components are increased waist circumference, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hypertension (130/85mmHg) and fasting glucose of ≥110 mg/dL.[2]

Obesity, insulin resistance, physical inactivity, advanced age and hormonal imbalance has been suggested as the underlying risk factors for the development of metabolic syndrome.[3] Thyroid hormones play an important role in regulation of energy homeostasis, glucose and lipid metabolism. Thyroid functions affect Met Syn parameters including HDL cholesterol, triglycerides (TG), blood pressure and plasma glucose.Overt hypothyroidism leads to an increase in plasma cholesterol levels and blood pressure and subclinical hypothyroidism showed comparable but less pronounced association.[4] Thyroid function and components of metabolic syndrome are influenced by genetic, geographic, dietary and other factors.This study aimed to investigate the relationship between the thyroid dysfunction and components of the metabolic syndrome in the patients visiting to B. P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal for thyroid function testing.

## MATERIALS AND METHODS

A hospital based cross-sectional study conducted in the Department of Biochemistry, BPKIHS,in collaboration with Department of Internal Medicinein the period ofone year. One hundred and eighty eight patients fulfilling inclusion and exclusion criteria were included in the study with their consent. Patients diagnosed with known diabetes, severe liver, heart and kidney failure, receiving any medication that may alter thyroid function and lipid metabolism, pregnant women and with an abdominal mass or asciteswere excludedfrom this study. A structured questionnaire used to collect the demographic variables of all study participants.Anthropometric measurements (height, weight, waist circumference) and blood pressure measured using the calibrated instruments. After 8 to 12 hours, fasting venous blood samples collected by venipuncture in all the subjects into a plain vial. Serum separated by centrifugation (Remi Research centrifuge, Model R-23) at 2500 rpm for 15 minutes.Serum divided into two aliquots for further analysis, one aliquots for thyroid function tests (fT3, fT4, TSH) and another for Triglycerides, HDL-c and fasting glucose estimation.Competitive ELISA used to measure serum fT3 and fT4andmeasured Sandwich ELISAfor serum TSH estimation (HUMAN Kit, Germany). Fasting Glucose, triglycerides and HDL-c were assayed using random access discrete clinical chemistry analyzer (MERK, Vitalab Selectra E).Ethical clearance obtained from Institutional Review Committee, BPKIHSas per institutional guideline.

## RESULTS

One hundred eighty eight subjects were enrolled in this study, out of them 49 (26.06%) were male and 139 (79.93%) female. The male and female ratio was 1.283. Studysubjects were divided into two groups, i.e. metabolic syndrome (Met Syn) and Non Metabolic Syndrome (Non Met Syn) based on the components of the metabolic syndrome.About one third the study participant were diagnosed as Met Syn out of them 4.78% (n=9)were male and 27.65% (n=52) were female.Based on the thyroid function test, study subjects were classified into euthyroid, hyperthyroid and hypothyroid group. Around two-third of the study subjects were euthyroid followed by 10.10 % (n=19) hyperthyroid and 22.34% (n=42) hypothyroid.Among these groups metabolic syndrome was found more common in euthyroid (n=41) and hypothyroid (n=18) as compared to hyperthyroid (n=2) (Table 1).

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**Table 1: Comparison of metabolic syndrome in thyroid groups.**

| | Met Syn (n=61) | Non Met Syn (n=127) | p Value* |
|---|---|---|---|
| **Euthyroid** | 41 (67.21%) | 86 (67.71%) | <0.05 |
| **Hyperthyroid** | 2 (3.27%) | 17 (13.38%) | |
| **Hypothyroid** | 18 (29.50%) | 24 (18.89%) | |

* Chi-square test was appliedto test the significance considering p<0.05 at 95% confidence interval.

In hyperthyroid group, both non-metabolic syndrome and metabolic syndrome groups had increased $fT_3$ and $fT_4$ levels where as TSH was significantly decreased as compared to euthyroid group. In hypothyroid group, both non-metabolic syndrome and metabolic syndrome groups had decreased $fT_3$ and $fT_4$ levels where as TSH was significantly increased as compared to euthyroid group. This difference was statistically significant (p<0.05) as depicted in Table 2.

**Table 2 Thyroid function tests between the metabolic syndrome and non-metabolic syndrome subjects.**

| Thyroid Status | | $fT_3$ (pg/mL) | $fT_4$ (ng/dL) | TSH (mIU/L) |
|---|---|---|---|---|
| **Euthyroid** | **Non Met Syn** | 2.987 ± 0.54 | 1.51 ± 0.26 | 3.08 ± 1.57 |
| | **Met Syn** | 2.81 ± 0.61 | 1.50 ± 0.27 | 3.45 ± 1.77 |
| **Hyperthyroid** | **Non Met Syn** | 7.68 ± 3.91* | 4.03 ± 1.91* | 0.18 ± 0.11* |
| | **Met Syn** | 8.87 ± 5.33* | 2.97 ± 0.81* | 0.17 ± 0.13* |
| **Hypothyroid** | **Non Met Syn** | 2.98 ± 0.76 | 1.29 ± 0.29 | 14.09 ± 10.18* |
| | **Met Syn** | 2.70 ± 0.66 | 1.44 ± 0.33 | 11.70 ± 8.93* |

* Independent t test was applied to test the significance considering p <0.05 at 95% confidence interval.

Systolic blood pressure and serum triglyceride weresignificantly increased in metabolic syndrome hypothyroid group as compared to the euthyroid metabolic syndrome group (133.06±12.50 mmHg vs 129.90±10.03 mmHg, p<0.05 and 276.11±241.95 mg/dL vs 251.34±184.30 mg/dL, p<0.05).Rest of the components of the metabolic syndrome were comparable in both groups. Similarly, serum serum triglyceride was significantly decreased in metabolic syndrome hyperthyroid group as compared to the euthyroid metabolic syndrome group(102.00±53.75 mg/dL vs 251.34±184.30 mg/dL, p<0.05) and other components were comparable but statistically not significant different. Comparisons of the components of metabolic syndrome in hypothyroid and hyperthyroid metabolic syndrome group found that systolic blood pressure and serum triglyceride were statistically significant difference between these two groups (133.06±12.50 mmHg vs 120.00±14.14 mmHg, p<0.05 and 276.11±241.95 mg/dL vs 102.00±53.75 mg/dL, p<0.05). and rest of the components were comparable. Comparisons of the components of the metabolic syndrome in euthyroid, hypothyroid and hyperthyroid groups as depicted in table 3.

**Table 3: Comparison of components of metabolic syndrome in euthyroid, hyperthyroid and hypothyroid groups.**

| Components of Met Syn | Euthyroid | | Hypothyroid | | Hyperthyroid | |
|---|---|---|---|---|---|---|
| | Non Met Syn | Met Syn | Non Met Syn | Met Syn | Non Met Syn | Met Syn |
| **WC (Inch)** | 31.07±4.59 | 35.07± 4.02 | 32.57±4.67 | 34.17± 4.75 | 29.76 ±3.80 | 34.50±4.95 |
| **SBP (mmHg)** | 122.15±11.34 | 129.10±10.03 | 119.17±8.16 | 133.06±12.50* | 117.35±7.10 | 120.00±14.14 * |
| **DBP (mmHg)** | 80.00±8.98 | 86.46 ±6.35 | 79.38 ±8.25 | 88.06 ±7.88 | 78.24 ±5.57 | 85.00 ±7.07 |
| **FG (mg/dL)** | 86.58 ±13.84 | 116.29±45.89 | 85.88±10.99 | 110.28±52.06 | 104.29±27.47 | 187.50 ±84.15 |
| **TG (mg/dL)** | 117.81±55.80 | 251.34±184.30 * | 114.75±52.20 | 276.11±241.95 * | 122.47±53.70 | 102.00±53.75 * |
| **HDL-C (mg/dL)** | 40.05 ±1.78 | 40.73 ±1.58 | 40.21 ±1.59 | 40.89 ±2.00 | 39.59 ±2.29 | 39.00 ±2.83 |

* Independent t test was applied to test the significance considering p <0.05 at 95% confidence interval.

Free triiodothyronine was negatively but statistically not significantly correlated with waist-circumference, systolic blood pressure, diastolic blood pressure, triglycerides and HDL cholesterol but significant positive correlation was found with fasting glucose (r=0.236, p=0.001). Similar finding was observed in fT4 except in systolic blood pressure (r=-0.144, p=0.049) and fasting glucose (r=0.159, p=0.03).TSH showed positive correlation with waist-circumference, systolic blood pressure, diastolic blood pressure, triglycerides and HDL cholesterol and showed negative correlation with fasting glucose (r=-0.006, p=0.940) (table 4).

**Table 4: Correlation of fT3, fT4 and TSH with the components of metabolic syndrome.**

| Particulars | fT3 (ng/mL) | fT4 (ng/dL) | TSH (mIU/L) |
|---|---|---|---|
| **WC (Inch)** | r=-0.114, p=0.12 | r=-0.085, p=0.248 | r=0.096, p=0.192 |
| **SBP (mmHg)** | r=-0.182, p=0.13 | **r=-0.144, p=0.049** | r=0.089, p=0.225 |
| **DBP (mmHg)** | r=-0.140, p=0.05 | r=-0.095, p= 0.195 | r=0.103, p=0.158 |
| **FG (mg/dL)** | **r=0.236, p=0.001** | **r=0.159, p=0.03** | r=-0.006, p=0.940 |
| **TG (mg/dL)** | r=-0.103, p=0.159 | r=-0.065, p=0.375 | r=0.106, p=0.148 |
| **HDL-C (mg/dL)** | r=-0.142, p=0.052 | r=-0.142, p=0.052 | r=0.010, p=0.893 |

* Pearson's correlation was applied to test the correlation between the variables considering p <0.05 at 95% as statistically significant.

## DISCUSSION

Metabolic syndrome is a complex diseased condition characterized by several abnormalities including central obesity, impaired glucose tolerance, hypertension, low high-density lipoprotein cholesterol (HDL-C) level and hypertriglyceridemia. Insulin resistance is supposed to be the central pathophysiological phenomenon underline this clustering. The insulin resistance has characteristics of endocrine and metabolic disturbances along with inflammatory and prothrombic state. Thyroid has ubiquitous effects, influences in the function of most organs, and markedly stimulates the basic metabolic rate and the metabolism of carbohydrate, lipids and proteins. Cardiovascular system is very sensitive to thyroid function and both hyperthyroidism and hypothyroidism mostly presented as cardiovascular manifestation. On the other hand, the relation between metabolic syndrome and thyroid dysfunction is not clearly identified yet. The results ofthis study revealed a various effect of thyroid status on the components of metabolic syndrome.

The percentage of metabolic syndrome in male and female were 4.78% and 27.65% respectively and the overall percentage of metabolic syndrome was 32.43%.Out of total 188 study subjects, 127, 19 and 42 were in euthyroid, hyperthyroid and hypothyroid groups respectively. Among these groups metabolic syndrome was found more common in euthyroid groups (n = 41) followed by hypothyroid (n = 18) and hyperthyroid (n = 2). This finding is comparable to the study done by Uzunlulu et al.[5] Both overt and subclinical hypothyroidism unfavorably affects biochemical parameters.[4]and reported that these abnormalities can be reversed by levothyroxine replacement therapy.[6, 7] Similar study done in female subjects in same settings revealed that, hyperthyroidism is protective for the development of metabolic syndrome.[5] It shows that the influences of thyroid function on lipid metabolism extend in to the euthyroid range.

Serum triglyceride is significantly increased in metabolic syndrome group in both euthyroid and hypothyroid but significantly decreased in hyperthyroid in comparison to non-metabolic syndrome group. Other components were not statistically significant. This result is consistent with previous study.[8] The combination of deranged triglycerides and HDL-c level is the hallmark of metabolic syndrome and can be explained through the metabolic pathway. Thyroid hormone has significant effect on the synthesis, mobilization and degradation of lipids, especially degradation affected more than synthesis during thyroid hormone excess. This results in a decrease in the storage of lipids and an increase in plasma concentration and finally increased synthesis of TG in liver because of increased availability of free fatty acids, glycerol mobilized from adipose tissues.[9]Free triiodothyronine and fT4 showed significant positive correlation with fasting blood glucose but statistically not significant negatively correlation with waist-circumference, systolic and diastolic blood pressure, triglycerides and HDL cholesterol. TSH showed positive correlation with waist-circumference, systolic and diastolic blood pressure, triglycerides and HDL cholesterol but negatively correlated with fasting glucose.

Thyroid hormones have pleitropic effects upon regulation of energy homeostasis, lipid and glucose metabolism.[10-13] We evaluated a potential relationship between serum thyroid hormone levels and metabolic syndrome because hypothyroidism and hyperthyroidism are likely to change behavior and physical activity, and may obviate the relationship between thyroid hormones and components of Met Syn.[14, 15]Several possible explanations were proposed for this association. Firstly, it could be possible that thyroid hormones may play a role in the development of Met Syn. Insulin resistance generally considered the basis of Met Syn, and there is a positive relationship between numbers of Met Syn components and severity of insulin resistance.[16] Secondly, it could be possible that underlying pathogenetic factors in the Met Syn led to low circulating free thyroxine levels. Recently, chronic inflammation was proposed as important etiologic factor. Increased adipose tissue and circulating levels of inflammatory cytokines, including tumor necrosis factor and interleukin-6 in obese and diabetic subjects.[17] In patients with nonthyroid illness, thyroid function was suppressed by activated cytokines, as negative correlation was observed .between circulating thyroid hormones and cytokine concentrations.[18] Finally, several epidemiologic studies have shown that Met Syn poses a significant risk for atherosclerosis, even higher than diabetes mellitus.[19]Thyroid hormones could increase cardiac oxygen consumption and whole blood volume, both of which might exacerbate the heart workload, lowered thyroid hormone levels would then become an adaptive response of human bodies to the preexisting cardiovascular disorders.[20]

## CONCLUSIONS

It is conclusion, thyroid dysfunction is associated with an increased risk of Met Syn in the Nepalese population. It can be postulate that a maladaptive thyroid hormone response affecting the components of Met Syn may lead to it, T2DM, coronary artery disease and more metabolic abnormalities.

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