

Subclinical hypothyroidism has no association with insulin resistance indices in adult females: A case-control study

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Abstract. Longitudinal studies have indicated an association between thyroid function and insulin resistance (IR) or a neutral relationship. Both the lowest tertile of free thyroxine (fT4) and the highest tertile of free triiodothyronine (fT3) were found to be associated with IR in cross-sectional studies. The aim of the present study was to analyze the association between IR and subclinical hypothyroidism in a female adult population from Bucharest, Romania. This is a retrospective pilot case-control study that included female patients examined by two endocrinologists and a diabetologist in an outpatient clinic. The retrospective follow-up had a one-year duration and included the evaluation of thyroid function tests and IR indices based on fasting insulinemia and C-peptide. The study included 176 women, 91 with subclinical hypothyroidism, with a median age of 60±17 years and a mean body mass index (BMI) of 27.79±4.76 kg/m². The majority of the population (50%) was diagnosed with autoimmune thyroiditis, and 17.05% with goitre. The univariate logistic regression using hypothyroidism as the explaining variable found no evidence of a significant relationship between a decreased thyroid function and IR (OR 1.32; P=0.36). Metabolic syndrome was probably the most important determinant of IR in the population group studied. Thus, it was not the thyroid function *per se*, but the

coexistence of other elements of this syndrome that prevailed in determining IR. Advantages to the study are the design that permitted evaluation of IR and the thyroid function at different moments in time as well as the uniformity of the blood tests. The multivariate analyses were adjusted for age, lipid profile and treatment; however, one limiting factor was the absence of other hormonal blood tests. In summary, there was no association between the thyroid function tests (TSH, fT4) and IR indices in adult Romanian women in a case-control study with one-year retrospective follow-up.

Introduction

Although no unanimous definition of insulin resistance (IR) exists, this condition can be described as the decreased capacity of hepatic, muscular and adipose tissue to make use of glucose in the presence of insulin levels that would normally elicit this process in healthy subjects (1). This phenomenon has been described in anabolic states such as obesity (2), inflammation (3), cancer (4), and is a core element of the metabolic syndrome (5), or type 2 diabetes mellitus (6). In an epidemiological study including a large Romanian population, there were higher levels of IR in metabolically unhealthy lean, and metabolically healthy obese patients vs. controls (7). In addition, longitudinal studies have indicated an association between thyroid function and IR (8,9). Both the lowest tertile of free thyroxine (fT4) (8) and the highest tertile of free triiodothyronine (fT3) (9) have been associated with IR in cross-sectional studies.

The loss of insulin sensitivity could be determined by a decreased insulin-dependent glucose utilization in all tissues (10), a reduction in muscle and liver glycogenolysis and gluconeogenesis (11,12), or interference with adipocyte-myocyte cross-talk (13). Another mechanism possibly involved in the indirect action on lipid metabolism fraction and subsequent lipotoxicity, leads to increased IR (14).

Moreover, the early administration of levothyroxine or metformin in subclinical hypothyroidism was associated

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Table I. General characteristics of the study population.

Variable	IR (n=91)	Non-IR (n=85)
Age (years) ^a	64±13.5	58±16
Glycemia (mg/dl) ^a	104.98±19.48	98.13±12.2
HbA1c (%) ^a	5.4±0.8	5.1±0.6
Total cholesterol (mg/dl)	185.68±58.07	199.61±53.79
HDLc (mg/dl)	63±29.5	68±25
LDLc (mg/dl)	96.3±58.6	110.6±52.34
TG (mg/dl) ^a	121.86±52.39	83.37±43.48
TSH (μUI/ml)	4.11±4.53	2.99±3.6
fT4 (ng/dl)	1.1±0.19	1.08±0.18
Fasting insulin (μUI/ml) ^a	9.21±9.6	5.32±4.87
Fasting C-peptide (ng/ml) ^a	1.55±1.9	1.38±0.73
HOMA-IR1 (insulin) ^a	2.62±2.81	1.29±1.2
HOMA-IR2 (insulin) ^a	1.32±1.32	0.71±0.67
HOMA-IR1 (C-peptide) ^a	2.96±1.32	2.40±0.53
HOMA-IR2 (C-peptide) ^a	1.60±1.5	1.05±0.55

^aP<0.05. IR, insulin resistance; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HbA1c, glycosylated hemoglobin; HDLc, high-density cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides; TSH, thyroid-stimulating hormone; fT4, free thyroxine.

with improved IR in some (15,16), but not all (17,18) studies. Consequently, the aim of the present study was to analyze the association between subclinical hypothyroidism (SHO) and IR in a female adult population from Bucharest, Romania.

Case study

A pilot, retrospective, case-control study was designed that included female patients examined by two endocrinologists and a diabetologist in an outpatient clinic in Bucharest, Romania. The patients presented for a routine evaluation of obesity, thyroid disease or osteoporosis. Patients that were analyzed by the same laboratory and had the complete hormonal and biochemical blood parameters were included. The variables considered were: glycemia (mg/dl), glycosylated hemoglobin (HbA1c) (%), total cholesterol (mg/dl), high-density (HDLc) and low-density lipoprotein cholesterol (LDLc) (mg/dl), triglycerides (TG) (mg/dl), thyroid-stimulating hormone TSH (μUI/ml), free thyroxine-fT4 (ng/dl), fasting insulin (μUI/ml) and fasting C-peptide (ng/ml). Previous values (within one year) for these blood tests were searched retrospectively for each patient.

The study followed the Helsinki Declaration. Approval was obtained from the Ethics Committee of the Diabetes Department of 'Carol Davila' University of Medicine and Pharmacy (National Institute of Diabetes, Nutrition and Metabolic Diseases N. C. Paulescu), Bucharest, Romania.

Patient data. Data regarding age, weight, height, comorbidities and concomitant treatment were collected. Body mass index (BMI) was estimated as weight (kg)/height (m)². IR evaluation was carried out as follows. The homeostatic model assessment HOMA-IR1 equation (insulin)=fasting glycemia (mg/dl) x fasting insulin (μUI/ml)/405; HOMA-IR1

(C-peptide)=1.5 + fasting glycemia (mmol/l) x [fasting C-peptide (nmol/l)/2800 (19), and HOMA-IR2 (insulin), HOMA-IR2 (C-peptide)] was calculated with HOMA-IR software version 2.2.3, available online (20). The cut-off value for defining IR was at 2.5 (19).

Microsoft Office Excel[®] file (Microsoft Corp.) was used to create the database. Inferential statistical analyses were carried out with the R computing and programming environment v. 4.0.3 [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>], under an RStudio local terminal, v. 1.1.456.

Assuming that the probability of the exposure variable (hypothyroidism) in women from the general population is ~8% (21), with a 1:1 ratio for cases and controls, a prevalence of 25% of IR (22), and 80% power, a minimum (total) sample size of 150 was necessary for a univariate logistic regression model using a score test and a minimum (total) sample size of 187 for the same model using a Wald test, to be able to detect an odds ratio of 4 (log OR, 1.39). For the multivariate analysis, the sample size needed was much larger, but the pilot study data allowed for the assessment of such a study and more precise calculations for such a study. Statistical power was computed using the 'sample size logistic case-control' R package V.0.0.6 (23). A P-value (two-tailed) <0.05 was considered significant.

Following univariate analysis (IR as a function of the presence or absence of hypothyroidism), a pre-specified multivariate model including BMI, age, and parameters of the lipid profile (total cholesterol, LDLc, HDLc, and TG) as covariates (including relevant interactions) was developed. Assessment of the model fit was performed using specific functions from the 'LogisticDx' R package [Osius and Rojek's tests, Stukels tests, the area under the receiver-operating curve (AUC)

Table II. Comparison of the hypothyroidism and control groups, according to IR risk factors.

Risk factor	Cases (n=91) [mean (SD) or %]	Controls (n=85) [mean (SD) or %]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P-value (Wald-test)
HDLc	67.8 (18.0)	71.4 (19.8)	0.99 (0.97-1.00)	1.05 (1.00-1.11)	0.064
LDLc	110.0 (41.5)	103.0 (37.5)	1.00 (0.99-1.00)	1.03 (0.99-1.07)	0.088
BMI	28.3 (4.40)	27.4 (5.07)	1.24 (1.14-1.34)	1.52 (1.22-1.89)	<0.001
TG	119.0 (62.4)	102.0 (37.8)	1.01 (1.01-1.02)	1.08 (1.02-1.14)	0.004
Age	59.8 (10.6)	60.4 (14.4)	1.04 (1.01-1.06)	1.03 (1.00-1.06)	0.075
Hypoth	100%	0%	1.32 (0.73-2.38)	1.09 (0.54-2.21)	0.803
HDLc*LDLc	NA	NA	1 (1.00-1.00)	1.00 (1.00-1.00)	0.049
BMI*TG	NA	NA	1 (1.00-1.00)	1.00 (1.00-1.00)	0.011

IR, insulin resistance; Hypoth, hypothyroidism; NA, not applicable; SD, standard deviation; OR, odds ratio; CI, confidence interval; HDLc, high-density cholesterol; LDLc, low-density lipoprotein cholesterol; BMI, body mass index; TG, triglycerides.

and others] (24). Interaction plots were generated using the 'interplot' R package (25).

Results

In total, 176 women, of whom 91 had subclinical hypothyroidism (SHO) with a median TSH of 5.6 ± 2.66 vs. 1.63 ± 1.06 uIU/ml compared with controls were included. The median age in our population was 60 ± 17 years, and the mean BMI was 27.79 ± 4.76 kg/m². The majority of our population (50%) was diagnosed with autoimmune thyroiditis, and 17.05% with goiter, based on previous antibody measurements and thyroid echography. In the entire population, 8.52% underwent a thyroidectomy, and 52.84% were treated with a levothyroxine substitute. Although >50% of the women had concomitant treatment, the thyroid hormone levels were not in target. The general characteristics of the population are presented in Table I.

The univariate logistic regression using hypothyroidism as the clarifying variable found no evidence of a significant relationship between a decreased thyroid function and IR (OR, 1.32; $P=0.36$).

The second level of our analysis was to adjust for variables most likely to be associated with IR: The lipid profile (HDLc, LDLc, TG), BMI, and age; total cholesterol was not included in the model as it was highly correlated with the LDLc ($r=0.89$, 95% CI 0.85-0.91). The unadjusted and adjusted OR for the different covariates are provided in Table II and Fig. 1.

Leaving out the six most influential observations resulted in some changes in the model. The ORs for the BMI and TG were slightly increased (1.74 and 1.10), and the effect of age became significant (OR, 1.06; $P=0.005$) after eliminating the outliers in another model different from that in Table II. Instead, the P-values for the HDL:LDL interaction, as well as the individual effect of LDL and HDL, increased considerably beyond the conventional threshold of significance ($P=0.15$, 0.22 and 0.36, respectively). Although the influence of IR on LDLc was moderate, there was a small difference between groups, leading to the inclusion of this variable in the analysis. The interaction effect between HDL and LDL is described in Fig. 2.

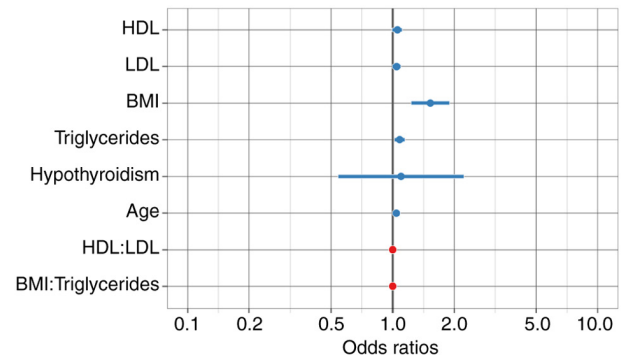


Figure 1. The odds ratio for the main risk factors associated with insulin resistance, with 95% Wald confidence intervals. HDLc, high-density cholesterol; LDLc, low-density lipoprotein cholesterol; BMI, body mass index; TG, triglycerides.

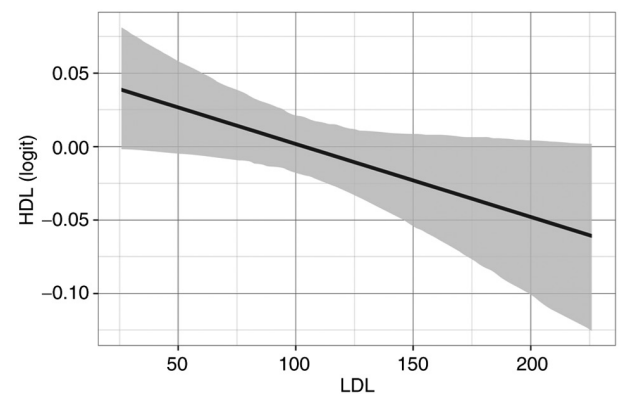


Figure 2. Interaction plot describing the variation of the HDLc coefficient (logit) as a function of LDLc value. At the lowest LDLc values the OR for HDLc is ~1.05, whereas at the highest values, OR was ~0.90. The dark grey band corresponds to the 95% confidence interval. HDLc, high-density cholesterol; LDLc, low-density lipoprotein cholesterol; OR, odds ratio.

The later evolution (over a period of one year) towards clinically manifested hypothyroidism and diabetes, respectively, was assessed, but no significant effect was found for the two variables ($P=0.62$ and 0.83, respectively).

Discussion

The data regarding insulin sensitivity and resistance in the course of thyroid dysfunctions remain controversial (11,22,26-28). In a previous cross-sectional study in the Romanian population, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) predicted a thyroid-stimulating hormone (TSH) increase in obese patients with newly diagnosed thyroid pathology (29). This led to the design of a case-control study in order to assess the relationship between the two parameters in time (two determinations at a one-year interval).

The absence of a significant correlation between IR and thyroid function may be related to the relatively small sample size as opposed to other studies (11,26-29). The sample size considerations assumed a relatively large effect (an OR of ~4.0). To detect an OR of 1.32 in a case-control study such as the current one, as suggested by the data, a sample size of over 5,000 patients would be needed. Another explanation is the level of thyroid hormone itself, i.e.; the median TSH was smaller than that in other studies that included patients with subclinical hypothyroidism (SHO) (5.6 vs. 7.37 or 8.9 uUI/ml) (11,27). The interference of hormones or metabolites leading to IR that were previously described in some populations including cortisol (29), prolactin (17), leptin (28), adiponectin (28,30), homocysteine (31), or autonomic nervous system stimulation (17) cannot be excluded. These additional hormones were not evaluated in the present study.

Metabolic syndrome is probably the most important determinant of IR in our population. In women with SHO, some components of metabolic syndrome [central obesity, triglycerides (TG)] are more prevalent (32). Accordingly, TG and BMI were different between the SHO and controls in the present study, compared with the HDL-LDL interaction which became insignificant after eliminating outliers. Thus, not the thyroid function per se, but the coexistence of other elements of this syndrome prevail in determining IR. Other authors have reached the same conclusion (30).

Age is another confounder that was included in our multivariate analysis. In pubertal children, IR may be related to increased TSH (33), but in adolescents with risk factors for diabetes, there was no correlation between the two factors (34).

Although the overall balance tends to favor the existence of a relationship between hypothyroidism and IR, this hypothesis is based on small observational studies. The advantages to the present study are the design that permitted us to evaluate the IR and the thyroid function at different time periods. The same laboratory analyzed the uniformity of the blood tests. The susceptibility for recall and information bias was reduced because of direct access to the laboratory database. Multivariate analyses for age, lipid profile and treatment were adjusted; however, one of the limits was the absence of other hormonal blood tests (the control of other extraneous variables is incomplete, as for all case-control studies). In addition, the relatively small sample size may influence the results.

In summary, no association between thyroid function tests (TSH, fT4) and IR indices were found in adult Romanian women in a case-control study with one-year retrospective follow-up. This relationship may be influenced by the TSH level, being evident only in values over a certain cut-off (7 uUI/ml).

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Availability of data and materials

Restrictions apply to the availability of these data. The database is available with author's permission.

Authors' contributions

RAS, CIT, and CG realized the concept of the study. RA, RAS are responsible for methodology. RA, RAS, and CS performed the formal analysis. RAS and SDS performed data acquisition and curation and are responsible for confirming the authenticity. RAS, AC, APS, and RA prepared the original draft. CG, RAS, RA, RIŞ.vS, IPT, SDS, and CS reviewed and edited the draft. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of the Diabetes Department of 'Carol Davila' University of Medicine and Pharmacy (National Institute of Diabetes, Nutrition and Metabolic Diseases N. C. Paulescu; approval no. 2/20.03.2017), Bucharest, Romania.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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