Lipid Profile in Thyroid Autoimmunity - A Study among Reproductive Age Group Females of Central Kerala

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ABSTRACT

BACKGROUND
One of the most common causes of thyroid dysfunction among women is autoimmunity, especially in fertile age group. Thyroid hormone disorders are associated with a number of biochemical abnormalities including dyslipidaemia, metabolic dysfunctions, spontaneous miscarriage, and preterm delivery. Dyslipidaemia is one of the most common metabolic abnormalities present in patients with thyroid disease. The purpose of this study was to find the association between anti-thyroid peroxidase antibody (anti-TPO) and dyslipidaemia in reproductive age group females from Central Kerala.

METHODS
A total of 200 asymptomatic women, all in reproductive age group, from a tertiary hospital in Kerala participated in this study. Demographic data and detailed medical history of the participants were collected. Anti-TPO and thyroid stimulating hormone (TSH) were measured using chemiluminescence immunoassay system. Serum lipid profile was estimated using fully automated random-access clinical chemistry analyser EM - 360. Continuous variables were compared between the groups using Mann–Whitney U-test. P value lesser than 0.05 was considered as statistically significant.

RESULTS
The mean age of the subjects was 32.92 ± 11.82 years. A total of 47 participants (23.5 %) were anti-TPO positive. Abnormality in lipid profile was present in 72.34 % (N = 34) of the anti-TPO positive participants. In the anti-TPO positive group, 51.06 % of the participants had hypercholesterolemia. In the anti-TPO positive group, anti-TPO levels show a statistically significant correlation with total cholesterol and triglyceride levels (P = 0.07 and P < 0.01). A total of 9 % (N = 18) had thyroid stimulating hormone (TSH) values greater than normal range (0.34-4.25 µIU/mL) suggesting presence of hypothyroidism. TSH values were also significantly associated with lipid profile in the anti-TPO positive group. Both thyroid autoimmunity and dyslipidaemia can affect fertility, pregnancy and other reproductive outcomes.

CONCLUSIONS
Women should be screened for autoimmune antibodies and associated biochemical abnormalities to estimate and reduce the risk of cardiovascular morbidity, negative pregnancy outcomes and infertility.

KEY WORDS
Thyroid Autoimmunity, Anti-TPO Antibody, Dyslipidaemia
Thyroid dysfunctions, namely hypothyroidism or hyperthyroidism, are the most common metabolic disorder in general population, and can be detected in a subclinical or overt form. Autoimmunity is one of the most frequent cause of thyroid dysfunction in women of reproductive age. About 5–15% of euthyroid women have thyroid antibodies like anti-thyroid peroxidase antibody and are at increased risk of developing thyroid dysfunction. The presence of anti-TPO antibodies is relatively high in women of child bearing age.

Thyroid dysfunctions remain asymptomatic in most of the cases and hence, American Thyroid Association has recommended routine population screening for early detection and treatment of the condition. Subclinical hypothyroidism has a high conversion rate into overt hypothyroidism.

Thyroid hormone disorders are associated with a number of biochemical abnormalities due to the effect of thyroid hormones in all major metabolic pathways. These include dyslipidemia, metabolic dysfunctions, spontaneous miscarriage and preterm delivery.

Thyroid dysfunction is also a known cause of infertility along with many other factors like hyperprolactinemia. Autoimmune thyroiditis is prevalent in women with polycystic ovary syndrome, specifying the importance of screening for anti-TPO antibodies in women, especially in their reproductive age.

Thyroid hormones have a major effect in all aspects of lipid metabolism and is known to cause a number of qualitative and quantitative changes in lipids. Dyslipidemia is one of the most common metabolic abnormalities in patients with thyroid diseases. Existing data suggest that thyroid dysfunctions are associated with increased cardiovascular risk due to hemodynamic alterations and an elevated risk of atherosclerosis. In thyroid dysfunctions, lipid profile changes are established, however, lipid profile changes in thyroid autoimmunity is not well known. There is paucity of data on biochemical profile and prevalence of thyroid dysfunctions from India. Data from Kerala is negligible with respect to anti-TPO antibodies and its association with different biochemical abnormalities.

The aim of this study is to find association between anti-TPO antibody and dyslipidemia in reproductive age group females from Central Kerala. The objectives of the study are 1). To determine the changes in serum lipid profiles and thyroid autoimmunity in females belonging to the fertile age group and 2). To find the association between these two parameters in these women.

**METHODS**

This study is cross sectional study conducted on 200 asymptomatic females in reproductive age group, all of whom were either students or staff of a tertiary healthcare centre. The study was conducted from September 2015 to August 2016.

**Inclusion Criteria**

Adult female (students or staff) of a tertiary healthcare center in Central Kerala

**Exclusion Criteria**

Potential participants were excluded if they were-
- Pregnant.
- Had already diagnosed thyroid disease
- Currently receiving thyroid medications
- Currently on anti-lipidemic medications
- Not willing to participate in the study

Enrolment was done based on the inclusion and exclusion criteria. Study subjects were counselled separately about the study and a written consent was procured from them. Demographic data like age was recorded along with a detailed medical and family history using a semi-structured questionnaire. General physical examination including vitals (temperature, pulse, blood pressure, etc.) were also noted. Serum samples of participants were processed for lipid profile, TSH and anti-TPO antibody. Venous blood samples were collected in the morning between 7:00 am to 10:00 am after an 8 - 12 hour fast, and then promptly centrifuged and analysed. The levels of serum TSH and anti-TPO antibody were determined in all subjects on the same day of blood sampling. Institutional Ethics Committee of Thirssur Medical College Hospital approved the study.

Thyroid stimulating hormone and anti-TPO were measured using chemiluminescence immunoassay system Roche Colas E411. The concentrations of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were estimated using fully automated random access clinical chemistry analyser EM - 360. Appropriate calibrators were used for validating the test.

Serum lipids were classified as per National Cholesterol Education Program-Adult Treatment Panel III Guidelines. According to these guidelines, hypercholesterolemia is defined as total cholesterol (TC) value > 200 mg/dl, high-density lipoprotein (LDL) as > 100 mg/dl, hypertriglyceridemia as triglyceride (TG) value > 150 mg/dl, and low high-density lipoprotein (HDL) as < 40 mg/dl. Dyslipidemia is defined as the presence of one or more than one abnormal serum lipid values. For analyses of anti-TPO antibodies, the reference value taken was < 35 IU/mL. And for serum TSH, 0.34 - 4.25 µIU/mL was considered as the reference range. Hypothyroidism state of the participants was analysed on the basis of TSH level alone due to economic constraints.

Participants were grouped into two on the basis of anti-TPO levels – anti-TPO positive and anti-TPO negative. Participants with anti-TPO antibody values above 35 IU/mL were considered anti-TPO positive. Exploratory analysis was done using EPI Info version1. TSH and anti-TPO levels were analysed using multivariate linear regression models after log transformation due to skewness of their distribution in their original scale. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented as absolute numbers and percentage. Mann-Whitney U-test was used for comparison of continuous variables between the two groups. Differences between
groups were assessed with chi-square or Fisher’s exact test for categorical variables as appropriate. \( P < 0.05 \) was taken as statistically significant.

**RESULTS**

In this cross-sectional study, 200 participants from the department were evaluated for the presence of anti-thyroid peroxidase antibody and serum lipid profile and TSH. The mean age (mean ± SD) of the participating women was 32.92 ± 11.82 years. More than half of the participants in the study were staff of the department, while the rest were students. About 17 % of the participants had a family history of thyroid disorders. Most of them had regular menstrual cycle and only 7 % reported to have irregularities in periods.

Anti-TPO had a high mean value among the participants of the study (68.12 IU/mL). A total of 47 participants (23.5 %) were anti-TPO positive. Mean age of the anti-TPO positive group was 34.56 ± 12 years, while that of anti-TPO negative group was 32.43 ± 11.77 years.

The mean values of TC among the participants was 198.17 mg/dL, while that of TG was 105.15 mg/dL. Average LDL in the study group was 118.88 mg/dL and HDL was 58.38 mg/dL. Lipid abnormality was present in 72.34 % (N = 34) of the anti-TPO positive participants. In the anti-TPO positive group, 51.06 % (N = 24) of the participants had hypercholesterolemia, whereas in the anti-TPO negative group, 40.79 % (N = 62) had hypercholesterolemia which was not statistically significant (\( P = 0.65 \)). In anti-TPO positive group, 6.38 % had hyperglyceridaemia; whereas in the anti-TPO negative group, 5.26 % (N = 8) had hyperglyceridaemia. There was a significant association between the triglycerides and anti-TPO antibodies (\( P = 0.03 \)). Likewise, in anti-TPO positive group, 14.9 % (N = 7) had hyper LDL cholesterol (LDL-C); while in TPO negative, one fourth of the patients had hyper LDL-C which was not statistically significant. None of the participants from anti-TPO positive group had low HDL-cholesterol (HDL-C), while 3.9 % of the anti-TPO negative group had low HDL-C.

The mean TSH value was 9.69 ± 11.37 µIU/mL. TSH value was 38.89 ± 10.59 years. Mean TSH value was 9.69 ± 11.37 µIU/mL. More than half of the participants in the group (N = 10) had high anti-TPO levels (mean ± SD = 192.68 ± 244.28 IU/mL). TSH and anti-TPO antibodies had a statistically significant correlation (R = 0.192, \( P = 0.006 \)). There was a statistically significant correlation between TSH and anti-TPO when the participant had a family history of thyroid disorders (R = 0.630, \( P = 0.028 \)).
(Anti-TPO – anti thyroid peroxidase antibody; TC – total cholesterol; TSH – thyroid stimulating hormone).

Among the anti TPO positive group participants, 34 % (N = 16) had TSH values and TC values within normal range, but in 13 % (N = 6) of them TSH values were > 4.25 μIU/mL even when TC values were within acceptable range. In the same group, 38 % (N = 18) had high TSH values with normal TC values, whereas 9 % (N = 4) had both TSH and TC values higher than normal. While comparing the TSH values with serum TG levels, more than half of the participants (55 %) had normal values for both TSH and TG. A total of 6 participants (13 %) showed higher values of TSH when serum TG levels were well within normal range. In this group of anti TPO positive participants, 17 % (N = 8) recorded high TG values but had normal TSH levels. Among the 47 anti-TPO positive participants, 9 % (N = 4) had both TSH and TG values higher than normal. Among the 34 participants with normal TSH values, 11 (23 %) of them had serum LDL-C values well within range, while close to 50 % (N = 23) had high LDL-C levels. A total of 10 participants (21 %) who had high levels of TSH, 4 (9 %) had serum LDL-C values while the rest (21 %) had high serum LDL-C levels.

Statistically significant association was present between TSH values and serum TC levels in the anti-TPO positive group (R = 0.028, P < 0.05). TSH levels were also associated with TG levels in this group of participants (R = 0.002, P < 0.05). LDL-C levels in the same group were statistically associated with TSH values (R = 0.05, P < 0.05) too. None of the participants had lower than normal serum levels of HDL-C.

| Total cholesterol | TSH Range | Total |
|-------------------|-----------|-------|
|                   | < 0.34    | 0.34 - 4.25 | > 4.25 |
| Within TG range   | 2         | 16       | 6      | 24     |
| High              | 1         | 10       | 4      | 23     |
| Total             | 3         | 34       | 10     | 47     |

| Total glycerides  | TSH Range | Total |
|-------------------|-----------|-------|
|                   | < 0.34    | 0.34 - 4.25 | > 4.25 |
| Within TG range   | 2         | 26       | 6      | 34     |
| High              | 1         | 11       | 4      | 13     |
| Total             | 3         | 34       | 10     | 47     |

| Total LDL-C       | TSH Range | Total |
|-------------------|-----------|-------|
|                   | < 0.34    | 0.34 - 4.25 | > 4.25 |
| Within TG range   | 0         | 24       | 6      | 32     |
| High              | 3         | 34       | 10     | 47     |

Table 3. TSH and Lipid Measures in Anti-TPO Positive Group

(Anti-TPO – anti thyroid peroxidase antibody; TC – total cholesterol; TG- Total glycerides; LDL-C – LDL cholesterol; TSH – thyroid stimulating hormone)

DISCUSSION

Thyroid dysfunctions related to autoimmunity are one of the most common causes of thyroid diseases. In general population, 8 – 27 % are reported to have anti-TPO antibodies and a high titre of these antibodies is present in 89.9 % of patients with autoimmune thyroid disorders. One of our earlier studies showed that one in four women in the reproductive age to be having higher levels of anti-TPO antibodies. Most of these women were euthyroid and asymptomatic. Anti-TPO positivity can progress to overt hypothyroidism and decrease the quality of life in women.

While many studies are available regarding the effects of anti-TPO antibodies in subclinical hypothyroid women, very few relate to euthyroid fertile females. A study on 1000 euthyroid Indian women showed a higher prevalence of infertility, anaemia and pre-term delivery in anti-TPO positive euthyroid group. Anti-TPO antibodies can cross the placenta, and also lead to vasculo-placental complications including postpartum haemorrhage, placental abruption, postpartum thyroiditis and pre-eclampsia. New-born babies are susceptible to thyroid dysfunctions like hypothyroidism as these thyroid antibodies cross the placental barrier. TSH values are also known to be elevated in women with infertility when compared to control population. Thyroid autoantibodies were indicated as a marker of at-risk pregnancy in a study conducted in 552 women in their first trimester of pregnancy. Women in thyroid autoantibody-positive group had a higher rate of miscarriage (17 %) when compared to those who did not have thyroid autoantibodies (8.4 %). Moreover, in a cross-sectional study conducted in 187 women with unexplained infertility, TSH levels were found to be high when compared to control group.

Thyroid dysfunctions may cause symptoms that affect the quality of life of a woman. Thyroid disorders are associated with dyslipidaemia and this is known to confer risk of cardiovascular diseases. Mustaq et al. reported an increase in serum TC, LDL-C, HDL-C, or TG in patients with thyroid dysfunction. Similarly, dyslipidaemia was significantly associated with anti-TPO positivity in other studies, especially in women with thyroid dysfunction. A recent retrospective study investigating the association of serum lipids and anti-thyroid antibody positivity in 7688 participants with normal TSH levels shows positive association between thyroid antibodies and increasing LDL-C and decreasing HDL-C (P < 0.05). This large study indicates that serum lipids may be predictors of thyroid autoimmunity even in women with normal TSH levels.

TSH is a pituitary gland hormone that plays a significant role in the normal functioning of thyroid glands. Increased TSH levels may also lead to dyslipidaemia. In our study, TSH levels, though within normal range, were higher in anti-TPO positive group subjects when compared to that of anti-TPO negative group. This increase in the TSH values may be due to the elevated risk of thyroid dysfunction in anti-TPO positive people. Studies from Kerala are negligible regarding the degree of lipid changes in thyroid dysfunctional groups. This study was an attempt to determine the association of anti-TPO antibodies and dyslipidaemia in reproductive age women with high levels of anti-TPO antibodies.

In this cross-sectional study, triglycerides were significantly associated with anti-TPO antibodies in the group with thyroid antibodies when compared to the anti-TPO negative group. Other studies, most of which were conducted on subclinical hypothyroid women, also observed significantly high serum values of triglycerides in patients with increased anti-TPO antibodies. Lai et al. in a study on 1534 Chinese adults with subclinical hypothyroidism, observed similar increase in triglycerides. But in an Indian study conducted by Kumar et al. in Uttar Pradesh, triglycerides were only marginally elevated in patients with subclinical hypothyroidism. Anti-TPO antibodies were found to have a statistically significant association with hyperlipidaemia in yet another Indian study conducted by Jaseem et al. on women with thyroid dysfunction. Our study shows that serum TSH levels also have a significant association with lipid levels, including TC, TG, LDL-C, in the anti-TPO positive group. Similar association was recorded by
Saranya in 96 patients with thyroid dysfunction in Chennai.28 HDL-C did not have any significant association with thyroid autoimmunity in the participants of our study which was similar to the results presented by Hiregoudar et al. in a study conducted in Odisha, India.15

Variations in thyroid hormone affects the functioning of cardiovascular system and, thus, patients with thyroid dysfunctions or high levels of anti-TPO antibodies also have an elevated risk of developing coronary artery disease (CAD).29 Risk of CAD and all-cause mortality was higher in patients with thyroid disorders.30 Besides the evident effect on cardiovascular diseases, studies show dyslipidaemia as a major determinant of infertility.31,32 Importance of lipid homeostasis in female fertility is reported in a prospective cohort study conducted in US.33 In an observational study on fertile females in Aurangabad, India, significant correlation was observed between dyslipidaemia, fertility and thyroid dysfunctions.34 About 22 % of the participants in this study by Vikas et al. had menstrual irregularities while 10.5 % had infertility. Elevated levels of triglycerides before pregnancy are associated with increased risk of pregnancy complications including pre-eclampsia and gestational diabetes mellitus.35

Thus, thyroid autoimmunity is known to have association with pregnancy loss, pre-term birth, rate of miscarriage and even infertility. Further, dyslipidaemia is also a known cause for infertility and other pregnancy complications. Given the potential association of thyroid autoimmunity and dyslipidaemia with pregnancy outcomes and infertility, it is of prime importance to screen pregnant women for thyroid antibodies. And if found positive for this antibody, they must be examined for associated conditions, especially dyslipidaemia to improve fertility and pregnancy, when necessary. Screening for and treatment of thyroid dysfunction in fertile, asymptomatic women can lead to clinically important benefits. More studies, preferably large-scale population-based studies, are needed to assess the risk of thyroid autoimmunity and associated biochemical changes on fertility rate and other reproductive outcomes.

**CONCLUSIONS**

Association between autoimmune antibodies like anti-TPO antibodies and negative pregnancy outcomes are known from different studies. Abnormal lipid profile is also associated with infertility and pregnancy complications in females, including euthyroid women. Given these associations of biochemical profile of women with fertility and other reproductive outcomes, it is important to screen reproductive age women for autoimmune antibodies and dyslipidaemia for better understanding, prevention, and treatment of infertility and cardiovascular morbidities.

**Limitations of This Study**

Small sample size and differences in baseline characteristics of the participants are two limitations of this study.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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