การศึกษาค่าอ้างอิงระดับฮอร์โมนไทรอยด์ในซีรัม ของคนไทยที่มีภาวะอ้วน

ปิยะรัตน์ เลิศตระกูล[1, 2] ถวัลย์ ฤกษ์งาม[1, 3] และ นริสา เก่งตรง บดีรัฐ[1, 3*]

[1]บัณฑิตศึกษา สาขาเทคนิคการแพทยมหาบัณฑิต ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์ (ศูนย์รังสิต) จังหวัดปทุมธานี

[2]งานภูมิคุ้มกันวิทยา กลุ่มงานพยาธิวิทยา โรงพยาบาลตำรวจ ปทุมวัน กรุงเทพมหานคร

[3]ภาควิชาเทคนิคการแพทย์ คณะสหเวชศาสตร์ มหาวิทยาลัยธรรมศาสตร์ (ศูนย์รังสิต) จังหวัดปทุมธานี

บทคัดย่อ

การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อประเมินค่าอ้างอิงของฮอร์โมนไทรอยด์ในคนไทยที่มีภาวะอ้วน โดยศึกษาในผู้ที่มารับการตรวจสุขภาพประจำปีที่โรงพยาบาลตำรวจ จำนวน 400 ราย อายุระหว่าง 18-50 ปีที่มีภาวะอ้วน โดยคำนวณจากค่าดัชนีมวลกายที่มากกว่า 25 กิโลกรัมต่อตารางเมตร ตัวอย่างวิจัยแบ่งเป็น 3 กลุ่มย่อยตามอายุ คือ 18-30 ปี 31-40 ปี และ 41-50 ปี ผลการศึกษา พบว่า ระดับฮอร์โมน TSH ในกลุ่มอายุ 41-50 ปี ที่มีภาวะอ้วนมีค่าสูงขึ้นอย่างมีนัยสำคัญ เมื่อเทียบกับกลุ่มตัวอย่างอายุน้อย โดยระดับฮอร์โมนไทรอยด์ (FT3 และ FT4) ในเพศชายมีค่าสูงกว่าในเพศหญิงอย่างมีนัยสำคัญ แต่ไม่พบความแตกต่างของระดับฮอร์โมน TSH ระหว่างเพศชายและเพศหญิง การศึกษานี้ใช้ค่าอ้างอิงในคนไทยที่มีภาวะอ้วน โดยคิดจากค่าการตรวจวัดในช่วง 2.5^{th}-97.5^{th} percentile ของระดับฮอร์โมน TSH เท่ากับ 0.31-5.93 มิลลิยูนิตต่อลิตร ค่า FT3 เท่ากับ 0.20-0.39 นาโนกรัมต่อเดซิลิตร และค่า FT4 เท่ากับ 0.93-1.73 พิโคกรัมต่อมิลลิลิตร โดยสรุป ความอ้วนมีผลทำให้ระดับ TSH เพิ่มขึ้นเล็กน้อย ดังนั้นควรประเมินการทำงานของต่อมไทรอยด์ในผู้ที่มีภาวะอ้วนอย่างเหมาะสม เพื่อป้องกันการวินิจฉัยผิดและใช้ยารักษาโดยไม่จำเป็น

คำสำคัญ: ภาวะอ้วน ค่าอ้างอิง ฮอร์โมนไทรอยด์

***ผู้รับผิดชอบบทความ E-mail address:** narisa.k@allied.tu.ac.th

รับบทความ: 20 มิถุนายน 2561 แก้ไขบทความ: 16 กรกฎาคม 2561 รับตีพิมพ์บทความ: 8 สิงหาคม 2561

Reference Interval of Serum Thyroid Hormone in Obese Thais

Piyarat Lerttrakul,[1, 2] Thaval Rerkngarm[1, 3] and Narisa Kengtrong Bordeerat[1, 3*]

[1]*Graduate Program of Medical Technology, Faculty of Allied Health Science, Thammasat University, Rangsit Campus, Pathum Thani Province, Thailand*
[2]*Department of Immunology, Police General Hospital, Bangkok, Thailand*
[3]*Department of Medical Technology, Faculty of Allied Health Science, Thammasat University, Rangsit Campus, Pathum Thani Province, Thailand*

Abstract

The aim of this study was to evaluate the reference intervals of TSH, FT3, and FT4 in obese Thais. The cross-sectional study consisted of 400 subjects who were recruited after undergoing routine health check-ups at the Police General Hospital. The subjects, age 18-50 years with BMI ⩾ 25 kg/m^2, were divided into three sub-groups: 18-30 years, 31-40 years and 41-50 years. The results showed that thyroid hormone (FT3 and FT4) levels were higher in males than in females. TSH levels in obese, 41-50 years age group were significantly higher than those in the younger age groups. However, no statistical significance of TSH was shown between males and females. The reference intervals (p2.5-97.5) for TSH, FT3 and FT4 were 0.31-5.93 mIU/L, 0.93-1.73 pg/mL and 0.20-0.39 ng/dL, respectively. In conclusion, obesity may impact the range of normality of TSH. The reference intervals for thyroid hormones are needed to be determined for each specific population. Slightly elevated TSH concentrations in the obese could be considered acceptable, with no need for thyroxine treatment.

Keywords: Obesity, Reference interval, Thyroid hormone

***Corresponding author E-mail address:** narisa.k@allied.tu.ac.th

Received: June 20, 2018 Revised: July 16, 2018 Accepted: August 8, 2018

Introduction

Obesity is a serious health problem accompanied by many hormonal changes[1]. It has a complex pathophysiology characterized by interaction of genetic, environmental and physiological factors[2]. Thyroid dysfunction is well known in the pathogenesis of obesity. Weight gain is frequently seen in hypothyroidism and the treatment causes mild weight loss[3]. Serum thyroid stimulating hormone (TSH) is the most sensitive indicator of thyroid dysfunction. Abnormal TSH levels occur during the development of hypothyroidism, earlier than the detection of triiodothyronine (T3) and thyroxine hormone (T4) abnormalities[4]. Subclinical thyroid diseases are diagnosed based on laboratory evaluation of abnormal TSH levels, with normal levels of T4, free T4 (FT4), free T3 (FT3) and few, if any, clinical signs and symptoms. The interpretation of these hormonal changes in obesity and their distinction from real pathological endocrine alterations can be challenging. The clinical observations mentioned above raise the questions whether TSH change within physiological limits is associated with obesity and whether there is a link between adipose tissue and hypothalamic-thyroidal axis[5].

In this aspect, previous reports have consistently demonstrated a positive correlation between obesity and serum TSH levels[6-7]. Along with TSH concentrations, people with obesity have higher levels of FT3[8-9]. Although the relationship between adipose tissue and thyroid function is not completely understood, the hypothesis of the hypothalamic pituitary thyroid adipose axis, in which fat accumulation may induce an increase in TSH production as a mechanism to compensate for energy expenditure, has been proposed[10]. As moderately increased TSH levels may be a reaction to adipose accumulations rather than the cause of weight gain[11], these findings challenge the diagnosis of subclinical hypothyroidism in obesity. Reference value for TSH in normal BMI population may be inadequate when classifying hypothyroidism in certain ranges of individuals with obesity, which could lead to over treatment.

This study was aimed to evaluate the reference intervals of TSH, FT3 and FT4 in obese Thais. Sex and age were also considered when evaluating the distribution of serum TSH, FT3 and FT4 levels in different groups.

Materials and Methods

The present cross-sectional study consisted of subjects who were recruited after undergoing routine health check-ups during October 2016 to January 2018 at the Police General Hospital in Bangkok. This study was performed in accordance with the ethical standard approval from the ethics review committee at Thammasat University (No.190/2560). The most commonly used criteria for obesity classification, established by the World Health Organization (WHO) in 2000, is defined by BMI values as following;

underweight (BMI < 18.5 kg/m^2), normal-weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), obesity (BMI 30-39.9 kg/m^2) and morbid obesity (BMI > 40 kg/m^2). A total of 2,300 healthy subjects between 18 and 50 years of age with BMI ⩾ 25 kg/m^2 were enrolled in this study. A total of 1,723 subjects were excluded from the present study due to a prior history of documented thyroid dysfunction, a history of medicine use that could influence thyroid function (thyroid hormones, estrogen or glucocorticoids) and/or a family history of thyroid disorders. Moreover, 172 subjects with missing data and five subjects with outliers (⩾ 5 × standard deviation above the mean) for TSH and FT4 concentrations were also excluded resulting in a final study population of 400 different individuals (200 men; 200 women).

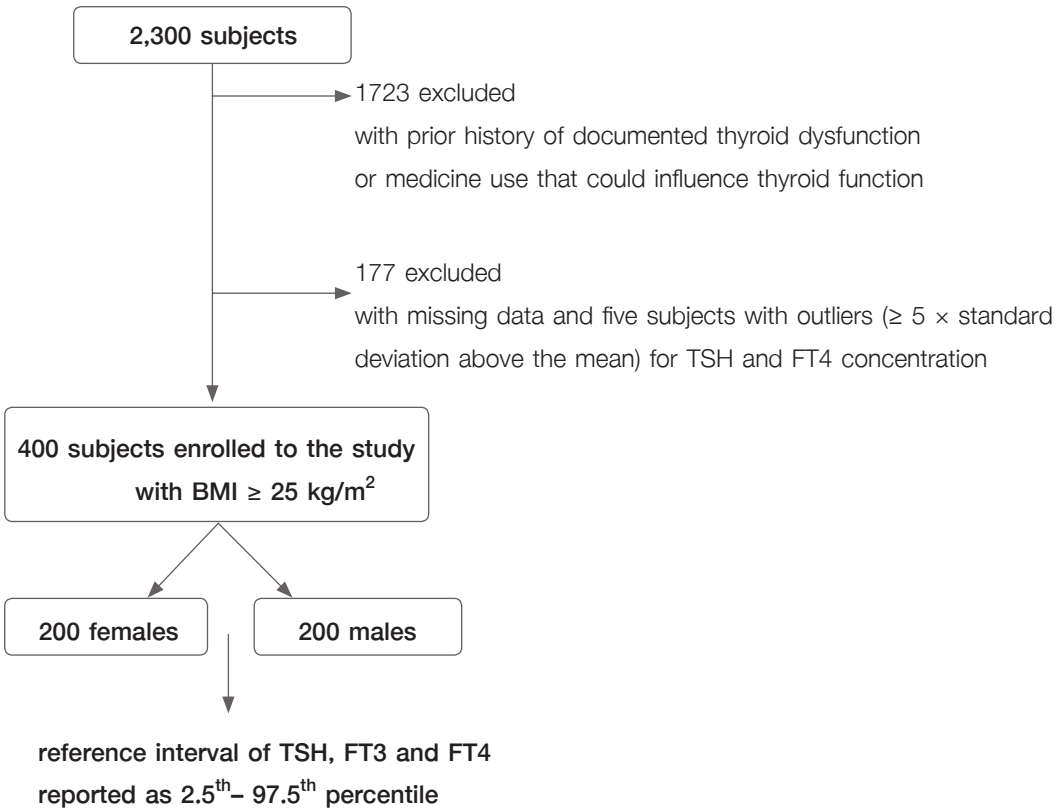

Fig. 1 Recruitment of obese Thais for determining reference interval of serum TSH, FT3 and FT4

Serum analysis

TSH, FT3 and FT4 were measured by electrochemiluminescence immunoassay on a Cobas e601 analyzer (Roche Diagnostics, Switzerland). The assay had intra-assay and inter-assay precision between 1.31%-7.1% and 3.60%-8.30%, respectively. The corresponding normal range of serum TSH, FT3 and FT4 are 0.27-4.2 mIU/L, 0.93-1.91 pg/mL and 0.2-0.44 ng/dL, respectively. These values correspond to the 2.5^{th} and 97.5^{th} percentiles of results obtained from a total of 516 healthy test subjects examined[12].

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS, Chicago IL, USA). The Kolmogorov-Smirnov test was used for Gaussian distribution analysis. The data were reported as median and empirical percentiles for non-Gaussian distribution. Comparisons of the upper limits of TSH for different age groups and genders were calculated by Mann-Whitney U test and Kruskal-Wallis one way ANOVA. *P*-values less than 0.05 indicated statistical significance.

Results

Characteristics of study samples

A total of 400 individuals, 200 women (50%) and 200 men (50%), free of thyroid disease according to the above criteria were enrolled in the analysis. Demographic characteristics of the study samples are given in Table 1. Median age of the samples was 42.5 ± 7.35 years. Median weight and BMI were 75.52 ± 13.81 kg and 27.6 ± 3.85 kg/m^2. For the total samples, median TSH, FT3 and FT4 were 2.36 ± 2.09 mIU/L, 0.30 ± 0.07 pg/mL and 1.29 ± 0.21 ng/dL, respectively. Median BMIs were not significantly different among age groups (18-30, 31-40 and 41-50 years).

Table 1 Demographic data of all samples. The data were reported as median±SE.

Characteristics	All samples	Male	Female	*p*-value
Number of samples (n)	400	200	200	
Age (years)	42.5 ± 7.45	42.7 ± 7.35	42.3 ± 7.57	0.556
Weight (kg)	75.52 ± 13.81	81.20 ± 1.78	69.83 ± 12.41	< 0.01*
BMI (kg/m^2)	27.6 ± 3.85	27.9 ± 3.76	27.4 ± 3.93	0.255
TSH (mIU/L)	2.36 ± 2.09	2.09 ± 1.79	2.64 ± 3.67	0.055
FT3 (pg/mL)	0.30 ± 0.07	0.31 ± 0.07	0.29 ± 0.07	< 0.01*
FT4 (ng/dL)	1.29 ± 0.21	1.34 ± 0.21	1.24 ± 0.21	< 0.001*

Effects of age and gender on TSH, FT3 and FT4 levels in the study samples

The associations between TSH, FT3 and FT4 potentially confounding factors, such as age and gender were analyzed. The data on thyroid hormone levels of all age groups are shown in Fig. 2 The median of TSH for all age groups (18-30, 31-40 and 41-50 years) in women were 2.14 ± 0.76, 1.630 ± 1.27 and 2.220 ± 1.30 mIU/L, and in men were 1.66 ± 0.92, 1.94 ± 1.09 and 1.62 ± 1.05 mIU/L, respectively. The median of FT3 for all age groups (18-30, 31-40 and 41-50 years) in women were 0.285 ± 0.175, 0.288 ± 0.04 and 0.285 ± 0.05 pg/mL, and in men were 0.33 ± 0.031, 0.315 ± 0.05 and 0.307 ± 0.08 pg/mL, respectively. The median of FT4 for all age groups (18-30, 31-40 and 41-50 years) in women were 1.24 ± 0.234, 1.27 ± 0.174 and 1.20 ± 0.20 ng/mL, and in men were 1.43 ±

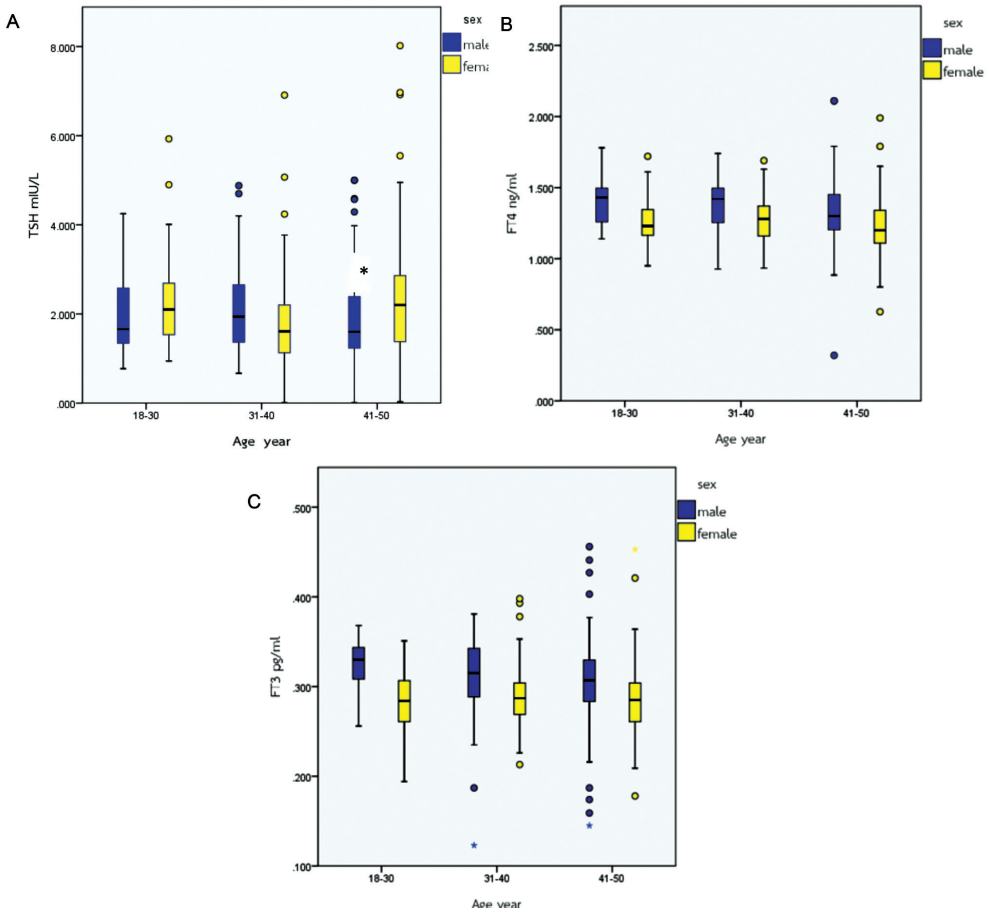

Fig. 2 Median concentrations of TSH (A), FT4 (B) and FT3 (C) according to age and gender in the study samples. Data are median ± standard error. Blue bar represents male data and yellow bar represents female data. *ANOVA test significance between age group: $p<0.05$.

0.177, 1.42 ± 0.197 and 1.30 ± 0.225 ng/mL, respectively. From the results, 41-50 years age group had the highest 97.5th percentile of TSH (5.93 mIU/L) when compared with other age groups (p<0.05). Median FT3 and FT4 concentrations were not significantly different by age groups. According to gender comparison, median FT3 and FT4 concentrations were significantly higher in males than in females (0.31 ± 0.07 pg/mL *vs.* 0.29 ± 0.07 pg/mL and 1.34 ± 0.21 ng/dL *vs.* 1.24 ± 0.20 ng/dL, respectively). In contrast, the serum TSH did not show any significant gender-dependent.

Reference interval of TSH, FT3 and FT4 levels in obese Thais

The 2.5th-97.5th percentile of TSH derived from the study samples was 0.31-5.93 mIU/L, which was higher than the upper limit specified by the assay manufacture. In contrast, the reference interval of FT3 and FT4, 0.20-0.39 pg/mL and 0.93-1.73 ng/dL, respectively, were similar to the reference intervals provided by the manufacturer, (Table 2).

Discussion

This is the first report defining a reference interval for serum thyroid hormone concentrations; TSH, FT3 and FT4, in obese Thai population. A new upper limit of the TSH reference range was found for Thais, 5.93 mIU/L, which was higher than the upper reference limit (4.24 mIU/L) provided by the assay manufacturer. In addition, the upper limit was higher than those reported in the national health examination survey, which has established reference intervals of thyroid function tests in Thais[13]. The reference intervals (2.5th-97.5th percentile) reported in the survey were 0.34-5.11 mIU/L and 0.98-1.79 ng/dL for TSH and FT4, respectively. In particular, the proportion of individuals in 41-50 years age group with obesity would have been 40% elevated TSH levels if the standard ranges of normality for normal weight people had been applied. The 97.5th percentile of TSH values increased with age and this was most evident among those age 40 years and older.

Table 2 Reference intervals (2.5th and 97.5th Percentiles) for FT3, FT4 and TSH by gender

Hormones	Female (N=200)		Male (N=200)		Total (N=400)	
	2.5th Percentiles	97.5th Percentiles	2.5th Percentiles	97.5th Percentiles	2.5th Percentiles	97.5th Percentiles
FT3 (pg/mL)	0.21	0.39	0.187	0.381	0.20	0.39
FT4 (ng/mL)	0.80	1.65	0.982	1.750	0.927	1.730
TSH (mIU/L)	0.29	6.97	0.46	5.50	0.31	5.93

The results also demonstrated that the changes in the thyroid hormone profile associated with age in obese people are concordant with previous reports, consistently revealing a positive correlation between age and TSH but not FT3 and FT4[14]. In addition, normal or slightly higher than normal ranges of TSH have been associated with enhancement of FT4 to FT3 conversion in previous epidemiological studies[15, 16], which is also concordant with the increased activity of deiodinases in response to increasing TSH concentrations reported in *in vivo* studies[17]. Such a causal role of BMI-to-fat mass ratio in the induction of increased TSH production is confirmed by prospective data, showing how the modifications in thyroid function in subject with obesity reverts after weight loss induced by bariatric surgery and hypocaloric diet[18]. The link between adipose tissue and the hypothalamic-thyroid axis could be mediated by adipokines produced by adipose tissue, which has been shown to stimulate the release of TSH by the pituitary[19]. The corresponding changes in thyroid function secondary to weight accumulation could be more pronounced in individuals with obesity[20]. Scientists supporting the idea that body adiposity correlates with increased plasma TSH levels in euthyroid subjects have proposed that upper limit of normal TSH concentration may be presumed as 2.5 mIU/L and upper values may resemble subclinical hypothyroidism[21].

In the present study, the upper limit of TSH tended to increase with age and was most pronounced among individuals age $\geqslant 40$ years. The findings on the association between age and TSH are consistent with previous studies. With aging, the set point for TSH secretion is altered, resulting in higher serum TSH concentration. TSH bioactivity declines with age, so that a greater circulating concentration of immunoreactive TSH required to maintain the same circulating T4 concentrations. The TSH increase could also arise from diminished responsiveness of the thyroid gland to TSH, so that higher TSH is required to maintain the same circulating T4 levels. An age-specific TSH range would be beneficial to very old individuals[22]. Therefore, elevated TSH with normal levels of FT4 in obese people might be concerned as normal obese people. This situation may cause risk of adverse effects from treatment of levothyroxine. Moreover, the present result can directly confirm the association of high TSH level in obese as our exclusion criteria had rejected persons who had prior history of documented thyroid dysfunction, history of medicine use that could influence thyroid function (thyroid hormones, estrogen or glucocorticoids) and/or a family history of thyroid disease.

There were no differences in median TSH levels between males and females, which was inconsistent with the findings of the previous study[23]. Interestingly, the results showed that reference range of TSH for females

had higher upper limit. This may be supported by relationships between body adiposity and plasma TSH levels in female subjects[24].

The strength of our study was that we had been able to study a wide range of sample of thyroid-disease-free individuals representative of the healthy obese (BMI > 25 kg/m^2) population in Thailand. However, there were several limitations in the study. Although thyroid disease was excluded by clinical and laboratory evaluation, thyroid ultrasound was not performed to confirm the subjects as being free of autoimmune thyroid disease. Iodine status was not assessed in this study. It should also be noted that the reference intervals reported here could not be compared with different assays. Further research is required to extend these analyses to greater number of subjects and other confounders such as level of obesity, smoking and diet.

In conclusion, according to our results, BMI is associated with changes in thyroid function that may impact the range of normality of TSH. In particular, the population with obesity might be inappropriately classified if the standard ranges of normality for normal-weight people were applied when defining hypothyroidism. Wider cohorts of subjects with obesity are needed to confirm our finding.

Conflicts of the interest statement

The author declares that they have no conflicts of interest.

References

1. Douyon L, Schteingart DE. Effect of obesity and starvation on thyroid hormone, growth hormone, and cortisol secretion. Endocrinol Metab Clin North Am 2002; 31: 173-89.
2. Knudsen N, Laurberg P, Rasmussen LB, *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.
3. Naumann KU, Furer J, Kaser L, Vetter W. Hypothyroidism, Main symptoms: fatigue, weight gain, depression, myalgia, edema. Praxis 2007; 96: 1411-9.
4. Spencer CA, LoPresti JS, Patel A, *et al*. Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. J Clin Endocrinol Metab 1990; 70: 453-60.
5. Schaffler A, Binart N. Scholmerich J, Buchler C. Hypothesis paper: Brain talks with fat-evidence for a hypothalamiv-pituiatary-adipose axis? Neuropeptides 2005; 39: 363-7.
6. Karavani G, Strich D, Edri S, Gillis D. Increase in thyrotropin within the near normal range are associated with increase triiodothyronine but not increased thyroxine in the pediatric age group. J Clin Endocrinol Metab 2014; 99: E1471-E1475.

7. Tiller D, Intermann T, Greiser KH, *et al*. Association of serum thyrotropin with anthropometric markers of obesity in the general population. Thyroid 2016; 26: 1205-14.
8. Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C, Stamatelopoulos K. Free thyroxine is an independent predictor of subcutaneous fat in euthyroid individuals. Eur J Endocrinol 2009; 161: 459-65.
9. Lambrinoudaki I, Armeni E, Rizos D, *et al*. Indices of adiposity and thyroid hormones in euthyroid postmenopausal women. Eur J Endocrinol 2015; 173: 237-45.
10. Marzullo P, Minocci A, Tagliaferri MA, *et al*. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab 2010; 95: 3965-72.
11. Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013; 5: 40-4.
12. Roche Diagnostics. TSH and FT4 Reagent Kit Literature for Cobas e601. Roche Diagnosis Mannheim: 2011.
13. Sriphrapradang C, Pavarangkoon S, Jongjaroenprasert W, Chailurkit LO, Ongphiphadhanakul B, Aekplakorn W. Reference ranges of serum TSH, FT4 and thyroid autoantibodies in the Thai population: the national health examination survey. Clin Endocrinol (Oxf) 2014; 80: 751-6.
14. Nannipieri M, Cecchetti F, Anselmino M, *et al*. Expression of thyrotropin and thyroid hormone receptors in adipose tissue of patients with morbid obesity and/or type 2 diabetes: effects of weight loss. Int J Obes (Lond) 2009; 33: 1001-6.
15. Lee JJ, Pedley A, Marqusee E, *et al*. Thyroid function and cardiovascular disease risk factors in euthyroid adults: a cross-sectional and longitudinal study. Clin Endocrinol (Oxf) 2016; 85: 932-41.
16. Strich D, Karavani G, Edri S, Gillis D. TSH enhancement of FT4 to FT3 conversion is age dependent. Eur J Endocrinol 2016; 175: 49-54.
17. Valdés S, Maldonado-Araque C, Lago-Sampedro A. Population-Based National Prevalence of Thyroid Dysfunction in Spain and Associated Factors: Diabetes Study. Thyroid 2017; 27: 156-66.
18. Janssen IM, Homan J, Schijns W, *et al*. Subclinical hypothyroidism and its relation to obesity in patients before and after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2015; 11: 1257-63.

19. Silvestri E, Schiavo L, Lombardi A, Goglia F. Thyroid hormones as molecular determinants of thermogenesis. Acta Physiol Scand 2005; 184: 265-83.
20. Mantzoros CS, Ozata M, Negrao AB, *et al.* Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. J Clin Endocrinol Metab 2001; 86: 3284-91.
21. Rotondi M, Leporati P, Rizza MI, *et al.* Raised serum TSH in morbid-obese and non-obese patients: effect on the circulating lipid profile. Endocrine 2014; 45: 92-7.
22. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab 2005; 90: 5483-8.
23. Kahapola-Arachchige KM, Hadlow N, Wardrop R, Lim EM, Walsh JP. Age-specific TSH reference ranges have minimal impact on the diagnosis of thyroid dysfunction. Clin Endocrinol (Oxf) 2012; 77: 773-9.
24. Vadiveloo T, Donnan PT, Murphy MJ, Leese GP. Age- and gender-specific TSH reference intervals in people with no obvious thyroid disease in Tayside, Scotland: the Thyroid Epidemiology, Audit, and Research Study (TEARS). J Clin Endocrinol Metab 2013; 98: 1147-53.