Int J Endocrinol Metab 2009; 1: 12-19

ORIGINAL ARTICLE

Trends of Serum Thyrotropin Concentration and Associated Factors in Urban Pakistan (Karachi)

Riaz M[a], Salman A[a], Fawwad A[a], Iqbal Hydrie MZ[b], Yakoob Ahmadani M[a], Basit A[a], Shera AS[c]

[a]Department of Medicine, Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, [b]Department of International Health, Institute of General Practice and Community Medicine, Faculty of Medicine, University of Oslo, Norway, Baqai Institute of Diabetology and Endocrinology [c]WHO Collaborating Centre for Diabetes, Karachi, Pakistan

This investigation aimed at assessing trends of TSH levels and associated factors in apparently normal subjects of urban Pakistan (Karachi).

Materials and Methods: The survey was conducted in 2004 in Lyari, Karachi. Using a geographical imaging system, 85, 520 households were identified, of which 532 were randomly selected; 867 adults aged≥25 years consented to take part in the study. Blood samples from 324 subjects were available for analyses. Subjects with previous history of thyroid disorders were excluded.

Results

Conclusion: This spectrum of TSH levels highlighted a high prevalence of increased serum TSH levels in the population studied, a trend that was associated with obesity and various lipid abnormalities. Further population based studies are needed to correlate these findings with clinical parameters of hypothyroidism.

Key Words: Thyrotropin, Sub-clinical hypothyroidism, Obesity

Received: 02.12.2008 **Accepted**: 04.02.2009

Correspondence: Mussarat Riaz, Consultant Physician, Department of Medicine, Baqai Institute of Diabetology and Endocrinology, Baqai Medical University, Karachi, Pakistan

E-mail: research@bideonline.com

Introduction

Hypothyroidism, a common endocrine disorder resulting from deficiency of thyroid hormones, is more prevalent in females than males.[1] It is usually a primary process in which the thyroid gland produces insufficient amount of thyroid hormones. The most common cause of hypothyroidism worldwide is iodine deficiency, with an overall prevalence of hypothyroidism reported to be 2–5%.

The estimated prevalences of hypothyroidism and sub-clinical hypothyroidism in Paki-

stan are 4.1 and 5.4% respectively.[2] In India, the reported prevalence of hypothyroidism is 25%.[2,3] In the United States, the estimated prevalence of thyroid disease among people taking thyroid medications is 5%.[4,5]

The overall sensitivity of TSH is (98%) and specificity is (92%), emphasizing the importance of using TSH in screening of subjects for early detection of sub-clinical hypothyroidism, to decrease the cardiovascular risks and to improve the overall outcome, by reduction in the morbidity and mortality related to hypothyroidism.[6-8]

It has been reported that elevated TSH is associated with severe obesity.[9] The Framingham offspring study also demonstrates the association of raised TSH with weight gain and the efficacy of using TSH in early detection of sub-clinical hypothyroidism.[10]

The American Association of Clinical Endocrinologists (AACE) recommends TSH measurement in women of child bearing age before pregnancy or during the first trimester.[11]

One of the largest studies to date on the prevalence of thyroid disease, the Colorado Thyroid Disease Prevalence Study reported the prevalence of sub-clinical thyroid dysfunction to be 5%.[12]

The American Thyroid Association recommends the measurement of thyroid function in all adults after the age of 35 years and every 5 years thereafter, which clearly underscores the importance of screening in early detection of sub-clinical hypothyroidism.

This study aimed as determining trends of TSH levels and associated factors in an apparently normal urban population of Karachi as per ATA definition, were in the "at risk" category.

Abstract

: Mean age of subjects was 40.8±14.13 years, 68.2% were females, mean values of waist circumference of males and females were 85.5±16 cm and 87.8±15.7 cm respectively. Fifty-nine (18.2%) subjects had TSH>6.0 (mU/L) based on the ELISA laboratory reference range, used for the estimation of TSH. Based on the American Thyroid Association (ATA) guidelines, 159 (49.07%) subjects had TSH<2.5, while 76 (23.45%) subjects with TSH between 2.5-4.0 mU/L as per ATA definition, were in the "at risk" category. Thirty subjects (9.26%) had TSH levels between 4.1–6.0 mU/L. A significant correlation was found between TSH levels and waist circumference, whereas a weak, non significant one was observed between TSH and waist hip ratio. A strong association between overweight (BMI >23) and elevated serum TSH concentration (TSH>4.1 mU/l) was also observed.

Materials and Methods

This is a sub-study of the Lyari survey which was conducted to estimate the prevalence of metabolic syndrome in urban Pakistan.[13] The study was conducted between July and December 2004, by generating a computerized random sample of households in Lyari Town, Karachi, Pakistan, using a Geographical Imaging System.

The Lyari Town Geographical Imaging System (GIS) was developed by the Population Census Office, Statistics Bureau Sindh, and a research organization to define the geopolitical boundaries and population density of Lyari Town (2004 estimated population, 700,000). This was done by dynamically linking the national census database to a purpose-built GIS. This GIS ascribed unique identification numbers to 85,520 households. From among the initial households selected, 532 households were randomly selected using GIS software and maps.

If members of a selected household were absent or refused to participate, then the third door to the right of that house (while facing the door of the original house) was approached and consent for participation was sought. In case of further refusal or absence, the next consecutive door to the right was selected; 867 adults≥25 years , consented to take part in the study. These people were interviewed by the field teams, and their anthropometric measurements were taken and blood samples were collected; 324 samples were available for analyses. Subjects with a history of thyroid disorders, or being currently treated were excluded from the study, as were pregnant patients.

Anthropometry*:* Body weight (kg), height (cm), waist and hip circumference were measured in the standing position with subjects wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight divided by height in meters squared (kg/m^2). Overweight and obesity were defined as BMI between 23–24.9 kg/m^2 and ≥25 kg/m^2 respectively.[14] Waist circumference was measured at the level of the umbilicus, while hip circumference was measured midway between the highest point of the iliac crest and the lowest ribs. The measurements were taken in cms and the waist hip ratio was calculated as weight / hip circumference. The

cutoff values of waist circumference were ≥90 cms in men and ≥80 cms in women.

Two blood pressure readings were taken and a mean value was used for the final measurement.

Laboratory Assays*:* After an 8 hour fast, plasma levels of insulin, glucose and lipid profile were measured, results which are presented elsewhere;[15] plasma levels of TSH (mU/L) reference range (0.27–6.0) were also determined by an immune analysis (ELISA), with a detection limit of about 0.1 mU/L.

Statistical analysis

All data were recorded in forms developed using TeleForm® version 6.01, optical character recognition software. Baseline characteristics of the sample are presented as mean±SD and TSH values are given as median.

Chi-square analyses were performed to examine the association between TSH and other associated factors. Association between TSH and BMI is shown by scatter plot, and its significance is given by P value.

Results

Description of anthropometric and biochemical parameters are provided in Table 1.

Mean age of subjects was 40.8±14.13 years. Of subjects, 104 (32.1%) were males and 220 (67.9%) were females. Mean values of waist circumference in males and females were 89.5±16 cm and 87.8±15.7 cm respectively; female subjects were younger, but had higher BMI values. Males were older and had higher waist circumference and blood pressure. In our study group, 59 (18.2%) subjects had TSH >6.0 mU/L, based on the laboratory reference range. High serum TSH levels (4.1–6.0 mU/L) were found in 30 (9.26%) subjects, while 76 (23.45%) subjects had TSH levels between 2.51–4.0 mU/L; in 145 (44.75%), TSH levels were between 0.1-2.50 mU/L and in 14 (4.32%) TSH levels ≤0.1 mU/L were observed (Table 2).

Table 1. Baseline characteristics of the sample

	Males n= 104 (32%)	**Females n= 220 (68%)**	**Overall n = 324**
Age (yrs)	45.1±15.7	38.7±12.8	40.8±14.1
Waist Circumference (cm)	89.5±16.0	87.8±15.7	88.3±15.8
Waist-to-hip ratio	0.93±0.11	0.91±0.16	0.91±0.14
BMI (kg/m_2)	23.9±7.2	26.0±7.0	25.3±7.1
Systolic blood pressure (mmHg)	127.3±18.5	124.3±19.6	125.2±19.3
Diastolic blood pressure (mmHg)	84.2±11.7	79.9±13.6	81.2±13.2

* Mean±SD

Table 2. Categories of TSH, according to American Thyroid Association (ATA) guidelines

TSH (mU/L)	Males n (%) median	Females n (%) median	Overall n median
≤0.1	4 (29)	10 (71)	14
	0.02	0.1	0.1
0.1-2.5	53 (37)	92 (63)	145
	1.0	0.9	1.0
2.5-4.0	53 (70)	23 (30)	76
	3.0	2.9	3.0
4.0-6.0	8 (27)	22 (73)	30
	4.9	4.5	4.7
>6.0	16 (27)	43 (73)	59
	9.85	9.2	9.2
Overall	104 (32)	220 (68)	324
	2.15	2.8	2.6

Although a significant correlation was found between TSH and BMI (p=0.00025) and waist circumference (Fig 1), a weak and non significant correlation was seen between TSH and waist hip ratio. A strong association was observed between overweight (BMI>23) and high serum TSH levels, which were also associated with various lipid abnormalities (Table 3).

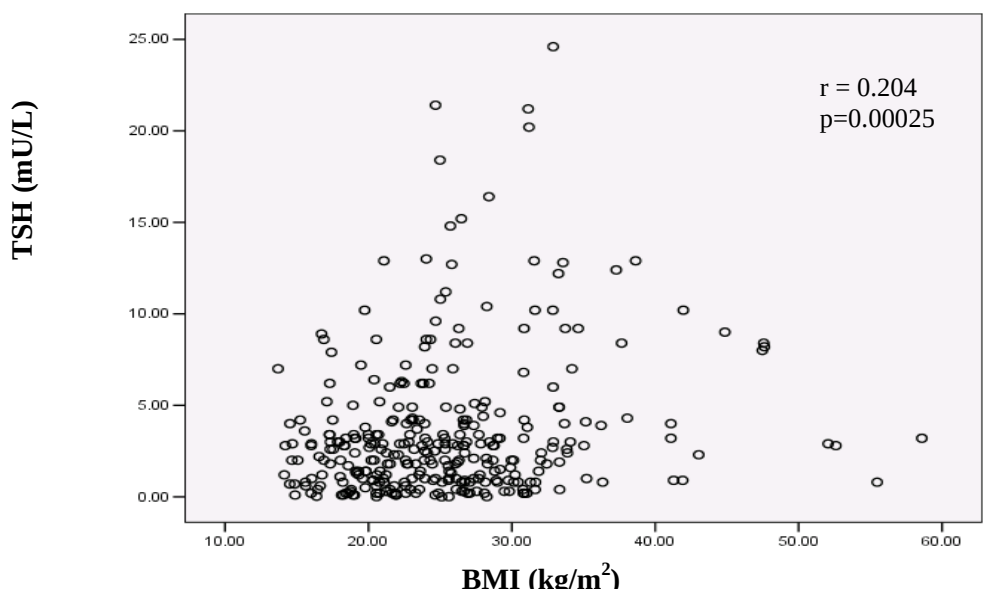

Fig.1. Association between TSH and BMI

Table 3. Association of TSH with overweight/ obestity and lipid abnormalities

	TSH (mU/L) according to ATA*			
	< 2.5	**2.5–4**	**4-6**	**≥ 6**
Over weight (BMI >23 kg/m2)	3.36 (0.04)†	0.41 (0.3)	8.37 (0.003)	7.27 (0.005)
Obesity (BMI >25 kg/m2)	1.72 (0.11)	0.26 (0.35)	3.0 (0.05)	2.48 (0.07)
High TG (>150 mg/dL)	0.01 (0.51)	0.65 (0.25)	0.06 (0.46)	0.01 (0.512)
Low HDL (male <40mg/dL)	0.28 (0.37)	0.14 (0.444)	0.42 (0.341)	0.25 (0.412)
Low HDL (female <50mg/dL)	0.54 (0.268)	0.29 (0.341)	0.02 (0.494)	0.31 (0.345)
High LDL (>100 mg/dL)	0.36 (0.312)	0.22 (0.364)	0.06 (0.45)	0.006 (0.525)
High cholesterol (>160 mg/dL)	0.85 (0.2)	0.46 (0.29)	0.024 (0.48)	0.009(0.51)

* ATA Laboratory reference for TSH, 0.27-6.0 mU/L; † Chi Square (P value)

Discussion

Our study showed a high prevalence of increased serum TSH levels in the urban population of Karachi, Pakistan, strongly supporting the previously reported correlation between serum TSH levels and the degree of obesity.[15] Sub-clinical hypothyroidism is defined by normal serum free T_4 levels and serum TSH levels above the upper limit of the reference range.[16]

Serum level of TSH is a reliable index of the biological activity of thyroid hormones. Being the prime regulators of energy balance, the contribution of thyroid hormones in obesity has been the subject of numerous clinical studies. Measurement of serum level of TSH has been a consistent component of various studies on the relationship between thyroid function and obesity.[17]

The detrimental effects of elevated levels of serum TSH on the cardiovascular system have been reported and follow up studies have shown an increase in the risk of development of overt thyroid dysfunction in subjects with high normal serum TSH levels.[18,19]

In our study, 89 (27.46%) subjects had relatively high TSH levels TSH>4.1 (mU/L). Variations in thyroid function are seen between individuals within the normal range, as documented by small individual variations in thyroid hormones and TSH.[20] Similarly, considerable differences may be seen in thyroid function among populations when estimated by median serum TSH levels; genetic and environmental factors play an important role in the development of such differences in thyroid functions;[21] such variations are probably caused by a number of primarily environmental factors of which iodine intake level seems to be of major importance.[22,23]

The American Association of Clinical Endocrinologists (AACE) in January 2003 recommended that "doctors consider treatment for patients who test outside the boundaries of a narrower margin, based on a target TSH level ranging between 0.3 and 3.0; AACE believes the new range will result in proper diagnosis for millions of Americans who suffer from a mild thyroid disorder, but have gone untreated until now".[11] Based on the AACE guidelines, the number of subjects having

high serum TSH levels increased from 89 (27.46%) to 132 (40.74%) which is quite significant. TSH>6 (mU/L) was found in 59 (18.2%) subjects as per the laboratory reference range.

The importance of diagnosing mild thyroid disorder and sub-clinical hypothyroidism cannot be underestimated because if not treated, they can severely compromise the quality of life. Untreated thyroid disease can cause or contribute to various health problems like weight problems and obesity, heart disease, elevated cholesterol, osteoporosis, infertility, miscarriages and depression.

Increased serum TSH levels in our study were also associated with increase in BMI. In subjects with BMI of 25 or more the mean TSH values were >6.0 mU/L, a finding that correlates with various other clinical studies.[17,24,25]

It is not known at the present time whether an increased TSH level favors the deposition of fat or, on the contrary, the excessive accumulation of fatty tissue increases TSH secretion. There is an established association between overt thyroid dysfunction and weight changes because weight gain is a constant phenomenon in hypothyroidism.[26] Various studies have concluded that weight gain increases serum levels of TSH, while others showed no relationship between TSH and body weight.[15,27-29]

A cross sectional study found a higher BMI among women with sub-clinical hypothyroidism of borderline statistical significance, whereas the opposite association was found among men;[30] the spectrum of TSH levels in the given population highlighted a high prevalence of sub-clinical hypothyroidism in the community.

We observed a high frequency (18.82%) of increased serum TSH levels in the urban population of Lyari Town in the city of Karachi. All the major ethnic groups in Pakistan reside in this locality with a mixed socioeconomic status. Our study area is not an endemic area for iodine deficiency. Furthermore the salt used by the general population of Karachi including Lyari is fortified with iodine.

To mention study limitations, this is a small community based observational study with a small sample size, therefore the observations cannot be generalized for the Pakistani population as a whole; however this study is helpful in interpreting trends of TSH in the urban community. Another limitation of our study is that we did not measure free thyroxine levels. Also high TSH levels were not correlated with clinical parameters. Nonetheless serum TSH concentrations are generally considered to be the most sensitive marker of thyroid function and serum levels of TSH are used to detect thyroid disease and monitor the effectiveness of treatment.[10]

The association between increased serum TSH levels and obesity with resultant adverse effects on physical and mental health necessitates the early detection and treatment of this condition.

To conclude the spectrum of TSH levels observed a high prevalence of increased serum TSH levels in the population, a trend that is associated with obesity and various lipid abnormalities. Further population based studies are needed to correlate these findings with clinical parameters of hypothyroidism.

References

1. Bharaktiya S. Hypothyroidism. Medscape's Continually Updated Reference. 2007 Oct. Available From: URL:http://www.emedicine.com/med/topic1145.htm#section~Introduction

2. Khan A, Khan MMA, Akhtar S. Thyroid disorders, etiology and prevalence. Pak J Med Sci 2002; 2: 89-94.

3. Saha PK, Baur B, Gupta S. Thyroid stimulating hormone measurement as the confirmatory diagnosis of hypothyroidism: A study from a tertiary-care teaching hospital, Kolkatta. Indian J Community Med 2007; 32: 139-40.
4. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87: 489-99.
5. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526-34.
6. Danese MD, Powe NR, Sawin CT, Ladenson PW. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. JAMA 1996; 276: 285-92.
7. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000; 160: 1573-75.
8. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001; 86: 4585-90.
9. Moulin de Moraes CM, Mancini MC, de Melo ME, Figueiredo DA, Villares SM, Rascovski A, et al. Prevalence of subclinical hypothyroidism in a morbidly obese population and improvement after weight loss induced by Roux-en-Y gastric bypass. Obes Surg 2005; 15: 1287-91.
10. Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med 2008; 168: 587-92
11. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al; American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002; 8: 457-69.
12. Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FD, Clark P, et al. Prevalence of subclinical thyroid dysfunction and its relation to socioeconomic deprivation in the elderly: a community-based cross-sectional survey. J Clin Endocrinol Metab 2006; 91: 4809-16.
13. Hydrie MZ, Shera AS, Fawwad A, Basit A, Hussain A. Prevalence of Metabolic Syndrome in Urban Pakistan (Karachi): Comparison of Newly Proposed International Diabetes Federation and Modified Adult Treatment Panel III Criteria. Metab Syndr Relat Disord 2009; 7: 119-24.
14. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. Nutrition 2004; 20: 482-91.
15. Knudsen N, Laurberg P, Rasmussen LB, Bülow I, Perrild H, Ovesen 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.
16. Cooper DS. Clinical practice. Subclinical hypothyroidism. N Engl J Med 2001; 345: 260-5.
17. Bastemir M, Akin F, Alkis E, Kaptanoglu B. Obesity is associated with increased serum TSH level, independent of thyroid function. Swiss Med Wkly 2007; 137: 431-4.
18. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000; 132: 270-8.
19. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 291: 228-38.
20. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endo Metab 2002; 87: 1068-72.
21. Hansen PS, Brix TH, Sørensen TI, Kyvik KO, Hegedüs L. Major genetic influence on the regulation of the pituitary- thyroid axis; a study of health Danish twins. J Clin Endocrinol Metab 2004; 89: 1181-7.
22. Knudsen N, Bulow I, Jorgensen T, Laurberg P, Ovesen L, Perrild H. Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. Eur J Endocrinol 2000; 143: 485-91.
23. Laurberg P, Bülow Pedersen I, Knudsen N, Ovesen L, Andersen S. Environmental iodine intake affects the type of nonmalignant thyroid disease. Thyroid 2001; 11: 457-69.
24. Näslund E, Andersson I, Degerblad M, Kogner P, Kral JG, Rössner S, et al. Associations of leptin, insulin resistance and thyroid function with long-term weight loss in dieting obese men. J Intern Med 2000; 248: 299-308.
25. Roti E, Mineli R, Salvi M. Thyroid hormone metabolism in obesity. Int J Obes Relat Metab Disord 2000; 24 Suppl 2: S113-5.
26. Krotkiewski M. Thyroid hormones in the pathogenesis and treatment of obesity. Eur J Pharmacol 2002; 440: 85-98.
27. Krotkiewski M. Thyroid hormones and treatment of obesity. Int J Obes Relat Metab Disord 2000; 24 Suppl 2: S116-9.

28. Ritz P, Dumas JF, Salle A, Simard G, Malthiery Y, Rohmer V. Thyroid hormones and obesity. Ann Endocrinol 2002; 63: 135-39.
29. Tagliaferri M, Berselli ME, Calò G, Minocci A, Savia G, Petroni ML, et al. Subclinical hypothyroidism in obese patients: relation to resting energy expenditure, serum leptin, body composition, and lipid profile. Obes Res 2001; 9: 196-201.
30. Lindeman RD, Romero LJ, Schade DS, Wayne S, Baumgartner RN, Garry PJ. Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey. Thyroid 2003; 13: 595-600.