Original Article

A study of retinal changes in women with polycystic ovarian syndrome

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Purpose: To compare the optical coherence tomography (OCT)-based retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) thickness at the posterior pole, and total macular thickness of women with the polycystic ovarian syndrome (PCOS) versus healthy reproductive age group females. **Methods:** The study included 110 eyes of 55 diagnosed cases of PCOS (study group) and 110 eyes of 55 healthy reproductive age group (15–49 years) females (control group). All patients underwent a detailed ophthalmological evaluation followed by an OCT to measure their retinal thicknesses**.** The body mass index (BMI) of patients was noted and compared with the retinal thickness. Also, the lipid profile and serum testosterone levels of PCOS patients were recorded. **Results:** The retinal thicknesses in the two study were similar and there was no statistically significant difference. However, on stratification with BMI, it was seen that in patients with BMI>30 kg/m^2, the superior Retinal Nerve Fibre Layer (RNFL) was significantly thicker in the PCOS group as compared with the control group (P = 0.0006). The mean serum testosterone level in patients with PCOS was 141.3 ± 23.2. Also, 65.45% of patients had a serum testosterone level of more than 70 ng/dL. The mean HDL cholesterol in patients with PCOS was 38.1 ± 15.6. The mean LDL cholesterol in PCOS patients was 98.4 ± 21.7, and the mean total cholesterol in PCOS patients was 153.6 ± 27.3. **Conclusion:** Androgens have a trophic action on nerves, which could explain the increased RNFL thickness in these patients.

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Polycystic ovary syndrome (PCOS) is one of the most frequent endocrine disorders in women of the reproductive age group.[1,2] The prevalence of the disease is 4–26% worldwide.[3,4] It presents with a variety of symptoms caused due to hyperandrogenism and ovulatory dysfunction.[4,5] It may be associated with metabolic syndrome, insulin resistance, glucose intolerance, type 2 diabetes, cardiovascular disease, obesity, and dyslipidemia.[6-8]

The relationship between eye changes in PCOS is unexplored, especially in the Indian population. Because PCOS is known to be associated with metabolic syndrome and changes in glucose metabolism, it is interesting to study retinal changes in these patients as compared to healthy females of the reproductive age group. Target organs in these patients experience an unopposed hyperestrogenemic effect that cannot be counteracted by progesterone. They respond to estrogen by producing certain proteins (e.g., cathepsin D, alpha- 2-macroglobulin, and aromatase cytochrome P45), which are involved in vital cellular functions such as differentiation, proliferation, and maturation. As expected, ocular tissues such as the ciliary body and retinal pigment epithelium show the presence of most of these proteins. Androgens have also been studied to affect gene expression and lipid synthesis in meibomian glands, making them a target organ for these hormones.[9,10]

Initial studies in patients with PCOS have demonstrated increased retinal nerve fiber layer (RNFL) thickness around the optic nerve compared with healthy women and its association with the presence of hyperandrogenism. The hormonal effects have also been said to cause aqueous layer deficiency and evaporative dry eye disease.[11-15]

The aim of this study was to compare optical coherence tomography OCT-based RNFL and ganglion cell layer (GCL) thickness at the posterior pole, and total macular thickness in women with PCOS versus healthy reproductive age group females.

Methods

The study was a cross-sectional comparative study and included 55 patients who were diagnosed cases with PCOS according to Rotterdam's criteria, 2013, and 55 healthy reproductive age group females to serve as the control group. The study was conducted in the Department of Ophthalmology in collaboration with the Department of Obstetrics and Gynecology. The patients diagnosed with PCOS were advised to visit the Department of Ophthalmology.

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The Rotterdam criteria require the presence of two of the following:[16,17]

1. Hyperandrogenism (clinical or biochemical)
2. Ovulatory dysfunction (oligo or anovulation)
3. Polycystic ovaries on Ultrasound (USG) (At least one ovary with i) 12 follicles of 2–9 mm ii) volume >10 mL.

Patients giving written informed consent to inclusion and participation in the trial were included in the study.

Exclusion criteria were women with other endocrine disorders, renal or liver failure; chronic users of drugs that might interfere with the metabolism of carbohydrates, lipids, and with renal function (such as diuretics, antihypertensives, antilipemic agents, and corticosteroids); smoking; alcohol consumption; or illicit drug use, women who had undergone any ocular surgery, women not giving written informed consent and uncooperative patients in whom the parameters could not be measured.

A detailed history regarding the onset of symptoms, if any, duration, progression, and any associated complaints were assessed. The presence of symptoms resulting from hyperandrogenism and ovulatory dysfunction were excluded from the control group. Hirsutism is the most reliable marker of clinical hyperandrogenism. Ovulatory dysfunction presents clearly in the form of oligomenorrhea or amenorrhea.[2] Because Rotterdam's criteria require any two of the three above parameters for a diagnosis of PCOS, excluding the first two by history would be sufficient to exclude the presence of PCOS in the control population. History regarding any major medical illness or addiction was also recorded. The demographic details of the patient were recorded. These patients included treatment-naïve patients, patients solely on lifestyle modification, and also those on oral contraceptive pills. The treatment duration was variable. The baseline parameters including visual acuity (both unaided and best corrected) using Snellen's charts, intraocular pressure (IOP) with applanation tonometer, central corneal thickness with the help of an autorefractometer, and Schirmer's test with Schirmer's strip were performed. The patients then underwent a thorough slit-lamp examination to evaluate the anterior segment; Ocular Surface Staining Score (OSSS) and tear film break-up time were measured. Patients were looked for any evidence of meibomian gland dysfunction (MGD). This was followed by a dilated fundus examination with a + 90D lens. Indirect ophthalmoscopy with a +20 D lens was also performed. After recording all these findings, a three-dimensional 3D OCT using Topcon Spectral Domain OCT Machine was performed.

Images of the OCT-based retinal nerve fiber layer thickness at the disc and macula were taken. For the disc, the values from the quadrant-wise map were noted and for the macula, the superior and inferior RNFL thickness were noted. OCT-based evaluation of the ganglion cell layer thickness at the macula was done and the superior and inferior GCL+ (ganglion cell layer + inner plexiform layer) thickness values were noted. OCT-based central macular thickness was measured using a 3D macular scan.

In addition to these parameters, the height and weight of patients were recorded and the body mass index (BMI) was calculated. For PCOS patients, the serum testosterone levels and the lipid profile of the patients were also noted.

Results

A total of 110 patients were enrolled in the study. 55 patients were diagnosed with PCOS according to Rotterdam's Criteria that formed the study group and 55 patients were healthy reproductive age group females satisfying the inclusion and exclusion criteria.

In all, 81.8% of patients in the PCOS group and 89.09% of patients in the control group resided in urban areas. Three PCOS patients and five controls had a history of hypothyroidism. A family history of systemic diseases (Diabetes Mellitus [DM], Hypertension [HTN], Coronary Artery Disease [CAD], Chronic Kidney Disease [CKD], etc.) was found in 18 PCOS patients and 17 controls. The difference between the two groups was not statistically significant [Table 1].

Clinical evidence of hyperandrogenism was found in 35 (63.63%) PCOS patients (history of hirsutism). Oligo/anovulation was found in 39 (79.90%) patients (irregular menstrual cycles, dysmenorrhea). Thirty-four patients (61.81%) had evidence of polycystic ovaries on ultrasound.

The mean age of patients was significantly lower in the PCOS group as compared to that in the control group.

In all, 63.64% of PCOS patients had an unaided distance visual acuity of 0.00 on the logMAR scale, whereas 49.09% of controls had the same. The BCVA was 0.00 on the logMAR scale in all our patients. Among the PCOS patients, 21% had no refractive error, 46% had a refractive error of <2D, and 33% had a refractive error between >2–4D. Among the controls, 17% had no refractive error, 36% had a refractive error of <2D, and 47% had a refractive error between >2 and 4D.

The Intraocular Pressure (IOP), Central Corneal Thickness (CCT), Schirmer's test, Tear Film Break-Up Time (TBUT), and Ocular Surface Staining Score (OSSS) were comparable between the two groups in our study.

Table 2 shows the SD-OCT parameters that were analyzed. We analyzed the peripapillary RNFL thickness, the RNFL thickness at the macula, the total macular thickness, and the GCL + thickness.

The RNFL thickness was uniformly distributed among the two study groups both at the disc and the macula as there was no significant difference between the two.

Table 1: Demographic details of the study population

	Case	Control	*P*
Age			
Mean+SD	26.32±5.84	32.09±7.83	0.236
Residence			
Urban	45 (81.81%)	49 (89.09%)	0.279
Rural	10 (18.18%)	6 (10.90%)	
Systemic History			
Hypothyroidism	3 (5.45%)	5 (9.09%)	0.304
Others	4 (7.27%)	3 (5.45%)	
Family History			
DM	8 (14.5%)	9 (16.3%)	0.806
HTN	4 (7.27%)	4 (7.27%)	
Others	6 (10.9%)	4 (7.27%)	

We then stratified the patients according to BMI dividing them into two groups. Group 1 included patients with BMI < 30 kg/m^2, Group 2 included patients with BMI > 30 kg/m^2.

The RNFL thickness was then compared. Interestingly, in patients with BMI >30 kg/m^2, the superior RNFL was significantly thicker in the PCOS group as compared with the control group (P = 0.0005) [Table 3].

Multiple linear regression was also carried out using age, BMI, and the presence or absence of a diagnosis of PCOS as independent variables and retinal thicknesses as the dependent variables. However, we did not obtain any statistically significant results.

We also studied the serum testosterone and lipid profile of our PCOS patients.

The mean serum testosterone level in patients with PCOS was 141.3 ± 23.2. Braunstein *et al.*[18] gave the reference ranges for testosterone in premenopausal women. The serum testosterone levels in clinics were divided into normal or raised depending on lab values for our lab. In all, 65.45% of patients had a serum testosterone level of more than 70 ng/dL [Table 4]. The PCOS group was then subdivided into those with serum testosterone levels <70 ng/dL and >70 ng/dL and the retinal thicknesses were compared. However, we did not find any significant results in doing so.

The mean HDL cholesterol in patients with PCOS was 38.1 ± 15.6. The mean LDL cholesterol in PCOS patients was 98.4 ± 21.7 and the mean total cholesterol in PCOS patients was 153.6 ± 27.3 [Tables 5 and 6].

However, because these parameters were studied retrospectively, similar data for the control group were not available to us.

Table 2: Retinal thicknesses among our study groups

Variables	Case (Mean±SD)	Control (Mean±SD)	*t*	*P*
Peripapillary RNFL thickness				
I	243.54±10.64	243.01±9.29	0.276	0.782
S	226.23±14.16	223.72±12.86	0.972	0.333
N	148.30±6.96	147.45±6.93	0.645	0.52
T	163.01±10.73	162.29±10.78	0.354	0.723
Macular RNFL thickness				
I	72.85±4.87	72.89±5.03	0.038	0.969
S	66.61±4.57	66.85±4.73	0.266	0.79
Central macular thickness (CMT)	366.18±10.67	364.54±9.89	0.833	0.406
GCL+				
I	141.09±11.51	139.98±11.12	0.513	0.608
S	139.18±11.44	137.98±13.07	0.512	0.609

Table 3: Superior RNFL Thickness Among the Two Groups After Stratification According to BMI

BMI (kg/m^2)	SUP RNFL thickness		*t*	*P*
	Case (Mean±SD)	Control (Mean±SD)		
<30	96.57±12.68	105.62±3.56	3.062	0.128
>30	119.27±12.76	103.47±15.25	4.564	0.0005

Discussion

The aim of this study was to compare OCT-based RNFL and GCL thickness at the posterior pole, and total macular thickness in women with PCOS and healthy reproductive age group females.

The study recorded the RNFL thickness at the disc and the macula, the total macular thickness, and the GCL + thickness. The GCL + included the GCL + inner plexiform layer thickness.

The patients were then stratified into two groups according to BMI.

There was no significant difference in the total macular thickness between the two groups. Edvan *et al.* did a significant study where they found that in the absence of insulin resistance, there were no statistically significant differences among the means of the measurements of the total macular thickness between the studied groups.[11]

Our study found no significant difference in the RNFL thickness at the disc and the macula. This could be due to the fact that patients in our study were relatively younger, which means that they were diagnosed earlier.

However, on stratification according to BMI, we found that the superior RNFL thickness in the PCOS group was significantly thicker than that in the control group. Stratified analysis of the remaining retinal thicknesses did not reveal any significant results.

The RNFL in patients with PCOS was significantly thicker in the superior quadrant and those with BMI >30 kg/m^2. This was in concurrence with studies conducted earlier by Edvan *et al.*,[11] Demir *et al.*[13] and Açmaz *et al.*[12] who also found a similar result. This could be due to the fact that

Table 4: Serum testosterone values among the PCOS patients

	Case (Mean±SD)	Range (mg/dL)	No of patients
Testosterone (ng/dL)	138.3±23.2	<70	19 (34.54%)
		>70	36 (65.45%)

Table 5: Lipid profile of the PCOS patients

	Case (Mean±SD)	Range (mg/dL)	No. of patients
HDL (mg/dL)	43.4±15.6	>50	24 (46.63%)
		<50	31 (56.36%)
LDL (mg/dL)	99.5±21.7	<100	26 (47.27%)
		>100	29 (52.72%)
Total Cholesterol (mg/dL)	198.7±27.3	<200	27 (49.09%)
		>200	28 (50.90%)

Table 6: Abbreviations with full forms

Abbreviation	Full Form
GCL	Ganglion Cell Layer
RNFL	Retinal Nerve Fiber layer
AVG	Average
CMT	Central Macular Thickness
BMI	Body Mass Index
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein

androgens have a trophic effect on the nerves and this could suggest that PCOS has a protective effect on the RNFL. The hyperestrogenemic effect in PCOS cannot be balanced by progesterone and induces changes in the target organs. Ogueta *et al*.[9] described estrogen-induced proteins (e.g., cathepsin D, alpha-2-macroglobulin, and aromatase cytochrome P45), which play an important role in vital cellular functions such as differentiation, proliferation, and maturation. Most of these proteins are found in ocular tissues such as the ciliary body and the retinal pigment epithelium.

Our study found no significant difference between the RNFL thickness at the macula. This was in contrast to the study conducted by Edvan *et al*.[11] where they found significant thickening in the temporal inner macula (TIM), the inferior inner macula (IIM), the nasal inner macula (NIM), and the nasal outer macula (NOM). In another study conducted by Acmaz *et al*., nasal outer macula (NOM) and temporal outer macula (TOM) were statistically thicker in the PCOS group than in the control group. Fovea center thickness and temporal inner macula were, however, significantly thinner in the PCOS group than in the healthy control group. Therefore, it seems that the effect of PCOS on the macula is not clear and needs further studies.

Açmaz *et al*.[12] measured the choroidal thickness in patients with PCOS using an Enhanced Depth Optical Coherence Tomography(EDOCT) and found a significantly thicker choroid in patients with PCOS. Our study was, however, limited by the use an SD OCT, which does not measure the choroidal thickness.[13]

PCOS is characterized by an irregular menstrual cycle, ovulatory dysfunction, and hyperandrogenism. Metabolic alterations, insulin resistance, and obesity are often seen in patients with PCOS. Insulin resistance can cause diabetic eye changes in women with PCOS. However, we did not find any diabetic eye changes in our PCOS patients.

In addition to the above, we assessed the IOP, CCT, Schirmer's test, and TBUT in these patients.

There was no significant difference in the IOP and CCT among the two groups. Meibomian glands are a target organ of androgen hormones, which have been shown to regulate gene expression and lipid synthesis in these tissues.[14] Androgen deficiency may lead to MGD and evaporative dry eye syndrome. Estrogen is an antagonist of meibomian gland function and may promote the development of evaporative dry eyes.[14] This was consistent with the studies done by Adıyeke *et al*.[14] and Demir *et al*.[13] who did not find any significant difference between the IOP of the groups. However, in the study done by Karaca *et al*., a significant difference was found between the Central Corneal Thickness (CCT) among the two groups where the CCT in patients was found to be significantly thicker in PCOS patients.

Previous studies conducted by Bonini *et al*.[19] and Yavas *et al*.[20] found no significant difference between the values of Schirmer's test between the two study groups. Our study also failed to find a significant difference. However, in the study conducted by Karaca *et al*., a significantly lower Schirmer's test value was found in PCOS patients. Interestingly, TBUT was found to be significantly lower in PCOS patients in all three studies, unlike our study. This could be explained by the fact that factors such as high temperature and windy climate that are present in our study region, would cause patients with dry eyes to be equally distributed in our study and control groups. In all, the higher prevalence of dry eyes in our study region could be a confounding factor.

We also assessed the OSSS and found no significant difference between the two groups. This was consistent with the above findings. However, no other studies have evaluated the same.

Conclusion

Our results suggest that hyperandrogenemia can modify the RNFL in patients with PCOS. A limitation of our study would be that PCOS was not ruled out biochemically in the control group. Treatment of PCOS can probably ameliorate symptoms of dry eyes in these patients. However, further studies need to be done with a larger sample size to confirm the posterior segment changes in these patients and compare the effect of treatment on the parameters that we assessed.

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Conflicts of interest

There are no conflicts of interest.

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