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## Is subclinical hypothyroidism increasing exogen obesity in children?

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**ÖZET**

**Amaç:** Obez çocuklarda tiroid fonksiyonları ve subklinik hipotroidi değerlendirilmesi amaçlandı.

**Gereç ve yöntemler:** Kırk üç obez çocuk ve kontrol grubu olarak benzer yaşta 17 idiopatik boy kısalığı olan çocuk, antropometrik ölçümler, bazal tiroid stimule edici hormon (TSH), serbest triiodotronin (sT3), serbest tiroksin (sT4), total tiroksin (TT4), total triiodotronin (TT3) düzeyleri ve tirotropin salgılatıcı hormon (TRH) uyarı testine TSH yanıtı ile değerlendirildi.

**Sonuçlar:** Obez ve kontrol grubunun, yaş, kemik yaşı, bazal TSH, sT3, sT4, TT4 düzeyleri arasında fark saptanmadı. Obez grubun TT3 düzeyleri kontrol grubundan anlamlı olarak yüksekti (p=0.009). TSH düzeylerinin maksimum artışı ve pik TSH düzeyleri, obez grupta, kontrol grubuna göre anlamlı olarak düşüktü (sırasıyla p=0.021, p=0.04). Obez grup, TSH yanıtına göre değerlendirildiğinde; Grup 1 (Anormal artış gösteren TSH yanıtı olanlar) ve grup 2 (TSH yanıtı normal olanlar) olarak ikiye ayrıldı. Grup 1'in bazal TSH'sı, grup 2'den anlamlı olarak yüksekti (p<0.001).

**Karar:** Bazal TSH düzeyleri yüksek olan obez çocuklarda TRH uyarı testi subklinik hipotroidizmi belirlemede yardımcı olabilir.

**Anahtar Kelimeler:** Çocuklar, obezite, subklinik hipotroidi, tirotropin salgılatıcı hormon uyarı testi.

**ABSTRACT**

**Background:** We aimed to evaluate thyroid functions and subclinical hypothyroidism in obese children.

**Methods:** Forty three children with exogenous obesity and 17 aged matched idiopathic short stature children (control group) were studied with anthropometric indices and basal thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), total thyroxine (TT4) and total triiodothyronine (TT3) levels and they all underwent thyrotropin releasing hormone (TRH) stimulation test to determine TSH response.

**Results:** There were no significant difference in age, bone age, basal TSH, fT3, fT4, TT4 levels between obese and control group. Total triiodothyronine levels of obese group were significantly higher than control group (p=0.009). The maximum increment of TSH levels (□ TSH) and peak TSH levels in obese group were significantly lower than the control group (p=0.021, p=0.04 respectively). We evaluated obese children for TSH response and divided them into two groups; obese group 1 ( TSH response abnormally elevated) and obese group 2 (TSH response were normal), basal TSH levels of group 1 were found significantly higher than group 2 (p<0.001).

**Conclusion:** Thyrotropin releasing hormone stimulation test may be helpful to determine subclinical hypothyroidism in exogen obese children, if basal TSH levels were elevated.

**Key words:** Children, obesity, subclinical hypothyroidism, thyrotropin releasing hormone stimulation test.

## INTRODUCTION

Childhood obesity is a multifactorial complex syndrome. Genetic, intrauterin, enviromental, dietary, familial and social factors are the risk factors for obesity. Generally, childhood obesity is exogenous and less than 10% of obese children are related with endocrine and genetic factors (1-5).

Thyroid function tests are generally in normal ranges in obesity, TT3 and fT3 levels may be high. The basal serum levels of TSH are generally in normal ranges but TSH response to exogenous TRH stimulation can be normal, blunted or augmented due to the hypothalamo-pituitary-thyroid axis activity alterations (5-6). The potential defects of thyroid function in obesity may be related to adaptation of hypothalamopituitary axis to obesity and nutritional related factors (7).

Subclinical hypothyroidism is characterized as normal serum thyroxine and triiodothyroidine levels and high basal TSH levels and/or augmented TSH response to exogenous TRH stimulation (8-9).

We aimed to evaluate thyroid function and subclinical hypothyroidism in obese children.

## MATERIAL AND METHOD

Fourty three children with exogenous obesity recruited to the study. The obese children due to endocrine disorders as hypoparathyroidism, Cushing disease, Bardet Biedl syndrome, Prader Willi syndrome... etc. and children with known iodine deficiency, thyroiditis, thyroid antibody positivity or any other thyroid disease were excluded from the study. The study was approved by the Ethics Committee of Ministry of Health Ankara Education and Research Hospital and informed consent was obtained from children's parents before examination.

We compared obese children to 17 otherwise healthy but idiopathic short stature children (control group), who had been evaluated with thyrotropin releasing hormone (TRH) stimulation test.

Thyrotropin releasing hormone (TRH) stimulation tests were performed to all obese and short statured children in the morning after at least 8 hours fasting period, through a polyethylene intravenous cannule with bolus injection of 5 µg/kg ( maximum 200 µg) synthetic TRH with in 1-2 minutes. Before TRH administration, blood samples were collected for basal levels of TSH, fT3, fT4, TT3, TT4. After TRH administration, blood samples were collected for TSH levels at 20., 40., 60. minutes. Thyroid function tests were measured with chemiluminesans method, Immulite 2000® Immunoassay. Normal basal TSH levels were between 0.7 and 6.4 uIU/ml and the normal peak TSH response to TRH stimulation was less than 20 uIU/ml. We defined the peak TSH levels more than 20 uIU/ml as augmented response (11,12). Only four children had nausea after TRH injection immediately and they recovered spontaneously in a few minutes.

Antropometric measurement of all children was performed by the same clinician who was training pediatrics, with the same weighing machine and stadiometer in pediatric endocrinology policlinic. Puberty was evaluated with Tanner stages by the same clinician. Also due to their chronological age, height and weight measurements, body mass index (BMI) [BMI= body weight (kg) / body surface (m<sup>2</sup>)], ideal body weight for height and relative weight of both obese children and control group were calculated. By the BMI charts of World Health Organisation (WHO), obesity was defined as a BMI> 95. percentile and relative weight > 120 % (2). We also evaluated the bone age with Greulich Pyle skeletal development atlas with left hand radyograms (10).

Statistical analyzes were studied with SPSS 11 programe with Mann Whitney U test, independent samples t test and chi-square test.

## RESULTS

We compared 43 obese children [boys (n: 19, 42%) and girls (n: 24, 55.8%) ] with 17 idiopathic short children [boys (n:13, 76.5%), girls (n: 4, 23.5%)] (control group).

There wasn't any statistically significant difference between two groups for bone age and chronologic age.

**Table 1:** Median chronologic age, bone age, basal TSH, peak TSH,  $\Delta$  TSH, TT3, TT4, fT3, fT4 levels of obese and control groups.

	Obese group (n=43)	Control group (n=17)	P values
Median chronologic age (year)	10.8 (4.16-15.4)	12 (2.75-15.4)	P=0.73
Median bone age (year)	11 (3.5-16)	10 (2-15)	P=0.68
Basal TSH (uIU/ml)	2.46 $\pm$ 1.5	2.8 $\pm$ 1.9	P=0.61
Peak TSH (uIU/ml)	13.68 $\pm$ 8.8	16.02 $\pm$ 5.9	P=0.04
$\Delta$ TSH (uIU/ml )	11.2 $\pm$ 7.7	13.2 $\pm$ 4.1	P=0.021
TT3 (ng/dl)	149.5 $\pm$ 33.4	128.6 $\pm$ 33	P=0.009
fT3 (pg/ml)	4.08 $\pm$ 0.8	3.99 $\pm$ 0.9	P= 0.72
TT4 (ug/dl)	8.89 $\pm$ 1.7	8.42 $\pm$ 1.6	P= 0.59
fT4 (ng/dl)	1.27 $\pm$ 0.2	1.21 $\pm$ 0.1	P=0.78

Mean body weight of obese subjects was 61.03  $\pm$  19.76 kg, median relative weight was 145% (123% - 264% ) and median BMI was 27.3 kg/m<sup>2</sup>( 19.7 kg/m<sup>2</sup> - 50 kg/m<sup>2</sup> ), BMI percentile of all obese subjects were over 95 percentile.

Relative weight, BMI percentile and height were significantly higher in obese group (p< 0.001).

In obese group, 19 (42.1%) patients and in control group 13 (76.5%) patients were prepubertal.

Although mean fT4, TT4 and fT3 were not statistically different between study and control groups, mean TT3 levels were significantly higher in obese group (p=0.009) (Table 1).

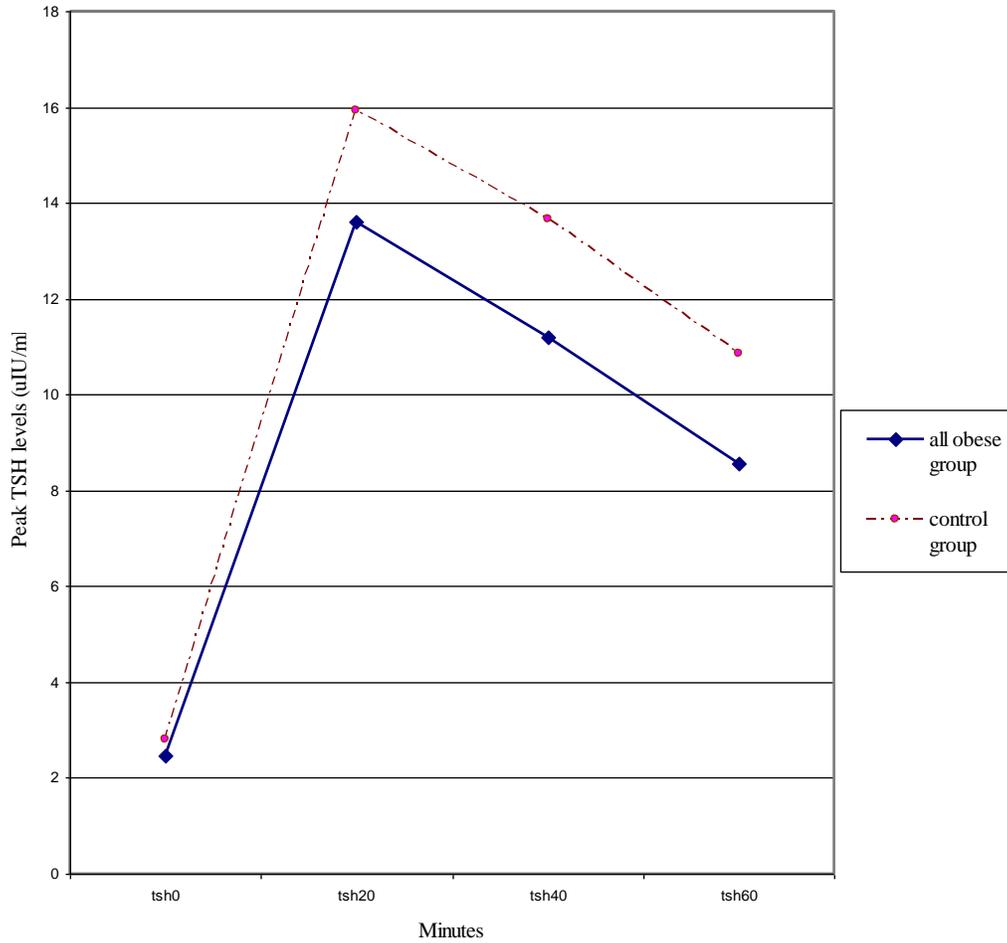
There wasn't any significant difference between obese and control groups for basal TSH levels (p=0.61) but mean peak TSH and  $\Delta$  TSH levels of obese subjects were significantly lower than control group on TRH stimulation test (p=0.04, p=0.021 respectively) (Table1).

We determined augmented TSH response to TRH stimulation, in 7 (16%) obese patients and in 3 (12%) control patients, and there wasn't a significant difference between two groups (p=0.58). The peak TSH responses were seen at 20. and 40. minutes in both of the groups and no delayed response was determined.

In obese group, we also compared subjects due to TSH response to TRH stimulation; seven (16.2%) children had augmented TSH response (defined as group 1), and 36 (83.7%) children had normal TSH response (defined as group 2) to TRH stimulation.

There was no significant difference between group1 and 2, for chronologic age, bone age, relative weight, height (Table 2). Basal levels of fT3, fT4, TT3, TT4 didn't differ between two groups, but basal TSH levels of group 1 were significantly higher than group 2 (p<0.001) (Table 2). In group 1 who had augmented TSH response to TRH stimulation, only one patient had high basal TSH level (7.91 mIU/l), but the other six subjects had normal basal TSH levels.

We evaluated the thyroid volumes of obese patients by ultrasonographically. All obese patients' thyroid volumes were normal respect to their body weights.



**Figure 1:** TSH response of all obese group and control group.

## DISCUSSION

In this study we aimed to evaluate the hypothalamic-pituitary-thyroid axis and determine whether there is subclinical hypothyroidism in obese children.

It's known that TSH response to TRH stimulation might be normal, blunted or augmented in obese children (13-18).

Mancini et al, found blunted TSH response to TRH stimulation in obese adults (18). In our study although the mean peak TSH and mean  $\Delta$  TSH levels were significantly lower than control group, no blunted response was observed.

Lala et al, compared 47 obese children with age matched short stature children and they found that peak TSH levels of obese group were significantly higher than control group (14). In another study, which compared obese children with 17 short stature children, there wasn't any difference for basal and peak TSH levels. They thought that short statured children as a control group might be effect the results (15) Also we enrolled short children as a control group in our study, we determined statistically significantly lower peak TSH values in obese group and no difference in basal TSH levels.

**Table 2:** Mean chronologic age, bone age, relative weight, height, basal TSH, peak TSH, Δ TSH, TT3, fT3, TT4, fT4 levels of obese group 1 and obese group 2.

	Group 1 (n=7)	Group 2 (n=36)	P values
Girls/boys (n)	6/1	18/18	P=0.176
Chronologic age (years)	11.6 (8.6-13.8)	10.6(4.16-15.4)	P= 0.78
Bone age (years)	10 (6.8-14)	11.5(3.5-16)	P= 0.87
Relative weight (%)	142 (126-169)	145 (123-264)	P=0.65
Height (cm)	154 (130-161)	147.5(110-173)	P=0.23
Prepubertal/pubertal (n)	¾	16/20	p=0.93
Basal TSH (uIU/ml)	4.37 ± 1.6	2.09 ± 1.2	P<0.001
Peak TSH (uIU/ml)	30.3 ± 7.5	10.4± 4.2	P<0.001
Δ TSH (uIU/ml)	25.9 ± 6.4	8.3 ± 3.61	P<0.001
TT3 (ng/dl)	142.8 ± 34.3	150.8 ± 33.6	P= 0.31
fT3 (pg/ml)	4.16 ± 0.7	4.07 ± 0.8	P= 0.17
TT4 (ug/dl)	8.07 ± 1.5	9.05 ± 1.7	P=0.23
fT4 (ng/dl)	1.08 ± 0.2	1.3 ± 0.2	P=0.22

In different studies, basal TSH levels (within normal ranges) of obese children were reported to be significantly higher than control group (6,7,19-22). In our study there was no difference between control and obese group with respect to basal TSH levels but peak and delta TSH levels of control group were significantly higher than obese subjects (p=0.04, p= 0.021 respectively). This result may be due to the control group which included short stature children. But we determined that obese patients with augmented response to TRH, had higher basal TSH levels

than who had a normal TSH response to TRH (p<0.001), so we thought that the increments of TSH may be an important signal of thyroid disorder in obese children.

It is still unknown whether the augmented response of TSH is the result of hypothalamo-pituitary axis abnormality or subclinical hypothyroidism. Although this has been tried to be explained with several studies, there aren't still enough data for obese children. Several reports support that variability of TSH response to TRH is due to the disorder of hypothalamo-pituitary axis. Coiro et al, studied with obese adults to evaluate if the serotonergic disorders effect TSH response to TRH. They determined a significant decrease of TSH response after fenfluramine administration in the group who had an augmented response to TRH. They informed that obese patients who had normal basal TSH levels but augmented TSH response to TRH stimulation should be evaluated by a second TRH stimulation test after fenfluramine administration for a more reliable diagnosis. However there wasn't any reason of augmented response of TSH to TRH, so it could be affected from the neuroendocrine disorders of hypothalamopituitary axis (13). On the other hand, another study revealed no difference in TSH response before and after fenfluramine administration (15).

In different studies, obese subjects had high or normal TT3 and TT4 levels respect to control groups, also TT4 and fT4 levels were inversely correlated with body weight (6, 15,19-24), but we didn't find any difference in fT3, fT4, TT4 between obese and control group.

Total T3 levels are diet sensitive and have a positive correlation with energy expenditure and basal metabolic rate. Calorie intake (especially carbohydrate intake) effects T3 metabolism. In fasting, T3 level decreases and with overfeeding T3 level increases (22-24). In our study TT3 levels were significantly higher in obese group. Our obese subjects were exogen obese and due to their overfeeding T3 levels might be elevated. If TT3

increment was due to thyroid binding globulin levels, both TT4 and TT3 would be elevated. So, determining increased TT3 levels but normal TT4 levels, should make us think some other factors. Also thyroid hormone binding capacity of serum carrier proteins can be altered by changes of nutritional status (7). Increased thyroid hormone concentrations could point to hormone resistance. Both TSH and peripheral thyroid hormones increase in obesity and there is a decreased negative feedback between them and also T3 receptors decreases (25).

Hypothalamopituitary thyroid axis and leptin, a signal of adipose tissue storage are closely related (26). Serum leptin concentrations tend to be high in obese patients. It might contribute to an increase of formation of proTRH and trigger a TRH dependent elevation of pituitary TSH stimulation. So, slightly increased TSH levels in obesity might be due to increased leptin production (27). If we could have studied leptin levels, it would be more useful for us to evaluate the relationship between thyroid hormones and obesity.

As it's known, mild variations of thyroid hormones can affect the resting energy expenditure and cumulative weight gain, so thyroid hormone replacement may be beneficial for subclinical hypothyroidism, but still controversial (9). Reinehr et al determined that there was a significant decrease in T3 and T4 levels but not any significant change in TSH levels after weight loss (26). Diet treatment was compared with diet combined thyroid hormone treatment in a study and combined treatment appeared to be more effective for weight loss (19,28). However, it was shown that TSH response to TRH stimulation became normal after diet treatment in obese subjects (29). Also a significant TSH decrease was shown after weight reduction surgery, but no change in FT3 levels (30).

In childhood obesity, adaptation of diet and exercise treatment is too hard and presence of

subclinical hypothyroidism makes weight loss more difficult. As a result, if basal TSH levels of exogenous obese children are elevated, TSH response to TRH may be augmented, so basal TSH may be a determining factor. Exogenous obese children can be evaluated for subclinical hypothyroidism when their TSH levels are closer to the upper ranges.

## REFERENCES

1. Gahagan S. Overweight and Obesity. in Kliegman RM, Stanton B, Geme JS, Schor N, Behrman RE, eds. Nelson Textbook of Pediatrics, 19<sup>th</sup> Ed. United States of America: Elsevier, 2011; 179-87.
2. Dennis M, Styne MD. Childhood and adolescent obesity prevalence and significance. *Pediatr Clin North Am* 2001; 48 (4): 823-54.
3. Maffei C. Aetiology of overweight and obesity in children and adolescents. *Eur J Pediatr* 2000; 159 (s1): 35-44.
4. Rolland-Cachera MF. Childhood obesity: Current definitions and recommendations for their use. *Int J Pediatr Obes*, 2011; 6: 325-31.
5. Alemzadeh R, Lifshitz F. Childhood obesity. In Lifshitz F. eds. *Pediatric endocrinology* 5th ed. New York: Informa Healthcare, 2007; 1: 1-25.
6. Aypak C, Türedi O, Yüce A, Görpeliöğlu S. Thyroid-stimulating hormone (TSH) level in nutritionally obese children and metabolic co-morbidity. *J Pediatr Endocrinol Metab*. 2013; 26: 703-8.
7. Stichel H, Allemann ID, Gruters A. Thyroid function and obesity in children and adolescents. *Horm Res* 2000; 54: 14-9.
8. Kabadi UM. Subclinical hypothyroidism, natural cause of the syndrome during a prolonged follow up study. *Arch Intern Med* 1993; 153: 957-61.
9. Kaplowitz PB. Subclinical hypothyroidism in children: Normal variation or a sign of a failing thyroid gland? *Int J Pediatr Endocrinol* 2010; 281453 Available from URL: <http://www.ijpeonline.com/content/2010/1/281453> [Accessed 2011 Aug 8]
10. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2<sup>nd</sup> ed. California: Stanford University press, 1959: 62-187
11. Nicholson JF, Pesce M. Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics, 16<sup>th</sup> ed. Philadelphia: W.B.Saunders Co, 2000; 2181-2228.
12. Synder PJ, Utiger RD. Response to thyrotropin releasing hormone in normal man. *J Clin Endocrinol Metab* 1972; 34: 380-5.
13. Coiro V, Passeri M, Capretti L, et al.. Serotonergic control of TSH and PRL secretion in obese men. *Psychoneuroendocrinol* 1990; 15 (4): 261-8.
14. Argenio G, Bernini G, Vivaldi MS, et al.. Effect of fenfluramine on prolactin and thyroid stimulating hormone response to thyrotropin releasing hormone in obese and normal women. *Eur J Clin Pharmacol* 1990; 39 (1): 13-16.
15. Lala V, Jamias P, Yogananda CS. Thyrotropin response to thyrotropin releasing hormone in children and adolescents with obesity. *Pediatr Res* 1984; 18 (169A): 442.

16. Lala VR, Ray A, Jamias P, Te D, Orteza N, Fiscina B, Noto R. Prolactin and thyroid status in prepubertal children with mild to moderate obesity. *J Am Coll Nutr* 1988; 7: 361-6.
17. Cacciari E, Frejaviile E, Balsamo A, et al. Disordered prolactin secretion in obese child and adolescents. *Arch Dis Child* 1981; 56: 386-9.
18. Mancini A, Fiumara C, Conte G, et al.. Pyridostigmine effects on TSH response to TRH in adult and children obese subjects. *Horm Metab Res* 1993; 25: 309-11.
19. Marras V, Casini MR, Pilia S, Carta D, Civolani P, Porcu M, Uccheddu AP, Loche S. Thyroid function in obese children and adolescents. *Horm Res Paediatr.* 2010;73:193-7
20. Marhawa RK, Tandon N, Garg MK, Ganie MA, Narang A, Mehan N, Bhadra K. Impact of body mass index on throid functions in Indian children. *Clin Endocrinol* 2013; 79: 424-8.
21. Ünüvar T, Anık A, Catlı G, Esen I, Abacı A, Büyükgebiz A, Böber E. Isolated hyperthyrotropinemia in childhood obesity and its relation with metabolic parameters. *J Endocrinol Invest.* 2014 Jun 12. [Epub ahead of print]
22. Emokpae MA, Adaleke SI, Uwumarongie HO. Subclinical hypothyroidism in childhood obesity and its correlation with lipoproteins. *Afr J Med Sci.* 2011; 40: 361-5.
23. Krotkiewski M. Thyroid hormones in the pathogenesis and treatment of obesity. *Eur J Pharmacol* 2002; 440: 85-98.
24. Proces S, Delgrange E, Borghet TV, Jamart J,Donckier JE. Minor alterations in thyroid function tests associated with diabetes mellitus and obesity in outpatients without known thyroid illness. *Acta Clinica Belgica* 2001; 56: 86-90.
25. Reinehr T, Andler W. Thyroid hormones before and after weight loss in obesity. *Arch Dis Child* 2002; 87: 320-3.
26. Korbontis M. Leptin and the thyroid. A puzzle with missing pieces. *Clin Endocrinol* 1998; 49: 569-72.
27. Pinkney HJ, Goodrick JK, Johnson BA, Lightman LS, Coppack WS, Vidya MA. Leptin and the pituitary thyroid axis: A comparative study in lean obese hypothyroid and hyperthyroid subjects. *Clin Endocrinol* 1998; 49: 583-8.
28. Abraham RR, Densem JW, Davies P, Davie MWJ, Wynn V. The effects of triiodothyronine on energy expenditure, nitrogen balance and rates of weight and fat loss in obese patients during prolonged caloric restriction. *Int J Obes.* 1985; 9: 433-42.
29. Carlson EH, Drenick JE, Chopra JI, Hersman MJ. Alterations in basal and stiumulated thyrotropin, prolactin and thyroid hormones in starved obese men. *J Clin Endocrinol Metab* 1977; 45: 707-13.
30. Chikunguwo S, Brethauer S, Nirujogi V, et al. Influence of obesity and surgical weight loss on thyroid hormone levels. *Surg Obes Relat Dis.* 2007;3:631-5.