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ASSOCIATIONS OF SERUM TESTOSTERONE WITH DIABETIC RETINOPATHY AMONG DIABETIC MEN AND WOMEN: A CASE-CONTROL STUDY

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ABSTRACT

Aim: Sex steroid hormones are essential for reproductive function, but can also affect the physiology of a non-reproductive system, such as that of eye, and are probably the cause of the large majority of known sex differences in function and disease. The aim of this study is to measure the levels of serum testosterone and to study the relationship with diabetic retinopathy. **Subjects and Methods:** To meet the aim a hospital-based, cross-sectional study was conducted on 120 eyes of 60 diabetic patients, who were referred from the Rajiv Gandhi Center for Diabetes and Endocrinology to the Retina Clinic, Institute of Ophthalmology, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh. Serum testosterone, blood sugar fasting, blood sugar post-prandial, glycated hemoglobin was measured in subjects with diabetic retinopathy and subjects without diabetic retinopathy. In addition, correlation of serum testosterone with age, duration of disease, blood pressure, glycemic profile and sex steroid hormonal status of subjects with diabetic retinopathy **Results:** The mean serum testosterone level was found to be significantly higher ($p<0.05$) in subjects with diabetic retinopathy (DR) as compared to subjects without diabetic retinopathy (DR). A significant positive correlation of serum testosterone was found with blood sugar fasting (BSF) ($p<0.01$), HBA1c ($p<0.05$), serum progesterone ($p<0.01$) whereas a significant negative correlation was found with serum estrogen ($p<0.01$), serum LH ($p<0.01$) and serum FSH ($p<0.01$). However when the various stages of diabetic retinopathy was compared with serum testosterone, it was found maximum in the severe NPDR category, whereas minimum in moderate NPDR category, with a non-significant result ($p >0.05$). **Conclusion:** A possible susceptibility and association of high levels of serum testosterone with diabetic retinopathy encourages further studies needed for justification of the quantum of influence of serum testosterone and other sex hormones have, in relation to gender with regard to progression of diabetic retinopathy as well as diabetic duration and blood glucose control to understand the mechanism of progression of diabetic retinopathy.

KEYWORDS: Sex steroid hormone, testosterone, diabetic retinopathy, blood sugar fasting, blood sugar post-prandial, glycated hemoglobin.

1. INTRODUCTION

Approximately, 382 million people across the world have been estimated to have DM in 2013 and if no action is taken this number will rise to 592 million by 2035 (International Diabetes Federation, 2017). WHO estimates that 19% of the world's diabetic population lives in India and 80 million people in India will have diabetes by the year 2030 (Yau et al., 2012). All people with diabetes mellitus (both Type I and Type II) are at risk to develop Diabetic retinopathy (DR). Diabetic retinopathy (DR), neuropathy, nephropathy are common complications in all types of diabetes. Among these, DR is one of the most common and specific microvascular complications of diabetes. It has been seen that patients having DR are 25 times more at risk of blindness than a non-diabetic individual. Diabetic retinopathy is an important cause of blindness and occurs as a result of long-term accumulated damage to the small blood vessels in the retina. 2.6% of global blindness can be attributed to diabetes (Bourne et al., 2013).

The eye was long considered a "sexually neutral" structure, meaning that it was believed that there were no differences in ocular physiology and pathology between the sexes. Today, however, we know that differences among sexes exist both in the physiology and in the pathology of the eye (Wickham et al., 2010). In fact, the eye is a target for sex steroid hormones as demonstrated by the large presence of sex steroid hormone receptors (SSHRs) (Wickham et al., 2010). The SSHRs' mRNAs

are present everywhere in the eye: cornea, lens, iris, ciliary body, retina, lacrimal gland, meibomian gland, conjunctiva (Gupta et al., 2005). In all these locations, estrogen receptor α (ERα), estrogen receptor β (ERβ), progesterone receptor, and androgen receptor (AR) mRNAs have been detected. The distribution of sex steroid hormone receptors (SSHRs) in the eye varies by sex and age, which partly explains the difference in the epidemiology of certain eye diseases (Mellon et al.,2001). PCR assay, Western blot, and immunohistochemical analysis have demonstrated the presence of ER-α protein in the retina and RPE of young women, but not in postmenopausal women or men (Ogueta et al., 1999). In addition to androgen receptor (AR) mRNA (Wickham et al., 2010), the AR protein is present in the lachrymal and meibomian glands, the cornea, the bulbar conjunctiva, the lens, and the retinal pigment epithelium (RPE), together with 5α-reductase (the enzyme converting testosterone into the more powerful dihydrotestosterone, DHT) type 1 and 2 mRNA (Wickham et al., 2010). The mammalian retina has the ability of synthetize neurosteroids (pregnenolone, progesterone, dehydroepiandrosterone, desoxycorticosterone, 3 alpha, 5 alpha-tetrahydrodesoxycorticosterone, 3-alpha-hydroxy-5alpha-dihydroprogesterone, 17-hydroxyprogesterone, and 17-hydroxypregnenolone) from cholesterol, as demonstrated by using retinal explants, thus excluding interferences from circulating steroids (Guamieri et al., 1994). The steroidogenic enzymes are found in retinal neurons, glial cells, and photoreceptors in amounts similar to those observed in other part of the CNS (Mellon et al., 2001). Enzymes' concentration is greatest in the internal nuclear layer, which is considered the principal site of retinal steroids' synthesis (Cascio et al., 2015).

Sex-related differences in eye anatomy and physiology are reflected in disease processes (Zetterberg 2016). Dissimilarities in ocular physiopathology exist between human males and females (Gupta et al., 2015). These differences can be observed in the lacrimal and other eye-associated glands, the ocular surface, the crystalline lens, and the retinochoroid complexes. Sex steroid hormone (estrogen, progesterone, and androgen) actions, various physiological condition, such as age, menstrual cycles, pregnancy and menopause or andropause, hormone milieu changes, can affect the vision. Sex-related differences in the prevalence of diabetic retinopathy are associated with the difference in the prevalence of diabetes. Though more men than women are affected by type 1 diabetes (Wandell et al., 2013) no study to date has found a significant difference in its prevalence (Chaturvedi et al., 2001, Klein et al., 2009). Similarly, no statistically significant sex-related differences in the prevalence of diabetic retinopathy associated with type 2 diabetes have been established, though some studies have suggested that it is more frequent among men (Kostev et al., 2013, Looker et al., 2012). Various other risk factors besides sex alone need to be taken into account (Ozawa et al., 2015). This leads us to new area of study of sex steroid hormones and diabetic retinopathy.

2. SUBJECTS AND METHODS

2.1 Subjects

This cross-sectional study was conducted getting an approval from the Ethical Committee, Jawaharlal Nehru Medical College and Hospital, A.M.U., Aligarh, and was according to the Declaration of Helsinki. An informed written consent was taken from each patient and/or patient attendant before participation in the study. The study population was drawn from the diabetic subjects who attended the Rajiv Gandhi Center for Diabetes and Endocrinology, and subsequently were referred to the Retina Clinic, Institute of Ophthalmology, of the same hospital, for their ocular evaluation. Total of 60 patients with diabetes mellitus II were enrolled. The patients were divided into two groups: the first group served as the study group and comprised of diabetic patients with diabetic retinopathy. The second group served as the control group and comprised of diabetic patients without diabetic retinopathy.

2.2 Methods

A clinical history was taken with the help of a structured questionnaire including- demographic data, duration of diabetes, treatment taken, presence of any other complications of diabetes, addictions, dietary habits, family history of diabetes, and blood pressure. The laboratory profile of each subject comprised of Blood sugar (both fasting [greater than or equal to 126mg/dL in diabetics] and 2-hour Post-prandial [greater than or equal to 200mg/dL), HbA1C (greater than or equal to 6.5 % in diabetes), sex hormones (reference range values): serum Total Testosterone; Male: 3.0-12.0 ng/ml, Female: 0.07-0.65 ng/ml. The sex hormones were assessed by Beckman Coulter, Access 2, which uses the chemiluminescence immunoassay technique (Cinquanta, L., Fontana, D. E., & Bizzaro, N, 2017).

The patients with media not clear (where fundus photograph is not possible), with rheumatoid arthritis, lupus, and other autoimmune disorder, systematic inflammation, major depressive disorder, malignancies, history of chemotherapy or radiotherapy within past 1 year, taking medications which interferes either with sex hormones and/or treatment for diabetes and 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 were excluded from the study. A diagnosis of diabetic retinopathy was made when a patient exhibited a minimum of one microaneurysm in any field, as well as hemorrhages (dot, blot or flame shaped) and maculopathy (with or without clinically significant macular edema). The diagnosis of proliferative diabetic retinopathy was made only if there is neovascularization.

2.3 Statistical Analysis

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

3.1 Personal and demographic characteristics of study subjects

Table 1 represents the personal and demographic characteristics of subject with diabetic retinopathy (Case) and subject without diabetic retinopathy (Control) subjects. Both among cases and control, 60.0% of the subjects were male and 40.0% of the subject were female. 76.66% of the subject with diabetic retinopathy (Case) are found to be non-vegetarian and 23.33% are vegetarian whereas 73.33% of the subject without diabetic retinopathy (Control) are found to be non-vegetarian and 26.66% are found to be vegetarian.

83.33% of the subject with diabetic retinopathy (Case) belonged to the urban area and 16.66% belonged to the rural area whereas 75.0% of the subject without diabetic retinopathy (Control) belonged to the urban area and 6.0% belonged to the rural area. 86.66% of the subject with diabetic retinopathy (Case) were found to be non-smoker and 13.33% were smoker whereas 90% of the subject without diabetic retinopathy (Control) were found to be non-smoker and 10.0% were smoker.

Table 1: Personal and demographic characteristics of study subjects.

Variables	CASE (With DR) n (%) (N = 30)	CONTROL (Without DR) n (%) (N = 30)
Gender		
Male	18(60)	18(60)
Female	12 (40)	12 (40)
Dietary habits		
Vegetarian	07(23.33)	8(26.66)
Non-vegetarian	23(76.66)	22(73.33)
Area of residence		
Rural	5(16.66)	6(25.0)
Urban	25 (83.33)	24 (75.0)
Addiction		
Smoker	04(13.33)	03(10)
Non-smoker	26(86.66)	27(90)
Marital status		
Unmarried	0 (0.0)	0 (0.0)
Married	29(96.66)	28 (93.33)
Divorced/Widowed/Separated	1(3.33)	2 (6.66)

3.2 Physical characteristics of study subjects

Table 2 exhibits Physical characteristics of subject with diabetic retinopathy (Case) and subject without diabetic retinopathy (Control). The mean age of subjects with diabetic retinopathy (DR) was found to be insignificantly lower (p>0.05) as compared to the mean age of subjects without diabetic retinopathy. The mean duration of diabetes mellitus (in years) for the subjects with diabetic retinopathy (DR) was found to be significantly higher (p<0.05) as compared to the duration of diabetes mellitus for the subjects without diabetic retinopathy. The mean blood sugar fasting (BSF) and the mean blood sugar postprandial (BSPP), both were significantly higher (p<0.05) in the subjects with diabetic retinopathy as compared to the mean blood sugar fasting in subjects without diabetic retinopathy. Also the mean glycated hemoglobin (HBA1c) was significantly higher (p<0.05) in the subjects with diabetic retinopathy as compared to the glycated hemoglobin (HBA1c) in the subjects without diabetic retinopathy.

Table 2: Physical characteristics of study subjects.

Variables	CASE (With DR) Mean ± SD (N = 30)	CONTROL (Without DR) Mean ± SD (N = 30)	p value
Age (years)	57.10±10.76	57.86±9.58	p >0.05
Duration of Diabetes Mellitus (years)	14.66±3.63	12.93±2.74	**p<0.05**
Blood sugar Fasting (mg/dL)	131.50 ± 25.88	117.93 ± 19.75	**p<0.05**
Blood sugar post-prandial (mg/dL)	189.96 ± 31.06	171.36 ± 28.64	**p<0.05**
Glycated Haemoglobin (%)	8.19 ± 1.29	7.52 ± 1.11	**p<0.05**

3.3 Serum Testosterone levels among study subjects

Table 3 represents the serum testosterone levels among the study subjects. The mean serum testosterone level was found to be significantly higher ($p<0.05$) in subjects with diabetic retinopathy (DR) as compared to subjects without diabetic retinopathy (DR).

Table 3: Serum Testosterone levels among study subjects.

Variables	CASE (With DR) Mean ± SD (N = 30)	CONTROL (Without DR) Mean ± SD (N = 30)	p value
Serum Testosterone (ng/mL)	3.75±2.75	2.47±1.94	p<0.05

3.4 Comparison of the stage of diabetic retinopathy (DR) with serum testosterone and level of glycemic control among study subjects

Table 4 exhibits different stage of diabetic retinopathy was compared with serum testosterone. Serum testosterone was found maximum (5.32±1.75ng/mL) in the severe NPDR category, whereas minimum (2.16±2.29ng/mL) in moderate NPDR category. However results were found to be non-significant (p >0.05). The blood sugar fasting (BSF) was maximum in mild-moderate PDR category (150.00±14.14 mg/dL), whereas minimum in mild NPDR category (114.66±14.22 mg/dL). The blood sugar postprandial (BSPP) was found maximum in mild-moderate PDR category (205.00±31.06 mg/dL), whereas minimum in moderate NPDR category (182.72±32.84 mg/dL). The Glycated hemoglobin (HBA1c) was found to be maximum in the severe NPDR category (8.60±1.35%), whereas minimum in mild NPDR category (7.86±1.39%). However all these results were found to be non-significant (p >0.05).

Table 4: Comparison of the stage of diabetic retinopathy (DR) with serum testosterone and level of glycemic control among study subjects

Variables	Mild NPDR	Moderate NPDR	Severe NPDR	Mild-Moderate PDR	p value
Serum Testosterone (ng/mL)	3.81±3.52	2.16±2.29	5.32±1.75	3.74±2.75	p<0.05
Blood sugar Fasting (mg/dL)	114.66±14.22	126.54±30.87	142.27±21.81	150.00±14.14	p<0.05
Blood sugar post-prandial (mg/dL)	195.50±48.03	182.72±32.84	191.45±20.82	205.00±31.06	p<0.05
Glycated Haemoglobin (%)	7.86±1.39	7.92±1.31	8.60±1.35	8.45±0.07	p<0.05

3.5 Correlation of serum Testosterone with age, duration of disease, blood pressure, glycemic profile and sex steroid hormonal status of subjects with diabetic retinopathy

Table 5 represents the correlation of serum testosterone with age, duration of disease, blood pressure, glycemic profile and sex steroid hormonal status of subjects with diabetic retinopathy. A negative correlation was found with duration of diabetes mellitus, systolic blood pressure, diastolic blood pressure, serum estrogen, serum LH, serum FSH, and a positive correlation was found with age of patient, blood sugar fasting (BSF), blood sugar post prandial (BSPP), glycated hemoglobin (HBA1c) and serum progesterone. However the results were found to be significant for blood sugar fasting (BSF) ($p<0.01$), HBA1c ($p<0.05$), serum estrogen ($p<0.01$), serum progesterone ($p<0.01$), serum LH ($p<0.01$) and serum FSH ($p<0.01$).

Table 5: Correlation of serum Testosterone with age, duration of disease, blood pressure, glycemic profile and sex steroid hormonal status of subjects with diabetic retinopathy.

TESTOSTERONE	Age	Duration	SBP	DBP	BSF	BSPP	HBA1c	Estro	Progest	LH	FSH
r value	.134	-.085	-.043	-.050	.471	.263	.446	-.891	.558	-.790	-.831
p value	>0.05	>0.05	>0.05	>0.05	**p<0.01**	>0.05	**p<0.05**	**p<0.01**	**p<0.01**	**p<0.01**	**p<0.01**

4. DISCUSSION

The aim of our study was to measure the level of serum testosterone in the patient with diabetic retinopathy. Sex hormone has drawn attention recently due to its association with type 2 diabetes mellitus, increased cardiometabolic risk and metabolic syndrome (Santoro et al., 2010; Haring et al., 2010; Vikan et al., 2010).In the present study serum levels of serum testosterone was measured and compared in 30 patients having diabetes mellitus without diabetic retinopathy (Controls) and another 30 patients having diabetes mellitus with diabetic retinopathy (Cases).

The mean serum testosterone level was found to be maximum in patients with diabetic retinopathy (DR) (3.75±2.75 ng/mL) and minimum in patients without DR (2.47±1.94 ng/mL) with significant results ($t=2.079$, $p<0.05$). Our results show testosterone is significantly higher in patients with diabetic retinopathy. It has also been reported that the testosterone firstly causes increased expression of VEGF (Vascular Endothelial

Growth Factor)(Srivastava BK & Rema M, 2005). Secondly, testosterone has been reported to cause an increased expression of artery thromboxane A2 and activated renin-angiotensin system (Dubey et al., 2002, Orshal and Khalil 2004). Thirdly high levels of testosterone enhance cell adhesion of leukocytes to retinal capillary endothelial cells (Hammes and Porta 2010). Fourthly, Dihydrotestosterone (DHT) increased the expression of VCAM-1 in male human endothelial cells, as the leukocyte integrins are the principle attachment proteins of leukocytes whose corresponding ligands on endothelial cells are ICAM and VCAM-1 (Death et al., 2004). All these possible effects of testosterone in presence of a setup of hyperglycemia, which itself is a condition associated with increased oxidative stress, advanced glycation end products, and increased VEGF activity can result in impaired autoregulation and retinal hyperperfusion resulting in diabetic retinopathy as supported by our findings of a high level of testosterone in patients with diabetic retinopathy.

The testosterone levels found in patients with diabetic retinopathy and without diabetic retinopathy in our study is not coherent with the suggestions of a cohort study conducted in Germany that reported a low total testosterone concentration to be associated with increased risk of Type II diabetes mellitus in men (Sabine et al., 2010) and a Finnish study in elderly population that reported higher levels of testosterone independently predicted a reduced risk of type 2 diabetes in elderly men (Salminen et al., 2015). The variation in the results may be due to the fact that the association between testosterone levels and the risk of Type II diabetes and its complication is not completely independent of other variables, such as exposure time, adiposity, insulin resistance or sex hormone binding globulin (SHBG) levels. This is because a substantial fraction of circulating testosterone is bound to SHBG and in our study, total testosterone has been measured as compared to free testosterone concentration which is a more sensitive and active marker for insulin resistance or atherosclerosis.

When serum testosterone levels were correlated to other sex steroid hormones and to the clinical correlates of patient, then a significant negative correlation was found with serum estrogen($r=-0.891$, $p<0.01$), serum LH($r= -0.790$, $p<0.01$) and serum FSH ($r=-0.831$, $p<0.01$) and a significant positive correlation was found with blood sugar fasting (BSF)($r=0.471$, $p<0.01$), HBA1c ($r=0.446$, $p<0.05$), serum progesterone ($r=0.558$, $p<0.01$) respectively. Our findings of significant positive correlation of testosterone to blood sugar fasting (BSF) and glycated hemoglobin (HBA1c) and negative correlation with estrogen further emphasizes that in settings of poor glycemic control testosterone may nullify the somewhat protective effect of estrogen and increase the risk for diabetic retinopathy. Further in the study when the different stage of diabetic retinopathy was compared with serum testosterone then it was reported that serum testosterone was found the maximum (5.32±1.75 ng/mL) in the severe NPDR category, whereas minimum (2.16±2.29 ng/mL) in moderate NPDR category. The results were found to be non-significant.

5. CONCLUSION

The mean serum testosterone level was found to be significantly higher in patients with diabetic retinopathy as compared to patients without diabetic retinopathy. A significant positive correlation of serum testosterone was found with blood sugar fasting (BSF), HBA1c, serum progesterone whereas a significant negative correlation was found with serum estrogen, LH and FSH. A possible susceptibility and association of high levels of serum testosterone with diabetic retinopathy encourages further studies needed for justification of the quantum of influence of serum testosterone and other sex hormones have, in relation to gender with regard to progression of diabetic retinopathy as well as diabetic duration and blood glucose control to understand the mechanism of progression of diabetic retinopathy.

REFERENCES

1. Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Global Health, 2013; 1: e339-e349.
2. Cascio C, Deidda I, Russo D, Guarnieri P. The estrogenic retina: the potential contribution to healthy aging and age-related neurodegenerative diseases of the retina. Steroids, 2015; 103: 31–41. doi:10.1016/j.steroids.2015.08.002
3. Cascio C, Russo D, Drago G, Galizzi G, Passantino R, Guarnieri R, et al. 17b-estradiol synthesis in the adult male rat in retina. Exp Eye Res., 2007; 85(1): 166–72. doi:10.1016/j.exer.2007.02.008
4. Chaturvedi N, Sjoelie AK, Porta M, Aldington SJ, Fuller JH, Songini M, et al. Markers of insulin resistance are strong risk factors for retinopathy incidence in type 1 diabetes. Diabetes Care, 2001; 24(2): 284–9. doi:10.2337/ diacare.24.2.284
5. Cinquanta, L., Fontana, D. E., & Bizzaro, N. Chemiluminescent immunoassay technology: what does it change in autoantibody detection? Auto-immunity highlights, 2017; 8(1): 9.
6. Death, A. K., K. C. McGrath, M. A. Sader, S. Nakhla, W. Jessup, D. J. Handelsman and D. S. Celermajer. Dihydrotestosterone promotes vascular cell adhesion molecule-1 expression in male human endothelial cells via a nuclear factor-kappaB-dependent pathway. Endocrinology, 2004; 145(4): 1889-1897.
7. Dubey, R. K., S. Oparil, B. Imthurn and E. K. Jackson. Sex hormones and hypertension. Cardiovascular Research, 2002; 53(3): 688-708.
8. Guarnieri P, Guarnieri R, Cascio C, Pavasant P, Piccoli F, Papadopoulos V. Neurosteoidogenesis in

rat retina. J Neurochem, 1994; 63(1): 86–96. doi:10.1046/ j.1471-4159.1994.63010086.x
9. Gupta N, Gupta R. Diabetic Retinopathy- an Update. Journal of International Medical Sciences Academy, 2015; 28(1): 54-58.
10. Gupta PD, Johar K, Nagpal K, Vasavada AR. Sex hormone receptors in the human eye. Surv Ophthalmol, 2005; 50(3): 274–84. doi:10.1016/j.survophthal. 2005.02.005
11. Hammes, H. P. and M. Porta. Experimental Approaches to Diabetic Retinopathy. Karger, 2010; 20: 1-8.
12. International Diabetes Federation. (2017). Diabetes Atlas.8th Edition.
13. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin epide- miologic study of diabetic retinopathy XXIII: the twenty-five-years incidence of macular edema in persons with type 1 diabetes. Ophthalmology, 2009; 116(3): 497–503. doi:10.1016/j.ophtha.2008.10.016
14. Kostev K, Rathmann W. Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis. Diabetologia, 2013; 56(1): 109–11. doi:10.1007/ s00125-012-2742-7
15. Looker HC, Nyangoma SO, Cromie D, Olson JA, Leese GP, Black J, et al. Diabetic retinopathy at diagnosis of type 2 diabetes in Scotland. Diabetologia, 2012; 55(9): 2335–42. doi:10.1007/s00125-012-2596-z
16. Mellon SH, Griffin LD, Compagnone NA. Biosynthesis and action of neurosteroids. Brain Res Brain Res Rev., 2001; 37(1–3): 3–12. doi:10.1016/ S0165-0173(01)00109-6
17. 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.
18. Orshal, J. M. and R. A. Khalil. Gender, sex hormones, and vascular tone. American journal of physiology. Regulatory, integrative and comparative physiology, 2004; 286(2): R233- 249.
19. Ozawa GY, Bearse MA Jr, Adams AJ. Male-female differences in diabetic retinopathy? Curr Eye Res., 2015; 40(2): 234–46. doi:10.3109/02713683.2014. 958500
20. Sabine Schipf, Robin Haring, Nele Friedrich, Matthias Nauck, Katharina Lau, Dietrich Alte, Andreas Stang, Henry Völzke & Henri Wallaschofski. Low total testosterone is associated with increased risk of incident type 2 diabetes mellitus in men: results from the Study of Health in Pomerania (SHIP), The Aging Male, 2011; 14(3): 168-175.
21. Salminen, M., Vahlberg, T., Räihä, I., Niskanen, L., Kivelä, S. and Irjala, K. Sex hormones and type2 diabetes in the elderly. Geriatrics & Gerontology International, 2015; 15: 559-564.
22. Srivastava BK and Rema M, (2005).Does Hypertension Play a Role in Diabetic Retinopathy? JAPI, 53.
23. Wandell PE, Carlsson AC. Time trends and gender differences in incidence and prevalence of type 1 diabetes in Sweden. Curr Diabetes Rev.,2013; 9(4): 342–9. doi:10.2174/15733998113099990064
24. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand, 2000; 78(2): 146–53. doi:10.1034/j.1600-0420.2000. 078002146.x
25. Yau JW, Rogers SL et al. Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care, 2012; 35: 556-64.
26. Zetterberg M. Age-related eye disease and gender. Maturitas, 2016; 83: 19–26. doi:10.1016/j.maturitas.2015.10.0