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Original article

Relationship between thyroid hormones, resting energy expenditure and cardiometabolic risk factors in euthyroid subjects

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SUMMARY

Background & aims: Whereas hypothyroid subjects have a decreased resting energy expenditure (REE), it is unknown whether REE is associated with TSH in euthyroid subjects. It is also uncertain whether there is an association between cardiometabolic risk factors and TSH among euthyroid subjects. The primary aim was to test whether REE and TSH are associated in euthyroid subjects. The second aim was to evaluate the association between TSH and cholesterol, HDL-cholesterol, triglycerides, glucose and blood pressure.

Methods: 885 Caucasian euthyroid subjects (75% women) aged 18–79 years and with a median body mass index of 28.6 kg/m^2 were consecutively studied at our Research Center. REE was measured using a canopy-equipped indirect calorimeter. Multivariable regression of 25th, 50th and 75th percentiles was used to evaluate the association between the outcomes (REE, cholesterol, HDL-cholesterol, triglycerides, glucose and blood pressure) and the predictors (TSH, FT4 and FT3) controlling by gender, age and body mass index.

Results: REE was not associated with TSH, FT4 and FT3 at any percentile. On the contrary, a positive association between TSH and triglycerides was evident at all percentiles. A positive association between FT3 and HDL-cholesterol was also present but only at the 75th percentile.

Conclusions: REE is not associated with TSH in euthyroid subjects. It is however positively associated with triglycerides confirming the findings of recent population studies.

1. Introduction

Thyroid hormones regulate energy homeostasis by acting both in peripheral tissues and the central nervous system [1,2]. Overt hypothyroidism is associated with decreased resting energy expenditure (REE) and weight gain while hyperthyroidism is associated with increased REE and weight loss [3,4]. Even if patients undergoing treatment for hypothyroidism show measurable changes of REE with small changes in levothyroxine dosage [5], the relationship between thyroid hormones and REE in euthyroid subjects is widely unknown. A lack of association between REE and TSH has been reported in euthyroid subjects with severe obesity [6] but no data are now available on the REE-TSH association in non-obese euthyroid subjects.

Hypothyroidism is associated with an increase of many cardiovascular risk factors, i.e. dyslipidemia, hyperglycemia and hypertension, and may predispose to atherosclerosis [7,8]. It is however uncertain whether cardiovascular risk factors are associated with TSH among euthyroid subjects. In the largest study of lipid profile performed so far in euthyroid subjects, Meisinger et al. found a positive association between TSH and triglycerides that was independent from gender and a positive association between TSH and cholesterol in women [9]. Similar findings were recently reported by Garduño-Garcia et al. [10] in a Hispanic population, together with an association between TSH and insulin and HOMA-IR but not with glucose [10].

We performed a large cross-sectional study to evaluate the REE-TSH relationship among euthyroid subjects and to evaluate also the association of TSH with total cholesterol, HDL-cholesterol, triglycerides, glucose and blood pressure.

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Table 1
Measurements of the study subjects.

	Women ($n = 664$)			Men ($n = 221$)			Total ($n = 885$)		
	P_{25}	P_{50}	P_{75}	P_{25}	P_{50}	P_{75}	P_{25}	P_{50}	P_{75}
Age (years)	36	45	55	39	47	57	37	46	55
Weight (kg)	64.8	72.8*	82.8	83.7	93.0	103.4	67.4	77.6	90.1
Height (m)	1.57	1.62*	1.66	1.71	1.75	1.81	1.59	1.64	1.71
BMI (kg/m^2)	25.1	27.9*	32.0	27.6	30.1	33.6	25.8	28.6	32.4
Waist (cm)	82	91*	100	99	106	116	85	95	104
REE (Kcal/day)	1281	1388*	1509	1644	1802	1956	1320	1460	1650
REE: weight (Kcal/kg)	17.4	18.8	20.7	18.1	19.2	20.4	17.6	19.0	20.6
TSH (mU/l)	1.26	1.76	2.46	1.23	1.71	2.21	1.26	1.74	2.40
FT4 (pg/ml)	9.50	10.6*	11.9	9.90	11.1	12.1	9.60	10.8	12.0
FT3 (ng/ml)	2.77	3.05	3.37	2.99	3.29	3.56	2.80	3.10	3.42
Cholesterol (mg/dl)	186	210	237	183	207	235	185	210	237
HDL-cholesterol (mg/dl)	51	60*	71	40	45	53	47	57	68
Triglycerides (mg/dl)	64	86*	119	85	121	173	68	94	131
Glucose (mg/dl)	84	90*	97	89	97	106	85	92	100
Systolic BP (mm Hg)	110	120*	130	120	130	140	110	120	130
Diastolic BP(mm Hg)	70	75*	80	75	80	90	70	80	85

*$p < 0.001$ *vs.* males at P_{50} regression.
Abbreviations: $P_{25} = 25^{th}$ percentile; $P_{50} = 50^{th}$ percentile; $P_{75} = 75^{th}$ percentile; BMI = body mass index; REE = resting energy expenditure from indirect calorimetry; TSH = thyroid stimulating hormone; FT4 = free thyroxine; FT3 = free triiodothyronine, BP = blood pressure.

2. Subjects and methods

2.1. Study design

We consecutively studied euthyroid subjects who came to ICANS (International Center for the Assessment of Nutritional Status) voluntarily between January 2008 and December 2011 to obtain an assessment of nutritional status and cardiometabolic risk. Inclusion criteria were age ≥18 years and presence of euthyroidism. Euthyroidism was operationally defined as a value of TSH between 0.2 and 4.2 ng/ml. Exclusion criteria were psychiatric disease, cancer and chronic disease (e.g. heart failure). The institutional review board approved the study procedures and each subject provided written informed consent. The study was carried out according to the Declaration of Helsinki.

Clinical examination, anthropometry, indirect calorimetry and blood samples for laboratory examinations were performed on the same day.

2.2. Clinical examination and anthropometry

All subjects underwent a clinical examination before being enrolled into the study. Anthropometric measurements were taken by the same operator following international guidelines [11]. Weight was measured to the nearest 100 g and height to the nearest 0.1 cm using a balance with incorporated stadiometer (SECA 711, SECA, Hamburg, Germany). BMI was calculated as weight (kg)/stature (m)^2 and classified according to the World Health Organization [12]. Waist circumference was measured at the midline between the last rib and the iliac crest [12].

2.3. Indirect calorimetry

REE was measured using an open-circuit ventilated-hood system (Sensor Medics Vmax29, Sensor Medics, Anaheim, CA) in the post-absorptive state (≥12 h from fasting) and in a thermo-neutral environment (24–26 °C). The subjects lying in a horizontal position remaining awake for at least 20 min prior to perform the measurement. At least 30 min of respiratory gas exchange data were collected with the first 10 min being discarded to allow acclimation of the subject [13]. REE was calculated as the average of at least 20 min of gas exchange using Weir's equation [14].

2.4. Laboratory measurements

Fasting cholesterol, HDL cholesterol, triglycerides and glucose were measured using an enzymatic method (Cobas Integra 400 Plus, Roche Diagnostics, Rotkreuz, Switzerland). Fasting TSH, FT4 and FT3 were measured using immunoenzymatic method (Cobas E 411, Roche Diagnostics, Rotkreuz, Switzerland). Blood pressure was measured by a physician using a random-zero mercury sphygmomanometer following JNC 7 guidelines [15].

2.5. Metabolic syndrome

The metabolic syndrome (MS) was diagnosed using the harmonized international definition [16]. Large waist was defined as waist circumference ≥102 cm in men and ≥88 cm in women, low HDL-cholesterol as HDL-cholesterol <40 mg/dl in men and <50 mg/dl in women, high triglycerides as triglycerides ≥150 mg/dl, high blood pressure as systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and high glucose as glucose ≥100 mg/dl. MS was defined as 3 or more of the above components.

2.6. Statistical analysis

Continuous variables are reported as 25th, 50th and 75th percentiles because of non-Gaussian distributions. Categorical variables are reported as counts and percentages. All continuous variables besides age were winsorized using a tail of 0.01. This implies that values under the 1st or over the 99th internal percentile were put equal to the 1st or 99th percentile, respectively. Winsorization limits the influence of outliers and increases the generalizability of the results [17,18]. Between-gender comparisons of continuous variables were performed using univariable regression of the 50th percentile of the outcome with gender (0 = female; 1 = male) as predictor [19]. Multivariable regression of 25th, 50th and 75th percentiles was used to evaluate the association between the outcomes [REE (kcal/day), total cholesterol (mg/dl), HDL-cholesterol (mg/dl), triglycerides (mg/dl), glucose (mg/dl), systolic blood pressure (mm Hg) and diastolic blood pressure (mm Hg)] and the predictors [TSH (mUI/l), FT4 (pg/ml) and FT3 (ng/ml)] using gender (0 = female; 1 = male), age (years/10) and BMI (kg/m^2) as covariates [19]. We used multivariable running plot sand multivariable fractional polynomials to test whether the relationship

Table 2
Frequency of normal weight, overweight and obesity and of the metabolic syndrome and its components.

	Women		Men		Total	
	n	%	*n*	%	*n*	%
Body mass index						
Normal	159	24.0	12	5.4	171	19.3
Overweight	271	40.9	95	43.0	366	41.4
Obesity class I	154	23.2	78	35.3	232	26.2
Obesity class II	56	8.4	23	10.4	79	8.9
Obesity class III	23	3.5	13	5.9	36	4.1
Total	663	100.0	221	100.0	884	100.0
Large waist						
No	268	40.4	85	38.5	353	39.9
Yes	396	59.6	136	61.5	532	60.1
Total	664	100.0	221	100.0	885	100.0
High triglycerides						
No	579	87.2	143	64.7	722	81.6
Yes	85	12.8	78	35.3	163	18.4
Total	664	100.0	221	100.0	885	100.0
Low HDL						
No	523	78.8	168	76.0	691	78.1
Yes	141	21.2	53	24.0	194	21.9
Total	664	100.0	221	100.0	885	100.0
High blood pressure						
No	434	65.4	76	34.4	510	57.6
Yes	230	34.6	145	65.6	375	42.4
Total	664	100.0	221	100.0	885	100.0
High glucose						
No	528	79.5	133	60.2	661	74.7
Yes	136	20.5	88	39.8	224	25.3
Total	664	100.0	221	100.0	885	100.0
Metabolic syndrome						
No	517	77.9	121	54.8	638	72.1
Yes	147	22.1	100	45.2	247	27.9
Total	664	100.0	221	100.0	885	100.0

between response variables and continuous predictors were non-linear [20,21]. We found that all relationships were linear and modeled accordingly. *P* value <0.05 was considered statistically significant. Statistical analysis was performed using STATA 13.0.

3. Results

Table 1 gives the measurements of the 885 Caucasian subjects that were consecutively enrolled into the study.

Seventy-five percent of the subjects were women ($n = 664$). Women had lower weight, height, BMI and waist circumference than men ($p < 0.001$ for all). REE was lower in women ($p < 0.001$) but this difference disappeared after standardization on body weight. There was no between-gender difference in TSH and FT3 but FT4 was lower in females than in males ($p < 0.001$). Women had also higher values of HDL and lower values of triglycerides, glucose, systolic blood pressure and diastolic blood pressure ($p < 0.001$ for all).

Table 2 reports the frequency of normal weight, overweight and obesity and that of MS and its components.

41.4% of the subjects were overweight, 26.2% had class I obesity, 8.9% class II obesity and 4.1% class III obesity. Above normal waist circumference was present in 60.1% of cases, high triglycerides in 18.4%, low HDL in 21.9%, high blood pressure in 42.4%, high fasting glucose in 25.3% and MS in 27.9% of cases.

Tables 3, 4 and 5 report the coefficients obtained from the regression of the 50th percentile of REE and cardiovascular risk factors *vs.* TSH, FT4 and FT3 comparing by age, gender and BMI.

Supplementary Tables 6, 7 and 8 report the coefficients obtained from the regression of the 25th percentile of REE and cardiovascular risk factors *vs.* TSH, FT4 and FT3 comparing by age, gender and BMI.

Supplementary Tables 9, 10 and 11 report the coefficients obtained from the regression of the 75th percentile of REE and cardiovascular risk factors *vs.* TSH, FT4 and FT3 controlling for age, gender and BMI.

No association was found between REE and TSH at all percentiles. The only cardiometabolic risk factor to be associated with TSH was blood triglyceride concentration. Such association was positive and evident at all percentiles. FT3 was associated to HDL cholesterol at the 75th percentile but not at the 25th and 50th percentiles.

4. Discussion

Based on our knowledge, this is the first study to systematically investigate the association between thyroid hormones and REE in a large sample of euthyroid subjects with BMI ranging from normal weight to class III obesity. We found no association between REE and TSH in our euthyroid subjects. Our findings agree with those of Tagliaferri and colleagues who found that, in severely obese subjects, REE and TSH are not associated in the presence of euthyroidism [6].

Hypothyroidism is characteristically associated with increased LDL-cholesterol while HDL-cholesterol may be normal or increased owing to a decreased activity of the thyroid-dependent enzymes

Table 3
Association between thyroid stimulating hormone, resting energy expenditure and cardiovascular risk factors.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	REE Kcal/day	Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	Triglycerides (mg/dL)	Glucose (mg/dL)	SBP (mm Hg)	DBP (mm Hg)
TSH (mU/l)	7	2	1	**6****	0	0	1
	[−8,21]	[−1,6]	[−0,2]	**[2,10]**	[−1,1]	[−1,2]	[−0,2]
Male	369***	−3	−13***	36***	5***	7***	4***
	[337,400]	[−10,5]	[−16,−11]	[24,48]	[3,7]	[5,9]	[3,6]
Age (years/10)	−47***	10***	1**	4**	3***	3***	1***
	[−57,−36]	[8,12]	[0,2]	[1,7]	[2,3]	[2,4]	[1,2]
BMI (kg/m^2)	22***	−0	−1***	2***	1***	1***	1***
	[19,24]	[−1,0]	[−1,−1]	[1,2]	[0,1]	[1,1]	[1,1]
Constant	961***	174***	83***	6	64***	82***	50***
	[867,1055]	[155,193]	[75,90]	[−16,28]	[59,69]	[76,88]	[46,53]
Observations	885	885	885	885	885	885	885

95% confidence intervals in brackets.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
Bold values represents $p = 0.008$
Values are regression coefficients and 95% confidence intervals obtained from multivariable regression of the 50th percentile of the outcome (numbered from 1 to 7) *vs.* thyroid stimulating hormone, gender, age and body mass index.
Abbreviations: REE = resting energy expenditure; SBP = systolic blood pressure; DBP = diastolic blood pressure; TSH = thyroid stimulating hormone; BMI = body mass index.

Table 4
Association between free thyroxine, resting energy expenditure and cardiovascular risk factors.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	REE Kcal/day	Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	Triglycerides (mg/dL)	Glucose (mg/dL)	SBP (mm Hg)	DBP (mm Hg)
FT4 (pg/mL)	1	−1	0	−1	0	0	0
	[−6,8]	[−2,1]	[−0,1]	[−3,0]	[−0,1]	[−0,1]	[−0,1]
Male	365***	−3	−13***	34***	5***	6***	4***
	[334,396]	[−10,5]	[−16,−11]	[23,44]	[3,7]	[4,8]	[3,6]
Age (years/10)	−48***	10***	1**	4**	3***	3***	1***
	[−58,−38]	[8,12]	[0,2]	[1,7]	[2,3]	[2,4]	[1,2]
BMI (kg/m^2)	22***	−0	−1***	2***	1***	1***	1***
	[19,25]	[−1,0]	[−1,−1]	[1,3]	[0,1]	[1,1]	[1,1]
Constant	953***	182***	81***	27	63***	78***	48***
	[837,1070]	[157,206]	[71,91]	[−3,58]	[56,69]	[71,86]	[42,53]
Observations	885	885	885	885	885	885	885

95% confidence intervals in brackets.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Values are regression coefficients and 95% confidence intervals obtained from multivariable regression of the 50th percentile of the outcome (numbered from 1 to 7) *vs.* free thyroxine, gender, age and body mass index.
Abbreviations: REE = resting energy expenditure; SBP = systolic blood pressure; DBP = diastolic blood pressure; FT4 = free thyroxine; BMI = body mass index.

Table 5
Association between free triiodothyronine, resting energy expenditure and cardiovascular risk factors.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
	REE Kcal/day	Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	Triglycerides (mg/dL)	Glucose (mg/dL)	SBP (mm Hg)	DBP (mm Hg)
FT3 (ng/mL)	8	2	2	5	0	1	−1
	[−18,33]	[−4,8]	[−1,4]	[−2,12]	[−1,2]	[−1,4]	[−2,1]
Male	363***	−4	−14***	31***	5***	7***	4***
	[331,394]	[−12,3]	[−16,−11]	[20,42]	[3,7]	[4,9]	[3,6]
Age (years/10)	−47***	11***	1**	4**	3***	3***	1**
	[−58,−37]	[8,13]	[0,2]	[2,7]	[2,3]	[2,4]	[0,2]
BMI (kg/m^2)	22***	−0	−1***	2***	1***	1***	1***
	[19,25]	[−1,0]	[−1,−1]	[1,2]	[0,1]	[1,1]	[1,1]
Constant	944***	170***	80***	−0	63***	78***	52***
	[819,1070]	[144,197]	[71,89]	[−30,30]	[56,70]	[70,87]	[46,59]
Observations	885	885	885	885	885	885	885

95% confidence intervals in brackets.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Values are regression coefficients and 95% confidence intervals obtained from multivariable regression of the 50th percentile of the outcome (numbered from 1 to 7) *vs.* free triiodothyronine, gender, age and body mass index.
Abbreviations: REE = resting energy expenditure; SBP = systolic blood pressure; DBP = diastolic blood pressure; FT3 = free triiodothyronine; BMI = body mass index.

cholesteryl-ester transfer protein and hepatic lipase [22–24]. Hypothyroidism is also associated with a lower removal rate of triglycerides from plasma [25] and thyroid replacement therapy restores normal lipid metabolism [26]. Our findings are in agreement with those of Meisinger and colleagues [9] who, in a study of 13,517 subjects from four European cohorts, found that increasing TSH levels were associated with increasing levels of triglycerides in euthyroid subjects. On the other hand, we did not detect any association of TSH with total cholesterol. We found however a positive association between FT3 and HDL. Such association was however restricted to the 75th percentile of HDL and because we are the first to report it, it certainly needs confirmation in external populations. Associations of TSH with plasma triglycerides and cholesterol including HDL cholesterol were also recently reported by Garduño-Garcia and colleagues in a cross-sectional study of 3148 Mexican subjects [10].

Hyperglycemia is common in overt hypothyroidism. Thyroid hormones intervene in glucose homeostasis by regulating hepatic gluconeogenesis and by controlling the expression of glucose transporter 4 and the activity of Amp-activated protein kinase and acetyl CoA carboxylase in muscle [27,28]. Despite the well-known actions of thyroid hormones on carbohydrate metabolism, studies in humans have provided conflicting results. As Garduño-Garcia et al. [10], we found no association between TSH and blood glucose. However, we did not perform insulin measurements in our subjects, so we cannot test whether TSH and HOMA-IR are associated in our subjects as they are in those studied by Garduño-Garcia et al. [10]. Also hypertension is common in hypothyroidism and the coexistence of hypertension and lipid disorders might contribute to accelerate atherosclerosis [29]. We found however no association between SBP and DBP in our euthyroid subjects.

Although this is the first study that systematically investigate the REE-TSH relationship in a large sample of euthyroid subjects with varying degrees of BMI, it is not without limitations.

First, it was performed in a self-selected sample of Caucasian subjects. Even if this limitation is common to most of the available studies on thyroid hormones, its results may not extend to the general population and to non-Caucasian subjects. On the other hand, this is the first study on REE to consider normal-weight and overweight individuals in addition to obese individuals. Second, we did not measure insulin so that even if we can exclude an association of TSH with glucose in the presence of euthyroidism we cannot do the same for insulin or HOMA-IR [10]. Third, a cross-sectional study such as the present one does not offer the possibility to study the association between changes of REE and those of thyroid hormones as allowed by a cohort study [30].

In conclusion, we found no association between TSH and REE measured by indirect calorimetry in a large sample of euthyroid

subjects with a wide range of BMI. We confirm however that TSH levels with the euthyroid range are associated with triglycerides.

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Contributors

AS carried out the design of the study, collection and interpretation of data and drafted the manuscript. CC, AL and LV carried out collection of data and the manuscript revision. GB carried out the statistical analysis. AB and SB carried out the design of the study, interpretation of data and the manuscript revision. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2014.07.014.

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