The relationship between serum thyroid stimulating hormone (TSH) level within normal reference range and metabolic syndrome

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Abstract: Introduction: The effect of thyroid dysfunction on cardiometabolic profile is well known; increased total cholesterol, triglyceride, low density cholesterol (LDL-C), fasting blood glucose, blood pressure (BP), and decreased high density cholesterol (HDL-C) are characteristic effects of hypothyroidism. Most of these changes are components of metabolic syndrome (Mts). Studies exploring the association between elevated thyroid stimulating hormone levels and metabolic syndrome in euthyroid subjects are limited, that is why we conducted this study to explore this vague area. **Methods:** In this case control study, 100 subjects were studied (80 patients with Mts as the case group, and 20 subjects without Mts as the control group). Subjects had TSH level within reference range (⩾ 0.35 mu/ml⩽4.12mu/L). The parameters that were examined included body mass index (BMI), waist circumference (WC), blood pressure, serum level of high density lipoprotein cholesterol (HDL-C), serum triglycerides (TG) level, and serum level of thyroid stimulating hormone (TSH). **Results:** We found no association between serum TSH level within normal reference range and the presence of Mts; but there was significant positive correlation between serum triglycerides level (TG) and serum TSH level in patients with TSH level < 2.5 mu/L and ⩾ 0.35 mu/L (P=0.003). Negative correlation was found in the same group of patients between serum TSH level and both of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (P=0.014 and P=0.043 respectively). Also, the study identified negative correlation between serum level of TSH within normal reference range and DBP among all patients (P=0.038). **Conclusion:** This study revealed no association between serum TSH level within normal reference range and the presence of Mts.

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1. Introduction

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: raised fasting plasma glucose, impaired glucose tolerance or diabetes mellitus, abdominal obesity, low HDL-C, high triglycerides and high blood pressure (Eckel et al., 2005). It is estimated that around 20-25 percent of the world's adult population have the metabolic syndrome and they are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome have a fivefold greater risk of developing type 2 diabetes (Stern et al., 2004). The underlying cause of the metabolic syndrome continues to challenge the experts but both insulin resistance and central obesity are considered significant factors (Tajik et al., 2014; Carr et al., 2004).Genetics, physical inactivity, ageing, a pro-inflammatory state and hormonal changes may also have a causal effect, but the role of these may vary depending on ethnic group (Saad et al., 1991). The effect of thyroid dysfunction on lipid and glucose metabolism and blood pressure is well known; increased total cholesterol, triglyceride, LDL-C, fasting blood glucose, blood pressure, and decreased HDL-C are characteristic effects of hypothyroidism (overt or subclinical) (Kutty et al., 1978). Associations between thyroid function and parameters of metabolic syndrome have been reported (Roos et al., 2007). However, studies exploring the association between elevated thyroid stimulating hormone levels and metabolic syndrome in euthyroid subjects are limited. Therefore, we aimed in this study to investigate the relationship between thyroid stimulating hormone and metabolic syndrome in euthyroid subjects.

2. Material and Methods

The case control study was carried out on 100 subjects with age above 18 years, 80 of them having metabolic syndrome, in Internal Medicine Department of Tanta University Hospital (Egypt). The study was focusing on subjects with TSH levels in normal range (0.35 to 4.12 mu/L), so subjects with TSH less than 0.35 mu/L or more than 4.12 mu/L were excluded. Metabolic syndrome was defined using the National Cholesterol Education Program, Adult Treatment Panel Ш (NCEP- ATP Ш) criteria. The included 100 subjects were divided into three groups: Group I

included 34 subjects with metabolic syndrome with TSH level ≤ 2.5 mu/L and ≥ 4.12 mu/L; Group II included 46 subjects with metabolic syndrome with TSH level < 2.5 mu/L and ≤ 0.35 mu/L; and Control groups I and II included 20 subjects who have none of the components of metabolic syndrome and they were euthyroid. Among controls, 10 of them had TSH level ≥ 4.12 and ≤2.5 mu/L (control group I), and the rest had TSH level <2.5 and ≤ 0.35 mu/L (control group II). The exclusion criteria were: people under 18 years, patients with thyroid dysfunction (treated or non-treated), and subjects on treatment for dyslipidemia, hypertension, and diabetes mellitus or on estrogen replacement therapy. All participants were subjected to through history taking and clinical examination. Weight and height were measured with the subjects wearing light clothing and no shoes; the body mass index (BMI) was also calculated (kg/m2) and waist circumference was measured using simple tape at the part of the trunk located midway between the lower costal margin and the iliac crest while the person is standing, with feet about 25-30 cm apart. The measurer stood beside the individual and fitted the tape snugly, without compressing any underlying soft tissues. The circumference was measured to the nearest 0.5 cm, at the end of a normal expiration. All the subjects were asked to rest at least 30 minutes and then blood pressure of their right and left arms was measured twice with a desk-model sphygmomanometer with the participants in a sitting position, there was a 3-min interval between the two measurements for each participant, and the mean value of the two measurements was used. We excluded participants with significantly unequal blood pressure in both arms.

Laboratory measurements were carried out on venous samples which were drawn after a fasting period of 14 hours, after consent given by the patient. Fasting plasma glucose was measured by the glucose oxidase technique. Total cholesterol, and TG were measured by enzymatic colorimetric technique. HDL–C was measured by precipitation of very low density lipoprotein and low density lipoprotein by phosphotungstate in the presence of magnesium ions, after centrifugation the supernatant contains HDL which was determined using the total cholesterol enzymatic reagent. TSH was measured using immunochemoluminescent assays by an automated analyzer. All blood samples were analyzed in the laboratory of the Tanta University Hospital. The protocol of this study was approved by the ethical committee of research of Tanta Faculty of Medicine. Consent was taken from all subjects and blood sampling was done under complete aseptic condition. Site of sampling was disinfected and sterilized according to the standards of infection control, and contaminated wastes such as gloves and syringes were collected in safety box to be incinerated. There were no other possible risks appeared during the course of the research, also, there were adequate provisions to maintain privacy of participants and confidentiality of the data.

3. Results

A total of 100 euthyroid subjects were recruited for the study, and were divided into study and control groups. The study groups included 80 subjects with metabolic syndrome. Study group I included 34 subjects with TSH level ≤ 2.5 mu/L and ≥ 4.12 mu/L, and study group II included 46 subjects with TSH level <2.5 mu/L and ≤ 0.35 mu/L. The control groups included 20 subjects without metabolic syndrome. Subjects were recruited for control group I (10 subjects, TSH level ≤ 2.5 mu/L and ≥ 4.12 mu/L.), and control group II (10 subjects, TSH level <2.5 mu/L and ≤ 0.35 mu/L). Table 1 shows demographic data of studied patients. The distribution of men and women in the study and control groups was not significantly different (p>0.05). Also, there was no significant difference of age between study group I and control group I (39.67 ± 10.81 and 36.5 ± 16.82 respectively, P = 0.479), but there was significant difference of age between study group II and control group II (39.04 ± 12.25 and 29.5 ± 11.15 respectively, P = 0 .028).

Table 2 shows the clinical data of studied patients. Weight, waist circumference and body mass index were significantly greater in the study groups as compared to the control groups (p ≥ 0.001 for the three parameters). Also, systolic BP and diastolic BP were significantly higher in study groups when compared to the control groups (p=0.035 and 0.046 respectively for study group I and control group I), and (p =0.003 and 0.001 respectively for study group II and control group II). On the other hand, there was no significant difference of height between study group I and control group I (162.12 ± 5.65 and 162.3 ± 6.18 respectively, p = 0.93) and between study group II and control group II (160.7 ± 5.94 and 163.5 ± 5.23 respectively, p = 0.174).

As shown in Table 3, fasting plasma glucose level was significantly higher in study group I than control group I, and in study group II than control group II (p=0.016 and 0.022 respectively), serum TSH level was significantly higher in study group I than in control group I((3.63 ± 0.504 and 3.06 ± 0.77 respectively, p = 0.031), while, the serum level of TSH was not significantly different between study group II and control group II (0.72 ± 0.41 and 0.91 ± 0.57 respectively, p>0.05), serum level of HDL-C was significantly lower in study group I than in control group I (45.03 ± 5.68 mg/dl and 50.2 ± 4.47mg/dl respectively, p=0.011), also, serum HDL-C level was

significantly lower in study group II than in control group II (43.66 ± 7.3 mg/dl and 56 ± 3.16 mg/dl, p≥0.001), but serum TG level was not significantly different between study groups and control groups (p>0.05). As seen in Table 4, the correlation of serum level of TSH with different parameters (age, weight, height, BMI, SBP, WC, fasting plasma glucose level, serum TG level and serum HDL-C level) among all studied subjects was insignificant (p> 0.05), but serum level of TSH had significant inverse correlation with DBP (p= .038).

Table 1. Demographic data of studied groups

Item	Group (I), n=34		Control(I), n=10		Test of sig.	*P*
	n	%	n	%		
Sex						
Male	4	11.8	2	20	Fisher's Exact Test	
Female	30	88.2	8	80	P=.606	
Age						
Mean ± SD	39.67±10.81		36.5±16.82		t=.715	.479
Min-Max	25-65		20-70			
Item	Group (II), n=46		Control(II), n=10		Test of sig.	*P*
	n	%	n	%		
Sex						
Male	7	15.2	1	10	Fisher's Exact Test	
Female	39	84.8	9	90	P=1	
Age						
Mean ± SD	39.04±12.25		29.5±11.15		2.264	.028*
Min-Max	19-65		20-59			

Table 2. Clinical data of studied groups

Item	Group (I), n=34		Control (I), n=10		t-test	*P*
	Mean ± SD	Min-Max	Mean ± SD	Min-Max		
Weight	96.19±14.41	80-141	63.1±5.404	50.70	7.07	≤0.001*
Height	162.12±5.65	154-175	162.3±6.18	151-172	0.09	0.93(NS)
WC	106.83±11.09	89-135	83.6±5.36	73-92	6.24	≤0.001*
BMI	36.59±5.09	31.2-56.1	23.91±.904	21.9-25	7.77	≤0.001*
Systolic BP	122.79±15.13	100-150	112± 6.32	100-120	2.18	.035*
Diastolic BP	78.67±9.64	60-90	72± 6.32	60-80	2.05	.046*
Item	Group (II), n=46		Control(II), n=10		t-test	*p*
Weight	94.22±13.77	72-123	64.4±5.08	58-74	6.71	≤0.001*
Height	160.7±5.94	153-172	163.5±5.23	155-172	1.38	0.174(NS)
WC	105.34±9.86	89-125	82.3±3.802	75-87	7.25	≤0.001*
BMI	36.38±4.42	30.4-48.7	24.07±1.17	21.3-25	8.67	≤0.001*
Systolic BP	124.56±14.41	100-160	110±8.16	100-120	3.07	0.003*
Diastolic BP	81.74±10.34	60-100	70±8.16	60-80	3.36	0.001*

Table 3. Laboratory data of studied groups

Item	Group (I), n=34		Control(I), n=10		t-test	*p*
	Mean ± SD	Min-Max	Mean ± SD	Min-Max		
F.P.G	141.5±57.78	65-274	95±8.34	72-99	2.516	0.016*
T.G	140.09±35.09	81-231	142.2±5.79	130-149	0.188	.852(NS)
H.D.L	45.03±5.68	28-53	50.2±4.47	41-55	2.645	0.011*
T.S.H	3.63±0.504	2.67-4.12	3.06±0.77	0.3-4.12	2.228	0.031*
Item	Group (II), n=46		Control(II), n=10		t-test	*p*
F.P.G	156.43±84.71	66-452	92.8±7.76	74-99	2.357	0.022*
T.G	142.07±51.73	59-290	119.2±28.48	75-148	1.348	0.183(NS)
H.D.L	43.66±7.3	29-56	56± 3.16	49-59	5.205	≤0.001*
T.S.H	0.72±0.41 Median=0.57	0.15-1.84	0.91±0.57 Median=0.38	0.38-1.87	Z=0.814	0.416(NS)

Table 5 shows that, serum level of TSH had insignificant correlation with age, weight, height, BMI, waist circumference, SBP, DBP, fasting plasma glucose level, serum TG level and serum HDL-C level in the study group I and control group I (p> 0.05). On the other hand, Spearman's rank correlation analysis in study group II (n=46) showed statistically significant inverse correlation of serum level of TSH with SBP and DBP (p = 0.014 and 0.043 respectively), but there was no significant correlation of serum level of TSH with age, weight, height, BMI, waist circumference, fasting plasma glucose level, serum TG level and serum HDL-C level (p> 0.05). Also as shown in Table 5, Spearman's rank correlation analysis in control group II (n=10) showed that serum level of TSH had significant positive correlation with serum TG level (p= 0.003), but had no significant correlation with age, weight, height, BMI, waist circumference, SBP, DBP, fasting plasma glucose level and serum HDL- Ch (p> 0.05).

Table 4. Correlation of T.S.H with different parameters among all subjects (n=100)

Item	r	*P*
Age	.012	.907
weight	-.103	.307
Height	.113	.261
BMI	-.150	.138
systolic BP	-.182	.070
Diastolic BP	-.207	.038*
WC	-.104	.304
F.P.G	-.111	.270
T.G	.003	.973
H.D.L	.029	.772

Table 5. Correlation of TSH with different parameters in all groups

Item	Group (I), n=34		Control(I), n=10		Group (II), n=46		Control(II), n=10	
	r	*P*	r	*P*	r	*P*	r	*P*
Age	.162	.359	.133	.714	-.219	.144	-.386	.270
weight	-.096	.589	.461	.179	-.045	.767	-.367	.297
Height	.066	.712	.294	.410	.088	.562	-.591	.072
BMI	-.212	.228	.542	.106	-.080	.595	.186	.608
WC	-.123	.488	.548	.101	-.135	.373	-.312	.380
SBP	-.170	.337	.530	.115	-.359	.014*	-.141	.698
DBP	-.163	.356	.530	.115	-.300	.043*	-.141	.698
F.P.G	.039	.826	.435	.209	.004	.979	.412	.237
T.G	-.212	.228	.548	.101	.065	.667	.834	.003*
H.D.L	-.123	.489	-.186	.607	.087	.564	-.208	.564

4. Discussion

Thyroid function affects lipid metabolism, carbohydrate metabolism and blood pressure which are also affected in MetS (Scheen, 2004). Studies have given evidence that thyroid function is associated with MetS in thyroid disease, and recently few studies have suggested that this association may extend into the normal reference range of thyroid function (Roos et al., 2007), but it is still controversial. In our study, study groups, and control groups did not demonstrate any association between serum TSH levels and the presence of metabolic syndrome. This finding applied for both sexes and cases with high normal and low normal TSH levels. We found that serum level of TSH had no significant correlation with weight, BMI, or waist circumference. Although the significant association between overt hypothyroidism and high adiposity has been demonstrated before, the issue is not clear for cases with TSH levels within normal limits (Portmann and Giusti, 2007). A meta-analysis by Souza and Schieri showed that 18 studies out of 29 on this topic have demonstrated a significant association between plasma TSH levels and adiposity, but those were not supported by the others (Souza and Sichieri, 2011). In this meta-analysis, the correlation between TSH and obesity has been found in 11 of the clinical studies and it has been valid for both sexes in presence of morbid obesity and only for females in presence of non-morbid obesity. As there are no different gender-specific cut-off values for normal plasma TSH, the correlation found only for obese women but not for men cannot be explained.

Likewise, we could not find any correlation between BMI and plasma TSH levels for both genders.

Scientists supporting the idea that body adiposity correlates with increasing plasma TSH levels in euthyroid subjects have proposed that upper limit of normal TSH levels may be presumed as 2.5 mIU/mL and higher values may resemble subclinical hypothyroidism (Wartofsky and Dickey, 2005). However in a wide population-based study conducted by Hamilton and co-workers, the upper limit of plasma TSH has been proposed as 4.0 mIU/mL for those with no thyroidal disease findings (Hamilton et al., 2008). In accordance with this study, we did not determine any difference in terms of body adiposity when a TSH cut-off level 2.5 mIU/mL was used. Some studies have pointed out the elevation of metabolic syndrome risk in euthyroid cases with the increasing TSH levels(Waring et al., 2011).However, another study has shown no increase of metabolic syndrome incidence even in subclinical hypothyroidism (Garduño-Garcia et al., 2010). In our work, there was no correlation between serum TSH level within normal reference range and the presence of metabolic syndrome or any component of metabolic syndrome except for BP. Different results of different studies including ours may be related to distributional differences of groups, sensitivity of TSH measurement techniques, changes in reference cut-off points and race differences of normal serum TSH levels with differences of definition of obesity, and metabolic syndrome (Schectman et al., 1991; Wulan et al., 2010; Lin et al., 2011). We observed no significant correlation between serum TSH levels and serum TG and serum HDL-C, except in subjects without metabolic syndrome and with low normal TSH value (0.35-2.4), as serum TSH level was positively correlated to serum level of TG. The effects of TSH within the reference range on serum lipid levels remain controversial. Evidence from two studies suggests that TSH within the reference range may be positively associated with total serum cholesterol (Pallas et al., 1991), and LDL- cholesterol (Bakker et al., 2001).

Recently, a large population-based study reported about the association between TSH at the upper limits of the normal range and lipid levels. In the fifth Tromso study (a cross-sectional epidemiological study of 5143 subjects), there was a positive association between serum TSH level and total cholesterol and LDL-C levels. However, this did not achieve statistical significance in women after adjusting for age and BMI (Iqbal et al., 2006). Another population-based study demonstrated that increased levels of TSH were associated with less favorable lipid levels within the reference range of TSH (Asvold et al., 2007). Some studies have also shown that thyroid function (free T4 or TSH) is not related to HDL-C (Park et al., 2009). Our study does not include free thyroid hormone levels, thyroid autoantibody levels, and it lacks reevaluation for patients who lost weight after life style interventions which can be regarded as the pitfalls of the study. However; serum TSH assay seems to be the most useful laboratory test in the initial evaluation of thyroid dysfunction in monitoring patients for thyroid disease. In addition, free thyroid hormone levels and autoantibody measurements are secondary diagnostic steps and are not mandatory for screening (Garber et al., 2012). Absence of correlation between serum TSH levels and obesity in the present study does not mean that TSH and thyroid hormones have no effect on adiposity. Recent studies have shown extra-thyroidal TSH receptors on adipose tissue (Sorisky et al., 2000). The TSH receptors found on rat preadipocytes have been demonstrated to play a role on adipocyte differentiation. Increasing TSH receptor expression in human subcutaneous adipose tissue has been shown to be parallel to the severity of obesity (Lu et al., 2012). These findings suggest that TSH-adiposity interaction may be related to local TSH receptor expression rather than fluctuating plasma TSH levels. Dentice and coworkers have defined the importance of type II deiodinase activity for myogenesis and muscle regeneration (Dentice et al., 2010). Boelen and colleagues have reported that local deiodinase activity can change as an adaptation for differing situations and this may regulate the local effects of thyroid hormones (Boelen et al., 2011). Additionally, differences in local expressions of thyroid hormone receptors may be related to adipogenesis similar to local TSH receptor expression. Accordingly, it has been demonstrated that obese cases had a significant rise in thyroid hormone receptor alpha-1 gene expression in subcutaneous fat tissue compared to omental fat tissue (Ortega et al., 2009). Researchers still arguing the relationship between serum TSH level and blood pressure in subjects with subclinical hypothyroidism and euthyroidism. Some researchers found that TSH positively correlated with SBP and/or DBP (Waterhouse et al., 2007; Saltiki et al., 2008), while some other researchers did not get such results (Takashima et al., 2007). One study of Annemieke Roos and colleagues showed that when TSH was within normal range, there was no correlation between TSH and SBP and DBP (Roos et al., 2007). Waterhouse et al., took 728 healthy women as subjects and found TSH positively correlated with SBP, with TSH increasing by 1mIU/L, SBP increased 1.53mmHg, but no correlation was found between TSH and DBP.

In our study, there was inverse correlation between low normal TSH levels (TSH= 0.35-2.4) and

blood pressure (Waterhouse et al., 2007). In this study, no correlation was observed between TSH and fasting plasma glucose. On the other hand, thyroid hormones influence carbohydrate metabolism, even in the euthyroid state. They regulate hepatic gluconeogenesis, lipogenesis, and lipolysis. Also, thyroid hormones modulate mRNA and protein expression of the glucose transporter 4, AMP activated protein kinase, and acetyl CoA carboxylase in skeletal muscle (Crunkhorn and Patti, 2008). Despite the known actions of thyroid hormones on carbohydrate metabolism, in vivo studies carried out in humans have provided inconclusive results. Roos et al., found no correlation between both TSH or FT4 values and insulin sensitivity (Roos et al., 2007). There is a study indicating that, in the euthyroid range, free T4 and free T3 rather than TSH are related to cardiovascular risk factors. Seemingly there is, at least in the euthyroid range, a discrepancy between effects that thyroid hormone has on peripheral tissues and the effect that the hormone has on central feedback inhibition of TSH release. Such a discrepancy may, for instance, originate from differences between the central and peripheral tissues in expression of thyroid hormone receptor isoforms, and in expression of type 1 and type 2 iodothyroninedeiodinase, with different catalytic properties (Croteau et al., 1996; Zhang and Lazar, 2000; Flamant and Samarut, 2003). Type 1 iodothyroninedeiodinase plays an important role in converting T4 to T3 within the thyroid gland itself, and in the liver and kidney, whereas type 2 iodothyroninedeiodinase is much more important in the brain, hypothalamus, and pituitary gland (Croteau et al., 1996; Jansen et al., 2005; Fliers et al., 2006). Of particular interest for a potential discrepancy is that expression of the thyroid hormone transporter monocarboxylate transporter 8 is thought to be of great importance for the uptake of thyroid hormone by thyroid hormone-sensitive neuronal cells (Heuer et al., 2005), whereas there is no evidence for a hypothyroid state in the liver of male patients with hemizygous mutations in monocarboxylate transporter 8 (Friesema et al., 2004). This suggests that liver cells take up thyroid hormone predominantly via other transporters, such as the Na/taurocholatecotransporting polypeptide and the organic anion transporting polypeptide families, which are expressed in the liver in particular (Hennemann et al., 2001). Polymorphisms in the TSH receptor have influenced ratios of plasma TSH and thyroid hormones, and can, therefore, also play a role in inducing a discrepancy between central and peripheral tissues (Peeters et al., 2003).

There are some limitations of our study. First, as this is a cross-sectional study, a cause and effect relationship could not be determined. Second, the number of subjects in the control groups was too small to stratify the TSH levels in those without metabolic syndrome, so we could not analyze the association between metabolic variables and level of TSH. Third, we did not measure, blood triiodothyronine levels, and the active form of thyroid hormone in tissues. Tri-iodothyronine acts in association with insulin to modulate glucose and lipid homeostasis (Kim et al., 2000). Also, the relationship between FT3 and obesity and body fat distribution has been reported (De Pergola et al., 2007). Forth, direct measures of insulin resistance were not undertaken in this study. However MetS is a well-known clinical expression of insulin resistance, which we studied. In conclusion, this study revealed no association between serum TSH level within normal reference range and the presence of Mts.

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References

1. Asvold, B. O.; Vatten, L. J.; Nilsen, T. I. and Bjoro, T., (2007): The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur J Endocrinol;156:181–6.
2. Bakker, S. J.; terMaaten, J. C.; Popp-Snijders, C.; Slaets, J. P.; Heine, R. J. and Gans, R. O., (2001): The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. Syndr and Relat Disord; 86: 1206–1211.
3. Boelen, A.; Kwakkel, J. and Fliers, E., (2011): Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection," Endocr Rev; 32(5): 670-693.
4. Carr, D. B.; Utzschneider, K. M. and Hull, R. L., et al. (2004): Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes; 53(8):2087-94.
5. Croteau, W.; Davey, J. C.; Galton, V. A. and St Germain, D. L., (1996): Cloning of the mammalian type II iodothyroninedeiodinase. A selenoprotein differentially expressed and regulated in human and rat brain and other tissues. J Clin Invest 1996; 98:405–417.
6. Crunkhorn, S. and Patti, M. E., (2008): Links between thyroid hormone action, oxidative metabolism, and diabetes risk? Thyroid; 18:227–237.

7. Dentice, M.; Marsili, A. and Ambrosio, R., et al. (2010): The FoxO3/type 2 deiodinase pathway is required for normal mouse myogenesis and muscle regeneration. J Clin Invest; 120 (11): 4021-4030.
8. De Pergola, G.; Ciampolillo, A.; Paolotti, S.; Trerotoli, P. and Giorgino, R., (2007): Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf); 67:265–9.
9. Eckel, R. H.; Grundy, S. M. and Zimmet, P. Z., (2005): The metabolic syndrome. Lancet; 365:1415–28.
10. Flamant, F. and Samarut, J., (2003): Thyroid hormone receptors: lessons from knockout and knock-in mutant mice. Trends Endocrinol Metab; 14:85–90.
11. Fliers, E.; Unmehopa, U. A. and Alkemade, A., (2006): Functional neuroanatomy of thyroid hormone feedback in the human hypothalamus and pituitary gland. Mol Cell Endocrinol; 251:1–8.
12. Friesema, E. C.; Grueters, A. and Biebermann, H., et al. (2004): Association between mutations in a thyroid hormone transporter and severe Xlinked psychomotor retardation. Lancet; 364:1435–1437.
13. Garber, J. R.; Cobin, R. H. and Gharib, H., et al.(2012): Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid; 22(12):1200-1235.
14. Garduño-Garcia, D. J.; Alvirde-Garcia, U. and López-Carrasco, G., et al. (2010): TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. Eur J Endocrinol; 163:2:273-278.
15. Hamilton, T. E.; Davis, S.; Onstad, L. and Kopecky, K. J., (2008): Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. JCEM; 93:4:1224-1230.
16. Hennemann, G.; Docter, R.; Friesema, E. C.; de Jong, M.; Krenning, E. P. and Visser, T. J., (2001): Plasma membrane transport of thyroid hormones and its role in thyroid hormone metabolism and bioavailability. Endocr Rev; 22:451–476.
17. Heuer, H.; Maier, M. K. and Iden, S., et al. (2005): monocarboxylate transporter 8 linked to human psychomotor retardation is highly expressed in thyroid hormone-sensitive neuron populations. Endocrinology; 146:1701–1706.
18. Iqbal, A.; Jorde, R. and Figenschau, Y., (2006): Serum lipid levels in relation to serum thyroidstimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromso Study. J Intern Med; 260: 53–61.
19. Jansen, J.; Friesema, E. C.; Milici, C. and Visser, T. J., (2005): Thyroid hormone transporters in health and disease. Thyroid; 15:757–768.
20. Kim, S. R.; Talbott, E. A.; Tull, E.; Vogt, M.; Andersen, S. and Kuller, L. H.,(2000): Contribution of abnormalities of thyroid hormones to type 2 diabetes. Diabetes Care; 23:260–1.
21. Kutty, K. M.; Bryant, D. G. and Farid, N. R., (1978): Serum lipids in hypothyroidism a reevaluation. J Clin Endocrinol Metab; 46:55-56.
22. Lin, S. X.; Carnethon, M.; Szklo, M. and Berton,i A., (2011): Racial/ethnic differences in the association of triglycerides with other metabolic syndrome components: the multi-ethnic study of atherosclerosis. Metab Syndr and Relat Disord; 9(1): 35-40.
23. Lu, S.; Guan, Q. and Liu, Y., et al. (2012): Role of extrathyroidal TSHR expression in adipocyte differentiation and its association with obesity. Lipids Health Dis 2012; 11: 17.
24. Ortega, F. J.; Moreno-Navarrete, J. M. and Ribas, V., et al.(2009): Subcutaneous fat shows higher thyroid hormone receptor-α1 gene expression than omental fat. Obesity; 17(12): 2134-2141.
25. Pallas, D.; Koutras, D. A. and Adamopoulos, P., et al. (1991): Increased mean serum thyrotropin in apparently euthyroidhypercholesterolemic patients: does it mean occult hypothyroidism? J Endocrinol Invest; 14: 743–746.
26. Park, H. T.; Cho, G. J. and Ahn, K.H., et al. (2009): Thyroid stimulating hormone is associated with metabolic syndrome in euthyroidpost menopausal women. Maturitas; 62:301–5.
27. Peeters, R. P.; van Toor, H. and Klootwijk, W., et al. (2003): Polymorphisms in thyroid hormone pathway genes are associated with plasma TSH and iodothyronine levels in healthy subjects. J ClinEndocrinolMetab; 88:2880–2888.
28. Portmann, L. and Giusti, V., (2007): Obesity and hypothyroidism: myth or reality? Revue Medicale Suisse; 3:105:859-862.
29. Roos, A.; Bakker, S. J. and Links, T. P., et al. (2007): Thyroid function is associated with components of the metabolic syndrome in

euthyroid subjects. J ClinEndocrinolMetab; 92:491-496.
30. Saad, M. F.; Lillioja, S. and Nyomba, B. L., et al. (1991): Racial differences in the relation between blood pressure and insulin resistance. NEJM; 324:733-9.
31. Saltiki, K.; Voidonikola, P.; Stamatelopoulos, K.; Mantzou, E.; Papamichael, C. and Alevizaki, M., (2008): Association of thyroid function with arterial pressure in normotensive and hypertensive euthyroid individuals: A cross-sectional study. Thyroid Res; 1(1): 3.
32. Schectman, J. M.; Kallenberg, G. A.; Hirsch, R. P. and Shumacher, R. J., (1991): Report of an association between race and thyroid stimulating hormone level. AJPH; 81:4:505-506.
33. Scheen, A. J., (2004): Prevention of type 2 diabetes mellitus through inhibition of the Renin-Angiotensin system. Drugs; 64:2537-65.
34. Sorisky, A.; Bell, A. and Gagnon, A., (2000): TSH receptor in adipose cells, HormMetab Res; 32(11-12): 468-474.
35. Souza, A. D. and Sichieri, R., (2011): Association between serum TSH concentration within the normal range and adiposity. Eur J Endocrinol; 165:1:11-15.
36. Stern, M.; Williams, K. and Gonzalez-Villalpando, C., et al. (2004): Does the metabolic Syndrome improve identification of individuals at risk of type 2 diabetes and / or cardio vascular disease? Diabetes Care; 27(11):2676-81.
37. Esra Tajik, Nor Afiah Mohd Zulkefli, Anisah Baharom, HalimatusSakdiahMinhat, Latiffah Abd Latiff. Contributing factors of obesity among stressed adolescents. Electronic physician, 2014; 6(1):771-778. Doi: 10.14661/2014.771-778.
38. Takashima, N.; Niwa, Y.; Mannami, T.; Tomoike, H. and Iwai, N., (2007): Characterization of subclinical thyroid dysfunction from cardiovascular and metabolic viewpoints. Circ J; 17: 191-195.
39. Waring, A. C.; Rodondi, N. and Harrison, S., et al. (2012): Thyroid function and prevalent and incident metabolic syndrome in older adults: the health, ageing and body composition study. Clinical Endocrinology; 76:6:911-918.
40. Wartofsky, L. and Dickey, R. A., (2005): The evidence for a narrower thyrotropin reference range is compelling. JCEM; 90:9:5483-5488.
41. Waterhouse, D. F.; McLaughlin, A. M.; Walsh, C. D.; Sheehan, F. and O'Shea, D., (2007): An examination of the relationship between normal range thyrotropin and cardiovascular risk parameters: a study in healthy women. Thyroid; 17(3): 243-248.
42. Wulan, S. N.; Westerterp, K. R. and Plasqui, G., (2010): Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. Maturitas; 65:4:315-319.
43. Zhang, J. and Lazar, M. A., (2000): The mechanism of action of thyroid hormones. Annu Rev Physiol; 62:439–466.

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