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Menopause modulates the association between thyrotropin levels and lipid parameters: The SardiNIA study

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ABSTRACT

Objective: Thyroid hormone influences lipoprotein metabolism. The role of menopausal status in this association has not been extensively studied. The aim of the present study is to evaluate the association between lipid parameters and mild elevations of thyrotropin (TSH), and whether menopause influences this relationship.
Study design: A cross-sectional study was conducted with a sample of 2,914 women (aged 14–102 years) from the SardiNIA study.
Main outcome measures: The association of TSH with blood lipid levels was examined using regression analyses, according to menopausal status.
Results: Postmenopausal women had lower serum TSH concentrations and higher levels of total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), and triglycerides than did premenopausal women ($p = 0.001$ or less for all). In premenopausal women, after adjusting for the confounders age, BMI, smoking, insulin and glycaemia, TSH showed a direct relation to the levels of total cholesterol ($\beta = 0.046$, $p = 0.010$), LDLc ($\beta = 0.044$, $p = 0.016$) and triglycerides ($\beta = 0.085$, $p < 0.001$), but no association with HDLc level. In the postmenopausal group, TSH was directly associated only with triglyceride levels ($\beta = 0.103$, $p = 0.014$).
Conclusions: The association between mild elevation of TSH and lipid levels is influenced by menopausal status. Further research is needed to clarify this finding.

1. Introduction

Thyroid hormones exert a wide range of effects in several systems including cardiovascular function. It has long been observed that overt hypothyroidism is associated with accelerated atherosclerosis but the role of subclinical hypothyroidism is not completely understood [1,2]. Thyroid hormone significantly influences lipoprotein metabolism, and overt hypothyroidism is a well-known cause of hyperlipidaemia [3]. Moreover, similar biochemical changes were also observed in subclinical hypothyroidism, in which high levels of thyrotropin (TSH) were associated with an increase of lipid abnormalities that were reversible by levothyroxine supplement therapy [4]. Recently, abnormalities in lipoprotein pattern have also been reported in subjects with TSH in the upper normal range [5], although with some gender difference [6]. Thus, serum lipids can change along with TSH levels even when thyroid hormone levels are normal.

Thus far, few large studies have investigated the association of TSH levels within the reference range with level of lipids in women in the general population. Menopause usually leads to changes in hormonal status, metabolism and lipid profile. Reduced oestrogen production from ovaries results in increased plasma cholesterol levels, both in total and low density lipoprotein cholesterol (LDLc), with a reduction in high density lipoprotein cholesterol (HDLc) [7]. The changes in lipid profile are thus similar to those observed in overt hypothyroidism, for which replacement therapy is mandatory. On the contrary, treatment of subclinical hypothyroidism is

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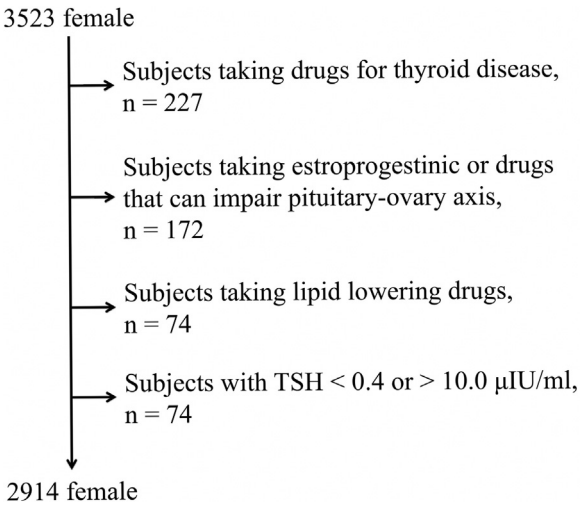

Fig. 1. Flowsheet of included cases.

not universally accepted, particularly in the elderly for whom mild TSH elevation may be a normal manifestation of aging.

The objective of this study was to investigate whether menopause might influence the relation between TSH and lipid parameters in a sample with normal or slightly elevated TSH.

2. Methods

2.1. Study population

This analysis is based on data from the SardiNIA study, a population-based survey that investigates genetic and phenotypic traits associated with aging [8]. Features of this project have been described elsewhere [9]. Briefly, all residents from four towns (Lanusei, Arzana, Ilbono, and Elini) in a valley in Sardinia (Italy), aged 14 years and older, were invited to participate. Since November 2001, participants had visited and their blood samples analysed about every 3 years, generating three complete surveys.

2.2. Exposure assessment and outcome assessment

A detailed medical history, which included age at menopause, a physical examination, anthropometric and biochemical measurements, was assessed by computer-aided face-to-face interviews. Physical examinations were performed by trained medical staff following a standardized procedure. We analysed data from a first visit of participants, focusing on women with normal or mildly elevated TSH (range 0.4–10.0 μIU/ml) and free thyroxine within the reference range. From the original cohort of 6,148 subjects, those who reported taking thyroid medications (thyroid hormone replacement or thyrostatics), lipid lowering drugs, or hormonal replacement therapy were excluded, yielding a final population of 2,914 (age 14–102 years), as shown in Fig. 1. Each participant signed an Informed Consent. All study methods were approved by the local ethics committee, Azienda Sanitaria Locale 4 (ASL4).

2.3. Covariates assessment

Venous blood samples were drawn between 7 and 8 a.m. after an overnight fast. Plasma triglycerides and total cholesterol were determined by an enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyser, Irving, TX, USA); HDLc by dextran sulphate–magnesium precipitation; and LDLc by the Friedewald formula. Serum TSH was assessed with the Siemens TSH assay (Immulite 2000) according to the manufacturer's instructions. The method is a solid-phase, two-site chemiluminescent immunometric assay (normal range 0.4–4.0 μIU/ml). Fasting plasma glucose concentration was measured by the glucose oxidase method (Beckman Instruments Inc., Fullerton, CA, USA). Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Smokers were defined as current consumers of at least one cigarette per day.

2.4. Statistical analysis

First, each parameter distribution gaussianity was assessed by the Shapiro-Wilk test. Because of skewed distributions, we calculated the sample descriptive statistics by using non-parametric tests, and reported results were expressed as median and 25th–75th percentiles. Distributions of categorical variables were expressed as absolute number and percentages. The Wilcoxon rank sum test was used to compare all continuous variables in women before and after menopause. Differences in frequencies were tested by the exact Fisher test. Because of the skewed distribution, lipid parameters were mathematically transformed (inverse normal transformation) for the regression analyses. Multiple linear regression tests were performed, separately, after stratifying the sample set by menopausal status, with each lipid parameter as a dependent variable and age, BMI, smoking, insulin, glycaemia as independent variables. Age at menopause was further included as independent variable only in models which analysed postmenopausal women. In a further analysis, we repeated the above analyses in women with serum TSH level within the normal range (TSH 0.4–4.0 μIU/ml). Collinearity was assessed by using the tolerance and variation-inflation factor (VIF). Collinearity was found if the tolerance was less than 0.1 and the VIF more than 10, respectively. Autocorrelation and heteroscedasticity were further tested with Durbin-Watson Test and Breusch-Pagan Test, respectively. Significance was set at $p < 0.05$ in Stata 12.0.

3. Results

Relevant features of the sample are in Table 1. Postmenopausal women had lower serum TSH, higher levels of total cholesterol, LDLc, HDLc, triglycerides, glycaemia and increased BMI compared to premenopausal subjects ($p = 0.001$ or less for all). To test the role of TSH on lipid parameters, multiple regression analyses were run (Table 2). In premenopausal women, after adjusting for the covariates age, BMI, smoking, insulin, glycaemia, TSH showed a direct relation with total cholesterol ($\beta = 0.046$, $p = 0.010$), LDLc ($\beta = 0.044$, $p = 0.016$), and triglycerides ($\beta = 0.085$, $p < 0.001$), but no association with HDLc ($\beta = -0.007$, $p = 0.720$).

In the postmenopausal group, TSH showed no relation with total cholesterol ($\beta = 0.032$, $p = 0.210$), LDLc ($\beta = 0.019$, $p = 0.470$), or HDLc ($\beta = 0.002$, $p = 0.940$). However, triglycerides were still positively associated with TSH ($\beta = 0.054$, $p = 0.028$).

In a separate analysis we tested the association between lipid parameters and TSH in women with TSH within the reference range (TSH 0.4–4.0 μIU/ml), stratified by menopausal status, as shown in Table 3. In premenopausal women TSH was directly related to total cholesterol ($\beta = 0.069$, $p = 0.008$), LDLc ($\beta = 0.057$, $p = 0.029$), and triglycerides ($\beta = 0.099$, $p < 0.001$). Again, HDLc showed no relation to TSH ($\beta = 0.018$, $p = 0.525$). In postmenopausal women TSH once more retained a positive relation with triglycerides ($\beta = 0.103$, $p = 0.014$), but no significant association with other lipid parameters ($p = 0.345$ or higher).

4. Discussion

Aging is usually associated with a worsening of lipid metabolism, both in men and in women [10]. LDLc progressively