Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

# Can oestrogen be a game changer in diabetic retinopathy progress: A novel study

**Asma Anjum**[1], **Saif Ahmed**[2], **Sheelu Shafiq**[3], **Abdul Waris**[1,*]

[1]*Dept. of Ophthalmology, Institute of Ophthalmology, Jawahar Lal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India*
[2]*College of Medicine, Al-Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia*
[3]*Rajiv Gandhi Center for Diabetes and Endocrinology, Jawahar Lal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India*

ARTICLE INFO

*Article history:*
Received 24-12-2022
Accepted 06-01-2023
Available online 30-03-2023

*Keywords:*
Diabetic retinopathy (DR)
Diabetic Mellitus (DM)
Diabetic eye disease (DED)
Serum Oestrogen
Blood Sugar fasting (BSF)
Chemical mesent immunoassay (CLIA)

ABSTRACT

**Aim:** To measure and correlate the levels of oestrogen in patients with diabetic retinopathy (DR).
**Materials and Methods:** A hospital based crossectional study of 60 patients (30 with DR, 30 without DR) with diabetes of more than 10 years was carried in our institute (JN Medical College, AMU). Serum oestrogen levels were measured in both the groups at Rajiv Gandhi Centre JNMCH & relevant statistical tests were conducted to compare both the groups.
**Result:** Serum oestrogen was maximum in patient without DR (64.02±46.40pg/mL) and minimum in patients with DR (42.34±34.8), the result was found to be significant (t = -2.047, P<0.05).
**Conclusion:** Oestrogen has a protective effect on diabetic retinopathy occurrence, through it has no statistically significant relation to its severity.



## 1. Introduction

Diabetic eye disease (DED) occurs as a direct result of chronic glucose levels causing damage to the retinal capillaries, leading to capillary leakage and capillary blockage. It may lead to loss of vision eventually, blindness. The spectrum of DED comprises diabetic retinopathy (DR), diabetic macular edema (DME), cataract, glaucoma, loss of focusing ability, and double vision. Diabetic macular edema is further a complication of retinopathy, which can occur at any stage. Diabetic retinopathy has a significant impact on people's quality of life and is associated with deterioration in physical well being. Besides the burden for people with diabetes, diabetic retinopathy is also responsible for significant healthcare expenditure.[1–3] Timely intervention in case of diabetic retinopathy can lower the disease burden by limiting the progression of reversible to irreversible visual loss and the role of early identification of risk factors and screening programme are indispensable.[4–6] In recent time sex hormones has been reported to be associated with diabetes mellitus, hypertension and cardiometabolic syndrome.[7] So we conducted a hospital-based, cross-sectional study titled "Diabetic retinopathy and it's correlation with sex hormons". The study population was drawn from the diabetic patients who attended the Rajiv Gandhi Centre for Diabetes and Endocrinology, and subsequently were referred to the Retina Clinic, Institute of Ophthalmology, of the same hospital, for their ocular evaluation. Aims of this study were

1. To indentify and accurately classify the patients of Diabetic Retinopathy.
2. To measure the levels of oestrogen in patient of Diabetic Retinopathy.

* *Corresponding author.*
*E-mail address*: waris_eye@yahoo.co.in (A. Waris).

https://doi.org/10.18231/j.ijceo.2023.010

3. To study the relationship between Diabetic Retinopathy and Oestrogen.

## 2. Materials and Methods

A total of 60 Diabetes Type II patients were included in the study. The patients were divided into two groups:

1. **Case group:** This group served as the case group and comprised of diabetic patients with diabetic retinopathy (30 patients).
2. **Control group:** This group served as the control group and comprised of diabetic patients without diabetic retinopathy (30 patients).

### *2.1. Inclusion criteria*

1. **Case group:** All diagnosed cases of diabetes mellitus type II (duration more than 10 years) with diabetic retinopathy and reasonably clear media who were referred to the Retina Clinic, Institute of Ophthalmology, Jawaharlal Nehru Medical College and Hospital, A.M.U., Aligarh from Rajiv Gandhi Center for Diabetes and Endocrinology, of the same hospital.
2. **Control group:** All diagnosed cases of diabetes mellitus type II without diabetic retinopathy and reasonably clear media who were referred to the Retina Clinic, Institute of Ophthalmology, Jawaharlal Nehru Medical College and Hospital, A.M.U., Aligarh from Rajiv Gandhi Center for Diabetes and Endocrinology, of the same hospital.

### *2.2. Exclusion criteria*

1. The patients with media not clear (where fundus photograph is not possible).
2. The patients who are on medications which interfere either with sex hormones and/or treatment for diabetes.
3. Rheumatoid arthritis, lupus, and other autoimmune disorder
4. Systematic inflammation
5. Major depressive disorder
6. Malignancies or history of chemotherapy or radiotherapy within the past 1 year.
7. The patients where fundus photography was not possible (in any particular eye or field) due to inadequate dilatation or inability of the subject to co-operate, properly.
8. Serum Oestrogen for females in follicular phase 57.0 – 227.0 pg/mL Preovulatory phase 127.0 – 476.0 pg/mL was considered by Beckman Coulter, Access 2 which uses chemiluminescene immunoassay technique, as normal range.

The study was approved by the ethical committee of Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh and was according to the Declaration of Helsinki. An informed written consent was taken from each patient before their participation in the study. A clinical history was taken with the help of a structured questionnaire including: demographic data, duration of diabetes, treatment taken, addiction, dietary habits, family history of diabetes, and blood pressure. A fundus photograph using Visucam 500 was taken for every patient and was secured as an objective evidence of the subjective findings seen on 78D/90D slit lamp biomicroscopy and indirect ophthalmoscope. The photographs were graded using the ETDRS grading system for the severity of retinopathy. The data was analyzed using Statistical Package for Social Sciences SPSS) 25.0 version (Chicago, Inc., USA). The Chi-square test was used to compare categorical variables. Unpaired t-test was used to compare the continuous variables between the two strata. The one-way analysis of variance (ANOVA) was used to compare more than two means. Pearson's correlation was done. The p-value<0.05 was considered significant. The results were shown as frequencies, percentages and mean ±SD.

## 3. Results

Serum estrogen in patients with diabetic retinopathy

**Table 1:** Comparison of serum estrogen between with diabetic retinopathy (DR) and without diabetic retinopathy (DR)

| Groups | Mean Estrogen ±SD (pg/mL) | t-value | p-value [1] |
|---|---|---|---|
| Case (with DR) | 42.34±34.81 | -2.047 | P=0.045* |
| Control (without DR) | 64.02±46.40 | | |

[1]Independent samples t-test, *Significant

As shown in Table 1, the mean serum estrogen was maximum in patients without DR (64.02±46.40 pg/mL) and minimum in patients with DR (42.34±34.81 pg/mL). The results were found to be significant (t=-2.047, p<0.05).

As shown in Table 2, different stage of diabetic retinopathy was compared with serum estrogen and was found that serum estrogen was maximum (58.20±46.14pg/mL) in mild NPDR category, whereas minimum (21.21±15.47pg/mL) in the severe NPDR category, However results were found to be non-significant ($F_{326}$=2.512, p>0.05).

As shown in the Table 3, when serum estrogen of patient with diabetic retinopathy was correlated with the demographic and clinical variable then a negative correlation was found with age of patient, duration of diabetes mellitus, systolic blood pressure, diastolic blood

**Table 2:** Comparison of the stage of diabetic retinopathy (DR) with serum estrogen

| Stage of Diabetic Retinopathy | Mean Estrogen ±SD (pg/mL) | F-value | p-value [1] |
|---|---|---|---|
| Mild NPDR | 58.20±46.14 | 2.512 | P= 0.081 |
| Moderate NPDR | 52.20±32.57 | | |
| Severe NPDR | 21.21±15.47 | | |
| Mild-Moderate NPDR | 56.75±60.03 | | |

[1]oneway ANOVA

**Table 3:** Correlation of serum estrogen

| Estrogen | Age | Duration | SBP | DBP | BSF | BSPP | HBA1c | TESTO | Progent | LH | FSH |
|---|---|---|---|---|---|---|---|---|---|---|---|
| r value[1] | .508** | .218 | .139 | .099 | .427* | .228 | .351 | .891 | .233 | .708** | .795** |
| p value[1] | .004 | .247 | .465 | .064 | .019 | .225 | .057 | .001 | .215 | .001 | .001 |

[1]pearson Correlation, *Significant at the 0.05 level, **Significant at the 0.001 level

pressure, blood sugar fasting (BSF), blood sugar post prandial (BSPP), glycated hemoglobin (HBA1c), serum testosterone, serum progesterone and a positive correlation was found with serum LH and serum FSH, However the results were found to be significant for age of patient (r = -0.508, p< 0.891), blood sugar fasting (BSF) (r = 0.427, p<0.01) and serum testosterone (r =-0.891, p<0.001), serum LH (r = 0.708, p<0.01) and serum FSH (r = 0.795, p<0.001), and found non-significant for duration if diabetes mellitus (r = -0.218, p>0.05), systolic blood pressure (r = -0.139, p>0.05), diastolic blood pressure (r = -0.009, p>0.05), blood sugar post prandial (BSPP) (r = -0.228, p>0.05), glycated hemoglobin HBA1c (r = -0.351, p>0.05) and serum progesterone (r = 0.233, p>0.05) respectively.

## 4. Discussion

In the present study the mean serum estrogen was found to be significantly (t = -2.047, p<0.05) low in patients with diabetic retinopathy (42.34±34.81pg/mL) as compared to patients without diabetic retinopathy (64.02±46.40 pg/mL) our findings show a significantly higher level of estrogen found in patients without diabetic retinopathy.[8–10] Firstly estrogen has been reported to stimulate the production of endothelial-derived nitric oxide (NO).[11,12] Estrogen increases gene expression of endothelial NO synthase (eNOS) and enhance eNOS activity (Ross et al., 2008; Novella et al., 2012; Kim et al., 2014).[13] Secondly, estrogen has been reported to inhibit rennin release and angiotensin-converting enzyme (ACE) and expression of ICAM-1 and VCAM-1 in the vascular endothelium during inflammation (Orshal and Khalil 2004; Villa balance et al., 2010).[14] Thirdly estrogen results in increased cyclooxygenase (COX-1) expression with resulting prostacyclin synthesis that is linked to vascular relaxation (McCrohonet al., 1999).[15] Thus estrogen may attenuate numerous factors that may lead to diabetic retinopathy in the setting of hyperglycemia as supported by our finding of a significantly high level of estrogen in patients without diabetic retinopathy.[16,17] However, no significant difference in the level of estrogen was found when the different stage of diabetic retinopathy was compared with serum estrogen. It was reported that serum estrogen was found the maximum (58.20±46.14pg/mL) in mild NPDR category, whereas minimum (21.21±15.47pg/mL) in the severe NPDR category, whereas minimum (21.21±15.47pg/mL) in the severe NPDR category and the difference in the mean value of serum estrogen in various stages of diabetic retinopathy was found to be non-significant (p > 0.05). Our finding shows a significant negative correlation of estrogen to age and postmenopausal state is significantly associated with the presence of dysglycemia independently of normal aging in this setting of dysglycemia along with deteriorating estrogen poses a risk for diabetic retinopathy. Estrogen also showed a significant negative correlation with blood sugar fasting (BSF) and testosterone which again emphasize upon the findings suggestive of increased risk for diabetic retinopathy in settings of high glucose and vascular changes mediated by testosterone in absence of ameliorating effects of estrogen.

## 5. Conclusion

The mean serum estrogen found to be significantly lower in patients with diabetic retinopathy (42.34±34.81pg/mL) as compared to patients without diabetic retinopathy (64.02±46.40pg/mL). The serum estrogen was found maximum in mild NPDR category (58.20±46.14pg.mL) and minimum in severe NPDR category (21.21±15.47pg.mL). With estrogen, a significant negative correlation was found with age of patient (r = -0.508, p<0.01), blood sugar fasting (BSF) (r = -0.427, p<0.05), serum testosterone (r = -0.891, p<0.001) and a significant positive correlation was found with serum LH (r = 0.708, p<0.01) and serum FSH (r = 0.795, p<0.01) respectively.

## 6. Carry Home Massage

1. Oestrogen has a protective impact on development of diabetic retinopathy.

2. Though it has no significant relation with severity of diabetic retinopathy.
3. Once oestrogen level falls after menopause the risk of DR increase.
4. Low level oestrogen therapy may have a positive impact on DR acuity in post menopause. Warrants a prospective study.

## 7. Source of Funding

None.

## 8. Conflict of Interest

None.

## References

1. Dandona R, Dandona L, Naduvilath TJ, Nanda A, Mccarty CA, Rao G. Population-based assessment of diabetic retinopathy in an urban population in southern India. *Br J Ophthalmol*. 1999;83(8):937–40.
2. Zheng Y, He M, Congdon N. The worldwide epidemic of diabetic retinopathy. *Indian J Ophthalmol*. 2012;60(5):428–31.
3. Gadkari SS, Maskati QB, Nayak BK. Prevalence of diabetic retinopathy in India: The All India Ophthalmological Society Diabetic Retinopathy Eye Screening Study 2014. *Indian J Ophthalmol*. 2016;64(1):38–44.
4. Grunwald JE, Brucker AJ, Schwartz SS, Braunstein SN, Baker L, Petrig BL, et al. Diabetic glycemia control and retinal blood flow. *Diabetes*. 1990;39(5):602–7.
5. Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, et al. Targeting intensive glycaemic control versus targeting conventional glycemic control for type 2 diabetic mellitus. *Cochrane Database Syst Rev*. 2013;11(11):CD008143. doi:10.1038/sj.ijo.0801748.
6. Joshi SR, Parikh RM. India; the diabetes capital of the world: Now heading towards hypertension. *J-Assoc Physicians India*. 2007;55:323–4.
7. Gupta PD, Johar K, Negpal K, Vasavada AR. Sex hormone receptors in the human eye. *Surv Ophthalmol*. 2005;50(3):274–84.
8. Kim KH, Bd Y, Bender JR. Endothelial estrogen receptor isoforms and cardiovascular disease. *Mol Cell Endocrinol*. 2014;389(1-2):65–70.
9. Haffiner SM, Klein R, Moss SE, Klein BE. Sex hormones and the incidence of severe retinopathy in male subjects with type I diabetes. *Ophthalmology*. 1993;100(12):1782–6.
10. Maurya RP, Gupta A, Singh A, Singh VP, Bosak S, Kumar A, et al. Gender, Sex hormones and Diabetic retinopathy. *Indian J Clin Exp Ophthalmol*. 2021;7(1):181–9.
11. Ogueta SB, Schwartz SD, Yamashita CK, Farber DB. Estrogen receptor in the human eye: influence of gender and age on gene expression. *Invest Ophthalmol Vis Sci*. 1999;40(9):1906–11.
12. Marin-Castaño ME, Elliot SJ, Potier M, Karl M, Striker LJ, Striker GE, et al. Regulation of Estrogen Receptors and MMP-2 Expression by Estrogen in Human Retinal Pigment Epithelium. *Invest Ophthalmol Vis Sci*. 2003;44(1):50–9.
13. Ross RL, Serock MR, Kahlil RA. Experimental benefits of sex hormones on vascular function and the outcome of hormone therapy in cardiovascular disease. *Curr Cardiol Rev*. 2008;4(4):309–22.
14. Orshal JM, Khalil RA. Gender, sex hormones, and vascular tone. *Am J Physiol Regul Integr Comp Physiol*. 2004;286(2):233–49.
15. Mccrohon RH, West SD, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, et al. High prevalence of sleep disorder breathing in patients with diabetic muscular edema. *Retina*. 2012;32(9):1791–8.
16. Novella S, Dantas AP, Segarra G, Medina P, Hermenegildo C. Vascular Aging in Women: is Estrogen the Foundation of Youth? *Front Physiol*. 2012;3:165.
17. Yuen KK, Kahn HA. The association of femal hormones with blindness from diabetic retinopathy. *Am J Ophthalmol*. 1976;81(6):820–2.

## Author biography

**Asma Anjum,** Senior Resident https://orcid.org/0000-0002-9625-3832

**Saif Ahmed,** Assistant Professor https://orcid.org/0000-0001-6403-526X

**Sheelu Shafiq,** Professor

**Abdul Waris,** Associate Professor https://orcid.org/0000-0002-3210-7633

**Cite this article:** Anjum A, Ahmed S, Shafiq S, Waris A. Can oestrogen be a game changer in diabetic retinopathy progress: A novel study. *Indian J Clin Exp Ophthalmol* 2023;9(1):49-52.