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Reference range thyroid-stimulating hormone is associated with physical activity energy expenditure in overweight and obese postmenopausal women: a Montreal-Ottawa New Emerging Team Study

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Abstract

Clinical and, to a lesser extent, subclinical hypothyroidism is associated with a variety of metabolic abnormalities, including increased body mass index, unfavorable lipoprotein profile, and increased biomarkers for atherosclerosis. Energy expenditure could act as a confounding factor in the association reported between thyroid-stimulating hormone (TSH) levels and cardiometabolic risk factors. The objective of the study was to investigate the relationship between reference range plasma TSH and energy expenditure as well as blood pressure, lipid, and inflammation parameters in women. One hundred four postmenopausal, overweight and obese, spontaneously euthyroid women were included in the study. We evaluated total energy expenditure by doubly labeled water, resting energy expenditure by indirect calorimetry, physical activity energy expenditure (PAEE = [total energy expenditure × 0.90] − resting metabolic rate), body weight, and percentage of fat mass by dual-energy x-ray absorptiometry. Blood pressure, plasma lipoproteins profile, and high-sensitivity C-reactive protein levels were also measured. Mean TSH was 2.39 ± 1.09 mIU/L. We observed that high-density lipoprotein cholesterol ($r = -0.20$, $P \leq .05$) was negatively associated with TSH, whereas systolic blood pressure ($r = 0.21$, $P \leq .05$) and apolipoprotein B ($r = 0.22$, $P \leq .05$) were positively correlated with TSH. However, these correlations were no longer significant after controlling for PAEE. A significant negative correlation was found between TSH and PAEE ($r = -0.23$, $P \leq .05$). Our results suggest that, although TSH in the reference range is associated with some cardiometabolic risk factors, this is in large part explained by lower PAEE. In turn, lower PAEE could increase the cardiometabolic risk.

1. Introduction

The interplay between thyroid, metabolism, and obesity has been the focus of several reports in recent years [1-3]. Overt hypothyroidism is associated with a variety of metabolic abnormalities, such as hypercholesterolemia, weight gain, and higher cardiovascular risk, as well as with lower resting energy expenditure (REE) [1-5]. However, extending these associations to *subclinical hypothyroidism*, defined as an elevated serum thyroid-stimulating hormone (TSH) with serum free thyroxine and free triiodothyronine levels within the reference range, has provided conflicting data [6]. The same is true for TSH at the upper limit of normal, as some epidemiologic evidence supports a narrower reference TSH range because of increased antithyroid autoimmunity and higher rate of progression to overt disease with TSH values between 3.0 and 4.5 mIU/L [7].

Several cardiovascular risks factors have been studied in relation to serum TSH within reference range. Conflicting

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results have emerged regarding associations between TSH and cardiovascular risk factors such as serum lipids [8], blood pressure [9-11], body composition [12,13], body mass index (BMI) [14-16], and insulin sensitivity [17], as well as coronary heart disease, which has been reported to be elevated [18] or unchanged [19].

Physical activity energy expenditure (PAEE) has been identified as a determinant of all-cause mortality in older adults [20,21], and thyroid hormones are known to be major determinants of energy balance [22]. Physical activity energy expenditure has not been studied in relation to thyroid status, as opposed to REE. Short-term, severe hypothyroidism in thyroidectomized patients awaiting radioactive iodine treatment of thyroid cancer has been associated with lower basal energy expenditure and increased percentage of body fat [5]. Resting energy expenditure was also found to be lower in obese patients with subclinical hypothyroidism, with TSH greater than 6 mIU/L [23]. Moreover, REE was found to be negatively correlated with an increase in TSH in the reference to subclinical range in patients chronically replaced with levothyroxine (LT_4) [24]. Exercise tolerance and muscle energy metabolism were identified as altered in subclinical hypothyroidism [25,26]. Improved insulin sensitivity after exercise is blunted by subclinical hypothyroidism in overweight or obese patients [27].

As the association between reference range TSH and PAEE has not been well studied, the aim of our study was to evaluate whether reference range plasma TSH is associated with energy expenditure, especially PAEE, as well as several cardiometabolic risk factors: serum lipid and lipoproteins concentrations, inflammation markers, glucose homeostasis, and blood pressure in a population of overweight and obese postmenopausal women. We hypothesized that upper range of normal plasma TSH levels might be associated with lower PAEE and higher body fat in this cardiometabolic at-risk population.

2. Material and methods

2.1. Subjects

The study sample consisted of 137 overweight and obese postmenopausal women, aged 46 to 70 years old, engaged in a weight loss study (Montreal-Ottawa New Emerging Team project) [28]. Women were eligible to participate if they met the following criteria: (1) BMI at least 27 kg/m^2, (2) cessation of menstruation for more than 1 year and a follicle-stimulating hormone level of at least 30 U/L, (3) nonsmokers, (4) low to moderate alcohol consumption (<2 drinks a day), (5) free of known inflammatory disease, (6) no use of hormone replacement therapy, and (7) sedentary (less than 2 h/wk of structured exercise). On physical examination or biological testing, all participants had no history or evidence of (1) cardiovascular disease, peripheral vascular disease, or stroke; (2) diabetes (75-g oral glucose tolerance test); (3) orthopedic limitations; (4) body weight fluctuation of ±2 kg in the last 6 months; (5) untreated thyroid or pituitary disease; (6) infection by medical examination along with a complete blood count; and (7) medications that could affect cardiovascular function and/or metabolism. Thirteen patients were excluded for overt de novo hypothyroidism and started on levothyroxine replacement, and 20 patients were excluded for previous chronic levothyroxine replacement. Our final cohort consisted of 104 women. After reading and signing the consent form, each subject had to come to the Laboratory of Metabolic Dysfunctions for a series of tests. This study was approved by the Université de Montréal ethics committee. One month before testing, weight stability within ±2 kg was verified by monitoring body weight for each subject on a weekly basis at our laboratory.

2.2. Anthropometric measurements and metabolic parameters

2.2.1. Body composition

Standing height was measured using a wall stadiometer (Perspective Enterprises, Portage, MI). Body weight and percentage of fat mass were measured using dual-energy x-ray absorptiometry (General Electric Lunar version 6.10.019, Madison, WI). Body mass index was calculated as body weight in kilograms divided by height in square meters.

2.2.2. Blood samples and blood pressure

After a 12-hour overnight fast, venous blood samples were obtained for measurements of fasting total serum cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and inflammation markers levels. Analyses were done on the COBAS INTEGRA 400 analyzer (Roche Diagnostic, Montreal, Quebec, Canada) for total cholesterol, HDL-C, and triglycerides. Total cholesterol, HDL-C, and triglycerides were used in the Friedewald formula to calculate low-density lipoprotein cholesterol (LDL-C) concentration. Serum apolipoprotein (apo) B and high-sensitivity C-reactive protein (hsCRP) were measured by immunonephelometry on IMMAGE analyzer (Beckman Coulter, Villepinte, France). Thyroid-stimulating hormone was measured by electrochemiluminescence. Sitting blood pressure was taken after the subjects rested quietly for 10 minutes using a Dinamap automatic machine (Welch Allyn, San Diego, CA).

2.2.3. Hyperinsulinemic-euglycemic clamp

The study began at 7:30 AM after a 12-hour overnight fast following the procedure described by DeFronzo et al [29]. An antecubital vein was cannulated for the infusion of 20% dextrose and insulin (Actrapid; Novo-Nordisk, Toronto, Ontario, Canada). The other arm was cannulated for sampling of blood. Three basal samples of plasma glucose and insulin were taken over 40 minutes. Afterward, insulin infusion was initiated at the rate of 75 mU/(m^2·min) for 180 minutes. Plasma glucose was measured every 10 minutes with a glucose analyzer (Beckman Instruments, Fullerton, CA) and maintained at fasting level with a variable infusion rate of 20% dextrose. Glucose disposal was calculated as the

mean rate of glucose infusion measured during the last 30 minutes of the clamp (steady state) and is expressed as milligrams per minute per kilogram of fat-free mass (FFM).

2.2.4. Doubly labeled water

Daily energy expenditure was determined using the doubly labeled water (DLW) method over a 10-day period [30]. The DLW experiments generated 5 urine samples per study: a predose sample was collected, 2 samples (16-24 hours later) were obtained after the $^{2}H_{2}^{18}O$ dose had initially equilibrated in the body, and 2 more samples were collected 10 days later. All samples were measured in triplicate for ^{18}O-water and ^{2}H-water. An Isoprime Stable Isotope Ratio Mass Spectrometer connected to a Multiflow-Bio module for Isoprime and a Gilson 222XL Autosampler (GV Instruments, Manchester, United Kingdom) were used for daily energy expenditure measurements. Data processing was performed with MassLynx 3.6 software (Waters Corp, Milford, MA). Stability test was performed each day before testing, giving a standard deviation of 0.026% for deuterium and 0.004% for ^{18}O. In addition, resting metabolic rate (RMR) and respiratory quotient were measured by indirect calorimetry. Concentrations of CO_2 and O_2 were measured using the ventilated hood technique with a SensorMedics Delta Track II (Datex-Ohmeda, Helsinki, Finland). Measurement of gas concentrations were then used to extrapolate 24-hour RMR using the Weir equation. Measurements were performed during 40 minutes; the first 10 minutes was considered as an acclimatization period, and the last 30 minutes was used for analyses. Assuming a thermal effect of feeding of 10%, PAEE was then calculated from the following equation: PAEE = (total energy expenditure × 0.90) − RMR.

2.2.5. Cardiorespiratory fitness (Vo_{2peak})

Subjects performed a graded exercise test on an ergocycle Ergoline 900 (Bitz, Germany) to voluntary exhaustion. During the test, power output was increased by 25 W every 2 minutes. Peak V_{O_2} (in liters per minute) was considered to be the highest value obtained during the test. Expired gas was analyzed during the exercise protocol using an Ergocard (software version 6; MediSoft, Dinant, Belgium) cardiopulmonary exercise test station. Three of the following criteria were required for a successful test: a respiratory exchange ratio higher than 1.1, heart rate within 10 beats per minute of maximal predicted heart rate value (220 − age), volitional cessation of exercise by the subject, and a plateau in oxygen consumption for 60 seconds.

2.2.6. Statistical analysis

The data are expressed as the mean ± standard deviation. We first verified the normality of the distribution of variables with a Kolmogorov-Smirnov test. Pearson correlations were first performed to examine the relationship between anthropometric and metabolic variables with TSH. Partial correlations were also used to control for PAEE. Subsequently, a 1-way analysis of variance was performed to compare mean differences among tertiles of plasma TSH levels. When significant differences were found, a Tukey post hoc test was performed to identify group differences.

3. Results

Anthropometric, hormonal, and metabolic characteristics of the subjects are presented in Table 1. We included overweight and obese women, with a mean BMI of 32.2 kg/m^2. The mean plasma TSH level was 2.39 mIU/L, and laboratory reference values were between 0.35 and 5.00 mIU/L.

The correlations between anthropometric, physiologic and metabolic parameters measured and plasma TSH levels are presented in Table 2. Thyroid-stimulating hormone was negatively correlated with HDL-C ($r = -0.20$, $P \leq .05$), whereas it was positively associated with apo B ($r = 0.22$, $P \leq .05$) and systolic blood pressure ($r = 0.21$, $P \leq .05$). However, when these variables were adjusted for PAEE, all the correlations were no longer significant. In addition, TSH was negatively correlated with PAEE ($r = -0.23$, $P \leq .05$). No correlation was found for other variables.

In Table 3, data are presented according to tertiles of normal plasma TSH levels. The third tertile represents the upper range of normal TSH, with values between 2.94 and 4.84 mIU/L. There was no significant difference between tertiles according to age or BMI. Women in the third tertile presented a significantly lower PAEE than women in the first tertile ($P \leq .05$). In addition, there was a significant difference between women in the first and second tertile of TSH for HDL-C ($P \leq .05$). Finally, systolic blood pressure was significantly different between women of the first and third tertile ($P \leq .05$); but the difference was also abolished when systolic blood pressure was adjusted for PAEE ($P = .06$). No differences between tertiles were observed for other parameters.

Table 1
Baseline characteristics of 104 euthyroid postmenopausal women

Variables	Mean ± SD	Range
TSH (mIU/L)	2.39 ± 1.09	0.34-4.84
Age (y)	57.5 ± 4.9	46.0-70.5
BMI (kg/m^2)	32.2 ± 4.79	26.1-48.5
Body weight (kg)	82.5 ± 13.5	56.4-130.4
Percentage of fat mass (%)	45.9 ± 4.6	36.5-57.9
Systolic blood pressure (mm Hg)	120.2 ± 13.4	92.0-159.0
Diastolic blood pressure (mm Hg)	76.2 ± 8.1	61.0-99.0
Total cholesterol (mmol/L)	5.5 ± 0.8	3.3-7.5
HDL-C (mmol/L)	1.5 ± 0.3	1.0-2.7
Triglycerides (mmol/L)	1.6 ± 0.7	0.5-4.5
LDL-C (mmol/L)	3.2 ± 0.7	1.8-5.0
Apo B (g/L)	1.0 ± 0.2	0.4-1.7
hsCRP (mg/L)	2.6 ± 1.9	0.3-9.1
Insulin sensitivity (mg/[min·kg FFM])	11.8 ± 3.1	4.7-22.9
Total energy expenditure (kcal/d)	2482 ± 401	1607-3572
RMR (kcal/d)	1307 ± 182	930-1850
PAEE (kcal/d)	932 ± 306	348-1697
Vo_{2peak} (mL/[kg·min])	17.7 ± 3.2	8.8-25.3

Table 2
Correlation between TSH and studied parameters

Variables	*r*	*P* value
Age	0.112	.257
BMI	0.083	.402
Body weight	0.032	.748
Percentage of fat mass	−0.061	.541
Systolic blood pressure	0.205[a]	.037
Diastolic blood pressure	0.156	.113
Total cholesterol	−0.068	.491
HDL-C	−0.202[b]	.040
Triglycerides	0.114	.247
LDL-C	−0.048	.631
Apo B	0.221[c]	.025
hsCRP	0.137	.175
Insulin sensitivity	−0.093	.360
Total energy expenditure	−0.141	.157
RMR	0.097	.328
PAEE	−0.230	.020
Vo_{2peak}	0.020	.841

[a] After adjustment for PAEE, $r = 0.190$.
[b] After adjustment for PAEE, $r = -0.161$.
[c] After adjustment for PAEE, $r = 0.167$.

4. Discussion

The objective of this study was to examine the relationship between plasma TSH concentration, within the reference range, and energy expenditure as well as cardiometabolic risk factors in euthyroid overweight and obese postmenopausal women using criterion standard methods. Our main finding is that lower PAEE might partly explain the association reported between reference range TSH concentrations and cardiometabolic risk factors in a population of overweight and obese postmenopausal women.

Table 3
Studied parameters according to TSH within reference range

Variables	TSH (mIU/L)		
	I: 0.34-1.66 n = 34	II: 1.67-2.91 n = 35	III: 2.94-4.84 n = 35
Age (y)	56.4 ± 4.7	58.0 ± 5.1	58.0 ± 4.9
BMI (kg/m^2)	31.1 ± 3.9	33.3 ± 5.3	32.2 ± 4.9
Body weight (kg)	79.9 ± 11.5	85.8 ± 15.4	81.8 ± 12.8
Percentage of fat mass (%)	45.4 ± 4.6	47.1 ± 4.6	45.1 ± 4.5
Systolic blood pressure (mm Hg)	116.1 ± 10.5	120.3 ± 13.2	124.2 ± 15.2*
Diastolic blood pressure (mm Hg)	73.9 ± 6.8	76.8 ± 8.4	77.8 ± 8.6
Total cholesterol (mmol/L)	5.6 ± 0.6	5.4 ± 0.9	5.4 ± 0.8
HDL-C (mmol/L)	1.7 ± 0.4	1.4 ± 0.2*	1.5 ± 0.4
Triglycerides (mmol/L)	1.4 ± 0.6	1.8 ± 0.7	1.6 ± 0.8
LDL-C (mmol/L)	3.3 ± 0.5	3.2 ± 0.8	3.2 ± 0.7
Apo B (g/L)	0.9 ± 0.2	1.0 ± 0.2	1.0 ± 0.2
hsCRP (mg/L)	2.4 ± 2.0	2.7 ± 1.9	2.7 ± 1.9
Insulin sensitivity (mg/[min·kg FFM])	12.2 ± 3.4	11.8 ± 3.1	11.4 ± 2.8
TEE (kcal/d)	2530 ± 372	2509 ± 447	2408 ± 378
RMR (kcal/d)	1266 ± 152	1328 ± 200	1327 ± 187
PAEE (kcal/d)	1022 ± 314	931 ± 315	847 ± 273*
Vo_{2peak} (mL/[kg BW·min])	18.2 ± 3.4	17.0 ± 3.3	18.0 ± 2.9

BW indicates body weight.
* Significantly different from group I ($P \leq .05$).

The negative correlation between plasma TSH levels and PAEE obtained in our study is of particular interest. Our results suggest that women who presented plasma TSH levels in the upper range of normal, which was not influenced by age or BMI, showed lower daily PAEE. Impaired response to exercise, notably through lower Vo_{2peak}, was previously shown in subclinical hypothyroidism [25]. In our population of obese postmenopausal women with TSH levels in the reference range, no correlation was found between TSH and Vo_{2peak}. However, one was found with PAEE. It seems that, although exercise tolerance is unaffected, the capacity to perform exercise is influenced by TSH levels at the upper level of normal. To our knowledge, no previous report has used DLW to study the association between reference range plasma TSH level and daily PAEE. Recent reports have revealed a strong association between PAEE evaluated by criterion standard methods and risk of mortality in an older adult population [20,21]. There is also evidence that higher PAEE could attenuate health risks related to obesity [31]. Accordingly, we also observed that PAEE was negatively associated with triglycerides and apo B levels in our study (data not shown).

We observed impairment of PAEE, whereas no effect was noted on REE. The latter observation was also reported by Tagliaferri et al [23], as only TSH values higher than the reference range were independently associated with REE in obese patients. Another group indicated that REE is very sensitive to changes in thyroid status of hypothyroid patients on varying doses of thyroid hormone replacement [24]. In our study, TSH levels all within reference range could explain the absence of effect on RMR.

In a group of euthyroid subjects, plasma TSH levels have been shown to be independently associated with LDL-C and HDL-C [17,32]. In the present study, we found a negative correlation between HDL-C and TSH values within reference range and a positive association between systolic blood pressure and TSH values, as demonstrated in earlier reports [9,17,32]. The positive correlation also found between apo B and TSH is noteworthy, apo B being an important indicator of cardiovascular risk [33]. However, these correlations were no longer significant when adjusting for PAEE. We did not find a correlation between hsCRP and TSH values within the defined range. This result is surprising considering that this new emerging cardiovascular risk marker predicted cardiovascular events irrespectively of lipid profile end points in a healthy population [34] and that CRP levels have been found to be elevated in subclinical hypothyroidism [35,36]. Physical activity energy expenditure was not associated with Vo_{2peak}, which is a strong predictor of mortality [37-39]. The low values of Vo_{2peak} obtained in women in our study may have limited our ability to observe this association. It is thus possible that overweight and obese postmenopausal women with higher levels of TSH within reference range

could be at higher cardiometabolic risk through lower PAEE. Lower PAEE could directly or through its effects on risk factors increase cardiovascular risk.

Unlike what has been reported in previous studies [12,15], we did not observe an association between BMI and TSH values. The mean BMI of our subjects may have been too low to allow us to observe a significant association between TSH and BMI. We could hypothesize that a higher degree of obesity may be related to higher levels of TSH. In accordance, it has been shown that TSH levels are higher in morbidly obese patients [40].

The present study has potential limitations. First, our cohort is only composed of nondiabetic, sedentary, overweight and obese postmenopausal women. Therefore, our findings are limited to this population. Second, we used a cross-sectional approach, which does not allow us to conclude to any causal associations between TSH and cardiovascular risk factors in our cohort. Finally, our sample size may have been too small to detect significant associations between TSH and some cardiometabolic risk factors. However, our results are strengthened by using criterion standard techniques to measure body composition and energy expenditure in a sample of well-characterized overweight and obese postmenopausal women.

5. Conclusion

In conclusion, our results suggest that, although reference range TSH is not strongly associated with conventional cardiometabolic risk factors, namely, lipid profile, inflammation markers, or BMI, TSH is correlated with lower PAEE. We suggest that higher TSH values in the reference range are associated with a lower PAEE that could consequently increase the cardiometabolic risk. Because studies investigating the association between TSH values within the reference range and cardiovascular events have reported either an increased [18] or no additional risk [19], further studies in larger and more diverse populations should be carried out to explore the impact of normal high TSH on PAEE and cardiovascular risk.

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References

[1] Cappola AR, Ladenson PW. Hypothyroidism and atherosclerosis. J Clin Endocrinol Metab 2003;88:2438-44.
[2] Staub JJ, Althaus BU, Engler H, et al. Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Am J Med 1992;92:631-42.
[3] Steinberg AD. Myxedema and coronary artery disease—a comparative autopsy study. Ann Intern Med 1968;68:338-44.
[4] Becker C. Hypothyroidism and atherosclerotic heart disease: pathogenesis, medical management, and the role of coronary artery bypass surgery. Endocr Rev 1985;6:432-40.
[5] Wolf M, Weigert A, Kreymann G. Body composition and energy expenditure in thyroidectomized patients during short-term hypothyroidism and thyrotropin-suppressive thyroxine therapy. Eur J Endocrinol 1996;134:168-73.
[6] Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008;29:76-131.
[7] Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995;43:55-68.
[8] Asvold BO, Vatten LJ, Nilsen TI, et al. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. Eur J Endocrinol 2007; 156:181-6.
[9] Asvold BO, Bjoro T, Nilsen TI, et al. Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. J Clin Endocrinol Metab 2007;92:841-5.
[10] Iqbal A, Figenschau Y, Jorde R. Blood pressure in relation to serum thyrotropin: the Tromso study. J Hum Hypertens 2006;20:932-6.
[11] Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction and blood pressure: a community-based study. Clin Endocrinol (Oxf) 2006;65:486-91.
[12] Iacobellis G, Ribaudo MC, Zappaterreno A, et al. Relationship of thyroid function with body mass index, leptin, insulin sensitivity and adiponectin in euthyroid obese women. Clin Endocrinol (Oxf) 2005; 62:487-91.
[13] Nyrnes A, Jorde R, Sundsfjord J. Serum TSH is positively associated with BMI. Int J Obes (Lond) 2006;30:100-5.
[14] De Pergola G, Ciampolillo A, Paolotti S, et al. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf) 2007;67:265-9.
[15] 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.
[16] Manji N, Boelaert K, Sheppard MC, et al. Lack of association between serum TSH or free T4 and body mass index in euthyroid subjects. Clin Endocrinol (Oxf) 2006;64:125-8.
[17] Bakker SJ, ter Maaten JC, Popp-Snijders C, et al. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab 2001;86:1206-11.
[18] Asvold BO, Bjoro T, Nilsen TI, et al. Thyrotropin levels and risk of fatal coronary heart disease: the HUNT study. Arch Intern Med 2008; 168:855-60.
[19] Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 2005;165:2467-72.
[20] Singer RB. Mortality in older adults in relation to daily activity energy expenditure. J Insur Med 2008;40:38-43.
[21] Manini TM, Everhart JE, Patel KV, et al. Daily activity energy expenditure and mortality among older adults. JAMA 2006;296: 171-9.
[22] Silvestri E, Schiavo L, Lombardi A, et al. Thyroid hormones as molecular determinants of thermogenesis. Acta Physiol Scand 2005; 184:265-83.
[23] Tagliaferri M, Berselli ME, Calo G, et al. Subclinical hypothyroidism in obese patients: relation to resting energy expenditure, serum

leptin, body composition, and lipid profile. Obes Res 2001;9: 196-201.
[24] al-Adsani H, Hoffer LJ, Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. J Clin Endocrinol Metab 1997;82: 1118-25.
[25] Caraccio N, Natali A, Sironi A, et al. Muscle metabolism and exercise tolerance in subclinical hypothyroidism: a controlled trial of levothyroxine. J Clin Endocrinol Metab 2005;90:4057-62.
[26] Monzani F, Caraccio N, Kozakowa M, et al. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. J Clin Endocrinol Metab 2004;89:2099-106.
[27] Amati F, Dube JJ, Stefanovic-Racic M, et al. Improvements in insulin sensitivity are blunted by subclinical hypothyroidism. Med Sci Sports Exerc 2009;41:265-9.
[28] Brochu M, Malita MF, Messier V, et al. Resistance training does not contribute to improve the metabolic profile after a 6-month weight loss program in overweight and obese postmenopausal women. J Clin Endocrinol Metab 2009.
[29] DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 1979;237:E214-223.
[30] Schoeller DA, van Santen E. Measurement of energy expenditure in humans by doubly labeled water method. J Appl Physiol 1982;53: 955-9.
[31] LaMonte MJ, Blair SN. Physical activity, cardiorespiratory fitness, and adiposity: contributions to disease risk. Curr Opin Clin Nutr Metab Care 2006;9:540-6.
[32] Boekholdt S, Titan S, Wiersinga W, et al. Initial thyroid status and cardio-vascular risk factors: the EPIC-Norfolk prospective population study. Clin Endocrinol 2009 [Accepted article:online].
[33] McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008;372:224-33.
[34] Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373:1175-82.
[35] Tuzcu A, Bahceci M, Gokalp D, et al. Subclinical hypothyroidism may be associated with elevated high-sensitive c-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J 2005;52:89-94.
[36] Christ-Crain M, Meier C, Guglielmetti M, et al. Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 2003;166:379-86.
[37] Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002; 346:793-801.
[38] Gulati M, Pandey DK, Arnsdorf MF, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation 2003;108:1554-9.
[39] Blair SN, Kohl III HW, Barlow CE, et al. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA 1995;273:1093-8.
[40] Michalaki MA, Vagenakis AG, Leonardou AS, et al. Thyroid function in humans with morbid obesity. Thyroid 2006;16:73-8.