ORIGINAL ARTICLE

RELATIONSHIP OF THYROID-STIMULATING HORMONE WITH METABOLIC SYNDROME IN A SAMPLE OF EUTHYROID PAKISTANI POPULATION

Muhammad Shahzad Saleem, Tanvir Ali Khan Shirwany*, Khurshid Ahmad Khan**

Department of Physiology, Shalamar Medical & Dental College, *Pakistan Red Crescent Medical & Dental College, **Allama Iqbal Medical College, Lahore, Pakistan

Background: Metabolic Syndrome is a group of factors that predispose to cardiovascular diseases. The prevalence of metabolic syndrome is rising rapidly. Recently, a few studies have suggested that lower thyroid function in the reference range may be associated with metabolic syndrome, but the issue remains unsettled. We aimed to elucidate the relationship between thyroid function and components of metabolic syndrome in a sample of euthyroid Pakistani population. **Methods:** This analytical, cross-sectional study was conducted at the Department of Physiology, University of Health Sciences, Lahore, Pakistan, and extended over a period of 12 months. It included 100 subjects with metabolic syndrome in the study group and thirty subjects without metabolic syndrome in the control group with age ranging 45–55 years. Both groups had normal thyroid function. After a detailed history and clinical examination, fasting blood was analysed for glucose, triglycerides, high density lipoprotein-cholesterol along with thyroid-stimulating hormone (TSH) and free thyroxine. **Results:** Serum TSH was significantly higher in study group than in control group (p=0.040). Serum free thyroxine values of study group were slightly but not significantly lower than those of control group. Serum TSH correlated significantly and positively with serum triglycerides in all subjects and with waist circumference and diastolic blood pressure in men. Serum TSH showed a positive and linear relationship with the number of components of metabolic syndrome (p=0.016) in all subjects. **Conclusion:** High-normal TSH is associated with metabolic syndrome and its components. There may be increased risk of cardiovascular diseases with high-normal TSH levels.

Keywords: Thyroid Stimulating Hormone, Metabolic Syndrome, Euthyroid

INTRODUCTION

Metabolic syndrome[1] (MS) is a group of risk factors that predispose to cardiovascular diseases (CVD). They include: central obesity, raised triglycerides (TG), low high-density lipoprotein cholesterol (HDL-C), raised blood pressure (BP) and raised fasting blood glucose. Presence of three or more of these risk factors indicates MS. It is also associated with a pro-thrombotic and a pro-inflammatory state.[2]

The MS has reached epidemic proportions in most countries.[3] Prevalence of MS in USA has been found to be 23.7%.[4] It is becoming one of the major health issues in developing countries including those of Asia which increasingly have chronic non-communicable diseases along with infectious diseases and under-nutrition. Prevalence of MS in Pakistan ranges between 18–46%.[5] Metabolic syndrome was found to be highly prevalent (77.2%) in an urban Indian diabetic cohort with greater prevalence in women than men.[6]

The increasing prevalence of MS is related to increase in obesity due to increasing caloric consumption and sedentary lifestyles.[7,8] Excess abdominal fat is more closely related to components of MS than total body fat. This is specially the case in Asian population, who may have a predisposition to abdominal obesity.[9] Insulin resistance is a common underlying pathogenic mechanism. It has been suggested that TG levels and TG/HDL-C ratio are surrogate markers for insulin resistance.[10] Also, multiple products are released from white adipose tissue, which have been implicated in development of MS. These include: non-esterified fatty acids (NEFAs), inflammatory cytokines, plasminogen activator inhibitor-1 and resistin.[11]

Variants of a number of genes affecting lipid and glucose metabolism, like the genes for β_3-adrenergic receptor, lipoprotein lipase and hormone sensitive lipase may increase the risk of MS.[12] Genetic predisposition interacting with environmental influences could plausibly lead to development of MS.[13]

It has been shown that MS and its components are associated with higher risk of cardiovascular diseases.[14] CVD has become the leading cause of death in many developing countries and 80% of worldwide deaths from CVD occur in these countries.[15]

Thyroid hormones affect lipid metabolism, carbohydrate metabolism, blood pressure and energy homeostasis.[16,17] Studies have given evidence of these effects of thyroid hormones in thyroid disease and recent data have suggested that there may be some association between serum thyroid function in the normal range and components of MS.[18]

Thyroid-stimulating hormone (TSH) correlates directly with insulin resistance, TG and indirectly with HDL-C in subjects within normal thyroid function.[19] Decreasing thyroid function in the normal range is associated with occurrence of obesity and hence can potentially contribute to the development of MS.[20] TSH levels were found to be significantly associated with MS in post-menopausal Korean women, who had normal thyroid function.[21] A cross-sectional study on South Indian patients demonstrated an association between hypothyroidism (overt and sub-clinical) and MS and showed that women with MS are at greater risk of developing hypothyroidism.[22]

The above limited evidence indicates that lower thyroid function in the reference range may be associated with MS. We proposed to elucidate the relationship of thyroid function with components of metabolic syndrome in euthyroid Pakistani subjects.

MATERIAL AND METHODS

This was an analytical, cross-sectional study that extended over a period of 12 months (from February 2009 to January 2010). It was conducted at the Department of Physiology, University of Health Sciences, Lahore, Pakistan. One hundred subjects with MS comprised the study group and 30 subjects without MS were in the control group. Age range was 45–55 years, both groups were clinically euthyroid and had normal thyroid function. Three or more of the following five criteria indicated MS[2]:

- Raised BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg) or drug treatment for raised BP.
- Central obesity (waist circumference ≥90 Cm in men and ≥80 Cm in women).
- Raised fasting blood glucose (≥100 mg/dl) or drug treatment for raised blood glucose.
- Raised serum TG (≥150 mg/dl).
- Low serum HDL-C (<40 mg/dl in men and <50 mg/dl in women).

Reference ranges for thyroid function tests[23]:

- Serum TSH: 0.465–4.68 mIU/l
- Serum free T_4: 10–28.2 ρmol/l

Subjects with thyroid disease, those with history of thyroid drug use, history of steroid use and those who have had thyroid surgery were excluded from the study. History was obtained from the subjects and clinical examination was conducted. Systolic and diastolic BP was measured after 5 minute rest. Waist circumference was measured at the level of top of the iliac crest in a horizontal plane, at the end of normal expiration.[2]

Five ml of venous blood was drawn in the morning after an overnight fast of 8–12 hours. Serum was separated after centrifugation, aliquoted and stored at a temperature of -80 °C until analysis.

Glucose level was measured on the day of sample collection by glucose oxidase method using Microlab® 300 semi automated analyser. Serum TG and HDL-C were measured by enzymatic-colorimetric technique using kits by AMP Diagnostics in Metrolab® 2300 automated analyser. Serum TSH and free T_4 levels were measured by immunodiagnostic method using kits by Ortho-Clinical Diagnostics, Johnson and Johnson, High Wycombe, United Kingdom, in Vitros® EciQ analyser. All subjects gave written informed consent to participate in the study.

The data were analysed using SPSS-16. Qualitative variables were expressed as percentage (%). The non-normally distributed quantitative variables were expressed as median (Interquartile Range: IQR) and the normally distributed quantitative variable was expressed as Mean±SEM. Chi-square test, Mann-Whitney U-test and independent-samples *t*-test were applied to observe group differences. Spearman's rank correlation was applied to observe correlations, $p<0.05$ was considered as statistically significant.

RESULTS

There were no significant differences between the median age of the study and control groups ($p=0.671$). Distribution of men and women along with menopausal status of the women in the study and control groups was not significantly different ($p>0.05$). Significantly greater number of subjects in the study group had history of diabetes, raised BP and dyslipidemia ($p<0.001$). History of CVD was present in 3% of study group subjects but none in the control group. This difference was not statistically significant ($p=0.340$). Subjects in the study group had significantly higher family history of diabetes and hypertension compared to the control group ($p=0.002$ and 0.005 respectively). Abdominal obesity was present in 94% of study group, and 66.70% of the control group subjects. This difference was statistically significant ($p<0.001$) (Table-1).

Median (IQR) waist circumference was significantly greater in the study group as compared to the control group ($p=0.003$). Median systolic BP, diastolic BP and fasting serum glucose were significantly higher in study group ($p<0.001$) when compared to the control group. Median serum TG were markedly higher in study group than in control group. This difference was statistically significant ($p<0.001$). Median (IQR) serum HDL-C in study group was 42.99 (38.11–48.22) mg/dl and in control group was 42.34 (38.14–56.23) mg/dl. This difference was not statistically significant ($p=0.270$). Median serum TG/HDL-C ratio was higher in study group compared to control group. This difference was statistically significant ($p<0.001$).

Median serum TSH was higher in study group than in control group. This difference was statistically significant ($p=0.040$). Mean±SEM serum free T_4 values of study group were 15.08±0.21 ρmol/l while those of

control group were 15.17±0.38 ρmol/l. This difference was not statistically significant (p=0.840) (Figure-1, Table-1).

Serum TSH had statistically significant positive correlation with serum TG but had statistically insignificant correlation with HDL-C. The correlation in all subjects, of serum TSH with waist circumference, SBP, DBP and serum glucose was statistically insignificant (Table-2).

Spearman's rank correlation analysis in men (n=56) showed statistically significant positive correlation of serum TSH with waist circumference and DBP, but no significant correlation was seen with SBP, serum glucose, serum TG and serum HDL-C (Table-3).

Spearman's rank correlation analysis in women (n=74) showed that serum TSH had statistically significant positive correlation with serum TG but had no significant correlation with waist circumference, SBP, DBP, serum glucose and serum HDL-C (Table-4).

Serum TSH showed statistically significant positive correlation with serum TG/HDL-C ratio in study group but not in control group. Serum TSH had statistically significant positive correlation with the number of components of MS of all subjects. As TSH values increased in a linear fashion, the number of components of MS increased (Figure-2).

Table-1: Baseline characteristics of the study and control groups

		Study group (n=100)	Control group (n=30)	*p*
Age (Years)		48 (46–51)	49.00 (46–52)	0.671
Gender	Male (%)	43	43.30	0.974
	Female (%)	57	56.70	0.974
Post menopausal (%)		43.86	47.06	0.816
History of Diabetes/IGT (%)		71	0	<0.001***
History of raised BP (%)		89	13.33	<0.001***
History of dyslipidemia (%)		56	3.33	<0.001***
History of CVD (%)		3	0	0.340
Family history of diabetes (%)		46	16.67	0.002**
Family history of hypertension (%)		34	10.00	0.005**
Abdominal Obesity (%)		94	66.70	<0.001***
Waist Circumference (Cm)		98 (93.25–104)	90 (84–100.5)	0.003**
Systolic BP (mmHg)		130 (130–150)	112.50 (110–121.25)	<0.001***
Diastolic BP (mmHg)		90 (80–90)	80 (70–80)	<0.001***
Serum Glucose (mg/dl)		134.50 (100.75–177.50)	78 (73–86.5)	<0.001***
Serum TG(mg/dl)		163.75 (132.28–251.12)	96.16 (75.98–152.35)	<0.001***
Serum HDL-C (mg/dl)		42.99 (38.11–48.22)	42.34 (38.14–56.23)	0.270
Serum TG/HDL-C ratio		4.17 (2.84–6.02)	2.45 (1.77–3.11)	<0.001***
Serum TSH (mIU/l)		1.80 (1.14–2.32)	1.61 (1.05–1.84)	0.040*
Serum free T_4 (ρmol/l)		15.08 ±0.21	15.17 ±0.38	0.840

Data are given as %, median (IQR) or Mean±SEM
*Significant at the 0.05 level, **Significant at 0.01 level, ***Significant at 0.001 level

Table-2: Correlation between serum TSH and components of MS in all subjects

	Serum TSH	
	Correlation Coefficient	*p*
Waist Circumference (cm)	0.118	0.180
Systolic BP (mm Hg)	0.001	0.989
Diastolic BP (mm Hg)	0.100	0.255
Serum Glucose (mg/dl)	0.019	0.830
Serum TG (mg/dl)	0.282	0.001**
Serum HDL-C (mg/dl)	-0.167	0.057

**Significant at 0.01 level

Table-3: Correlation between serum TSH and components of MS in men

	Serum TSH	
	Correlation Coefficient	*p*
Waist Circumference (cm)	0.314	0.018*
Systolic BP (mm Hg)	0.121	0.374
Diastolic BP (mm Hg)	0.361	0.006**
Serum Glucose (mg/dl)	0.019	0.830
Serum TG (mg/dl)	0.150	0.269
Serum HDL-C (mg/dl)	-0.101	0.460

*Significant at 0.05 level. **Significant at 0.01 level

Table-4: Correlation between serum TSH and components of MS in women

	Serum TSH	
	Correlation Coefficient	*p*
Waist Circumference (cm)	0.001	0.991
Systolic BP (mm Hg)	-0.106	0.369
Diastolic BP (mm Hg)	-0.097	0.410
Serum Glucose (mg/dl)	-0.039	0.742
Serum TG (mg/dl)	0.345	0.003**
Serum HDL-C (mg/dl)	-0.210	0.072

**Significant at 0.01 level

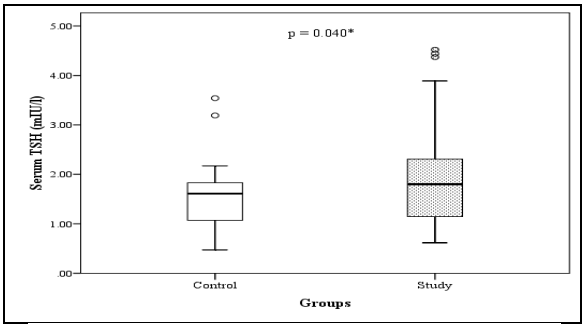

Figure-1: Comparison of median (IQR) serum TSH level of the study and control groups
(*significant at 0.05 level)

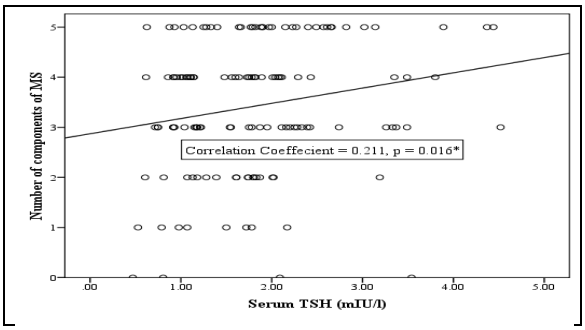

Figure-2: Correlation between TSH and number of components of MS in all subjects
*Significant at 0.05 level

DISCUSSION

Thyroid function affects lipid metabolism, carbohydrate metabolism and blood pressure which are also affected in MS.[16,17] Studies have given evidence that thyroid function is associated with MS in thyroid disease, and recently a few studies have suggested that this association may extend into the normal reference range of thyroid function.[18].

Serum TG and TG/HDL-C ratio, which are surrogate markers for insulin resistance[10], were significantly elevated in study group compared to control group. This indicates that the study group may have greater insulin resistance than the control group. Insulin resistance is said to be a common underlying abnormality in MS.[11] Roos *et al*[18] and Fernandez *et al*[24] demonstrated that TSH is associated with insulin resistance. Our study supports this observation.

In our study, TSH levels significantly positively correlated with waist circumference in men. Thyroid hormones affect thermogenesis[16] and body energy expenditure, so a lower thyroid function (free T_4) may potentially lead to obesity and associated increased waist circumference. Roos *et al*[18] showed a positive relationship of low normal thyroid function with waist circumference in both men and women.

Our study also showed that TSH levels significantly positively correlated with DBP in men. Low thyroid function can increase peripheral vascular resistance and activate the sympatho-adrenal system, leading to increase in BP, particularly DBP.[17] In the study by Park *et al*[21], correlation analysis showed a positive relationship of TSH with BP, in postmenopausal women.

In our study, TSH levels significantly positively correlated with TG levels in all subjects. This may be due to impaired lipolysis which accompanies increased TSH levels.[19] This confirms the finding of Fernandez *et al.*[24] However, Kim *et al*[25] showed that low normal thyroid function (free T_4) is negatively related to TG levels. The present study also showed positive correlation of serum TSH with serum TG in women. Park *et al*[21] showed similar finding in women but their subjects were postmenopausal, while our study included both pre- and postmenopausal subjects. Our study showed no correlation of serum TSH with serum HDL-C. Other studies[18,21,26] have also shown that thyroid function (free T_4 or TSH) is not related to HDL-C. Our study also showed that free T_4 correlated inversely with TSH, as expected. This is in keeping with the findings of Fernandez *et al*.[24]

Our study showed that TSH was significantly higher in the subjects with MS compared to those without MS. Free T_4 levels were not significantly different between the study and control groups. Park *et al*[21] also showed that TSH was associated with MS, but that study was done in postmenopausal women and did not include a control group.

Thyroid-stimulating hormone correlated positively with waist circumference and DBP in men, with TG in women, and in all subjects. So the relationship between TSH and MS and its components was different according to gender. This has also been shown in a previous study done in Chinese population.[25]

Our study has demonstrated that thyroid function decreased as the number of components of MS increased. This implies that subjects with lower thyroid function had greater number of components of MS. Therefore thyroid function in the low-normal range was related to increased presence of MS. A relationship between thyroid function (free T_4) and number of components of MS was shown by Lin *et al* in Chinese population.[26] Our study has shown a similar relationship but with thyroid function parameter of TSH instead of free T_4.

A higher history of CVD was seen in the study group compared to the control group, but the difference was insignificant and a relationship between TSH and CVD was not demonstrated. A prospective study including a large cohort may show a relationship of TSH with CVD.[27]

Thyroid-stimulating hormone is a much more sensitive indicator of thyroid function than thyroxine. Even very small changes in thyroid hormone levels lead to marked shift in TSH level. This would explain the presence of a relationship of MS with TSH but not with thyroxine in our subjects.[28]

There were several possible reasons for the presence of the positive relationship between low-normal thyroid function (high-normal TSH) and MS. One possibility was that low-normal thyroid function may have led to development of MS. Insulin resistance, which is said to be an underlying abnormality in MS, is enhanced by lower thyroid function. It has been demonstrated that thyroid hormones activate and stimulate the expression of some important candidates for regulating insulin sensitivity, including uncoupling protein, β-2 adrenergic receptor and peroxisome proliferator-activated receptor γ.[24,26] The stimulation of insulin sensitivity by thyroid hormones may only occur in the physiological range of thyroid function and hyperthyroidism could reduce insulin sensitivity.[26,29,30]

Another plausible explanation could be that a pathogenic abnormality of MS leads to low thyroid function.[26] Chronic inflammation has been proposed to be an important factor in the aetiology of insulin resistance and MS. Increased inflammatory cytokine levels including those of IL-6 and TNF-α were found in subjects with obesity and MS[11,26] Study by Shantha *et al*[22] on South Indian subjects showed that subjects with MS, who had sub-clinical hypothyroidism had a significantly elevated inflammatory marker (high

sensitivity C reactive protein). In non-thyroidal illness, inflammatory cytokines suppressed thyroid function by acting at the hypothalamic-pituitary or thyroid level.[26,31] Chronic inflammation in our subjects with MS may have suppressed their thyroid function.

The relationship between thyroid function and MS could be indirect, through a common underlying factor, which may have led to simultaneous changes in thyroid function and in components of MS. This factor could be genetic[24,25] or environmental.[24,25,32,33]

Our study has limitations. It is cross-sectional in design, so a causal relationship between low-normal thyroid function and MS cannot be ascertained. The sample size is small. Direct measures of insulin resistance were not undertaken in this study. However MS is a well known clinical expression of insulin resistance, which we studied. We also determined serum TG and TG/HDL-C ratio, which are recognised surrogate markers for insulin resistance. Systemic inflammatory markers like IL1, IL6 and TNF-α were not measured. We did not measure, blood tri-iodothyronine levels, the active form of thyroid hormone in tissues.[34] Tri-iodothyronine acts in association with insulin to modulate glucose and lipid homeostasis.[35]

CONCLUSIONS

Our results showed significantly higher serum TSH levels in subjects with MS compared to those without MS. Serum TSH correlated positively with components of MS. High-normal TSH is associated with MS and its components. There may be increased cardiovascular risk with high-normal TSH.

Future larger studies should also include direct measures of insulin resistance along with determination of inflammatory markers and blood tri-iodothyronine levels to further elaborate the relationship between thyroid function and MS.

ACKNOWLEDGEMENTS

The authors are thankful to the subjects for their participation in the study, staff of University of Health Sciences, and all other colleagues for their facilitation. The study was supported by a grant from the University of Health Sciences.

REFERENCES

1. Dysmetabolic syndrome X; Metabolic syndrome; code 277.7; [cited 27th July 2009] Available from: http://icd9cm.chrisendres.com/index.php?action=child&recordid=2128.
2. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel HR, Franklin BA *et al*. Diagnosis and management of the metabolic syndrome: an American heart association/ national heart, lung and blood institute scientific statement: executive summary. Circ 2005;112:285–90.
3. Grundy SM. Metabolic syndrome pandemic. Arterioscler Thromb Vasc Biol 2008;28:629.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. JAMA 2002;287:356–9.
5. Basit A, Shera AS. Prevalence of metabolic syndrome in Pakistan. Metabolic Syndrome and Related Disorders 2008;6(3):171–5.
6. Surana SP, Shah DB, Gala K, Susheja S, Hoskote SS, Gill N *et al*. Prevalence of metabolic syndrome in an urban Indian diabetic population using the NCEP ATP III guidelines. Journal of Association of Physicians of India 2008;56:865–8.
7. Mehboob F, Majeed MZ, Zaman SM. An impact of lifestyle and obesity on diabetes, hypertension and hyperlipidemia. J Fatima Jinnah Med Coll Lahore 2007;1:59–63.
8. Bonow RO, Eckel RH. Diet, obesity, and cardiovascular risk. N Engl J Med 2003;348:2057–8.
9. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world -a growing challenge. N Engl J Med 2007;356:213–5.
10. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med 2003;139:802–9.
11. Reaven G. Metabolic syndrome: pathophysiology and implications for management of cardiovascular disease. Circulation 2002;106:286–8.
12. Groop L. Genetics of the metabolic syndrome. British Journal of Nutrition 2000;83, Suppl.1:S39–48.
13. Roche HM, Phillips C, Gibney MJ. The metabolic syndrome: the crossroads of diet and genetics. Proceedings of the Nutrition Society 2005;64:371–7.
14. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, *et al*. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–9.
15. Reddy KS. Cardiovascular disease in non-western countries. N Eng J Med 2004;350:2438–40.
16. Krotkiewski M. Thyroid hormones in the pathogenesis and treatment of obesity. European Journal of Pharmacology 2002;440:85–98.
17. Fommei E, Iervasi G. The role of thyroid hormone in blood pressure homeostasis: evidence from short-term hypothyroidism in humans. J Clin Endocrinol Metab 2002;87:1996–2000.
18. Roos A, Bakker SJL, Links TP, Gans ROB and Wolffenbuttel BHR. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab 2007;92:491–6.
19. Asvold BO, Vatten LJ, Nilsen TIL, Bjoro T. The association between TSH within the reference range and serum lipid concentrations in a population based study, The HUNT study. European Journal of Endocrinology 2007;156:181–6.
20. Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesene L, *et al*. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab 2005;90:4019–24.
21. Park HT, Cho GJ, Ahn KH, Shin JH, Hong SC, Kim T, *et al*. Thyroid stimulating hormone is associated with metabolic syndrome in euthyroid post menopausal women. Maturitas 2009;62:301–5.
22. Shantha GPS, Kumar AA, Jeyachandran V, Rajamanickam D, Rajkumar K, Salim S, *et al*. Association between primary hypothyroidism and metabolic syndrome and the role of C reactive protein: a cross-sectional study from South India. Thyroid research 2009;2:2.
23. Ortho Clinical Diagnostics [homepage on the internet]; Vitros® immunodiagnostic products; FT4 and TSH reagent packs: instructions for use [cited Jan 21, 2008]; Available from: http://apps.orthoclinical.com/IFU/ContentPages/IntlSearchPage.aspx?culture=en-gb
24. Fernandez-Real JM, Lopez-Bermejo A, Castro A, Casamitjana R, Ricart W. Thyroid function is intrinsically linked to insulin sensitivity and endothelium-dependent vasodilation in healthy euthyroid subjects. J Clin Endocrinol Metab 2006;91:3337–43.

25. Kim BJ, Kim TY, Koh JM, Kim HK, Park JY, Lee KU, *et al*. Relationship between serum free T4 (FT4) levels and metabolic syndrome (MS) and its components in healthy euthyroid subjects. Clinical Endocrinology 2009;70:152–60.
26. Lin SY, Wang YY, Liu PH, Lai WA, Sheu WH-H. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. Metabolism: clinical and experimental 2005;54:1524–8.
27. Asvold BO, Bjoro T, Nilsen TIL, Gunnell D, Vatten LJ. Thyrotropin levels and risk of fatal coronary heart disease. Arch Intern Med 2008;168:855–60.
28. Goichot B, Sapin R, Schlienger JL. Subclinical hyperthyroidism: considerations in defining the lower limit of the thyrotropin reference interval. Clinical Chemistry 2009;55:420–4.
29. Al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. J Clin Endocrinol Metab 1997;82:1118–25.
30. Torrance CJ, Devente JE, Jones JP, Dohm GL. Effects of thyroid hormone on GLUT 4 glucose transporter gene expression and NIDDM in rats. Endocrinology 1997;138:1204–14.
31. Boelen A, Schiphorst MCP-T, Wiersinga WM. Soluble cytokine receptors and the low 3,5,3'-triiodothyronine syndrome in patients with non-thyroidal disease. J Clin Endocrinol Metab 1995;80:971–6.
32. Asvold BO, Bjoro T, Nilsen TIL, Vatten LJ. Tobacco smoking and thyroid function. Arch Intern Med 2007;167:1428–32.
33. Sari R, Balci MK, Altunbas H, Karayalcin U. The effect of body weight and weight loss on thyroid volume and function in obese women. Clinical Endocrinology 2003;59:258–62.
34. Brent GA. The molecular basis of thyroid hormone action. N Eng J Med 1994;331:847–53.
35. Kim SR, Talbott EA, Tull E, Vogt M, Andersen S, Kuller LH. Contribution of abnormalities of thyroid hormones to type 2 diabetes. Diabetes Care 2000;23:260–1.

Address for Correspondence:

Dr. Muhammad Shahzad Saleem, Department of Physiology, Shalamar Medical & Dental College, Lahore, Pakistan.
Cell: +92-345-4151578
E**mail:** mayo0052000@yahoo.com