

Association of thyroid peroxidase antibody and dyslipidemia in subclinical hypothyroidism

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ABSTRACT

Context: Subclinical hypothyroidism (SCH) is stated as mild thyroid failure, is more common as compared to overt hypothyroidism, is associated with different biochemical abnormalities such as dyslipidemia, and is also having high conversion rate into overt hypothyroidism in patients having thyroid peroxidase (TPO) antibody positive. Lipid abnormalities are controversial in SCH and there is lack of Indian studies showing correlation between lipid abnormalities and TPO positivity in SCH. Hence, we did this study to find the TPO positivity and associated dyslipidemia in SCH patients. **Materials and Methods:** It was a prospective observational study from January 2015 to December 2015 including fifty adult diagnosed SCH patients presented in outpatient department of Sri Balaji Action Medical Institute, Paschim Vihar, New Delhi. TPO positivity and different lipid abnormalities were studied in those fifty diagnosed SCH patients, and finally, association between TPO antibody and dyslipidemia was calculated. **Results:** Females were predominant (86%). TPO was positive in 56% SCH patients. Dyslipidemia was found in 100% of SCH patients with positive TPO antibody. In overall, TPO positive patients as well as TPO positive females, total cholesterol, triglyceride, and low-density lipoprotein were significantly high while high-density lipoprotein was insignificant. In males, no significant association was found. **Conclusion:** In SCH patients, dyslipidemia is significantly associated with TPO positivity, especially in females. Hence, early screening, diagnosis, and treatment of SCH patients are recommended to prevent further risks.

Keywords: Dyslipidemia, lipid profile, subclinical hypothyroidism, thyroid, thyroid peroxidase

Introduction

Subclinical hypothyroidism (SCH) is defined as a high serum thyroid-stimulating hormone (TSH) value with normal serum thyroxine (T₄) and triiodothyronine (T₃) values with few or no signs/symptoms of hypothyroidism.^[1]

SCH is more common than overt hypothyroidism. Elevated thyroid peroxidase (TPO) antibodies were found in 73% of SCH patients. As the value of TPO goes higher, the more rapid thyroid failure is there and since SCH patients with positive TPO antibody have around 5% per year conversion rate into overt hypothyroidism, it is important to screen and diagnose these patients at risk, and hence, TPO antibody measurement

is recommended as an integral part of the investigations done for SCH.^[2,3]

In overt hypothyroidism, lipid profile changes are well established; however, regarding lipid profile changes in SCH, there are controversial results and further there are very few Indian studies on this condition, especially in relation to positive TPO antibody.^[4-6] Thus, in this study, we tried to find out the correlation between dyslipidemia and TPO antibody in SCH patients.

Thyroid hormone replacement may prevent progression of SCH to overt hypothyroidism, may slow the coronary heart disease progression due to its beneficial effects on lipid and so, early diagnosis and early thyroxine treatment are recommended for such patients.^[7]

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Materials and Methods

Study population

We have enrolled fifty diagnosed SCH patients present in outpatient department of Sri Balaji Action Medical Institute.

Study design

A prospective observational study.

Inclusion criteria

- In this study, we have included patients having TSH ≥ 5 mIU and < 10 mIU having normal T3 and T4 levels
- Age > 18 years.

Exclusion criteria

- Age < 18 years
- Patients as a known case of overt hypothyroidism
- Patients taking any antithyroid medication
- Postthyroid surgery patients
- Patients who are taking iodine or iodide containing drugs
- Patients with history of external radiotherapy of neck
- Patients taking any antilipidemic drug
- Pregnant woman and those who are on oral contraceptives
- Patients having end-stage renal disease or postmyocardial infarction patients or patients with congestive heart failure or having diabetes mellitus or any other chronic illness.

Methodology

Written informed consent was taken from all patients. Enrolment was done as per inclusion and exclusion criteria. Demographic data such as age, gender, and address were noted. A detailed history, general physical examination including vitals (temperature, pulse, blood pressure, respiratory rate, etc.), and systemic examination were also recorded. Serum sample was processed for lipid profile and TPO antibody.

Lipid estimations were done using automated analyzer (Hitachi 902 fully automated biochemistry analyzer; Roche, Mannheim, Germany) and commercial kits (Roche, Mannheim, Germany).

We referred to the National Cholesterol Education Program-Adult Treatment Panel III Guidelines^[8] for serum lipids. According to these guidelines, hypercholesterolemia is defined as total cholesterol (TC) value > 200 mg/dl, high low-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 glucose level, we referred to Americans with the Disabilities Act Guidelines.^[9]

TPO antibody was analyzed using ECL kits from Roche (Germany) with normal value being < 60.00 U/mL. Participants with value ≥ 60.00 U/mL were considered as anti-TPO antibody positive.

Finally, the prevalence of TPO antibody and association between TPO antibody and lipid profile abnormalities were calculated in those fifty SCH patients.

Statistical analysis

Statistical analysis was performed by the SPSS statistical package (version 17.0, SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean \pm standard deviation, and categorical variables are 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.

Ethical considerations

Ethical clearance was obtained from the Institution's Ethical Review Board. Procedure required was venipuncture which was minimally invasive, routinely performed in most of the outpatients, and was done using strict aseptic precautions.

Results

In our study, age distribution with mean age was 48.70 ± 15.75 years.

Female predominance ($n = 43$) was there (86%) while only 14% ($n = 7$) were males [Table 1].

The anti-TPO antibody prevalence was found to be 56% ($n = 28$) [Table 2]. There was no association between sex distribution and TPO ($P = 1.000$).

Lipid abnormality was present in 100% ($n = 28$) of total TPO positive patients.

In TPO positive, 78.6% ($n = 22$) of patients had hypercholesterolemia; whereas in TPO negative, 27.3% ($n = 6$) of patients had hypercholesterolemia which was found to be statistically significant. Thus, there was significant association between TC and TPO ($P < 0.001$). We found that in TPO positive, 92.9% ($n = 26$) of patients had hyper LDL-cholesterol (LDL-C); whereas in TPO negative, 54.5% ($n = 12$) of patients had hyper

Table 1: Sex distribution

| Sex | n (%) |
|--------|-----------|
| Male | 7 (14.0) |
| Female | 43 (86.0) |
| Total | 50 (100) |

Table 2: Thyroid peroxidase distribution

| TPO | n (%) |
|-----------|-----------|
| ≥ 60 | 28 (56.0) |
| < 60 | 22 (44.0) |
| Total | 50 (100) |

TPO: Thyroid peroxidase

LDL-C which was found to be statistically significant. Thus, there was significant association between LDL and TPO ($P = 0.002$). Likewise in TPO positive, 71.4% ($n = 20$) of patients had hypertriglyceridemia; whereas in TPO negative, 45.5% ($n = 10$) of patients had hypertriglyceridemia which was also found to be statistically significant. Thus, there was significant association between TG and TPO ($P = 0.043$). 28.6% ($n = 8$) of patients had low HDL in TPO positive cases; whereas in TPO negative, 54.5% ($n = 12$) of patients had low HDL which found to be comparable. Thus, there was no significant association between HDL and TPO ($P = 0.063$) [Table 3 and Figure 1].

Hypercholesterolemia, hyper LDL-C, and hypertriglyceridemia were significantly associated with TPO positive group as compare to TPO negative group in females while it was not significantly associated with low HDL-cholesterol. However, among males, there was no significant association between any lipid abnormality and TPO [Tables 4-11 and Figures 2-9].

Table 3: Correlation between abnormal lipid and thyroid peroxidase

| Parameters | TPO | | P |
|----------------------|-------------------|-------------------|--------|
| | <60 (n=22), n (%) | ≥60 (n=28), n (%) | |
| TC ≥200 | 6 (27.3) | 22 (78.6) | <0.001 |
| HDL <40 | 12 (54.5) | 8 (28.6) | 0.063 |
| LDL ≥100 | 12 (54.5) | 26 (92.9) | 0.002 |
| TG ≥150 | 10 (45.5) | 20 (71.4) | 0.043 |
| Total abnormal lipid | 18 (81.8) | 28 (100.0) | 0.032 |

TPO: Thyroid peroxidase; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride

Table 4: Correlation between total cholesterol and thyroid peroxidase in male

| TC male | TPO | | P |
|---------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <200 | 2 (66.7) | 1 (25.0) | 0.486 |
| ≥200 | 1 (33.3) | 3 (75.0) | |
| Total | 3 (100) | 4 (100) | |

TPO: Thyroid peroxidase; TC: Total cholesterol

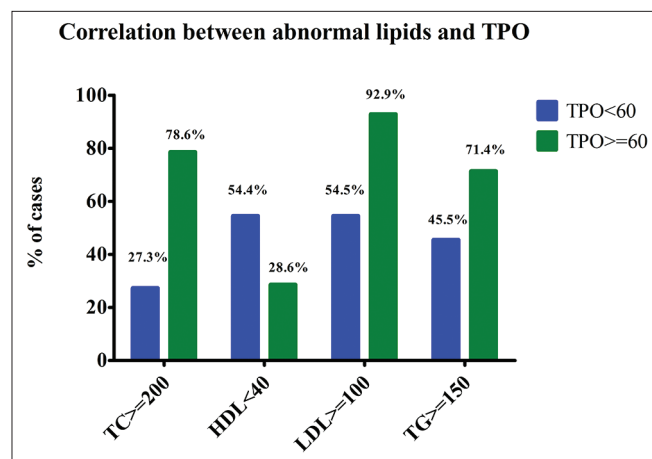


Figure 1: Correlation between abnormal lipid and thyroid peroxidase

Discussion

Hypothyroid state in body can cause symptoms, which reduces functional status and affect quality of life of the patient. SCH may be associated with dyslipidemia, neuromuscular and neuropsychiatric problems, and myocardial dysfunction and also can decrease the quality of life by its progression to overt hypothyroidism^[10] (even more with TPO positivity). These were some key factors which led this study to happen. Our study was a prospective observational study to look for the prevalence of TPO positivity and its association with dyslipidemia in SCH patients.

Our study showed female predominance with 86% of total study population while only 14% were male. This was similar to a study by Bandyopadhyay *et al.*^[11] where females constituted 78% of total study population.

We have found the prevalence of TPO antibody as 56% which was similar to a study by Asranna *et al.*^[12] where it was 50%. In a similar study by Bandyopadhyay *et al.*,^[11] it was 52%. However, in a study by Mohanty *et al.*,^[3] it was 73%. Hence, there are high rates of autoimmunity in such patients.

Table 5: Correlation between total cholesterol and thyroid peroxidase in female

| TC female | TPO | | P |
|-----------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <200 | 14 (73.7) | 5 (20.8) | 0.001 |
| ≥200 | 5 (26.3) | 19 (79.2) | |
| Total | 19 (100) | 24 (100) | |

TPO: Thyroid peroxidase; TC: Total cholesterol

Table 6: Correlation between high-density lipoprotein and thyroid peroxidase in male

| HDL male | TPO | | P |
|----------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <40 | 3 (100.0) | 1 (25.0) | 0.143 |
| ≥40 | 0 | 3 (75.0) | |
| Total | 3 (100) | 4 (100) | |

TPO: Thyroid peroxidase; HDL: High-density lipoprotein

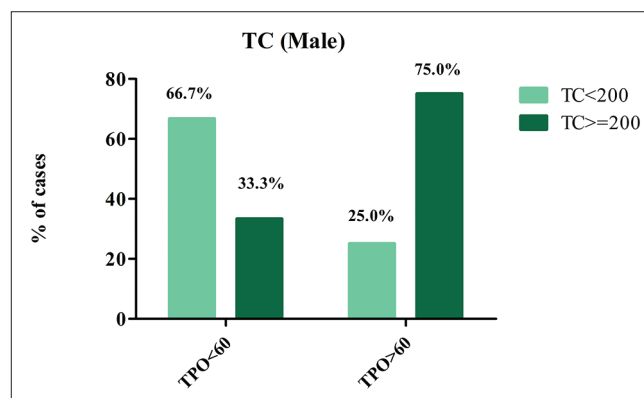


Figure 2: Correlation between total cholesterol and thyroid peroxidase in male

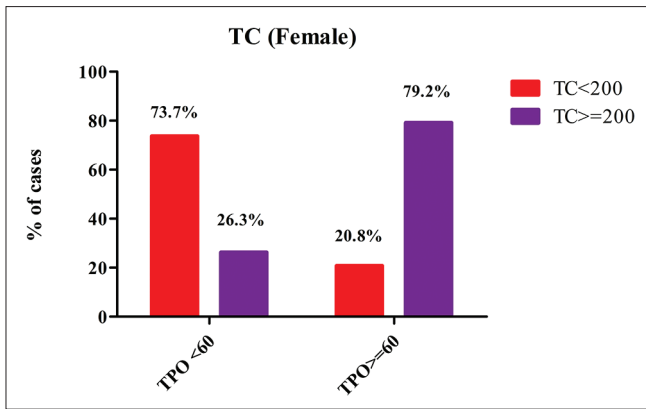


Figure 3: Correlation between total cholesterol and thyroid peroxidase in female

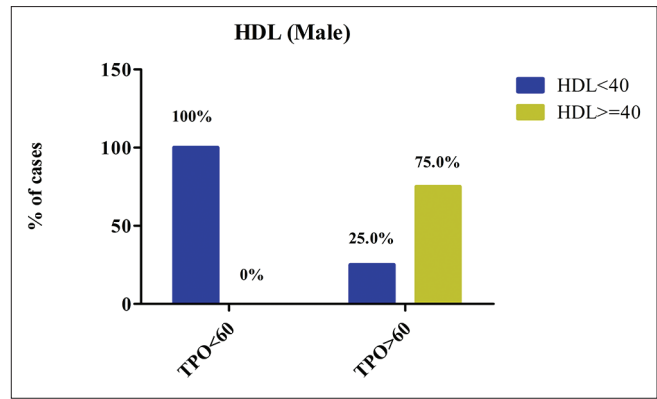


Figure 4: Correlation between high-density lipoprotein and thyroid peroxidase in male

Table 7: Correlation between high-density lipoprotein and thyroid peroxidase in female

| HDL female | TPO | | P |
|------------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <40 | 9 (47.4) | 7 (29.2) | 0.220 |
| ≥40 | 10 (52.6) | 17 (70.8) | |
| Total | 19 (100) | 24 (100) | |

TPO: Thyroid peroxidase; HDL: High-density lipoprotein

Table 9: Correlation between low-density lipoprotein and thyroid peroxidase distribution in female

| LDL female | TPO | | P |
|------------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <100 | 9 (47.4) | 1 (4.2) | 0.002 |
| ≥100 | 10 (52.6) | 23 (95.8) | |
| Total | 19 (100) | 24 (100) | |

TPO: Thyroid peroxidase; LDL: Low-density lipoprotein

Table 8: Correlation between low-density lipoprotein and thyroid peroxidase distribution in male

| LDL male | TPO | | P |
|----------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <100 | 1 (33.3) | 1 (25.0) | 1.000 |
| ≥100 | 2 (66.7) | 3 (75.0) | |
| Total | 3 (100) | 4 (100) | |

TPO: Thyroid peroxidase; LDL: Low-density lipoprotein

Table 10: Correlation between triglyceride and thyroid peroxidase distribution in male

| TG male | TPO | | P |
|---------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <150 | 0 | 3 (75.0) | 0.143 |
| ≥150 | 3 (100.0) | 1 (25.0) | |
| Total | 3 (100) | 4 (100) | |

TPO: Thyroid peroxidase; TG: Triglyceride

We found that in TPO positive cases, TC, LDL, and TG levels were significantly high while HDL level was comparable which was similar to a study by Bandyopadhyay *et al.*^[11] in which also TC, LDL, and TG levels in TPO positive cases showed statistically significant higher levels.

In females, hypercholesterolemia, hyper LDL-C, and hypertriglyceridemia were significantly associated with TPO positive group as compare to TPO negative group in our study; however, among males, there was no significant association between lipid abnormality and TPO in our study. Since studies on this condition are lacking, we have not found similar studies to compare this.

It has been shown that cardiovascular system has high sensitivity even to minimal variations in circulating thyroid hormone. Therefore, even subclinical hypothyroid state may be considered as a risk factor for the development of coronary artery disease (CAD).^[13] In the Rotterdam study, it was shown that the incidence of atherosclerosis was even higher in SCH if TPO antibody was positive.^[14] In a study, McQuade *et al.* have assessed the effects of hypothyroidism (TSH >10 μIU/L), moderate

SCH (TSH: 6.1–10 μIU/L), and mild SCH (TSH: 3.1–6.0 μIU/L) on different cardiovascular risk factors, CAD prevalence, and also all-cause mortality in patients who were at high risk for CAD. All-cause mortality was found to be higher in both genders in hypothyroid and moderate subclinical hypothyroid patients, but not in mild SCH cases.^[15]

Thus to finalize, our study has shown high prevalence of TPO positivity and also significant association of dyslipidemia with TPO positivity in SCH patients, especially in females. As these patients are at high risk of developing overt hypothyroidism, vascular diseases through dyslipidemia, endothelial and myocardium dysfunction, neuromuscular and neuropsychiatric problems as well as high all-cause mortality in future and so such patients need screening and thorough investigation for early diagnosis and appropriate treatment.

Hence, at primary care level by TSH testing, the screening of all suspected persons can be done and if they are found out to be SCH, must not be ignored, and must be examined and investigated further for possible bad effects, associated conditions, and complications of SCH, especially TPO

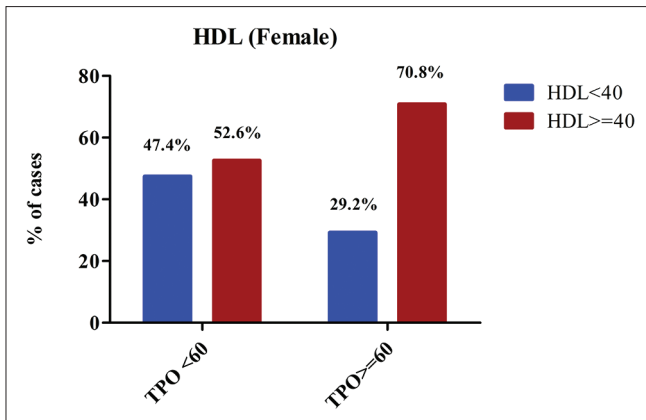


Figure 5: Correlation between high-density lipoprotein and thyroid peroxidase in female

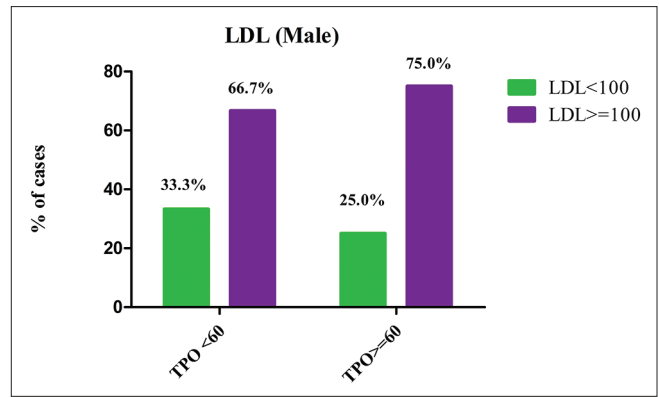


Figure 6: Correlation between low-density lipoprotein and thyroid peroxidase in male

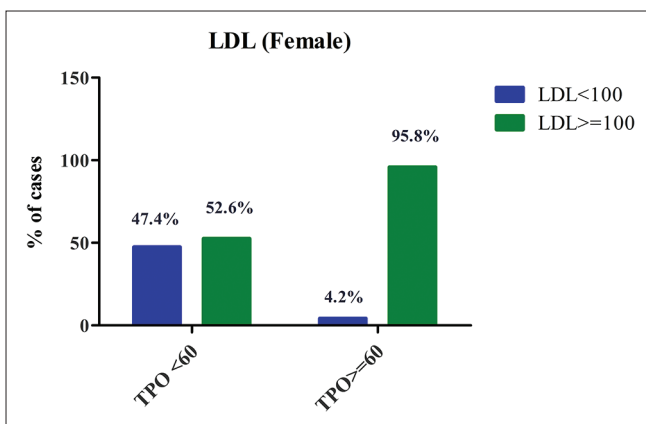


Figure 7: Correlation between low-density lipoprotein and thyroid peroxidase in female

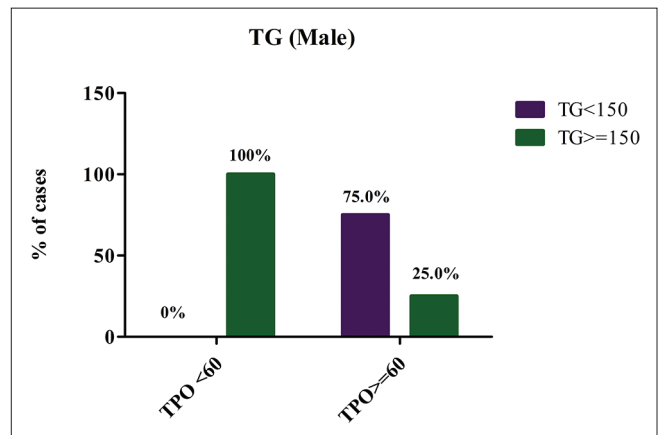


Figure 8: Correlation between triglyceride and thyroid peroxidase in male

Table 11: Correlation between triglyceride and thyroid peroxidase distribution in female

| TG female | TPO | | P |
|-----------|------------|------------|-------|
| | <60, n (%) | ≥60, n (%) | |
| <150 | 12 (63.2) | 5 (20.8) | 0.005 |
| ≥150 | 7 (36.8) | 19 (79.2) | |
| Total | 19 (100) | 24 (100) | |

TPO: Thyroid peroxidase; TG: Triglyceride

positivity and dyslipidemia. At primary care level, further treatment with levothyroxine can be started and follow-up of the patients can also be done on the basis of the American Thyroid Association and American Association of Clinical Endocrinologists Guidelines including criteria such as age of the patient, presence of symptoms, TPO positivity, presence of dyslipidemia, cardiovascular risk, pregnant patients, and infertile patients.^[16-18] Similarly, in my study also, there is high TPO positivity and dyslipidemia indicating the importance of these tests in deciding the prevention of complications and treatment of SCH patients. By early screening at primary care level and by starting appropriate therapy, such patients can be prevented from bad outcomes of SCH and can also be prevented from hospitalization due to such bad effects such as cardiovascular

events and other life-threatening complications. Since Indian studies in this field are lacking, we also recommend large-scale, multicenter studies for better understanding, prevention, and treatment of SCH patients.

Conclusion

Thus, we concluded from our study that SCH is more common in females, there is high prevalence of TPO antibody in SCH patients that means autoimmune etiology, dyslipidemia is significant if TPO positivity is there and females with SCH are more prone to develop dyslipidemia, especially with TPO positivity as compared to male. And so, we recommend early diagnosis of such patients and preventing them from further risks which can be done by early initiation of thyroid hormone replacement in such patients and their proper follow-up.

Acknowledgment

It is an honor and privilege to be associated with this work which has been a result of the focused and concerted efforts of our team. The study aims to contribute to the ever advancing field of medical science, bringing in newer concepts, and modes of treatment with each passing day.

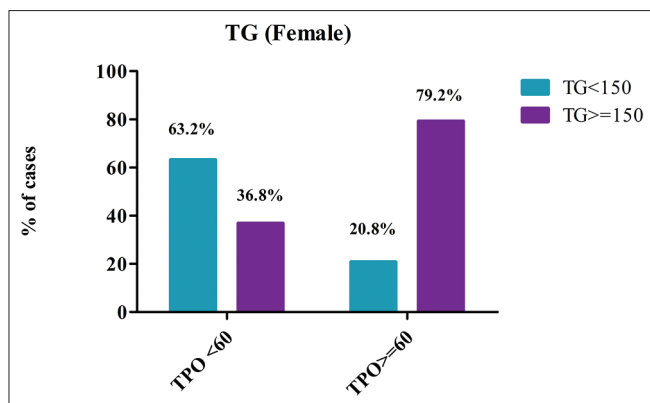


Figure 9: Correlation between triglyceride and thyroid peroxidase in female

First of all, I would thank almighty god who created all of us and gave us an inquisitive mind to ponder on his creation, and the so many possibilities of its variety, and yet, the similarities that exist beyond dimensions and species. I pray to him for the success of Science, to enable us to achieve the benefit out of it rather than creating modes of self-destruction. I thank him for enabling me to add a speck to this vast universe of knowledge with the help and support of my guide, my friends, my family, and last but not the least, our patients who are the center of the medical universe around which all our works revolve and toward which all our efforts trend. It gives me a great pleasure to express my heartfelt gratitude to my esteemed teacher and guide, Dr. Harkaran Singh, who has been the primary guiding force and inspiration behind this study.

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Conflicts of interest

There are no conflicts of interest.

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