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Diabetic Retinopathy and Sex Hormones

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Abstract: *Diabetic Retinopathy, also known as Diabetic eye disease, is a common complication of diabetes and a leading cause of legal blindness in working age adults.The longer a person has Diabetes,the h igher their risk of developing some ocular problem.After 10-15 years of Diabetes,nearly all patients with Type I diabetes and >60% of patients with type II diabetes have some degree of retinopathy.Various studies show certain dissimilarities in ocular physiopathology between human males and females. These differences can be observed in the lacrimal and other eye-associated glands, the ocular surface, the crystalline lens, and the retinochoroid complexes. Literature on the subject revealed that because of sex steroid hormone (estrogen, progesterone, and androgen) actions, various physiological conditions, such as age, menstrual cycles, pregnancy, and menopause or andropause, where the hormone milieu changes, affect vision. Timely diagnosis with the help of better screening and referral facilities, strict control of systemic parameters and timely management in the form of medical and surgical intervention can delay the sight threatening complication of diabetic retinopathy.*
Keywords: *blindness, diabetic retinopathy, eye, sex hormone*

I. Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes mellitus. It has been seen that patients having DR are 25 times more at risk of blindness than a non-diabetic individual.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 [1]. 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 [2].All people with diabetes mellitus are at risk those with Type I and those with Type II Diabetes.

The clinical hallmarks of Diabetic Retinopathy include increased vascular permeability leading to edema and endothelial cell proliferation. The earliest change seen in diabetic retinopathy includes a narrowing of retinal arteries associated with reduced retinal blood flow; dysfunction of blood retinal barrier leading to leaking of blood constituents into the retinal neuropile. Later the basement membrane of retinal blood vessels thickens, capillaries degenerate and lose cells particularly pericytes and vascular smooth muscle cells leading to loss of blood flow and progressive ischaemia and microscopic aneurysms which appear as balloon like structures jutting out from the capillary walls, which recruit inflammatory cells and leads to dysfunction and degeneration of neurons and glial cells of retina.

II. Progression Of Diabetic Retinopathy And Risk Factors

1. **Glycemic control:** Intensive glycemic control and decreasing the level of glycosylated haemoglobin, (HbA1c) is the most effective in delaying the progression of DR [3].
2. Hypertension: High blood pressure is a major risk factor for DR and Diabetic Macular Edema (DME). Progression of DR was associated with higher diastolic blood pressure at baseline and increases in diastolic blood pressure over 4 years of follow up [3].
3. **Nephropathy:** Wisconsin Epidemiological study of diabetic retinopathy (WESDR) study predicted about 95% increased risk of developing Diabetic Macular Edema in the presence of gross proteinuria (defined as microalbuminuria when there is an excretion of less than or equal to 300mg/dL/day and macroalbuminuria at greater than 300mg/dL/day) at baseline[3].
4. **Hyperlipidemia:** Early Treatment Diabetic Retinopathy Study (ETDRS) concluded that there is significant correlation between elevated cholesterol, high density lipids and triglycerides with faster development of hard exudates [3].
5. **Anemia:** A diabetic patient with less than 12 g/dl of haemoglobin has two fold increased risk of any grade of retinopathy and fivefold increase risk of developing severe grade of retinopathy in already established DR [3].
6. **Obesity:** An increase in Body mass index (BMI) significantly correlates with deterioration of HbA1C, decrease in HDL, increase in triglyceride and higher prevalence of hypertension.

7. Exercise: Exercise may have a beneficial role in reducing the risk of diabetic complication by direct and indirect mechanisms but physical exercise may have a detrimental effect on advanced DR. Loss of auto regulation in patients with proliferative diabetic retinopathy may increase the retinal arteriolar perfusion pressure to hemorrhagic threshold in these abnormal new vessels during exercise and may lead to intra-retinal, pre-retinal or vitreous haemorrhage. It was seen that 84% of vitreous haemorrhage were associated with exercise no more strenuous than walking [5]. Individually tailored exercise regimens are beneficial in the management of all forms of DM.

8. Pregnancy: Pregnancy is a well-established risk factor for progression of DR. Pregnant women with type 1 DM has twice the risk of development of DR than a non-pregnant diabetic female [3].

9. Obstructive Sleep Apnea (OSA): OSA has been found to be independent predictor of proliferative diabetic retinopathy even after adjusting for conventional risk factors and novel biomarkers of DR [6]. With comorbid conditions like obesity and hypertension, OSA further increases the risk of Proliferative DR [7].

10. **Cataract surgery:** Patients after cataract surgery show worsening of DR and especially, Diabetic Macular Edema [4].

11. Ethnicity

12. Cigarette smoking status.

III. Ocular Investigations and Treatment In Diabetic Retinopathy

3.1 Ocular Investigations in Diabetic Retinopathy

a. Fundus photography

b. Fundus fluorescein angiography

c. Optical Coherence Tomography

d. B Scan ultrasonography.

I.2 Treatment of Diabetic Retinopathy

a. Control of systemic parameters

b. Laser photocoagulation

c. Pharmacological agents- block the molecular target agents involved in the metabolic pathway in the pathogenesis of DR at various levels. These include Anti- vascular endothelial growth factors (Anti -VEGF), Corticosteroids, Protein kinase C inhibitors, Aldose reductase inhibitors, Somatostatinanalogues and Angiotensin converting enzyme (ACE) inhibitors.

d. Pars planavitrectomy (PPV)

IV. Overview of correlation of Sex Hormones with Diabetic Retinopathy

Various studies have been conducted to find out the correlation between sex hormones and diabetic retinopathy. Some studies have shown that sex hormone receptors are found in the human eye. Hence if the derangement in the sex hormones can be detected beforehand there are chances that we can prevent the changes occurring in the retina of the patients suffering from long standing diabetes.Interaction of steroid-receptor complexes with responsive genes containing a consensus sequence for receptor binding can result in either induction or repression of transcription, depending on the target gene and tissue. The broad range of estrogen-induced proteins identified to date may justify the multifaceted involvement of the steroid hormones in the control of processes such as cell proliferation, differentiation and development. Most of these proteins are found in human eye tissues such as retinal pigment epithelium (RPE), retina and ciliary body. These proteins seem to be coexpressed with estrogen receptors and thus, their regulation in the eye may be controlled by estrogens.

In a review, Gupta et al [4] studied the dissimilarities in ocular physiopathology exist between human males and females. These differences can be observed in the lacrimal and other eye-associated glands, the ocular surface, the crystalline lens, and the retinochoroid complexes. Literature on the subject revealed that because of sex steroid hormone (estrogen, progesterone, and androgen) actions, various physiological condition, such as age, menstrual cycles, pregnancy and menopause or andropause, where the hormone milieu changes, affect the vision. This review analyzes the relatively new area of hormones and vision. Earlier population studies such as the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) were done with predominantly white cohorts (Klein et al [25]; Klein et al [26]). The 25 year results of this WESDR showed that being male was an independent risk factor for the progression of diabetic retinopathy, although not a risk factor for the development of proliferative diabetic retinopathy or for visual impairment due to diabetes (Klein et al [26]).

A study by Haffner et al [8], suggested that changes in sex hormones may influence the development of diabetic retinopathy. They measured serum testosterone, estradiol, DHEA-S and sex hormone binding globulin levels in men and women with type I diabetes from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based study of diabetic complications. Serum testosterone concentrations were

significantly higher in male diabetic subjects with proliferative retinopathy than in male diabetic subjects with minimal or no retinopathy. No other statistically significant differences in sex hormones between subjects with and without proliferative retinopathy were observed. Although these results should be regarded as preliminary because of the small number of subjects, they support the hypothesis that testosterone concentrations may be associated with the development of retinopathy in type I diabetic patients.

The possibility that ethnicity or race played a role in gender differences in diabetic retinopathy was evaluated. The Los Angeles Latino Eye Study by Varma et al [30] showed that in Latinos with type 2 diabetes, males were more likely to develop diabetic retinopathy. A study in India by Raman et al [29] also demonstrated increased risk of diabetic retinopathy for men who develop diabetes over the age of forty. Yuen KK et al [9] examined the rates of blindness from diabetic retinopathy with or without other causes for persons in the Model Reporting Area (14 states) were determined in five-year intervals by sex. Diabetic males younger than 45 years of age had a higher rate of diabetic blindness than females under 45 years of age. However, for ages 45 and older, the risks of blindness among diabetics were approximately equal for men and women. These data were consistent with the hypothesis that the presence of female hormones improves the prognosis in diabetic retinopathy.

However, other studies in various ethnic groups show no gender differences. No gender difference was reported in proliferative diabetic retinopathy in Pima Indians by Nelson et al [28]. Haffner et al [16] compared Mexican-Americans in San Antonio to non-hispanic whites in Wisconsin found no gender differences in either group. Another study in India by Namperumalsamy et al [27] found no male predisposition to diabetic retinopathy. Schreiber G et al conducted a study in male diabetics (juvenile onset diabetes) with diabetic retinopathy and patients without diabetic retinopathy. The HCG and the LH-RH stimulation tests were performed and the results compared to those with normal metabolism and full vision. The findings can be interpreted as hypothalamic hypophysogonadal dysregulation in case of lowered basal testosterone, significantly inverse correlation to the relative responsiveness of Leydig's cells, lacking correlation between LH and testosterone as well as normal LH-RH test. Differences between patients with and without retinopathy were not detectable.

Major alterations in the levels of sex hormones are seen during puberty, it is important to note that the effect of the attainment of puberty on the development of retinopathy has evolved, but is not without controversy. Merimee [33] reported a clinical observation that diabetic dwarfs exhibit little retinopathy. Another observation reported by Bell [32] in a case study of agonadal (without ovaries) female twins demonstrated a lack of retinopathy after a long duration of very poorly controlled diabetes (A1c's as high as 15.6%). When trying to determine how puberty affects the prevalence of retinopathy, one must consider the endocrinological aspect during: 1) pre-puberty, 2) during puberty, and 3) after puberty.

In a study conducted by Robert P et al [12], the presence of background and preproliferative retinopathy in patients with type I diabetes was correlated with their pubertal development. In young diabetics with comparable disease duration (5 to 10 years), post pubertal children had a greater prevalence of retinopathy than those who were not sexually mature. This study was undertaken to investigate the relationship of the serum sex hormone-binding globulin (SHBG) levels with the plasma insulin concentration and with the insulin resistance in male subjects with noninsulin-dependent diabetes mellitus (NIDDM).The results suggested that insulin may directly affect the SHBG levels and that SHBG may constitute an index of the insulin resistance only in the hyperinsulinemic state.

Diabetic retinopathy presents a major problem during child bearing years and deleterious effects of diabetic retinopathy during pregnancy have been well documented. A study by Vargas et al [31] showed that 10% of all pregnancies have complications as a result of diabetes mellitus in United States. The occurrence and progression of retinopathy were related to the mean blood glucose levels and the serum concentrations of prolactin, human placental lactogen, estradiol and progesterone in pregnant insulin-dependent diabetic patients was shown by Larinkari J et al [11]. Throughout gestation, serum prolactin concentrations were significantly lower in diabetic patients than in healthy subjects. No correlation was found between serum prolactin values and the occurrence of retinopathy.

Further, the influence of hormonal alterations during pregnancy on the worsening of diabetic retinopathy, was studied by Soneetet al [14]. They examined the effects of estradiol (E2) and progesterone (P4) on the production of VEGF/VPF in bovine retinal pigment epithelial cells in culture. As the increase in serum P4 levels during pregnancy is reported to be greater in pregnant diabetic patients with progressive retinopathy, their findings suggested that P4 may contribute to the worsening of diabetic retinopathy during pregnancy by up-regulating intraocular VEGF levels.

In males, Kaushik et al [36] showed that men with higher levels of testosterone generally have better lipid profiles including high HDLs and lower triglycerides. Supplementation of testosterone in hypoandrogenesis is generally considered to decrease HDLs and only modestly affect LDLs as studied by

Mendelsohn and Karas [37]. Webb and Collins [38] reported that the lower levels of testosterone in men have also been linked to central adiposity, insulin resistance, hyperinsulinemia and type 2 diabetes.

In females, Mumford et al [39] found that total cholesterol and LDL levels were highest during the follicular phase of the menstrual cycle and were lower during the luteal phase. They found HDLs to be higher during the follicular and peri-ovulatory phases. In a meta-analysis of sex steroid use by transsexual individuals, Elamin et al [40] found a reduction in HDL in female to male patients receiving androgens and an increase in HDLs in male to female patients receiving estrogens. They also found triglyceride levels increased in both female to male patients receiving androgens and male to female patients receiving estrogens.

The association of sex hormones with atherogenic changes in lipoproteins and changes in glucose and insulin metabolism was showed by Steven M Haffner et al [13]. They examined the relation of total and free testosterone, sex hormone binding globulin, estrone, estradiol, and DHEA-SO4 to the 5-year IHD mortality in the older-onset diabetic subjects in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) in a matched diabetic subject-control design (two control subjects for every diabetic subject).This study suggests that alterations in sex hormones and DHEA-SO4 are unlikely to explain a major proportion of the variation in IHD mortality in diabetic subjects.

Testosterone is formed from its precursor androstenedione and to a lesser extent from DHEA. In males, testosterone is produced mainly by Leydig cells of the testes. Testosterone can be converted by peripheral tissues to the more active dihydrotestosterone (DHT) by the enzyme 5α-reductase or it can be converted into estradiol (E2) by an "A" ring aromatase. In the female ovary, testosterone secreted by thecal cells of the follicles is aromatized by granulosa cells into estradiol.

In males testosterone levels reach ≈250 ng/L by the second trimester of gestation. 2-3 months after birth, the levels fall to 50ng/L and remain low until puberty (age 12-17), when they rise to adult levels of 500-750ng/L. Levels of testosterone decline slowly after middle age, but inadequate testosterone levels can be augmented by hormone replacement therapy, as reported by Wilson et al [34]. Forest [35] studied that in females, testosterone levels are normally low: 30-50 ng/L throughout life. Serum testosterone is converted into inactive metabolites by the liver. Chaurasia RK et al [15] estimated the serum testosterone and follicle-stimulating hormone (FSH) levels using a radioimmunoassay technique in control subjects, diabetic patients without retinopathy and in patients with diabetic retinopathy. Testosterone levels were higher in the diabetic patients with and without retinopathy than in the control subjects. They were significantly higher in the diabetic patients with retinopathy compared with the levels in those without retinopathy and equally significantly elevated compared with the levels in the control group. Similarly, the FSH level was higher in the diabetic patients with retinopathy than in the control group and in those without retinopathy, although this increase was insignificant.

Whereas Haffner SM et al [16], measured the total testosterone, free testosterone, sex hormone-binding globulin, estradiol, and dehydroepiandrosterone-sulfate levels in men with type I diabetes participating in the 1984 to 1986 re-examination phase of the Wisconsin Epidemiologic Study of Diabetic Retinopathy, a population-based study of diabetic complications. Subjects who progressed to proliferative or preproliferative retinopathy 6 years later were compared with subjects who had little or no progression. Both groups were matched on initial level of retinopathy. Sex hormone-binding globulin concentrations (nmol/l) were significantly lower (reflecting increased androgenicity) in cases than in controls .Neither serum testosterone nor other sex hormones were related to the incidence of severe retinopathy. This relationship to low-serum sex hormone-binding globulin suggests that increased androgenicity may be associated with the progression of retinopathy in male subjects with Type I diabetes.

V. Conclusion

Diabetic Retinopathy, has emerged as a common cause of blindness in working age group adults and has a significant financial and health burden of the population. The longer a person has Diabetes, the higher their risk of developing some ocular problems, especially in cases of Type I diabetes. There are certain differences in the ocular pathophysiology of human males and females. These differences are mainly due to sex steroid hormones and physiological conditions, such as age, menstrual cycles, pregnancy, and menopause or andropause, where there is alteration of the hormone milieu that affects the vision.There is ample evidence that sex hormones do play a role in the development and progression of diabetic retinopathy in humans. Androgens can negatively affect lipid levels, blood glucose, and blood pressure. It is believed high glucose levels can induce oxidative stress through several mechanisms (Brownlee [18]; Cunha-Vaz [19]; Du et al.[20]). Nishikawa et al [23] found superoxides may be generated in the mitochondria, especially as a result of hyperglycemia.

Timely diagnosis with the help of better screening and timely management can delay the sight threatening complication of diabetic retinopathy. An indepth understanding of role of sex hormones in the development and progression of diabetic retinopathy is of importance. In case of Hormone replacement therapy in human females where estrogen replacement is only appropriate during certain peri-menopausal stages, estrogen may play

different roles depending on the stage of retinopathy. At an early stage the proliferation of endothelial cells induced by estradiol may be a benefit as a reparative mechanism; however, at a stage where proliferative retinopathy is threatening vision this increased proliferation and could lead to pathological vessel formation (Espinosa-Heidmann et al [21]; Grigsby et al [22]; Suzuma et al [24]).

So there is much yet to be learned about the role sex hormones play in the development and progression of diabetic retinopathy. Nonetheless, it is apparent that sex hormones do play a role at several different stages of retinopathy and that sex hormone stimulation or modulation, as appropriate, can offer promise to control diabetic retinopathy.

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