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Full Length Research paper

Correlation of serum free thyroxine with components of metabolic syndrome in euthyroid South Asian men and women

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Metabolic syndrome is a combination of risk factors for cardiovascular disease, whose prevalence is rising rapidly. Recently, a few studies have suggested that serum thyroxine, even in the reference range, may be associated with components of metabolic syndrome. However, this issue remains to be settled and has not been explored in the Pakistani population. So, we aimed to determine serum free thyroxine level and its relationship, if any, with components of metabolic syndrome in a euthyroid local population. This analytical, cross-sectional study included 130 euthyroid subjects (age range of 45 to 55 years). The subjects had their history taken and underwent clinical examination, after which, fasting blood was analysed for free thyroxine and thyroid stimulating hormone (chemiluminescence), along with glucose, triglycerides and high density lipoprotein cholesterol (using enzymatic methods). Free thyroxine showed a positive correlation with systolic and diastolic blood pressure in all subjects and with serum glucose in males, which was statistically significant (p = 0.022, p = 0.005 and p = 0.032, respectively). However, the correlation of serum free thyroxine with waist circumference, serum triglycerides and high-density lipoprotein cholesterol in males and with all components of metabolic syndrome in females was not significant. These results indicate that high-normal free thyroxine may be associated with raised blood pressure in all subjects and with raised glucose in males. Larger studies need to be done in Pakistani population to confirm our findings.

Key words: Free thyroxine, metabolic syndrome, correlation, euthyroid.

INTRODUCTION

Metabolic syndrome (MS) (Dysmetabolic syndrome X, ICD10CM, 2012) is a combination of risk factors for cardiovascular disease (CVD). Its diagnosis is indicated by the presence of at least three of the following five components: abdominal obesity, raised glucose, raised blood pressure (BP), raised triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) (Grundy et al., 2005). MS has become epidemic in most countries (Grundy, 2008). Prevalence of MS in the Greek population is 17.9% according to the National Cholesterol Education Program definition (Pitsavos, 2008). It is becoming one of the major public health problems in developing countries (Mohan and Deepa, 2006). A study on a group of urban Pakistanis found a prevalence of 34.8% (Alvi et al., 2011). The prevalence of MS in Iran is reported to be 41.6% according to the latest criteria (Delavari et al., 2009). The increasing MS prevalence is associated with excess consumption of calories and sedentary habits (Saidie, 2005; Bonow and Eckel, 2003). Asian populations are particularly susceptible to developing MS (Hossain et al., 2007). Insulin resistance is a common underlying causative mechanism (McLaughlin et al., 2003). Studies have indicated that MS and its components are linked to higher risk of CVD (Galassi et al., 2006).

Thyroid hormones have significant effects on energy balance, BP, metabolism of carbohydrates and lipids,

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which are also deranged in MS (Ayturk et al., 2009). Interestingly, recent studies have pointed to the fact that there may be some relationship between thyroid hormones and components of MS even in euthyroid individuals (Kim et al., 2009). Serum free thyroxine (T4) level in the normal range is inversely related to abdominal obesity and directly related to elevated BP, elevated fasting glucose and HDL-C levels; this relationship between serum free T4 and components of MS varies with age and gender (Kim et al., 2009; Roos et al., 2007). MS and insulin resistance is related to low free T4 in subjects with normal thyroid function and free T4 also has a significant negative association with total cholesterol and TG (Lin et al., 2005; Fernandez-Real et al., 2006).

The above limited evidence indicates that free T4 in the reference range may be associated with components of MS. However, little data is available on this association, particularly in South Asia. We proposed to elucidate the relationship of serum free T4 with components of metabolic syndrome (raised glucose, BP, TG, abdominal obesity and low HDL-C) in euthyroid South Asians of Pakistan.

MATERIALS AND METHODS

This analytical, cross sectional was conducted at the Department of Physiology, University of Health Sciences, Lahore, Pakistan. It comprised 130 euthyroid subjects (age range of 45 - 55 years), whose sampling was done by the non-probability, purposive technique. Subjects with history of thyroid disease, thyroid surgery, use of thyroid drugs and steroids were excluded from the study.

Definition of MS

Any three of the following five criteria (Grundy et al., 2005) indicated the presence of MS in our subjects: elevated BP (≥130 mm Hg systolic and ≥85 mm Hg diastolic) or drug treatment for elevated BP, central obesity (waist circumference ≥90 cm in men and ≥80 cm in women), elevated serum TG (≥150 mg/dl), low serum HDL-C (<40 mg/dl in men and <50 mg/dl in women) and elevated fasting blood glucose (≥100 mg/dl) or drug treatment for elevated blood glucose.

Reference ranges for thyroid function tests

According Ortho Clinical Diagnostics (2012), the reference range was given as: Serum TSH, 0.465-4.68 mIU/L and serum free T4: 10-28.2 pmol/L.

Data and sample collection

Each subject underwent a detailed history and clinical examination. BP was measured from the right arm of the subject in the sitting position after a rest of 5 min. Three BP readings were taken, the mean of which was recorded. Waist circumference was measured at a level of the top of the iliac crest in a horizontal plane, at the end of normal expiration (Grundy et al., 2005). In brief, 5 ml of venous blood was obtained in the morning following an overnight fast of 8 to 12 h and collected in vacutainer tubes. The serum was separated by centrifugation at 3000 revolutions per minute for 10 to 15 min, aliquoted and stored at a temperature of -80℃ until analysis.

Blood analysis

Glucose level was measured on the day of sample collection by the glucose oxidase method using kits by AMP Diagnostics (AMP Medizintechnik GmbH, Graz, Austria) in Microlab 300 (Merck) semi-automated analyzer. Serum TG was measured by an enzymatic-colorimetric technique using kits by AMP Diagnostics (AMP Medizintechnik GmbH, Graz, Austria) in Metrolab 2300 automated analyzer (Ortho Clinical Diagnostics, 2012; Burtis et al., 2006).

Serum HDL-C was measured by a direct enzymatic method (immunoinhibition technique) using kits by AMP Diagnostics (AMP Medizintechnik GmbH, Graz, Austria) in Metrolab 2300 automated analyzer. Serum TSH and free T4 levels were measured immunodiagnostically using kits (REF 148 7249 and 172 8872, respectively) by Ortho-Clinical Diagnostics, Johnson and Johnson, High Wycombe, United Kingdom, VITROS EciQ analyzer.

Ethical considerations

The study was conducted as per the Helsinki declaration of human rights (The World Medical Association homepage, 2012) and was approved by the ethical review committee of the University of Health Sciences, Lahore, Pakistan. Written informed consent was given by each subject for participation in the study.

Statistical analysis

The collected data was entered and analysed using Statistical Package for the Social Sciences (SPSS) version 16 software. Qualitative variables were expressed as percentage (%). Shapiro-Wilk test showed that our quantitative variables were not normally distributed except for serum free T4. So, the non-normally distributed quantitative variables were expressed as median (interquartile range: IQR) and the normally distributed quantitative variable was expressed as mean ± standard error of the mean (SEM). Spearman rank correlation was applied to observe correlations. A p value of <0.05 was considered as statistically significant.

RESULTS

As shown in Table 1, the median (IQR) age of the subjects (N = 130) was 48.00 (46.00 - 51.25) years. The gender distribution of the study subjects included 42.30% males and 57.70% females (Table 1). Moreover, the median (IQR) waist circumference of the subjects was 97 (90 - 103) cm. The median (IQR) systolic BP, diastolic BP and serum glucose were 130 (120 - 140) mm Hg, 80 (80 - 90) mm Hg and 113.50 (82.75-157.25) mg/dl, respectively. As also indicated in Table 1, the median (IQR) serum TG and HDL-C status of the subjects was 156.30 (105.08-230.25) mg/dl and 42.97 (38.14-48.43) mg/dl, respectively. Overall, 77% of all the subjects had MS (Table 1). The median (IQR) serum TSH of our subjects was 1.76 (1.13-2.21) mIU/L, while the mean ± SEM serum free T4 was 15.10 ± 0.18 pmol/L, as listed in Table 1.

Table 1. Baseline characteristics of the subjects.

Characteristics		Values (N =130)
Age (years)		48.00 (46.00 - 51.25)
Gender	Male (%)	42.30
	Female (%)	57.70
Waist Circumference (cm)		97 (90 - 103)
Systolic BP (mm Hg)		130 (120 - 140)
Diastolic BP (mm Hg)		80 (80 - 90)
Serum Glucose (mg/dl)		113.50 (82.75 - 157.25)
Serum TG (mg/dl)		156.30 (105.08 - 230.25)
Serum HDL-C (mg/dl)		42.97 (38.14 - 48.43)
MS (%)		77
Serum TSH (mIU/L)		1.76 (1.13 - 2.21)
Serum free T4 (pmol/l)		15.10 ± 0.18

Data are given as percentage (%), median (IQR) or mean ± SEM.

Table 2. Correlation between serum free T4 and components of MS in all subjects.

Components of MS	Serum free T4	
	Correlation coefficient	p value†
Waist Circumference	0.005	0.957
Systolic BP	0.200	0.022*
Diastolic BP	0.243	0.005**
Serum Glucose	0.172	0.05
Serum TG	- 0.132	0.134
Serum HDL-C	0.122	0.165

†Determined by Spearman rank correlation. *Significant at 0.05 level. **Significant at 0.01 level.

Spearman rank correlation analysis in all subjects showed that serum free T4 had statistically significant positive correlation with systolic BP (correlation coefficient = 0.200, p = 0.022) and diastolic BP (correlation coefficient = 0.243, p = 0.005) in all subjects (N = 130) (Table 2). However, the correlation of serum free T4 with waist circumference, serum glucose, serum TG and serum HDL-C in all subjects was statistically insignificant (correlation coefficient = 0.005, p = 0.957; correlation coefficient = 0.172, p = 0.05; correlation coefficient = -0.132, p = 0.134; correlation coefficient = 0.122, p = 0.165 respectively). Correlation analysis in males (N = 55) showed that serum free T4 had a significantly positive relationship with systolic BP, diastolic BP and serum glucose (correlation coefficient = 0.302, p = 0.023; correlation coefficient = 0.330, p = 0.013 and correlation coefficient = 0.287, p = 0.032, respectively) (Table 3). Serum free T4 had statistically insignificant correlation with waist circumference, serum TG and serum HDL-C (correlation coefficient = 0.060, p = 0.659; correlation coefficient = -0.087, p = 0.526 and correlation coefficient = 0.133, p = 0.328 respectively) (Table 3).

Additionally, Spearman rank correlation analysis in females (N = 75) showed serum free T4 to have no significant relationship with waist circumference (correlation coefficient = - 0.032, p = 0.784), systolic BP (correlation coefficient = 0.138, p = 0.242), diastolic BP (correlation coefficient = 0.201, p = 0.086), serum glucose (correlation coefficient = 0.086, p = 0.464), serum TG (correlation coefficient = -0.172, p = 0.144) and serum HDL-C (correlation coefficient = 0.087, p = 0.461) (Table 4).

DISCUSSION

There is paucity of data on the relationship between thyroxine and components of MS, particularly in the South Asian population. Thyroid hormones have marked effects on metabolism (carbohydrate and lipid), energy balance and BP which are also deranged in MS (Ayturk et al., 2009). A few recent studies have pointed to the fact that these effects of thyroid hormones may even be present in the normal range of thyroid function (Kim et al., 2009; Roos et al., 2007). The present study was conducted in order to determine the correlation between serum free T4 and components of MS in euthyroid South

Table 3. Correlation between serum free T4 and components of MS in males.

Components of MS	Serum free T4	
	Correlation Coefficient	p value†
Waist Circumference	0.060	0.659
Systolic BP	0.302	0.023*
Diastolic BP	0.330	0.013*
Serum Glucose	0.287	0.032*
Serum TG	- 0.087	0.526
Serum HDL-C	0.133	0.328

†Determined by Spearman rank correlation. *Significant at 0.05 level.

Table 4. Correlation between serum free T4 and components of MS in females.

Components of MS	Serum free T4	
	Correlation Coefficient	p value†
Waist Circumference	- 0.032	0.784
Systolic BP	0.138	0.242
Diastolic BP	0.201	0.086
Serum Glucose	0.086	0.464
Serum TG	- 0.172	0.144
Serum HDL-C	0.087	0.461

†Determined by Spearman rank correlation.

Asians of Pakistan.

In this study, serum free T4 showed a low but statistically significant direct correlation with systolic BP and diastolic BP, in all the subjects. This can be explained by the positive inotropic effect of thyroid hormones along with their ability to increase sympathetic system activity and angiotensinogen levels (Kim et al., 2009). Also, thyroid hormones cause peripheral vasodilation, decreasing peripheral vascular resistance, and in turn lead to stimulation of the renin-angiotensin-aldosterone system and consequent retention of sodium (Fommei and Iervasi, 2002). Some studies (Kim et al., 2009; Roos et al., 2007; Taneichi et al., 2011) have shown similar results, but studies by Lin et al. (2005) and Garduno-Garcia et al. (2010) are not in agreement. In the present study, serum free T4 correlated positively with serum glucose in males. A previous study has shown a similar finding in both males and females (Kim et al., 2009). Suggested mechanisms include decreased insulin secretion by pancreas and increased gluconeogenesis associated with increasing thyroxine levels (Kim et al., 2009). However, the study by Garduno-Garcia et al. (2010) done in a Hispanic population, showed a negative correlation between serum free T4 and glucose.

Another possible reason for the relationship between serum free T4 and components of MS could be indirect, through a common underlying factor, which may have led to simultaneous changes in free T4 and in components of MS. This factor could be genetic or environmental (Kim et al., 2009; Fernandez-Real et al., 2006). Serum free T4 correlated positively with BP in all subjects, and with serum glucose in males but not in females. So the relationships between serum free T4 and components of MS are different according to gender. This has been seen in a previous study in a Chinese population (Kim et al., 2009). Moreover, in our study, waist circumference, serum TG and HDL-C did not correlate with serum free T4 in males and in females. A study by Roos et al. (2007) in a Caucasian population showed a negative relationship of free T4 with waist circumference, TG and a positive association with HDL-C. Another study done in a Chinese population showed negative association of waist circumference with free T4 (in females and in males above 50 years of age), TG (in males below 50 years of age) and a positive relationship with serum HDL-C (Kim et al., 2009). The discordant results in our study may be due to the small sample size and the subjects being of South Asian origin. A larger study in the local population may clarify the relationships further.

Our study has limitations. It is cross-sectional in design, so a causal relationship between high-normal free thyroxine and components of 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. In addition, we did not measure, blood triiodothyronine levels; the active form of thyroid hormone in target tissues. It has been suggested

that triiodothyronine acts with insulin to modulate glucose and lipid homeostasis (Kim et al., 2000). The correlation between serum free T4 and BP in all subjects was statistically significant but low. This may also be due to the fact that the subjects were South Asian and the sample size was small.

In summary, our study has shown that high-normal thyroid function (free T4) is positively correlated with raised BP and with raised serum glucose levels in males. So, there may be increased risk of hypertension in subjects with high-normal thyroid function. Males with high-normal thyroid function may be at risk of developing raised blood glucose. Future large studies are required in the South Asian population to confirm and validate our findings.

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