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Research Article

Correlation between Body Mass Index and Thyroid Function in Euthyroid Individuals in Greece

Anastasios Milionis[1] and Charalampos Milionis[2]

[1] *Department of Endocrinology, Local Health Unit of N. Kosmos, Social Insurance Institute (IKA-ETAM), Machis Analatou and Lagoumitzi, 11744 Athens, Greece*
[2] *Directorate of Public Health, Region of Central Greece, Ainianon 2, 35100 Lamia, Greece*

Correspondence should be addressed to Charalampos Milionis; pesscharis@hotmail.com

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Although the effects of hypothyroidism and hyperthyroidism on body weight have been clearly demonstrated, there is no sufficient data on the relationship between the body mass index (BMI) and minor differences within the normal range of thyroid function. The present study aims to investigate the relationship of fluctuations of the thyroid stimulating hormone (TSH) and thyroid hormones with BMI in euthyroid subjects. The study included 736 euthyroid healthy individuals of known age, weight, height, and biochemical picture of the thyroid function. Individuals were classified according to BMI and thyroid hormones' values. The variations of normal thyroid function in euthyroid individuals were associated with body weight changes. A statistically significant positive correlation between BMI and thyroid function in women was found, while in men the correlation was not statistically significant. The alterations in thyroid function are mainly primary, while changes in body weight are secondary. The reason may be simple or multifactorial, and the biological mechanism is not completely known. Finally, the thyroid function disorders in conjunction with the strong influence of various environmental factors can increase body weight and lead to obesity.

1. Introduction

The relationship between thyroid function and body weight in euthyroid individuals has been given a great medical concern. Various researchers have studied the effect of the thyroid hormones on body mass index (BMI), and it has been demonstrated that overt thyroid dysfunction affects body weight. Clinical hypothyroidism causes an increase in body weight, while hyperthyroidism reduces it [1]. However, variations in thyroid function exist also between individuals with thyroid hormones' levels within the reference (physiologic) range [2]. These slight differences within the normal thyroid function may have important implications for the regulation of body weight and thus the prevalence of obesity. Although the optimal values for thyrotropin (TSH), T4 and T3 are not firmly established, there is a modern trend towards the narrowing of the reference normal range, especially for TSH [3]. In 2003, the American Association of Clinical Endocrinologists (AACE) defined the boundaries of the normal thyroid function and proposed the treatment of thyroid dysfunction when the serum TSH levels are off the narrow limits of 0.3–3.0 mIU/L [4].

Until now, data has led to the view that an increase in body weight can be attributed to diverse thyroid function (as it is expressed by TSH levels) even in euthyroid subjects [5, 6]. Furthermore, the Dan Thyr Study showed that BMI was positively correlated to serum TSH, negatively to serum free T4 (FT4) and had no correlation to serum free T3 (FT3) [7]. In another study, morbidly obese women (BMI > 40 kg/m^2) had higher TSH levels than others with moderate obesity (BMI < 40 kg/m^2), and TSH values were positively correlated to BMI in euthyroid subjects. In addition, lower FT4 values were accompanied by higher BMI values, but no relationship between BMI and FT3 was found [8]. Another study showed that morbidly obese subjects had higher levels of total T3 (TT3), FT3, total T4 (TT4), and TSH than those of the control group, probably as a result of the reset of their central thyrostat at higher level [9], whereas other researchers

showed that in overweight individuals with normal thyroid function the serum TSH levels and the grade of obesity were positively correlated [10].

FT4 has been closely associated with metabolic syndrome factors independently of insulin resistance. The serum FT4 (not TSH) was found to have a negative correlation with BMI. It was also negatively associated with total cholesterol and triglycerides and positively associated with HDL. The serum TSH levels were positively related only to triglycerides [11]. Moreover, FT4 was lower and TSH was higher in euthyroid hypertensive individuals compared with the corresponding normotensive individuals [12], while in euthyroid men the resting energy expenditure (REE) was found to be related to variations in the values of TT3 [13].

In contrast, other studies showed no relation between BMI and thyroid function in euthyroid individuals or patients with subclinical hypothyroidism [14, 15]. In a study among euthyroid women, the serum TSH values were not different between lean and obese euthyroid women and were not accompanied by a disorder of a lipidemic parameter which can be related to subclinical hypothyroidism, although there was a significant negative correlation between FT4 and BMI [16].

Finally, it is ascertained from the above that although a clear epidemiological association of thyroid function with body weight in euthyroid persons has not been completely established, the thyroid hormones may be an important determinant of the resting energy expenditure in people with normal thyroid function. In populations where physical activity is gradually reduced, a relatively small change in thyroid function can affect body weight. The present study aims at the detection of any correlations between the thyroid hormone values and the fluctuations of BMI and its parameters (weight and height).

2. Materials and Methods

2.1. Subjects. The study was conducted in the Department of Endocrinology of the IKA-ETAM (Social Insurance Institute) branch of N. Kosmos, Athens, Greece, and was approved by the administration of the institute. The study used the archives of the laboratorial exams of the department during the years 2009-2010.

The present study included 736 euthyroid persons, 616 females and 118 males (2 with missing information regarding gender were excluded from gender comparisons) who were clinically healthy. Detailed age, medical history, and smoking data were obtained. The selection of the sample followed certain criteria. The subjects did not suffer from any kind of thyroid disease or pathogenic condition that could affect the concentration of the thyroid hormones in the serum. Furthermore, they were not under any medication which could affect the thyroid function or the concentration of T4 and T3 in the serum. Any person with an abnormal TSH, TT3, TT4, FT3, or FT4 value was excluded. The individuals were subjected to the measurement of thyroid hormones for screening purposes. As regards age, the mean value ± standard deviation (median) was 52.5 ± 15.4 (54.0) years, weight 75.9 ± 17.5 (73.2) kg, and height 1.62 ± 0.09 (1.61) m, respectively. For subjects with valid height and weight measurements, BMI was calculated based on the following formula:

$$\text{BMI} = \frac{\text{Weight (Kg)}}{\left(\text{Height (m)}\right)^2}. \quad (1)$$

We created 4 classes of subjects according to BMI values: normal (BMI < 25), overweight (25 < BMI < 30), obese (30 < BMI < 35), and morbidly obese (BMI > 35). The hormone levels were measured by an enzymatic method, and the same assays were used for all the measurements. Normal values with the corresponding units were listed for TT3 (0.6–1.65 ng/mL), TT4 (4.4–11.0 μg/dL), FT3 (2.1–3.8 pg/mL), FT4 (0.7–1.7 ng/dL), and TSH (0.25–5.0 μIU/mL), respectively.

2.2. Statistical Methods. Descriptive statistics by gender (mean, standard deviation, median, quartiles, etc.) were used to present values for all continuous variables. Normality assumption was tested using the Kolmogorov-Smirnov test. Due to several deviations from normality, we used both parametric and nonparametric approaches. Specifically for bivariate correlation, we used Pearson's and Spearman's correlation coefficients to assess correlation between somatometric variables (height, weight, and BMI) with response variables FT3, FT4, TT3, TT4, and TSH. Correlation of somatometric characteristics with age was also computed to consider any plausible confounding effect of age. BMI was classified into 4 main categories (<25, 25–30, 30–35, and >35). Overweight (BMI > 25), obesity (BMI > 30), and morbid obesity (BMI > 35) percentages were calculated and presented as well.

BMI was treated as the main somatometric variable, so any difference by gender was considered, using contingency tables, presenting BMI classes, absolute and relative frequencies, along with the respective Chi-square P value (Fisher's exact test for 2 × 2 tables and Pearson's correction test for higher dimensional tables). Odds ratio was also computed and presented as point estimation and 95% confidence interval, for the odds of being overweight, obese, and morbidly obese (female versus male).

Bar charts were used to present mean levels for each thyroid hormone by BMI classes. In order to test basic thyroid hormone levels at different BMI classes, we used one-way ANOVA F-test along with post hoc Tukey test for multiple comparisons to specify any potential difference. Additionally, nonparametric Kruskal-Wallis test was used to verify the ANOVA F-test results. Using BMI, height, and weight as dependent variables, we fitted multiple linear regression models to detect statistically significant predictors. For BMI classes, we used bivariate logistic regression models to study the odds of being overweight (BMI > 25), obese (BMI > 30), and morbidly obese (BMI > 35) considering thyroid hormone levels and age as independent variables.

For all tests and confidence intervals, a significance level of 5% was used. For data management and statistical analysis, the statistical package SAS v. 9.0 was used.

Table 1: Descriptive statistics by gender for basic somatometric characteristics and thyroid parameters.

	Descriptive statistics by gender								
	n	Mean	Standard deviation	Median	1st quartile	3rd quartile	Min.	Max.	*P* value[†]
Age (years)									
Total	736	52.5	15.4	54.0	41.0	65.0	20.0	79.0	0.015[*]
Male	118	54.4	15.7	56.5	43.0	67.5	20.0	79.0	0.010[*]
Female	616	52.1	15.3	53.0	40.0	64.0	20.0	79.0	0.010[*]
Weight (kg)									
Total	736	75.9	17.5	73.2	62.2	86.1	38.1	142.3	0.020[*]
Male	118	85.8	18.5	82.5	72.6	97.0	54.0	142.0	0.010[*]
Female	616	74.1	16.7	72.0	61.7	83.7	38.1	142.3	0.010[*]
Height (m)									
Total	736	1.62	0.089	1.610	1.550	1.670	1.35	1.92	0.175
Male	118	1.70	0.096	1.700	1.630	1.780	1.45	1.92	0.150
Female	616	1.60	0.078	1.600	1.550	1.650	1.35	1.90	0.010[*]
BMI (kg/m^2)									
Total	736	29.05	6.31	28.46	24.52	32.84	14.38	53.15	0.250
Male	118	29.58	5.38	29.25	25.39	32.56	19.83	53.15	0.150
Female	616	28.96	6.48	28.13	24.37	32.88	14.38	51.42	0.010[*]
TT3 (ng/mL)									
Total	736	1.12	0.25	1.10	0.98	1.21	0.35	3.19	0.018[*]
Male	118	1.13	0.26	1.13	0.96	1.24	0.62	2.22	0.012[*]
Female	616	1.12	0.25	1.10	0.98	1.21	0.35	3.19	0.010[*]
TT4 (μg/dL)									
Total	736	7.30	1.44	7.30	6.42	8.10	0.83	13.20	0.320
Male	118	7.02	1.48	7.10	6.23	7.80	2.00	10.10	0.150
Female	616	7.37	1.40	7.40	6.50	8.19	1.20	13.20	0.024[*]
FT3 (pg/mL)									
Total	736	2.86	0.48	2.83	2.59	3.11	1.08	6.70	0.148
Male	118	2.92	0.50	2.90	2.59	3.22	1.23	4.20	0.150
Female	616	2.85	0.48	2.81	2.60	3.10	1.08	6.70	0.010[*]
FT4 (ng/dL)									
Total	736	1.15	0.78	1.07	0.96	1.21	0.52	14.15	0.020[*]
Male	118	1.08	0.24	1.06	0.93	1.17	0.52	2.12	0.010[*]
Female	616	1.17	0.85	1.08	0.97	1.21	0.63	14.15	0.010[*]
TSH (mU/L)									
Total	736	2.81	2.09	2.11	1.28	3.80	0.40	9.92	0.005[*]
Male	118	2.99	2.43	1.98	1.29	4.09	0.40	9.90	0.010[*]
Female	616	2.79	2.02	2.12	1.28	3.77	0.41	9.92	0.010[*]

[†]Kolmogorov-Smirnov normality test *P* value.
[*]Statistically significant result.

3. Results

Deviations from normal-Gaussian distribution were obvious for most of the numeric variables (somatometric and thyroid parameters) (Table 1). BMI was the main result variable (combining information from both height and weight), so apart from descriptive statistics, it was clear that we had to consider any possible effect modifiers, beginning with gender. Almost 7 out of 10 subjects (70.9%) were overweight or obese (BMI > 25), 4 out of 10 (39%) were obese (BMI > 30), while almost 2 out of 10 (17%) were morbidly obese (BMI > 35). BMI distribution (4 classes) differed indicatively between male and female subjects ($P = 0.078$). The prevalence of overweight obesity (BMI > 25) was statistically significantly higher in males (odds ratio or males versus females 1.72, $P = 0.027$). For BMI > 30 and BMI > 35, none of the differences were statistically significant (Table 2). BMI was significantly positively correlated with age, TT3, and TT4 in female patients, while for male patients only indicative correlations were detected through the use of nonparametric Spearman's correlation with FT3 (positively) and TSH (negatively). Weight was positively correlated with age, TT3, and TT4 in female patients, although the correlation coefficient was rather low ($P = 0.10$). For male patients, there was an

Table 2: BMI distribution among males and females.

	Male	Female	P value odds ratio Female versus male
BMI			
<25	24 (20.34%)	189 (30.68%)	
25–30	44 (37.29%)	190 (30.84%)	0.078
30–35	32 (27.12%)	130 (21.10%)	
>35	18 (15.25%)	107 (17.37%)	
Overweight			
No (BMI < 25)	24 (20.34%)	189 (30.68%)	0.027
Yes (BMI > 25)	94 (79.66%)	427 (69.32%)	0.58 (0.36–0.93)
Obesity			
No (BMI < 30)	68 (57.63%)	379 (61.53%)	0.471
Yes (BMI > 30)	50 (42.37%)	237 (38.47%)	0.85 (0.57–1.27)
Morbid obesity			
No (BMI < 35)	100 (84.75%)	509 (82.63%)	0.688
Yes (BMI > 35)	18 (15.25%)	107 (17.37%)	1.17 (0.68–2.01)

indicative correlation of weight with age (negative) and FT3 (positive). Height was negatively correlated with age for both male and female subjects. For male subjects only, height was also negatively correlated with FT4 and TT4 (Table 3).

Mean levels of TT3 and TT4 differed statistically significantly among different BMI classes (P value 0.037 and < 0.001, resp.). The overall trend for both TT3 and TT4 was increasing with BMI values (positive relation). The difference for TT3 mean level was statistically significant between the 1st and 4th BMI classes (BMI < 25 versus BMI > 35), while for TT4 statistically significant differences were detected between the 1st and 4th BMI classes (BMI < 25 versus BMI > 35) as well as between the 2nd and 4th BMI classes (BMI 25–30 versus BMI > 35) (Table 4). The above mentioned increasing trend of TT3 and TT4 was obvious. For FT3, while starting from high levels (for BMI < 25), mean level fell to the minimum (2.779) for BMI 25–30 and rose again for BMI 30–35 and > 35. On the other hand regarding FT4 and BMI, there was a clear (although not statistically significant) decreasing trend for higher BMI levels. For TSH, which is the main thyroid marker in terms of sensitivity and validity, there was only an indicative (negative) correlation with BMI only for male subjects. This decreasing trend with BMI was also obvious (although not statistically significant) for the total group of patients. This clear decreasing trend may be an indication of a general clinical (and not only statistical) mechanism present mainly for male subjects. Considering the low sample size for male subjects (compared to females), it was more than probable that this trend will be clearer for a higher sample size.

In the next step, we tried to include all predictors in separate models for BMI, height, and weight. In this way, we tried to imitate real effects, meaning that all of these factors act at the same time and interact with each other. Having all predictors in the same model, we had the chance to see step by step which are the most important factors in terms of statistical significance for BMI, weight, and height, respectively. Combining the information of all possible predictors for somatometric parameters (BMI, height, and weight), we used multiple linear regression models to detect the best set of predictors for each one of the above basic variables. For BMI as a dependent variable, TT4 and age were positively related with BMI. Specifically, for every additional unit of TT4, BMI increases by 0.608 units, while for every additional year of age, BMI increases by 0.076 units. For height as a dependent variable, gender and age were negatively related with height. Specifically, female subjects had 0.109 meters lower height compared to male subjects, while for every additional year of age, height decreases by 0.002 meters. For weight as a dependent variable, gender and TT4 were statistically significantly related with weight. Specifically, female subjects had 14.08 kg less weight compared to male subjects, while for every additional year of TT4, weight increases by 1.77 kg (Table 5).

Focusing on BMI classification, we used bivariate logistic models to study the effect of thyroid hormone levels and age to BMI. For the probability of BMI > 25 (overweight obesity), for every additional year of age, the chance of overweight obesity increases by 4.6%, while for every additional unit in TT3, the chance of overweight obesity increases 2.6 times. For the probability of BMI > 30 (obese), for every additional year of age, the chance of obesity increases by 2.5%, while for every additional unit in TT3, the chance of obesity increases 2.1 times. For the probability of BMI > 35 (morbid obesity), for every additional year of TT4, the chance of morbid obesity increases by 40.9%, while for every additional unit in FT4, the chance of morbid obesity decreases to 22.4% (almost 1/5) (Table 5).

4. Discussion

The correlation between BMI and the various thyroid hormones differed in both sexes. In women, there was a statistically significant association between BMI and TT3 and TT4, while in men BMI was positively associated with FT3 levels and negatively with TSH. BMI depends on fluctuations in

Table 3: Correlations somatometric measures with basic thyroid hormone levels.

Correlations	N	Pearson		Spearman	
		Coefficient	P value	Coefficient	P value
		BMI			
Female					
Age	594	0.21	<0.001*	0.25	<0.001*
FT3	339	0.04	0.445	0.08	0.161
FT4	393	−0.06	0.255	−0.04	0.442
TSH	616	−0.04	0.265	−0.04	0.265
TT3	432	0.15	0.002*	0.18	<0.001*
TT4	474	0.16	<0.001*	0.15	0.001*
Male					
Age	108	0.03	0.723	−0.01	0.880
FT3	62	0.16	0.219	0.22	0.082**
FT4	74	0.12	0.317	0.07	0.559
TSH	118	−0.15	0.103	−0.17	0.069**
TT3	84	0.06	0.565	0.11	0.308
TT4	89	0.16	0.128	0.12	0.273
		Weight			
Female					
Age	594	0.05	0.212	0.10	0.016*
FT3	339	0.02	0.676	0.09	0.098**
FT4	393	−0.04	0.456	0.00	0.929
TSH	616	−0.03	0.481	−0.05	0.229
TT3	432	0.16	0.001*	0.22	<0.001*
TT4	474	0.17	<0.001*	0.15	0.001*
Male					
Age	108	−0.11	0.238	−0.17	0.079**
FT3	62	0.14	0.275	0.23	0.072**
FT4	74	−0.05	0.677	−0.08	0.513
TSH	118	−0.14	0.122	−0.14	0.120
TT3	84	0.04	0.718	0.09	0.424
TT4	89	0.05	0.636	0.03	0.807
		Height			
Female					
Age	594	−0.38	<0.001*	−0.40	<0.001*
FT3	339	−0.02	0.672	0.01	0.915
FT4	393	0.05	0.319	0.05	0.295
TSH	616	0.02	0.585	−0.01	0.848
TT3	432	0.04	0.375	0.05	0.289
TT4	474	0.01	0.906	0.02	0.678
Male					
Age	108	−0.28	0.003*	−0.30	0.002*
FT3	62	−0.01	0.940	0.03	0.814
FT4	74	−0.31	0.007*	−0.27	0.021*
TSH	118	−0.05	0.570	−0.03	0.763
TT3	84	−0.05	0.678	−0.04	0.746
TT4	89	−0.18	0.098**	−0.22	0.041*

*Statistically significant correlations.
**Indicative correlations.

body weight and height. In our sample, changes in women's BMI were attributed mainly to weight changes and less to height changes, while in men the correlations were only indicative. In obese individuals, the correlation coefficients were much higher than in other categories of individuals. The serum T3 values were not correlated to BMI, and an increase in serum T3/T4 ratio was observed in individuals with increased BMI. These findings suggest that normal thyroid function may be associated with changes in BMI, but there is not a clear relationship. This interpretation can be simple or multifactorial. Moreover, the disorders of the thyroid function may be primary, and the BMI changes may be secondary or vice versa. During a progressive impairment of the thyroid function, the levels of TSH and thyroid hormones change until clinical hypothyroidism is presented. This may conceal a biological mechanism which justifies secondary changes in body weight.

The causal relationship between BMI and variations in thyroid function could be explained by the process of thermogenesis. Thyroid hormones increase thermogenesis through an increase in cellular activity to produce ATP [17]. The exact mechanism has not been determined. In order to increase energy consumption, thyroid hormones have been administered for the treatment of obesity with little success. The increase of the dosage for the achievement of the maximal desired effects led to side effects, and thus it was abandoned [18].

The relationship between TSH and BMI was investigated under the influence of adipose tissue signals. The leptin produced by cells has important effects on the central regulation of thyroid function through TRH. This is important for the downward adjustment of excess energy, but the importance of action under normal circumstances is unknown [19, 20]. There has been found a positive correlation between serum leptin and TSH which also means a positive correlation between BMI and TSH [21]. But if this is the responsible mechanism, there would also be an increase in T4 secretion. Instead, FT4 was decreased with increasing BMI. This probably means that the disorders of thyroid function (low FT4 and increased TSH) are primary, and BMI changes are secondary. The increase in BMI and fat mass may lead to increased serum leptin and to an expected positive correlation between TSH and leptin concentrations. Hypothetically, factors secreted from adipose tissue which directly stimulate the thyroid in a disastrous way could be responsible. The metabolites of estrogens could be one such factor, because the 2-methyloxy-estradiol has been shown to have a destructive effect in thyroid cells cultures [22]. Infection's cytokines which are released by visceral fat have been proven to inhibit the hypothalamic-pituitary axis [23]. This will lead to negative correlations between BMI and serum TSH and between BMI and serum T4.

Recent studies in humans and mammals have shown strongly that fat cells and precursor forms have receptors for TSH. The signal is transferred with the activation of cAMP-dependent kinase resulting in adipocyte precursor differentiation in adipocytes and lipogenesis [24–27]. The well-established expression of TSH receptors and the transfer of the message in adipocytes ensure that the possible positive

Table 4: One-way ANOVA by BMI level, for each thyroid parameter.

Mean values for	BMI class				ANOVA	Kruskal-Wallis	Tukey-post hoc test
	<25	25–30	30–35	>35	*F*-test *P* value	*P* value	Statistically significant differences
TT3	1.092	1.114	1.105	1.186	0.037	0.003	<25 versus >35
TT4	7.191	7.092	7.346	7.800	<0.001	0.006	<25 versus >35 25–30 versus >35
FT3	2.888	2.779	2.891	2.924	0.120	0.117	—
FT4	1.265	1.152	1.089	1.077	0.265	0.603	—
TSH	3.004	2.814	2.798	2.510	0.221	0.468	—

Table 5: Multiple linear regression of somatometric parameters, multiple bivariate logistic regression of BMI classes.

Dependent	Predictors	Coeff.	SE	*t*	*P* value	*Beta*
		Linear regression				
BMI	Intercept	20.85	1.625	12.83	<0.001	—
	TT4	0.608	0.186	3.27	0.001	0.137
	Age	0.076	0.017	434	<0.001	0.181
Height	Intercept	1.917	0.018	106.82	<0.001	—
	Sex (female versus male)	−0.109	0.008	−14.01	<0.001	-0.446
	Age	−0.002	0.0002	−10.34	<0.001	-0.329
Weight	Intercept	89.48	5.01	17.84	<0.001	—
	TT4	1.77	0.51	3.49	<0.001	0.14
	Sex (female versus male)	−14.08	1.98	−7.12	<0.001	−0.29

Dependent	Predictor	Coeff.	Lower 95% CL	Upper 95% CL	*P* value
		Logistic regression			
BMI > 25	Age	1.046	1.031	1.062	<0.001
	TT3	2.608	1.041	6.533	0.041
BMI > 30	Age	1.025	1.013	1.038	<0.001
	TT3	2.106	1.016	4.364	0.045
BMI > 35	TT4	1.409	1.120	1.774	0.004
	FT4	0.224	0.045	1.126	0.069

correlation between serum TSH and obesity has a biological significance. By observing that multiple pituitary hormone receptors are expressed in adipose tissue, it is ascertained that there is a possible "hypothalamic-pituitary-adipocyte axis." The positive correlation between TSH and obesity could be stable in the sense of downward regulation. Moreover, this axis may require a system of feedback regulation, and thus the positive correlation of serum TSH and obesity could be interpreted in reverse.

In conclusion, we have shown that variations of normal thyroid function are accompanied by differences in BMI perhaps due to the changes in the resting energy consumption. The high incidence of the pathological disorders in thyroid function combined with the strong influence of various environmental factors (diet, exercise, etc.) can increase weight with an unknown biological mechanism and lead to obesity. Further studies are required for a general assumption of the existence or nonexistence of a correlation between obesity and variations of normal thyroid function.

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