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Associations between the levels of thyroid hormones and lipid/lipoprotein levels: Data from National Health and Nutrition Examination Survey 2007–2012☆

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ABSTRACT

Data from National Health and Nutrition Examination Survey for the years 2007–2012 were used to investigate associations between thyroid hormones and lipid/lipoprotein levels for a representative sample of general US population aged ≥20 years. There were no statistically significant differences for adjusted high density lipoprotein levels among thyroid function groups, namely, subclinical hyperthyroid (SCHPR), clinical hyperthyroid (CHPR), euthyroid (EU), clinical hypothyroid (CHYP), and subclinical hypothyroid (SCHYP). For the general US population, positive associations for thyroid stimulating hormones (TSH) and negative associations for free thyroxine (FT4) levels were observed with total cholesterol (TC, $p < 0.01$), apolipoprotein B (APOB, $p < 0.01$), and triglycerides (TG, $p < 0.01$). A 10% increase in TC levels was associated with a 2% increase in TSH levels and 0.8% decrease in FT4 levels. Among EU subjects, TG levels were positively correlated with TSH ($p < 0.01$) and negatively correlated with FT4 ($p < 0.01$). For CHYP subjects, TG levels were negatively correlated with TSH ($p < 0.01$). For iodine deficient participants, low density lipoprotein levels (LDL) were lower for SCHPR when compared with EU or CHYP ($p < 0.01$). TC levels were usually lower for SCHPR than for EU, CHYP, and SCHYP but the differences were not necessarily statistically significant. For all participants and for iodine replete participants, TG levels for SCHPR were lower than for CHYP ($p < 0.01$). CHYP and SCHYP had higher levels of TG than other three thyroid function groups. APOB levels were lower for SCHPR than for EU and CHYP for all participants and for iodine replete participants ($p < 0.01$). There was a positive association between the four quartiles of thyroid stimulating hormones and TC, TG, and APOB. There was also an inverse association between the quartiles of free thyroxine levels and LDL, TC, TG, and APOB.

1. Introduction

Thyroid hormones have been suggested to influence lipoprotein metabolism (Delitala et al., 2016). Triglyceride (TG), ratio of triglyceride to high density lipoprotein cholesterol (HDL) and atherogenic index of plasma were reported to be significantly higher in subclinical hypothyroid (SCHYP) subjects as compared to euthyroid (EU) subjects in a hospital based case control study done among adult females in Southern India (James et al., 2016). In a study of 187 postmenopausal obese females conducted in an outpatient clinic in Poland, those with SCHYP were reported to have higher levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL), the ratio of LDL to HDL than the control group and among SCHYP group, positive association between thyroid stimulating hormone (TSH) and atherosclerotic index (Adamarczuk-Janczyszyn et al., 2016) was reported. Walsh et al. (2005), from a community based study conducted in Western Australia, reported higher unadjusted levels of TC ($p < 0.01$) and LDL ($p < 0.01$) in SCHYP subjects than EU subjects but statistical significance was not observed for adjusted levels of TC. Patients with SCHYP were reported to have higher levels of TC and LDL when compared with EU subjects and a positive correlation was observed between TSH, LDL and TC in subjects with SCHYP (Sharma et al., 2011). In a cross-sectional survey conducted among Hispanic subjects in five states of central Mexico, Garduño-Garcia et al. (2010) reported TC to be higher among SCHYP subjects as compared with EU subjects, TSH values were positively correlated with TC and TG, free thyroxine (FT4) levels were positively correlated with HDL. In a community based study in Iran among males and females aged ≥20 years, Alamdari et al. (2015), however, did not observe any differences in lipid profiles of SCHYP and EU subjects. Bansal and Yadav (2016) found higher levels of TC, TG,

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apolipoprotein B (APOB), and LDL associated with clinical hypothyroidism (CHYP) when compared with those without CHYP in a study conducted in a tertiary care hospital in Haryana, India. CHYP subjects were found to have higher TC levels than SCHYP subjects (Alamdari et al., 2015).

There were some differences in cut-offs used for TSH to define CHYP or SCHYP among the studies referred to above. For example, Adamarczuk-Janczyszyn et al. (2016) used a cut-off of 4.0 for TSH, Alamdari et al. (2015) used a cut-off of 5.06, and Bansal and Yadav (2016) used a cut-off of 6.0. However, in spite of the differences in cut-offs for TSH used by these authors and in spite of the fact that these studies were done in different parts of the world with possibly different levels of nutritional intake that may affect lipid profiles of, almost consistently, those with SCHYP and/or CHYP were found to have higher levels of one of the lipid/lipoprotein levels, namely, TC, TG, LDL, TG/HDL, or APOB. The only exception was the finding of no differences in lipid profiles of EU and SCHYP subjects (Alamdari et al., 2015) in an adult Iranian population.

Among obese EU individuals (TSH: 1.21–2.47 mIU/L) in Italy, Marzullo et al. (2016), reported free thyroxine levels (FT4) to be inversely associated with body mass index, insulin resistance, and TG and positively associated with HDL. In an adjusted analysis conducted in Italy, in premenopausal women, TSH was reported to have a positive association with TC, LDL, and triglycerides and in the postmenopausal group, TSH was reported to be positively associated only with TG (Delitala et al., 2016). In a population based study of 5205 Finns aged ≥30 years, TSH levels were reported to have positive associations with TC, LDL, APOB, and log triglycerides (Langén et al., 2016). Among EU males, serum free thyroxine (FT4) levels were reported to be inversely correlated with TC and TG, and in EU females, FT4 levels were reported to be positively associated with HDL and negatively correlated with TG and TG/HDL ratio and TSH levels were associated negatively with HDL (Alamdari et al., 2015).

The levels of fasting plasma glucose, HDL, and 25-hydroxyvitamin D levels were reported (Wang et al., 2016) to be significantly lower in obese patients complicated by mildly increased TSH than in obese patients with normal TSH ($p < 0.05$). Lee et al. (2016) used data from National Health and Nutrition Examination Survey (NHANES) for 2007–2012 for those aged ≥20 years and reported those with the lowest decile of urine iodine to be at higher risk of elevated TC and LDL and lower HDL/LDL ratio ($p < 0.04$) (AOR = 1.66, 95% CI: 1.18–2.33), than those who had urine iodine above the 10th percentile. Meng et al. (2015) used data from a large Chinese cohort and observed TSH to be positively associated with hyperlipidemia independent of free triiodothyronine (FT3) and FT4; males had relatively lower risk of hyperlipidemia in low TSH concentrations (< 0.3 μIU/mL), while females had relatively higher risks of hyperlipidemia in high TSH concentrations (> 4.0 μIU/mL). Bauer et al. (1998) reported white females aged ≥65 years to have high TSH associated with deleterious changes in HDL, LDL, and the ratio of LDL to HDL. After adjusting for gender, age, smoking status, fasting plasma glucose levels, FT3, and FT4, a positive correlation between TSH and TC level ($r = 0.095$, $p = 0.04$) among coronary heart disease patients was reported by Xu et al. (2012) and each 1 mIU/L increase in TSH was associated with a 0.015580712 mmol/L increase in TC. According to Xu et al. (2012), increases in TC associated with TSH are small but of clinical significance.

Thyroid dysfunction adversely affects the normal functioning of almost all human organs. Thyroid hormones T3 and T4 regulate protein, fat, and carbohydrate metabolism and are essential for the development and differentiation of all cells of the human body (Manna et al., 2013). They have an important role to play in the normal development of the brain (Bernal, 2005, 2007), lung (Bizzarro and Gross, 2004), heart (Danzi et al., 2005; Grover et al., 2005), and other organs in the human body. The overproduction of thyroid hormones T3 and T4 can lead to hyperthyroidism, and underproduction can lead to hypothyroidism. When hypothalamus senses the low circulating levels of T3 and/or T4, it releases thyrotropin-releasing hormone which stimulates pituitary to produce TSH. However, relatively high levels of TSH, even within the normal reference range, for example, among EU individuals, have been shown to be associated with higher mortality due to coronary heart disease (Asvold et al., 2012), higher risk of vascular dementia among ≥65 years old (Forti et al., 2012), increased arterial stiffness (Lambrinoudaki et al., 2012), increased risk of myocardial infarction (Westerink et al., 2012), and lower subendocardial viability ratio (Tatar et al., 2012). While studies referred to in the last few paragraphs do not necessarily indicate what is the magnitude of increase in TSH associated with a specific increase in the magnitudes of TC, TG, and/or LDL, a positive association between TSH and TC, TG, and/or LDL was almost always reported among EU as well as SCHYP subjects. It has also been reported that elevated values of TSH even within the normal range are a risk factor for mortality, heart failure, vascular dementia, and arterial stiffness as assessed by studies referred to above. Thus, a population based study rather than a community based study, for example, for US population that assesses associations between TSH/T3/T4 and lipid indicators is desirable.

To the best of this author's knowledge, a study that has investigated the association between the levels of thyroid hormones and lipid/lipoprotein levels has not been conducted for a representative sample of general US population. Consequently, this study was undertaken to study the associations between thyroid hormones and lipid/lipoprotein levels for general US population aged ≥20 years. Data from National Health and Nutrition Examination Survey (NHANES, www.cdc.gov/nchs/nhanes.htm) for the years 2007–2012 was selected for this purpose.

2. Materials and methods

Data from NHANES for the years 2007–2012 from demographic, body measures, fasting questionnaire, thyroid hormone, and lipid/lipoprotein files including APOB were downloaded and match merged by the ID of the NHANES participants. NHANES uses a complex, stratified, multistage, probability sampling designed to be representative of the civilian, non-institutionalized U.S. population based on age, sex, and race/ethnicity. Sampling weights are created in NHANES to account for the probabilities of selection and response as well as total U.S. population for certain combinations of gender, age, and race/ethnicity. All analyses completed for this study used sampling weights and design characteristics like stratification and clustering.

Data for six thyroid variables, namely, TSH, FT3, total triiodothyronine (TT3), FT4, total thyroxine (TT4), and thyroglobulin (TGN) were available. Data for lipids were available for high HDL, LDL, TC, TG, and apolipoprotein B (APOB).

Only those who were ≥20 years old, had fasted for at least 8 h, and had non-zero sampling weights were selected for analysis. In addition, those females who were pregnant at time of participation in NHANES and had missing values for TSH and/or FT4 were excluded from the database (Fig. 1). For the Access 2 (Beckman Coulter) method used to measure FT4, the normal range for FT4 was defined to be 0.6–1.6 ng/dL (https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/labmethods/thyrod_g_met_free_t4.pdf) and these were the normal values used for this study to classify thyroid status. For the Access 2 (Beckman Coulter) method used to measure TSH, the normal range for TSH was defined to be 0.24–5.4 μIU/mL (https://wwwn.cdc.gov/nchs/data/nhanes/2011-2012/labmethods/thyrod_g_met_tsh.pdf). However, for the purpose of this study, I used the reference limits for TSH as suggested by Surks et al. (2004). Thus, for the purpose of this study, normal reference range for TSH was defined to be 0.45–4.50 μIU/mL. Participants were classified in one of the five thyroid function categories. As previously described (Jain, 2015), subclinical hyperthyroidism (SCHPR) was defined as TSH ≤ 0.45 mIU/L and FT4 within its normal reference range of 0.6-1.6 ng/dL. Clinical hyperthyroidism (CHPR) was defined