Original Article

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Early menarche is independently associated with subclinical hypothyroidism: a cross-sectional study

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Abstract:

Background: Subclinical hypothyroidism (SH) is more frequent in females than males, with a female to male ratio ranging from 1.5 to 5 in the general population. The aim of this study was to evaluate for the first time the association of reproductive factors, particularly age at menarche, with SH risk.

Materials and methods: In a cross-sectional study, reproductive factors such as age at menarche, at menopause and at first birth, lactation, parity, full-term pregnancies, reproductive years, use of oral contraceptives and hormonal replacement therapy, somatometric data and insulin resistance parameters were recorded in 72 consecutive female patients with SH and 72 healthy female controls matched on age (± 5 years) and date of diagnosis (± 1 month).

Results: SH cases exhibited significantly younger age at menarche than controls (12.6 ± 1.2 vs. 13.3 ± 0.8 years, respectively, $p < 0.001$). Cases presented later age at first pregnancy with a lower number of full-term pregnancies ($p = 0.04$). Early age at menarche was independently associated with SH risk, above and beyond thyroid autoimmunity, body mass index (BMI), hip circumference (HC), homeostatic model assessment of insulin resistance and alcohol consumption [odds ratio (OR): 0.22, 95% confidence interval (CI): 0.11–0.44; $p < 0.001$].

Conclusions: It is possible that an interplay of early exposure to estrogens, as expressed by early menarche, and induction of thyroid autoimmunity may be associated with SH risk. More prospective studies shedding light on the role of estrogens in SH are required to confirm these findings.

Keywords: autoimmunity, estrogen, hypothyroidism, menarche, thyroid

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Introduction

Subclinical hypothyroidism (SH) is considered a mild thyroid dysfunction which can be diagnosed from elevated thyrotropin levels (TSH) in the presence of normal free triiodothyronine (fT3) and thyroxine (fT4) levels [1]. Hashimoto's thyroiditis (HT) is considered the most frequent determinant of progressive thyroid dysfunction and SH in adults [2], [3]. SH has been linked to cardiovascular disease (CVD), metabolic syndrome, atherosclerosis, dyslipidemia, diabetes mellitus (DM) type 2 and hypertension, particularly when TSH levels are above 10 mIU/L [2], [3], [4], [5].

There are few established risk factors for SH, with thyroid autoimmunity being the most important [5]. Because SH is consistently more frequent in women, with a female to male ratio ranging from 1.5 to 5 in the general population, reproductive, menstrual and hormonal parameters, particularly age at menarche, may be of paramount importance [6]. The aim of the present study was to explore for the first time the potential role of reproductive factors, particularly age at menarche, in SH risk among women living in the iodine-sufficient metropolitan region of Athens, Greece.

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Materials and methods

Study population

The study enrolled 72 consecutive women suffering from SH [thyroid stimulating hormone (TSH) level higher than 5 mIU/L measured at least twice in independent determinations and who were not receiving L-T4 treatment before the baseline visit] and 72 women as healthy control participants, coming to the outpatient clinic for an annual check-up examination, matched on age (± 5 years) and date of diagnosis (± 1 month) with cases, between February 2012 and December 2016 inclusive. All women were of Greek nationality residing in the same iodine-sufficient area (metropolitan area of Athens, Greece). The exclusion criteria included age less than 18 and above 75 years; any medications that could cause thyroid dysfunction; previous thyroidectomy; hypertension, CVD, renal or hepatic disease; autoimmune or endocrine disorders; muscular, neurologic or psychiatric disorders; cancer; pregnancy and post-partum period; anti-lipidemic drugs; and infection at the time period of blood sampling. All subjects were on an unrestricted diet.

Medical records were reviewed and interviews were performed by the same physician (TS), in order to obtain information on demographic characteristics, medical history, consumption of coffee and alcoholic beverages, tobacco smoking, physical exercise per week and reproductive factors such as age at menarche, menses characteristics (frequency, duration), age at menopause and at first birth, lactation, parity, full-term pregnancies, use of oral contraceptives and hormonal replacement therapy (HRT). Determination of weight, height, waist circumference (WC), hip circumference (HC), and blood pressure (BP) were performed by the same physician for all patients. Waist-to-hip ratio (WHR) was calculated and body mass index (BMI) was determined based on the equation: $\text{body weight (kg)}/\text{height}^2 (\text{m}^2)$. Body fat percentage was calculated based on the Deurenberg equation [7]. Each female participant was submitted to two BP measurements, with the same instrument, 5 min apart after 10 min of rest. BP was calculated based on the mean of two measurements. Interviews and measurements were accomplished under similar circumstances and at the same time in the morning (8–9.30 am). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Scientific and Ethics Committee of the hospital. All participants gave an informed consent before enrolment to the study.

Laboratory determinations

All blood draws were performed early in the morning after 12 h of fasting. Serum thyroid parameters (TSH, fT3, fT4, T3, T4, anti-thyroglobulin/TG antibodies and anti-peroxidase/TPO antibodies) and insulin were performed using electrochemiluminescent immunoassays (Cobas, Roche Diagnostics Corporation, Indianapolis, IN, USA). Homeostasis model assessment score of insulin resistance (HOMA-IR) was derived from the formula: $\text{Fasting serum insulin (mIU/L)} \times \text{fasting serum glucose (mmol/L)} / 22.5$.

Statistical analysis

The statistical analysis of the data was performed using IBM-SPSS® version 24 for Windows. Data were assessed through simple cross-tabulations and by using χ^2 test for categorical variables, t-test for normally distributed variables, and Mann-Whitney U for not normally distributed variables. Normality hypothesis was tested by using the Shapiro-Wilk test. Multiple logistic regression analysis was employed to identify independent significant determinants of SH occurrence (dependent variable) which were found in univariate analyses. Transformation in quartiles was performed for continuous variables not normally distributed. A two-sided p-value of less than 0.05 was considered significant.

Results

Descriptive categorical features and continuous clinical and laboratory parameters of all participants are presented in Table 1. A diagnosis of thyroid autoimmunity was more frequent in women with SH compared to controls ($p < 0.001$). Moreover, alcohol and coffee consumption were significantly higher in patients than controls ($p = 0.03$ and $p = 0.01$, respectively). As expected, women with SH had significantly higher levels of TSH, anti-TG and anti-TPO antibodies ($p < 0.001$) and similar levels of total T3, fT3 and fT4 (Table 1). Only total T4

was significantly lower in patients than controls ($p < 0.001$). Women with SH presented lower HC ($p = 0.01$) as well as elevated insulin and HOMA-IR than controls ($p < 0.05$).

Table 1: Clinical and Laboratory parameters of subclinical hypothyroidism cases ($n = 72$) and control participants ($n = 72$).

Categorical variables	Cases ($n = 72$) N, %	Controls ($n = 72$) N, %	p-Value
Education, years			0.74
6	8 (11.1)	4 (5.6)	
9	10 (13.9)	8 (11.1)	
12	32 (44.4)	36 (50.0)	
>12	22 (30.6)	24 (33.4)	
Smoking history			0.50
Non-smoker	40 (55.6)	36 (50.0)	
Ex-smoker	14 (19.4)	20 (27.8)	
Current smoker	18 (25.0)	16 (22.2)	
Alcohol consumption			0.03
Never	8 (11.1)	8 (11.1)	
Rarely (1–2 glasses per month)	12 (16.7)	24 (33.3)	
Weekly (1–2 glasses per week)	24 (33.3)	28 (38.9)	
Weekly (3–4 glasses per week)	20 (27.8)	8 (11.1)	
Coffee consumption			0.01
Never	4 (5.6)	0 (0.0)	
Few times per month	10 (13.9)	8 (11.1)	
Few times per week	6 (8.3)	20 (27.8)	
Daily	52 (72.2)	44 (61.1)	
Physical activity (≥ 2 h/week)	10 (13.9)	16 (22.2)	0.19
Presence of thyroid autoimmunity (yes, %)	21 (29.2)	4 (5.6)	<0.001
Continuous variables	Mean (SD)	Mean (SD)	
Age, years	48.6 (15.6)	49.9 (14.3)	0.74
Weight, kg	67.8 (11.4)	64.6 (8.2)	0.05
Height, m	1.64 (0.04)	1.64 (0.04)	0.87
BMI, kg/m ²	25.2 (4.0)	24.0 (3.1)	0.08
WC, m	0.81 (0.12)	0.84 (0.1)	0.15
HC, m	0.91 (0.1)	0.96 (0.73)	0.01
WHR	0.9 (0.08)	0.9 (0.06)	0.09
Fat, %	35.9 (5.9)	34.9 (4.9)	0.22
Fat mass, kg	24.8 (7.5)	22.8 (5.6)	0.06
Free fat mass, kg	42.9 (5.2)	41.8 (3.8)	0.20
SBP, mm Hg	128.4 (18.8)	125.8 (11.4)	0.27
DBP, mm Hg	80.1 (12.1)	79.7 (6.8)	0.84
Mean arterial BP ^a , mm Hg	96.2 (13.9)	95.1 (8.1)	0.47
TSH, mIU/L	8.5 (1.8)	2.7 (0.7)	<0.001
Free T3, pmol/L	4.76 (1.23)	4.76 (0.92)	0.94
Free T4, pmol/L	1802 (515)	1930 (386)	0.09
Total T3, nmol/L	2 (0.46)	2 (0.46)	0.45
Total T4, nmol/L	103 (23)	32 (17)	<0.001
Anti-TG Ab, kIU/L	56.5 (37.7)	34.5 (29.8)	<0.001
Anti-TPO Ab, kIU/L	26.4 (23.7)	13.1 (7.5)	<0.001
Glucose, mmol/L	4.63 (0.62)	4.46 (0.6)	0.09
Insulin, pmol/L	159.3 (36.6)	138.5 (22.2)	<0.001
HOMA-IR score	4.7 (1.6)	3.9 (0.9)	<0.001

Mean arterial BP = $(2 \times \text{DBP} + \text{SBP})/3$. Ab, antibody; BP, blood pressure; BMI, body mass index; DBP, diastolic blood pressure; HC, hip circumference; HOMA-IR, homeostasis model assessment score of insulin resistance; SBP, systolic blood pressure; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; WC, waist circumference; WHR, waist-to-hip ratio. Statistically significant results are given in bold.

Table 2 portrays reproductive factors of SH cases and controls. Overall, regarding reproductive factors, women with SH presented an earlier age at menarche ($p < 0.001$), an older age at first pregnancy ($p = 0.04$) and a lower number of full-term pregnancies ($p = 0.04$) than controls.

Table 2: Reproductive factors of subclinical hypothyroidism cases (n = 72) and control participants (n = 72).

Reproductive factors	Cases, n = 72	Controls, n = 72	p-Value
Continuous variables	Mean (SD)	Mean (SD)	
Age at menarche, years	12.6 (1.2)	13.3 (0.8)	<0.001
Age at menopause for menopausal women (n = 38 in cases and n = 44 in controls), years	45.0 (2.7)	44.3 (3.1)	0.55
Reproductive years for menopausal women (n = 38 in cases and n = 44 in controls), years	32.2 (3.0)	31.0 (3.3)	0.07
Menses duration, days	29.1 (1.9)	28.6 (1.7)	0.14
Period duration, days	5.07 (0.51)	5.08 (0.44)	0.84
Age at first pregnancy, years	29.6 (5.22)	28.27 (4.71)	0.04
Full-term pregnancies	1.75 (0.49)	2.02 (0.63)	0.04
Categorical variables	N, %	N, %	
Use of oral contraceptives (yes, %)	7 (9.7)	6 (8.3)	0.77
Hormone replacement therapy (yes, %)	3 (4.2)	3 (4.2)	1.00
Exogenous use of hormones ^a (yes, %)	10 (13.9)	9 (12.5)	0.81
Parity (yes, %)	40 (55.6)	44 (61.1)	0.50
Lactation (yes, %)	23 (31.95)	28 (38.89)	0.66
Menopausal (yes, %)	38 (52.8)	44 (61.1)	0.31

^aExogenous use of hormones: hormone replacement therapy and oral contraceptives. Statistically significant results are given in bold.

Table 3 depicts multiple logistic regression-derived adjusted odds ratios (OR) and 95% confidence intervals (CI) for associations of SH in relation to age, date of diagnosis (matching factors), age at menarche, BMI, HC, thyroid autoimmunity, HOMA-IR and alcohol consumption. There was statistically significant evidence that earlier age at menarche expressed by quartiles was associated with SH, before and after adjusting for the above mentioned parameters (OR = 0.22, 95% CI 0.11–0.44, $p < 0.001$). Also, thyroid autoimmunity, BMI, HC and alcohol consumption were associated with SH occurrence ($p < 0.05$).

Table 3: Association of age at menarche, alcohol consumption, autoimmune thyroid disease, BMI, HC and HOMA-IR with risk of subclinical hypothyroidism in 72 cases with subclinical hypothyroidism and in 72 controls matched on age and date of diagnosis; multiple logistic regression-derived, Odds Ratios and 95% Confidence Intervals.

Variables	Category or increment	p-Value	OR	95% CI
Age at menarche	1 quartile more	<0.001	0.22	0.11 – 0.44
BMI	1 kg/m ² more	0.03	1.21	1.02 – 1.43
HC	1 quartile more	<0.001	0.41	0.26 – 0.65
Thyroid autoimmunity	Yes vs. no	<0.001	45.27	5.84 – 350.79
HOMA-IR	1 SD more	0.12	1.66	0.89 – 3.11
Alcohol consumption	One category of alcohol consumption more	0.001	2.12	1.37 – 3.47

BMI, body mass index; HC, hip circumference; HOMA-IR, homeostasis model assessment score of insulin resistance; OR, odds ratio; SD, standard deviation; ^aAdjusted for age and date of diagnosis/blood draw (matching factors). SD, standard deviation. Statistically significant results are given in bold.

Discussion

To the best of our knowledge, this is the first study showing that early age at menarche was independently associated with SH risk. This study also confirms the strong association between thyroid autoimmunity and higher BMI with SH, as observed in many studies [2], [3], [5]. However, we did not find any independent associations between other reproductive factors and SH.

Early age at menarche has been linked to several disorders, such as metabolic syndrome, CVD, DM type 2, decreased bone mineral density, pre-eclampsia and breast cancer (BC) [8], [9], [10], [11], [12], [13], [14]. Besides, hypothyroidism has been associated with an increased risk of postmenopausal BC [15]. Menarche is influenced by genetic, nutritional, socio-economic, educational, ethnic, racial, environmental and geographical factors as

well as BMI and physical activity as seen in Figure 1 [16], [17], [18]. Nowadays, the age of menarche is decreasing due to many factors, such as style of living, diet, socio-economic and environmental factors, and educational level [16]. Women with a higher socio-economic profile presented lower age at menarche in contrast to those who were settled in low-income or rural areas with a lower educational level [17].

Figure 1: Age at menarche depends on genetic, nutritional, socio-economic, educational, ethnic, racial, environmental and geographical factors as well as BMI and physical activity.

Early menarche may be accompanied by an early exposure to estrogens which could trigger thyroid autoimmunity or may be associated with body fatness and insulin resistance which are also linked to subclinical hypothyroidism.

Puberty is considered a significant hormonal milestone in a woman's life that is characterized by alterations in the hypothalamus-pituitary-gonadal (HPG) axis, estrogens, adrenal androgens, growth hormone and insulin growth factor-I [18], [19]. Whilst it is unlikely that age at menarche per se is a causal determinant for SH, it could be a marker of an underlying pathway that confers an elevated risk. It is possible that early menarche accompanied by an early exposure to estrogens may trigger thyroid autoimmunity. It is well-known that autoimmune disorders, including thyroid autoimmunity, are more frequent in women than men with a female to male ratio of 1.5–5 [20]. Early menarche (age 12 or younger) was strongly associated with risk of systemic lupus erythematosus in big cohorts like Nurses Health Study (NHS) and NHS II [17]. Estrogen receptors are expressed in the majority of immune cells. Estrogens play a critical role in B-cell maturation and may have an after effect on the breakdown of immune tolerance observed in autoimmune disorders [21], [22]. Furthermore, estrogen receptors and earlier exposure to estrogens may influence the initiation and progression of thyroid autoimmunity. In vitro studies have shown that estrogens significantly increase proliferation, inflammation and invasive properties of thyroid cancer cell lines [5], [23], [24], [25]. Also, estrogen receptor levels were found to be higher in adenomatous goiter and follicular adenoma compared to normal thyroid glands [26]. Finally, another mechanism linking early menarche with SH risk may include body fatness, insulin resistance and other cardio-metabolic risk factors which are associated with early menarche in the majority of studies in Western countries [27], [28]. The abovementioned factors were also associated with SH risk [5], [29].

This study was appropriately and sufficiently powered to replicate prior established associations of the study parameters with SH risk and to produce new statistically significant associations with age at menarche. To minimize the possibility of potential uncontrolled exposures, we have included control subjects who were carefully matched to cases and drawn from the same study population of an iodine-sufficient area. However, this study presents noteworthy limitations to take into consideration. First of all, it was impossible to collect any somatometric data at childhood, as well as follow-up data, that may affect menarcheal age and negative health outcome of later life. Secondly, the cross-sectional nature of this study impedes conclusions as per the existence of a causal relationship, despite the fact that menarcheal age precedes SH. Third, menarcheal age was reported by recall; nevertheless, menarche is an important event in a woman's life, therefore, it is reliable throughout many years [30]. Although the cross-sectional design cannot demonstrate causality, it may raise reliable hypotheses to be bolstered and extended in future prospective and longitudinal studies. Finally, another limitation is the modest sample size of the study. However, we have calculated that based on our sample size of 72 cases and 72 controls the statistical power was 85% at the 0.05 level of significance in order to detect a

6-month (or 0.5 years) difference in age at menarche between groups. Nevertheless, this sample size was not eventually sufficient to perform subgroup analyses in menopausal women.

In conclusion, this study showed an independent association of early menarche with an increased risk of SH. Although it is still unclear how hormonal and reproductive factors are related to SH, this study may raise reliable hypotheses regarding the interplay of early exposure to estrogens, thyroid autoimmunity and BMI with SH risk as portrayed in Figure 1. Further larger prospective studies and genetic research of the association of reproductive factors with SH are needed. More investigation is warranted to explain the greater prevalence of SH and thyroid disorders amid women.

Author Statement

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Conflict of interest: None declared

Informed consent: All participants gave informed consent before enrolment to the study.

Ethical approval: The study was approved by the Scientific and Ethics Committee of the hospital.

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