An emerging relationship between circulating estradiol and thyroid autoimmunity in polycystic ovarian syndrome

Rehman, Anam; Altaf, Benash; Zahid, Hira; Tariq, Saba; Jawed, Shireen; Tariq, Sundus

DOI:
10.52764/jms.23.31.1.13

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Rehman, A, Altaf, B, Zahid, H, Tariq, S, Jawed, S & Tariq, S 2023, 'An emerging relationship between circulating estradiol and thyroid autoimmunity in polycystic ovarian syndrome', *Journal of Medical Sciences (Peshawar)*, vol. 31, no. 1, pp. 67-71. https://doi.org/10.52764/jms.23.31.1.13

ORIGINAL ARTICLE

AN EMERGING RELATIONSHIP BETWEEN CIRCULATING ESTRADIOL AND THYROID AUTOIMMUNITY IN POLYCYSTIC OVARIAN SYNDROME

Anam Rehman[1], Benash Altaf[1], Hira Zahid[1], Saba Tariq[2], Shireen Jawed[1], Sundus Tariq[3]

[1]Department of Physiology, Aziz Fatimah Medical and Dental College, Faisalabad - Pakistan

[2]Department of Pharmacology, University Medical and Dental College, Faisalabad - Pakistan

[3]Department of Physiology University Medical and Dental College, Faisalabad - Pakistan

ABSTRACT

Objectives: To find an association between circulating Estradiol and thyroid autoimmunity in females with polycystic ovarian syndrome (PCOS) and its impact on their health.

Materials and Methods: This study was conducted at Aziz Fatimah Medical and Dental College, after obtaining ethical approval from Institutional Ethical Committee (letter No. DME/568-19) from April to September 2017. Hundred PCOS females enrolled in the age range 17-35 years were taken who fulfilled inclusion and exclusion criteria. Blood samples were drawn and stored at Aziz Fatima Hospital, Faisalabad. All blood samples were analyzed for the levels of Estradiol, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free tetra-iodothyronine (FT4), and thyroid peroxidase antibody (TPO-Ab). The data was analyzed using SPSS 23.

Results: Of the total population, TPO-Ab was positive in 26% of study participants. It was observed that 64% and 40% of TPO-Ab positive subjects were in the Estradiol quartiles E3 and E4 respectively and none of them were found to be in E1 and E2 quartiles. We have found a significant association of the E2 with TSH, FT4, and TPO-Ab, however, no significant correlation was found between TSH and TPO-Ab. Beta coefficient (β) of 1.006 shows that higher E2 was significantly related to higher TPO-Ab titer with p-value = 0.002. Similarly, a significant but weak positive association was found between E2 and TSH. E2 was significantly negatively associated with FT4.

Conclusion: OEstradiol is positively associated with TPO antibodies and TSH and negatively associated with FT4 in PCOS patients. Our findings suggest that thyroid autoimmunity is commonly found in PCOS females.

Keywords: OEstradiol, Polycystic ovarian syndrome, Thyroid peroxidase antibody

This article may be cited as: Rehman A, Altaf B, Zahid H, Tariq S, Jawed S, Tariq S. An emerging relationship between circulating Estradiol and Thyroid Autoimmunity in Polycystic Ovarian Syndrom. J Med Sci 2023 January;31(1):67-71

INTRODUCTION

Autoimmune diseases are a major concern for health care providers globally in latest decades due to their associated comorbidities leading to high mortality rates.[1] The development of autoimmunity is a heterogeneous process. It is reported by previous research that the prevalence of autoimmune diseases is hiking in the current era including connective tissue diseases, autoimmune hepatitis, thyroid diseases, insulin-Dependent Diabetes Mellitus (IDDM) and skin diseases, etc. This auto-immune response is believed to be carried out due to the production of antibodies against own tissues and subsequently its destruction by the cytotoxic action of T cells.[2] In Pakistan, hypothyroidism is prevalent up to 4.1% and 5.4% in adults and children respectively. It is also reported that hypothyroidism and hyperthyroidism are more prevalent in females than in their male counterparts. Thyroid malfunctioning in subclinical hypothyroidism is interconnected with a raised risk of atherosclerosis and coronary artery diseases most probably also attributed to altered Estrogen levels.[3,4] Autoantibodies of the thyroid are not solely detectable in autoimmune thyroid disease (AITD) patients besides it they are also found in subjects who do not have evident altered thyroid function.[5]

Thyroid disorders are more rampant in females especially targeting the age of puberty and menopause. It is worrisome for the physicians that chances of thyroid carcinomas are more recurrent in women as compared to men. These findings are attributed to the altered levels of Estrogen in thyroid disorder pathogenesis.[6]Indirect role of Estrogen has been established on the thyroid affecting its

Correspondence
Dr. Anam Rehman
Assistant Professor
Department of Physiology, Aziz Fatimah Medical and Dental College, Faisalabad - Pakistan
Cell: +92-342-7398108
Email: doc.rehman158@gmail.com
Date Received: 23-11-2022
Date Revised: 18-02-2023
Date Accepted: 17-03-2023

hormonal economy, thence, enhancing the thyroxin binding globulin, and subsequently making thyroid hormone more pivotal in hypothyroid females. Estrogen has a direct effect on thyroid cells stimulating them and forming the thyroid nodule, it also causes an increased production of thyroid-binding globulins by the liver thereby decreasing the availability of free thyroid for the proper functioning of the body. [7] Normally progesterone is responsible for declining IL-6 and the production of antibodies. On the other hand, Estrogen decreases the activity of suppressor T-cells but enhances the action of B cells as well as secretion of IL-6, all contributing to autoimmunity in Hashimoto thyroiditis. Hence it is concluded by the researchers that imbalances in Estrogen and progesterone (a low progesterone/Estradiol ratio), may promote the development of Hashimoto thyroiditis in PCOS subjects resulting from the immune-stimulating effects of unbalanced Estrogen.[8]

MATERIAL AND METHODS

This Cross-sectional study was done at Aziz Fatimah Medical and Dental College from April 2017 to September 2017 after obtaining ethical approval from the institute with letter no. DME/568-19. It comprised 100 female participants. Female Subjects were recruited having PCOS on ultrasound with an age range of 17-35. However, subjects with hypothyroidism, taking thyroxin and hyperthyroidism, and subjects with thyroidectomy and hysterectomy were excluded from the study. 5ml of fasting blood samples were drawn under aseptic conditions following the protocol. Serum was separated in a centrifuge machine and saved in an Eppendorf tube and transferred to a freezer at -80 c till analysis. Anti-TPO antibodies were measured with help of CLIA cut of the range was taken less than 14 IU/ml. Estrogen was measured using CLIA cut-off value was taken15-112pg/ml. Data analysis was performed using SPSS version 23. Continuous data are expressed as mean ± S.D and median (IQR). Categorical data are expressed in frequencies and percentages. Shapiro Wilk test was applied for the normality of data. Data for Estradiol, TSH, and TPO Antibodies were not normally distributed and skewed. So, a non-parametric test was used for analysis. Spearman correlation coefficients were used to assess pairwise correlation. Regression analysis was done to assess the association between Estradiol and TPO antibodies, TSH, and FT4. A p-value of ≤ 0.05 was considered statistically significant. Spearman correlation was used to find a correlation.

RESULTS

This study comprised 100 Female participants having PCOS. The mean and SD of biochemical parameters are presented in table 1. Twenty-six percent of the subjects were positive for TPO-Ab. To assess the interrelation between serum E2 and the detectability of TPO antibodies, Participants were categorized into Estradiol (E2) quartiles. It was observed that 64% and 40% of TPO-positive subjects were in the E3 and E4 respectively and none of them were found to be in the E1 and E2 quartiles of E_2. (Table 2)

Spearman's correlation indicates a significant association of the E2 with TSH, FT4, and TPO antibodies, however, no significant association was found between TSH and TPO antibodies (Table 3). To assess the strength of this relation simple linear regression model for E_2, as independent variables, and the TPO antibodies titter, TSH, and FT4 as the dependent variable was used. The beta coefficient (β) of 1.006 shows that higher E_2 was significantly related to higher TPO antibodies titer with p-value = 0.002. Similarly, significant but weak positive association was found between the E2 and TSH (β =0.004, p-value 0.000). E2 was significantly negatively associated with FT4 (β = - 0.375, p value 0 .012). (Table 4) Estrogen (E_2) is in the dependent variable P value of ≤0.05 was taken as significant.

Table 1: Descriptive of Study Population (n=100)

Biochemical Parameters	Mean ± SD	Range	Median (IQR)
Estradiol(E_2)	70.69 ± 271.14	0.73 - 2550.0	4.77 (14.96)
Free Thyroxine (FT4)	9.13 ± 5.84733	0.02 - 25.90	3.42 (582)
Thyroid-stimulating Hormone (TSH)	6.7302±16.60	0.06 - 100.00	2.65(1.56)
Thyroid peroxide titer (TPO)	6.29 ± 5.48	0.73 - 20.00	3.91 (8.73)
Free triiodothyronine FT3	4.29 ± 4.07	3.50 - 1590	10.75 (10.85)

Table 2: Detectability of Thyroid Peroxidase Antibodies in Various OEstradiol (E2 Quartiles)

E2 Quartile	Positive TPO N(%)	Negative TPO N(%)
E1 (n= 25)	00(00)	25(100%)
E2 (n= 25)	00(00)	25(100%)
E3 (n=25)	16(64)	9(36)
E4 (n=25)	10(40)	15(60)

Table 3: Spearman's correlation between serum OEstradiol (E2), TSH and TPO antibodies

E2 vs TSH	**0.194**	**0.053**
E2 vs TPO antibodies	0.742	0.000
TSH vs TPO antibodies	0.072-	0.479
E2 Vs FT4	-.0450	0.000

Table 4: Regression Analysis of OEstradiol (E2) with dependent variables

Dependent variables	Beta Coefficients (β)	Std. Error	P value
TPO	1.006	0.002	0.002
TSH	.044	.005	0.000
FT4	-.375	.147	0.12

DISCUSSION

Polycystic ovarian syndrome (PCOS) and thyroid disorders are frequent growing ailments globally. The association between autoimmune thyroid disease and PCOS is more and more being recognized by researchers, and the reason for this link is yet unstipulated. Most of the researchers have suggested their bidirectional relationship.[9] Enhanced ovarian volume, as well as cystic changes in ovaries, have been stated in primary hypothyroidism.

Apart from this, several previous studies have documented a higher incidence of thyroid diseases in PCOS patients as compared to normal females. The link between thyroid autoimmunity and PCO is gaining interest among researchers, as accurate interrelation is yet to be known. Whether this occurs as a consequence of some common predisposing factors or a pathophysiological linkage among both of these disorders has not been elucidated to date.[9]

But a previous study, indicating the pathogenesis of PCOS reported a high prevalence of PCOS phenotype in adolescent girls with euthyroid Hashimoto Thyroiditis (HT), indicating the feasible impact of other aspects like autoimmunity as compared to hypothyroidism.[10]

Arduc et al., has explained that the hypothyroidism has deteriorated PCOS by lessening the sex hormone binding globulin level, raising the conversion of androstenedione to testosterone and aromatization to Estradiol, and decreasing the metabolic clearance of estrone and androstenedione leading to PCO.

Additionally, raised TSH level promotes its spillover effect on FSH receptors. Enhanced deposition of collagen in ovaries because of hypothyroidism has also been reported by Singla et al., [9, 10]

On the other hand, Chailurkit et al. stated extra thyroidal causes of thyroid autoimmunity that might be due to elevated Estradiol levels. Some researchers have suggested that androgens as well as osteogeneses have a significant impact on autoimmunity because of their aptitude of modulating immune response via their receptors.[11, 12] Numerous other previous studies also suggested imbalance among Estrogen and progesterone or Estrogen testosterone levels might be the contributing factors. Previous research was performed to highlight the association between PCO and Thyroid autoimmunity by investigating the relationship between hormonal imbalances in patients with PCOS versus control patients.

The authors concluded that imbalances in Estrogen and progesterone (a decreased progesterone/ Estradiol ratio), may promote the development of autoimmunity in PCO patients. Immune-stimulating effects of unbalanced Estrogen are directly involved in elevations of anti-TPO.[10,13]

Arduc A et al., also suggested that E_2 and progesterone seem to impede differently with expression and mass production of proinflammatory cytokines through activated macrophages and control downregulation of immune as well as inflammatory reactions.[10] Current study was conducted to find the emerging relationship between Estradiol and thyroid autoimmunity.

In our study, we found the presence of TPO antibodies in 26% of PCO females. Our results are in agreement with a previous study by Garelli et al. that also reported the presence of TPO antibodies in 27% of their PCO patients when compared to 8% in controls.[14]

Janssen et al also documented higher thyroid antibody levels in females with PCOs as compared to a control group. Additionally, Janssen et al., also reported that females with PCOs have larger thyroid volumes and

more hypoechogenic thyroid glands when compared to controls.[15] These finding reflects that thyroid autoimmunity is commonly found in PCO patient.

In the current study, circulating E2 was found to be related to TPO Ab in PCO females. Our finding is suggestive of a connection between E2 level and TPO Ab proposes that E2 might have an impact on thyroid autoimmunity pathogenesis in PCO females. Our results are supported by the previous study ascertaining a positive correlation between anti-TPO and Estradiol.[10]

To assess the relationship between serum E2 and detectability of thyroid autoantibodies, we classified the subjects into E2 quartiles and we noticed that a higher number of anti-TPO positive subjects were fall in upper two E2 quartile (E3 and E4), whereas none of the TPO positive subjects was found in lower E2 (E1 and E2) quartile. This study's finding suggests that Estrogen may be an aspect of causing autoimmunity. On the contrary, Chailurkit et al.

Found TPO antibodies almost equally in all four E2 quartiles suggesting no relationship between E2 and TPO antibodies. Our results are justified by Chen et al., a study carried out in China, which reported increased Anti-TPO antibodies with increasing Estrogen levels.[11, 12]

Our results of regression analysis show a significant positive association between E_2 and TPO antibodies. The beta coefficient of 1.006 shows that a 1-unit increase in Estradiol will increase the 1.006-fold increase in thyroid peroxide antibody level. Our results are reflecting that the increase in E_2 and subsequent increase in TPO antibodies, will result in the occurrence of thyroid autoimmunity Wang C et al., results showed that a 1-unit increase in TPOAb/TGAb, will increase the risk for developing autoimmunity increased by 1.265-fold.[16]

The current study found a significant but weak positive relation between TSH and Estradiol levels contrary to our results, Chailurkit et al., reported a negative association between E2 and TSH, but only in those whose TSH levels fell below the reference range.

The association between E2 and TSH may suggest the influence of E2 on thyroid function through thyroid autoimmunity. The present result did not find a significant association between OEstradiol and FT4, this study's results are per Chailurkit et al., who did not find an association between E2 and FT4 evident.[11]

CONCLUSION

OEstradiol is positively associated with TPO antibodies and TSH and negatively associated with FT4 in PCOS patients. Our findings suggest that thyroid autoimmunity is commonly found in females with PCOS.

REFERENCES

1. Mitratza M, Klijs B, Hak AE, Kardaun JW, Kunst AE. Systemic autoimmune disease as a cause of death: mortality burden and comorbidities. Rheumatology. 2021; 60(3):1321-30.
2. Kayar Y, Dertli R. Association of autoimmune diseases with celiac disease and its risk factors. Pak J Med Sci. 2019; 35(6):1548.
3. Shah N, Ursani TJ, Shah NA, Raza HM. Prevalence and Manifestations of Hypothyroidism among Population of Hyderabad, Sindh, Pakistan. PAB. 2021 Jul 13;10(3):668-75.
4. Iorga A, Cunningham CM, Moazeni S, Ruffenach G, Umar S, Eghbali M. The protective role of Estrogen and Estrogen receptors in cardiovascular disease and the controversial use of Estrogen therapy. Biol Sex Diff. 2017 Dec;8(1):1-6
5. Fröhlich E, Wahl R. Thyroid autoimmunity: role of anti-thyroid antibodies in thyroid and extra-thyroidal diseases. Frontiers in immunology. Front Immunol. 2017 May 9;8:521. doi: 10.3389/fimmu.2017.00521
6. Gietka-Czernel M. The thyroid gland in postmenopausal women: physiology and diseases. Prze Menopauzalny. 2017 Jun 30;16(2):33-7.
7. Santin AP, Furlanetto TW. Role of Estrogen in thyroid function and growth regulation. J Thyroid Res. 2011 Oct;2011.
8. Gaberščcek S, Zaletel K, Schwetz V, Pieber T, Obermayer-Pietsch B, Lerchbaum E. Thyroid and polycystic ovary syndrome. Endocrinol. 2015;172:R9-21.
9. Singla R, Gupta Y, Khemani M, Aggarwal S. Thyroid disorders and polycystic ovary syndrome: An emerging relationship. Indian J Endocrinol Metab. 2015 Jan;19(1):25.
10. Arduc A, Aycicek Dogan B, Bilmez S, ImgaNasiroglu N, Tuna MM, Isik S, Berker D, Guler S. High prevalence of Hashimoto's thyroiditis in patients with polycystic ovary syndrome: does the imbalance between Estradiol and progesterone play a role?. Endocr Res. 2015 Oct 2;40(4):204-10.
11. Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B. The relationship between circulating Estradiol and thyroid autoimmunity in males. Eur J Endocrinol 2014; 170:63–67
12. Chen Y, Chen Y, Xia F, Wang N, Chen C, Nie X, et al. A higher ratio of Estradiol to testosterone is associated with autoimmune thyroid disease in males. Thyroid. 2017 Jul 1;27(7):960-6.)
13. Gaberščcek S, Zaletel K, Schwetz V, Pieber T, Obermayer-Pietsch B, Lerchbaum E. Mechanisms in endocrinology: thyroid and polycystic ovary syndrome. Eur J Endocrinol. 2015;172(1):R9-21.
14. Garelli S, Masiero S, Plebani M, Chen S, Furmaniak J,

Armanini D, et al. High prevalence of chronic thyroiditis in patients with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol2013;169:248-51.

15. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gärtner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. Eur J Endocrinol 2004;150:363-9.

16. Wang C, Niu Q, Lv H, Li Q, Ma Y, Tan J, Liu C. Elevated TPO Ab is a Strong Predictor of Autoimmune Development in Patients of Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Case–Control Study. Diabetes, Metabolic Syndrome and Obesity: Onco Targets Ther. 2020;13:4369.)

CONFLICT OF INTEREST: Authors declare no conflict of interest

GRANT SUPPORT AND FINANCIAL DISCLOSURE: NIL

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Rehman A: Study design acquisition of data and manuscript writing. Revised and approved the article.

Altaf B: Data collection and statistical analysis. Revised and approved the article.

Zahid H: Study design acquisition of data and manuscript writing. Literature review.

Tariq S: Writing of results and referencing. Revise all intellectual contents of the article and approved.

Jawed S: Data analysis and interpretation results.

Tariq S: Formulate all tables. Literature review

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.