

EFFECT OF SATIETY ON TSH AND FREE THYROXINE LEVELS IN HEALTHY INDIVIDUALS AND PATIENTS WITH SUBCLINICAL AND OVERT HYPOTHYROIDISM



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BACKGROUND: Thyroid stimulating hormone (TSH) and thyroxine levels may change according to fasting — satiety status.

AIM: The aim of this study was to determine the effect of satiety on TSH and free thyroxine levels.

METHODS: This study was conducted in a tertiary hospital. According to previous TSH and thyroxine levels, groups of 30, 30 and 60 participants were designated as subclinical hypothyroidism, hypothyroidism, and control groups respectively. To obtain TSH and thyroxine results first phlebotomy was performed at 8 am while participants were in fasting state. Then participants were allowed to have non-standardized breakfast. Second phlebotomy was performed at 10 am while participants were in non-fasting state. Paired t-test and ANOVA were used to analyze the data.

RESULTS: The fasting TSH levels of the participants (2.57 ± 1.84 mIU/L) were significantly higher than the satiety TSH levels (2.04 ± 1.48 mIU/L) ($t = 8.566$, $p < 0.001$, $d = 0.80$). The fasting free thyroxine values (1.31 ± 0.38 mg/dl) of the participants were significantly lower than the satiety free thyroxine values (1.39 ± 0.35 mg/dl) ($t = -1.988$, $p = 0.049$, $d = 0.20$).

CONCLUSION: Knowing how TSH and free thyroxine tests are affected by satiety has the power to affect treatment of many patients. Our study has shown that both TSH and free thyroxine levels changed significantly according to satiety status.

KEYWORDS: *Thyroid function tests; thyroid hormones; fasting; phlebotomy; breakfast*

BACKGROUND

Thyroid function tests are used to measure and evaluate thyroid functions. Serum Thyroid Stimulating Hormone (TSH) level is the main test used for screening thyroid dysfunction [1].

TSH produced in the pituitary causes release of thyroxine (T4) and triiodothyronine (T3) from the thyroid gland. The circulating thyroid hormones bind to carrier proteins such as thyroxine binding prealbumin, albumin and thyroxine binding globulin. Thyroid hormones bind to nuclear receptors in target tissues and show their effect [2].

TSH is a glycoprotein hormone that is released in a pulsatile manner and can remain in the blood for a long time after release. Therefore, plasma TSH variations are small and relatively moderate [3, 4]. TSH is regulated essentially by T4. Increased T4 in the blood suppresses TSH levels. The degree of TSH suppression directly reflects the level of T4 in the blood. TSH is very sensitive to changes in thyroid function and there is a logarithmic relationship between thyroid function and serum TSH level. For example, 50% decrease in serum T4 levels causes an increase in TSH levels between 100-160%. Small changes in T4 level lead to excessive fluctuations of the serum TSH level. Therefore, TSH test can reflect even the smallest changes in thyroid function [5].

AIM

The aim of this study was to determine the effects of satiety on TSH and free thyroxine (fT4) values. Thus, it may contribute to the standard of measurement of thyroid function tests used for screening, diagnosis and monitoring of thyroid diseases.

METHODS

Study Area and Sampling

This quasi-experimental study was conducted on patients who applied to outpatient clinics of tertiary hospital of Çanakkale Onsekiz Mart (COMU) University Hospital between the dates of 1 August 2017 and 30 November 2017. The COMU University Hospital has 280 physicians and 677 beds and it is the only tertiary hospital in Çanakkale province in Turkey which has 519,793 inhabitants. The population of this study consisted of patients who applied to the outpatient clinics of the tertiary hospital.

The formula for related samples t-test was used to calculate sample size. For calculating the sample size, α error level was accepted as 0.05 and the power of the study was accepted as 90%. Means, standard deviations and correlation of TSH values from two previous studies were used [6, 7]. Sample size was calculated as 15 by G*Power (version 3.1) software [8].

The study was conducted in three groups. The first group was selected from patients without any disease (TSH and fT4 normal), the second group was selected from patients with subclinical hypothyroidism who did not receive thyroid hormone replacement (TSH high, fT4 normal), and the third group was with overt hypothyroidism (TSH high, fT4 low) received thyroid hormone replacement. According to the previous TSH – fT4 results and electronic recordings, patients were assigned into these groups until sufficient number of participants was reached for each group. The number of participants was 60 in the normal group and 30 each in subclinical hypothyroidism and primary hypothyroidism groups.



Individuals older than 18 years who gave their consent were included in the study. Pregnancy, chronic endocrinological disorders, thyroid diseases except those specified in the definition of groups, medicament use (steroid, dopamine, bromocriptine, somatostatin, prolactin inhibitors), history of previous thyroid operation, were the exclusion criteria of the study.

Application

Participants were invited to outpatient clinics of the tertiary hospital by telephone call and they were asked not to take any food or medicine after 12 pm. First phlebotomy was performed at 8 am while patients were at overnight fasting state. Then patients were allowed to have breakfast. Second phlebotomy was performed at 10 am while patients were satiated.

The study data consisted of socio-demographic data, fasting and satiety levels of TSH and fT4. Third generation ultra-sensitive chemi-luminometric method was used to measure TSH while radioimmunoassay method was used to measure fT4.

Informed Consent Statement: All participants' rights were protected, and written informed consents were obtained before the procedures according to the Declaration of Helsinki.

Ethical Approval: The research related to human use has been conducted in compliance with all the relevant national regulations, institutional policies and in accordance with the tenets of the Declaration of Helsinki, and has been approved by the Ethics Committee of Clinical Research of Çanakkale Onsekiz Mart University with the ID of 2017-09.

Statistical Analysis

After descriptive statistics, univariate tests were performed. Linearity was checked by scatter/dot graphs; homogeneity of variance was checked by Levene test. The normal distribution assumption was neglected on the basis of the central limit theorem since there were at least 30 people in each group [9]. Chi-square was used for categorical variables, independent t test, paired t test and ANOVA for continuous variables. In the cases of heteroscedasticity, the corrected t value for t test and Welch value for ANOVA was reported [9]. For hypothesis tests, $p < 0.050$ was accepted as the limit of significance. Test value, absolute p value and effect size were reported for all analyzes.

RESULTS

Of the participants, 94 (78.33%) were female and 26 (21.67%) were male. The mean age of the participants was 45.57 ± 17.64 years, and the mean body mass index was 23.79 ± 3.67 . Of the participants, 18 (15.00%) were primary school graduates, 6 (5.00%) were secondary school graduates, 14 (11.67%) were high school graduates, 61 (50.83%) were university graduates. On the other hand, 21 (17.50%) participants were literate without formal education. The details of the socio-demographic characteristics of the groups are given in Table 1.

The fasting TSH levels of the participants (2.57 ± 1.84 mIU/L) was significantly higher than the satiety TSH levels (2.04 ± 1.48 mIU/L) ($t = 8.566$, $p < 0.001$, $d = 0.80$). The fasting fT4 value (1.31 ± 0.38 mg/dl) of the participants was significantly lower than the satiety fT4 value

Table 1. Socio-demographic characteristics of the participants according to the groups

	Normal	Subclinical hypothyroidism	Hypothyroidism	Test Value, p Value, Effect Size
Age	42.23±17.31	45.83 ± 17.12	51.97 ± 17,58	F: 3.159 p: 0.046 η^2 : 0.051
Female gender	44 (73.33%)	27 (90.00%)	23 (76.67%)	χ^2 : 3.339 p: 0.188
Marital status				
Married	40 (66.67%)	20 (66.67%)	22 (73.33%)	χ^2 : 3.613 p: 0.461
Single	20 (33.33%)	10 (33.33%)	8 (26.67%)	
Education level				
University	37 (61.67%)	13 (43.33%)	11 (36.67%)	χ^2 : 5.902 p: 0.052
Other	23 (38.33%)	17 (56.67%)	19 (63.33%)	
BMI	22.81 ± 2.91	24.10 ± 4.76	25.46 ± 3.25	F: 5.772 p: 0.004 η^2 : 0.090
Chronic disease: +	25 (41.67%)	12 (40.00%)	11 (36.67%)	χ^2 : 0.208 p: 0.901
Family history of thyroid disease: +	9 (15.00%)	10 (33.33%)	10 (33.33%)	χ^2 : 5.502 p: 0.064

BMI: Body mass index, η^2 : eta square

Table 2. Subgroup analysis of TSH

	Fasting TSH (mIU/L)	Satiety TSH (mIU/L)	Statistics* (between fasting and satiety), Effect size
Normal	2.18 ± 1.2	1.78 ± 1.05	t: 8.352, p< 0.001, d: 1.10
Subclinical hypothyroidism	2.43 ± 1.76	2.02 ± 1.42	t: 4.000, p< 0.001, d:0.70
Hypothyroidism	3.50 ± 2.57	2.58 ± 2.07	t: 4.767, p< 0.001 d: 0.90
TOTAL	2.57 ± 1.84	2.04 ± 1.48	t: 8,566, p< 0.001. d: 0.80
Statistics** (between groups), Effect size	F: 3.536, p: 0.037, η²: 0.088	F: 2.092, p: 0.134, η²: 0.049	

d: Cohen's d, η²: eta square, *: Paired sample t test, **: ANOVA

Table 3. Subgroup analysis of fT4

	Fasting fT4 (mg/dl)	Satiety fT4 (mg/dl)	Statistics* (between fasting and satiety), Effect size
Normal	1.26 ± 0.19	1.37 ± 0.27	t: -3.093, p: 0.003, d: 0.40
Subclinical hypothyroidism	1.32 ± 0.44	1.44 ± 0.55	t: -1.453, p: 0.157, d: 0.30
Hypothyroidism	1.41 ± 0.56	1.38 ± 0.24	t: 0.280, p: 0.782, d: 0.05
TOTAL	1.31 ± 0.38	1.39 ± 0.35	t: -1.982, p: 0.049, d: 0.20
Statistics** (between groups). Effect size	F: 1.158, p: 0.324, η²: 0.025	F: 0.356, p: 0.701, η²: 0.006	

d: Cohen's d, η²: eta square, *: Paired sample t test, **: ANOVA

(1.39 ± 0.35 mg/dl) (t = -1.988, p = 0.049, d = 0.20). Statistically significant decrease of TSH levels was observed in all clinical groups, while significant fT4 increase was found only in the healthy group. Fasting and satiety levels of TSH and fT4 are provided in Table 2 and Table 3 respectively.

DISCUSSION

In our study, it was determined that TSH values measured in non-fasting state were significantly lower than fasting TSH values while fT4 values measured in non-fasting state were significantly higher than fasting fT4 values.

Studies in the literature [6, 7, 10–17] have shown that satiety causes a decrease in TSH in general, but this effect isn't seen in children [18]. In our study, the lowering effect

of satiety on TSH was observed in all normal, subclinical hypothyroid and hypothyroid groups as in previous studies [6, 14, 15]. Only for subclinical hypothyroid group the effect size was medium while for all other groups and in total the effect size was high.

One of the most likely reasons why the fasting TSH value is higher than the satiety TSH value is the suppression of TSH by an inhibitory hormone called somatostatin released after meals. Somatostatin, released within 90–120 minutes following food ingestion leads to decrease in plasma TSH [19]. Another confounding factor that may affect the TSH results is the time of phlebotomy. TSH peaks between 11 pm and 5 am due to diurnal and circadian variations. The plasma TSH value decreases in a nonlinear fashion towards the evening hours and reaches its minimum between 5 pm and 8 pm

in the evening. [20]. Kamat et al. have shown that the effect of satiety on TSH is related to the content of the food rather than its stomach-expanding effect [11]. However, in some studies, observations of similar TSH reduction without food suggest that this decrease may not be related to food [7, 16]. These studies suggest that the effects of meal content and diurnal-circadian variations on TSH are complex and intertwined. Although it is thought that the difference of measurement methods may be yet another confounding factor but it has been shown that the effect of satiety on TSH is not affected by measurement methods [16].

In many studies [6, 11, 14–16, 18], there was no significant effect of satiety on fT4 level while in our study it was determined that satiety can increase fT4 level only in the control group. But even this effect has small effect size. In a previous study related to the subject it was found that, similar to this study, satiety caused an increase in fT4 levels [13].

In addition to food intake, the fact that time of phlebotomy may cause changes in TSH levels revealed the necessity of implementing measurement standardization. At least during patient follow-up, performing each measurement at the same time may provide more accurate results.

It is difficult to interpret the results of previous studies because of the lack of effect size. In our study, the effect size was reported and cases with small effect sizes were determined, even if it was statistically significant. Due to the changes in TSH and fT4 measurement techniques over time, it is important that the findings are repeated with current methods.

The results of this study should be generalized with caution because this study was conducted only in a tertiary hospital. The content of breakfast was left to the preference of patients without any standardization and it might

be considered a limitation of our study. But researchers intentionally did not standardize the breakfast because such a restriction was not possible in daily life. Most important confounding factor of the study was time, but it is the general limitation of a quasi-experimental pre-post study.

CONCLUSION

TSH and fT4 tests are used frequently for both diagnostic research and patient follow-up. Knowing how TSH and fT4 tests are affected by daily fluctuation and fasting–satiety status has the power to affect treatment of many patients. Our study showed that both TSH and fT4 levels changed significantly with fasting–satiety status by revealing the effect size. Therefore, it is important to standardize the measurement of TSH and fT4. More studies are needed to determine whether the fasting or non-fasting levels of TSH and fT4 should be used for diagnosis and follow up of thyroid diseases.

ADDITIONAL INFORMATION

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