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The Role of Sex Hormones in Diabetic Retinopathy

Jeffery G. Grigsby[1], Donald M. Allen[2], Richard B. Culbert[3,4], Gerardo Escobedo[4], Kalpana Parvathaneni[1], Brandi S. Betts[1] and Andrew T.C. Tsin[1]
[1]*Department of Biology, University of Texas at San Antonio, San Antonio, Texas*
[2]*Department of Biology, University of Texas of the Permian Basin, Odessa, Texas*
[3]*Department of Surgery, Texas Tech School of Medicine, Midland, Texas*
[4]*Premier Retina Specialists, Midland, Texas*
[1, 2,3,4]*United States of America*

1. Introduction

The role sex hormones play in the etiologies of human proliferative diseases such as cancers of the breast and the male and female gonads have long been described (Beatson 1896; Lacassagne 1936; Love and Philips 2002). Lacassagne in 1937 suggested that "a therapeutic antagonist to the congestion of oestrone in the breast should be found to prevent breast cancer" (Lacassagne 1936). Finally, in 1962 Jenson et al. suggested an assay to detect the presence of estrogen receptor (ER) and suggested it be used to determine which breast cancers were susceptible to estrogen (Jensen 1962). Other human pathologies such as cardiovascular and autoimmune disease have also been linked to sex hormones (Ansar Ahmed et al. 1985; Mendelsohn and Karas 2005). Even though sex hormone receptors have been identified in the eye, the role that sex hormones play in the development of eye disease, such as that occurring with diabetes, is less described (Gupta et al. 2005). In this chapter, we hope to enlighten the reader about the presence of sex hormone receptors in various eye tissues, present how sex hormones are involved in the mechanisms that control the development of proliferative diabetic retinopathy and offer insight into areas where modulation of these mechanisms could be controlled by blockers of sex hormone receptors.

2. Epidemiology

2.1 Sex differences in the prevalence of retinopathy noted in epidemiological studies

The role of gender as a contributing factor in diabetic retinopathy has long been debated. Numerous and seemingly contradictory studies have shown either a male predisposition, a female predisposition, or no significant difference between the sexes in development or progression of diabetic retinopathy.

Earlier population studies such as the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) were done with predominantly white cohorts (Klein et al. 2008; Klein et al. 2010). 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. 2010). However, many other studies show no correlation between gender and either severity or progression of diabetic retinopathy (Janka et al. 1989; Klein et al. 1994; Lloyd et al. 1995). The possibility that ethnicity or race played a role in gender differences in diabetic retinopathy was evaluated. The Los Angeles Latino Eye Study showed that in Latinos with type 2 diabetes, males were more likely to develop diabetic retinopathy (Varma et al. 2007). A study in India also demonstrated increased risk of diabetic retinopathy for men who develop diabetes over the age of forty (Raman et al. 2011). However, other studies in various ethnic groups show no gender differences. No gender difference was reported in proliferative diabetic retinopathy in Pima Indians (Nelson et al. 1989). Comparing Mexican-Americans in San Antonio to non-hispanic whites in Wisconsin found no gender differences in either group (Haffner et al. 1988). Another study in India found no male predisposition to diabetic retinopathy (Namperumalsamy et al. 2009). Studies of Pacific Islanders have found no gender predisposition in prevalence or progression of diabetic retinopathy (Smith et al. 2007; Tapp et al. 2006). Asians in China and Singapore also demonstrated no gender differences in prevalence of diabetic retinopathy (Wang et al. 2009; Wong et al. 2008). A multi-ethnic study in the United States did not indicate an increased risk for males for retinopathy in white, black, Hispanic or Chinese cohorts (Wong et al. 2006). The Early Treatment of Diabetic Retinopathy Study (ETDRS) trial found increased risk for women to have progression of diabetic retinopathy, but this occurred only in one subgroup (Davis et al. 1998). All other subgroups showed no gender differences in progression of retinopathy or development of proliferative retinopathy, and therefore the differences in that subgroup were thought to be spurious.

This disparity of results indicates that there probably are other confounding factors that have not been considered in these studies. Variations in human leukocyte antigen (HLA) haplotypes may affect risk for diabetes and diabetic retinopathy (Rand et al. 1985). Unaccounted disparity in HLA expression between groups in studies may lead to apparent differences that are not actually present. The fact that most studies that do show an effect indicate a greater risk in men may indicate there is variable expression of a factor present in men, such as androgenic hormones, that may have accounted for the increased risk of progression of diabetic retinopathy.

2.2 Puberty

While the levels of sex hormones increase during puberty, it is important to remember that the levels of growth hormones and secondary growth factors also increase during puberty. In fact Merimee reported a clinical observation that diabetic dwarfs exhibit little retinopathy (Merimee 1990). Another interesting clinical observation reported by Bell 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%) (Bell 1995). When trying to determine how puberty affects the prevalence of retinopathy, one must consider the endocrinological environment of an individual: 1) pre-puberty, 2) during puberty, and 3)

after puberty. The search to determine the effect of the attainment of puberty on the development of retinopathy has evolved, but is not without controversy.

There has been much discussion on the presence of a pre-pubertal "grace period" from the development of retinopathy. One obvious consideration is that patients past puberty have had the disease longer. Some studies have suggested that puberty does not offer protection against the development of retinopathy, but that the infrequency of occurrence is related to the short duration of the disease during pre-pubescence (Constable et al. 1984; Knuiman et al. 1986; Porta et al. 2004; Szabo et al. 1967). Porta et al., in a retrospective analysis of 628 patients with diabetes and an onset of <29 years, found that retinopathy (determination of pubertal age was not available) may take longer to develop in patients who develop diabetes before puberty, but that after 20 years duration the prevalence of retinopathy is no longer influenced by the age of onset (Porta et al. 2004). In a previous prospective work, Porta et al. report that onset of diabetes before puberty could be an additional risk factor to the development of proliferative retinopathy (Porta et al. 2001).

Knowles et al. (1965) and Murphy et al. (1990) proposed there was a constant interval from the time of the adolescent growth spurt to the development of retinopathy and the years before this growth spurt were not an important consideration in the development of retinopathy. Further, Klein et al. (1985) found in a southern Wisconsin population-based study that the presence of retinopathy was more strongly associated with the duration of a patient's diabetes after the age of 13 than before it. Kostraba et al. also supported this conclusion, stating the "post-pubertal duration of IDDM may be a more accurate determinant of the development of microvascular complications and diabetes-related mortality than total duration" (Kostraba et al. 1989). Kernell et al. found "that children are at low risk before the age of 13 and before puberty" (Kernell et al. 1997). Using the Tanner scale of sexual maturity, Murphy et al., found no difference in the prevalence of retinopathy, considering pubertal status, in children with diabetes of less than 5 years duration, but did find post-pubescent youth with diabetes of 5 to 10 years duration were more likely to have retinopathy than prepubescent youth with the same duration of diabetes. They also found a higher rate of retinopathy in post-pubescent youth than prepubescent youth in the group of subjects with duration of diabetes greater than 10 years, but the numbers in the group of prepubescent youth were too small for statistical comparison. They determined that post-pubescent youth were 4.8X more likely to have retinopathy than prepubescent or pubescent youth when comparing subjects of the same age and duration of diabetes (Murphy et al. 1990). Many other studies reveal a protective effect of the pre-pubertal period for the development of retinopathy (Krolewski et al. 1986; Olsen et al. 2004; Svensson et al. 2004). Olsen et al. found in a Danish nationwide prospective study in patients followed for 8 years that, while the contribution of the pre-pubertal duration of type 1 diabetes does contribute to the development of retinopathy, it contributes only half as much as the post-pubertal period of time. (Olsen et al. 2004).

2.3 Pregnancy

The devastating effects of diabetic retinopathy during pregnancy have been well documented. Despite tight glycemic control, diabetic retinopathy presents a major problem during child bearing years. In the United States 10% of all pregnancies have complications as a result of diabetes mellitus (Vargas et al. 2010). Previously the prognosis for pregnancy

in women who have diabetes with microvascular disease was so poor that many physicians advised such patients to avoid or even terminate their pregnancies (Moloney and Drury 1982). Numerous articles have documented the acceleration of diabetic retinopathy during pregnancy, the pathogenesis of which still remains unclear (Klein et al. 1990; The Diabetes Control and Complications Trial Group 1993).

A myriad of physiologic events occur during pregnancy. Some studies show that the ability of the retina to autoregulate its blood flow is impaired (Ernest et al. 1983; Grunwald et al. 1984; Grunwald et al. 1995; Rassam et al. 1995). Other changes include hormonal, metabolic, immunologic, as well as differences in cardiovascular and hematologic systems (Chen et al. 1994; Rosenn et al. 1992; Schocket et al. 1999). After the first 3-4 weeks of a normal human pregnancy large quantities of estrogens are produced nearly exclusively by the placenta from dehydroepiandrosterone sulfate (DHEA). In the placenta it is desulfurylated, converted to androstenedione, aromatized to estrone and converted to 17-β estradiol (E2) before entering circulation. At full term half of the estradiol precursors are from the fetal circulation and half from the maternal. In addition, progesterone is formed in large amounts in the placenta from steroid precursors. Near full term this amount consumes what would be an equivalent of 1/4 to 1/3 of the daily low density lipoprotein (LDL) turnover of non-pregnant adults (Wilson et al. 1998). In fact, the extreme elevation of estrogen and progesterone is the greatest of the pregnancy associated endocrine alterations (Jovanovic-Peterson and Peterson 1991). Sone et al. found that while E2 levels at physiological concentrations did not increase VEGF concentrations in a human endometrial adenocarcinoma cell line, progesterone (P4) at physiological concentrations did significantly raise VEGF levels in bovine retinal pigment epithelial cells (Sone et al. 1996). Furthermore, Larinkari et al. have demonstrated that those pregnant patients with progressive retinopathy had progesterone and estradiol at the upper limits of the normal pregnancy ranges (Larinkari et al. 1982; Sone et al. 1996). Suzuma et al. found that E2 at normal physiological levels for pregnancy increased VEGFR-2 levels (Suzuma et al. 1999). Advanced glycation end-products (AGE) accumulate at an increased rate in hyperglycemia and have been implicated in the development of diabetic retinopathy. Tanaka et al. using human vascular endothelial cells found that the AGE receptor (RAGE) increases with exposure to E2 at normal pregnancy physiological levels and that this increase was blocked with the selective estrogen receptor modulator (SERM) tamoxifen (Tanaka et al. 2000).

3. Levels of testosterone, estrogen and progesterone

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 males, the conversion of testosterone to E2 by aromatase achieves masculinization of brain neurons (Wu et al. 2009). 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

(Wilson et al. 1998). In females, testosterone levels are normally low: 30-50 ng/L throughout life (Forest 1975). Serum testosterone is converted into inactive metabolites by the liver.

Levels of E2 are low in girls (1.6-2.6 pg/mL) but even lower in boys (0.4 to 1.1 pg/mL (Janfaza et al. 2006). During puberty (age 8-13) estrogen rises to adult levels and varies during the menstrual cycle. Estradiol shows a pre-ovulatory peak (190pg/ml) by day 14 of the cycle and peaks broadly (≈100pg/mL) during the luteal phase from days 18-25 (Levin and Hammes 2011; Thorneycroft et al. 1971). Progesterone is low except for a broad peak at 10 ng/mL during the luteal phase of the menstrual cycle. After menopause, E2 falls, reaching levels similar to those found in adult males (8-40 pg/mL) (Lee et al. 2006). Estrogen replacement can be used to ameliorate the side effects of low estradiol. Contraception employs small doses of an ethinylestradiol and progesterone, but studies have shown no relationship between current and past use of contraceptives and diabetic retinopathy (Klein et al. 1990).

4. Known sex hormone effects on vessel walls

4.1 General concepts

The role sex hormones play in the maintenance of the blood vessel walls has been an area of great interest recently. While much work has been done to elucidate the role of estrogen, the role of androgens has heretofore not received as much attention and consequently is not as well understood (Kaushik et al. 2010; Vitale et al. 2010). DHT has a higher affinity for AR and is converted from testosterone in target cells (Imperato-McGinley and Canovatchel 1992). Androgen receptors (AR) have been identified in vascular endothelial cells, vascular smooth muscle cells (VSM), macrophages and monocytes (Villablanca et al. 2010). Estradiol alone has little effect on the production of androgen receptor (Wynne and Khalil 2003). The concentration of AR is less in females than males and it appears to be regulated by a combination of estradiol and testosterone (Villablanca et al. 2010).

There are two estrogen receptors, ERα and ERβ, with overlapping distribution in body tissues. Each sub-type has several variants (Orshal and Khalil 2004). ERα and ERβ have been identified in the vasculature in endothelial cells, VSM, macrophages and monocytes (Villablanca et al. 2010). ERα is thought to promote protective effects to vascular injury. ERβ is believed to be the dominant form in VSM, especially in women (Mendelsohn 2002).

The two subtypes of progesterone receptor (PR), progesterone receptor A (PRA) and progesterone receptor B (PRB), have been found in vascular endothelial cells, VSM and macrophages (Thompson and Khalil 2003; Vazquez et al. 1999; Villablanca et al. 2010). The PRB subtype seems to have a role in gene transcription and cell proliferation of VSM (Pieber et al. 2001).

Sex hormones have gender-specific effects on cardiovascular risk factors such as lipid metabolism, obesity (central weight gain, i.e. android) and glucose metabolism possibly explaining the differences in cardiovascular disease (CVD) risk between men and women (Carani et al. 1997; Fonseca 2009; Liu et al. 2002; Vitale et al. 2010). All of these risk factors, along with blood pressure, are also risk factors of retinopathy and as such are another link between sex hormones and the development and progression of retinopathy (Cunha-Vaz 2011).

4.2 Vascular tone

For some time a correlation between blood pressure and progression of retinopathy has been noted in epidemiologic studies demonstrating that lower blood pressures result in less diabetic retinopathy. This has now been confirmed by large randomized studies (Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group 2005; The Diabetes Control and Complications Trial Group 1993; UK Prospective Diabetes Study Group 1998). It is well established that adolescent and premenopausal women have lower blood pressures than age matched males and that blood pressure in women rises after menopause. Systolic and diastolic blood pressures in men less than 60 years old are higher than in women by 6-7 and 3-5 mmHg (Dubey et al. 2002). Also blood pressure in women can be affected by the menstrual cycle, pregnancy and supplementation of estrogens (Mendelsohn and Karas 2005). While ERα and ERβ both mediate important effects on blood vessels animal studies indicate that ERβ controlled genes are the ones involved in arterial tone and blood pressure control (Vitale et al. 2010).

One way in which sex hormones interact with the walls of blood vessels is in the way they control vascular tone. Nitric oxide (NO) is a dilator and relaxant of blood vessels acting through its effects on VSM. It is produced by vessel endothelial cells in a reaction catalyzed by endothelial nitric oxide synthase (eNOS) requiring O_2 and NADPH where arginine is oxidized to citrulline, releasing NO (Berg et al. 2007). NO then diffuses from endothelial cells to VSM where it can activate guanylcyclase, producing cyclic GMP from GTP and triggering events leading to vessel dilation. Estrogen in both genomic and a non-genomic pathways can lead to the production of eNOS thus increasing production of NO. Furthermore, arterial endothelial NO release is greater in females than males (Orshal and Khalil 2004).

Less is known about the effects of androgens on blood pressure than are known about the effects of estrogens on blood pressure. (Dubey et al. 2002). Generally it has been found that androgen levels are inversely related to blood pressure (Kaushik et al. 2010). The Rotterdam population-based prospective study found an association toward higher blood pressure in the lower androgenic group, but this did not reach the predetermined level of significance in their study (Hak et al. 2002). The effect *in vitro* of testosterone on VSM is toward vasodilation and is mediated through the nitric oxide (NO) pathway (Kaushik et al. 2010). However, testosterone has also been linked to pro-hypertensive effects. In male spontaneously hypertensive rats testosterone has been found to increase the activity of tyrosine hydroxylase, the rate limiting enzyme in norepinephrine synthesis (Dubey et al. 2002). Furthermore, testosterone has been linked to increased expression of artery thromboxane A_2 resulting in enhanced coronary constriction (Dubey et al. 2002). In murine models hypertension has been prevented by orchidectomy. This normalization of blood pressure is reversed by supplementation of testosterone. These effects seem to be generated through AR since the AR blocker flutamide has been shown to eliminate the blood pressure difference between male and female mice (Kaushik et al. 2010).

Other research has looked at how the control of the renin-angiotension system is influenced by sex hormones. It has been proposed that testosterone may activate the renin-angiotension system and that E2 inhibits renin release and angiotension converting enzyme (ACE) (Orshal and Khalil 2004). The fact that there are no gender differences in the effectiveness of

ACE inhibitors when they are used to treat hypertension may mean that this male/female difference is insignificant (Kaushik et al. 2010). Normal physiological levels of E2 can result in increased cyclooxygenase (COX-1) expression with resulting prostacyclin synthesis in sheep fetal pulmonary artery and human umbilical vein endothelial cells (HUVEC). Prostacyclin synthesis is linked to vascular relaxation. Although several mechanisms have been proposed, COX inhibitors such as nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked to increased blood pressure (Orshal and Khalil 2004; Qi et al. 2002).

The effects of progesterone on vascular activity are not clear. In some tissues it has no effect while in others it can lead to vascular relaxation. The vasodilator effect of progesterone may be related to non-genomic relaxant effects (Orshal and Khalil 2004).

4.3 Lipids

Brown et al. found a "marked accumulation" of retinal exudate in patients with high triglyceride levels (Brown et al. 1984). Dodson and Gibson in a study on patients with type 2 diabetes found that hypercholesterolemia was a risk factor in the development of diabetic maculopathy (Dodson and Gibson 1991). In epidemiological studies Chew et al., and Klein et al. found that increased blood lipid levels are associated with diabetic retinopathy in that subjects with elevated lipids had a greater risk of developing high-risk PDR and a greater risk of vision loss from DME (Chew et al. 1996; Klein et al. 1991). Chowdhury et al. conclude that a toxic effect of LDL on pericytes could be enhanced by LDL glycation or oxidation (Chowdhury et al. 2002).

Although there has been some variation in study conclusions, epidemiological and observational studies have generally concluded that low endogenous testosterone levels in men are associated with lipid profiles consisting of decreased high-density lipoprotein (HDL) cholesterol levels and increased total cholesterol, triglycerides and LDL levels compared to normal or higher levels. This is referred to as Hypoandrogen Metabolic Syndrome (HAM) and often accompanies the metabolic syndrome of central obesity and insulin resistance (Kaushik et al. 2010). Multiple studies have reached a similar conclusion and found that men with higher levels of testosterone generally have better lipid profiles including high HDLs and lower triglycerides (Kaushik et al. 2010). Supplementation of testosterone in hypoandrogenesis is generally considered to decrease HDLs and only modestly affect LDLs (Mendelsohn and Karas 2005). Lower testosterone levels in men have also been linked to central adiposity, insulin resistance, hyperinsulinemia and type 2 diabetes (Webb and Collins 2010). Testosterone, acting through the adipocyte androgen receptors, increases expression of β-adrenergic receptor, protein kinase A, and lipase (Wu and von Eckardstein 2003).

The actions of estrogens on the blood lipid levels of women have been studied for many years. Lipid levels are affected by the action of endogenous sex steroid hormones and hormone replacement therapy (HRT) on liver lipoprotein metabolism. In an analysis of several studies Mumford et al. 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. 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 found triglyceride levels increased in both female to male patients receiving androgens and male to female patients receiving estrogens (Elamin et al. 2010).

After menopause it has been found that LDLs and triglyceride levels rise and HDL levels decrease. HRT appears to positively affect lipid levels by lowering total cholesterol, LDLs and raising HDLs, but negatively affects lipid levels by raising triglycerides (Mendelsohn and Karas 2005). Some controversy has arisen over the delivery method of HRT. Nanda et al. found that HRT transdermal therapy (estrogen 50 μg/day) had the advantage of lowering triglyceride levels as opposed to oral (conjugated equine estrogens 0.625mg/day) (Nanda et al. 2003). The Women's Health Initiative (WHI) trial and the Heart and Estrogen/Progestin Replacement Study (HERS) found that a favorable lipid profile developed using exogenous estrogens, but also found using estrogen with progestin was associated with elevated levels of CVD. Progesterone is believed to either have a neutral effect on lipids or to negatively affect estrogen's positive effects (Hulley et al. 1998; Mumford et al. 2011; Rossouw et al. 2002).

5. Sex hormone effects on specific components in the vessel wall

The events leading to the retinal damage associated with hyperglycemia such as the breakdown of the blood retinal barrier, vessel basement membrane thickening, formation of microaneursyms, hemorrhages, cotton-wool spots, capillary obliteration and acellular capillaries can be traced to the damage occurring to micro-vessel endothelial cells, pericytes and their surrounding basement membrane. It has been noted that these sequelae develop as a result of the early loss of capillary endothelial cells and pericytes in the retina (Cunha-Vaz 2011).

5.1 Endothelium

The initial recruitment of leukocytes into vasculature during the development of retinopathy involves a process referred to as rolling - the initial slowing and loose attachment of leukocytes to the vascular endothelium. This attachment is transient and reversible and its essential function is to slow down the leukocytes as they travel through the vessel lumen. The leukocyte integrins VLA-4, $\alpha_4\beta_7$-integrin, Mac-1 and LFA-1 are the principle attachment proteins of leukocytes whose corresponding ligands on endothelial cells are ICAM and VCAM-1. Rolling may be followed by activation of the leukocyte, adhesion to the endothelial cell and subsequent transendothelial migration through the vessel luminal layer of endothelial cells. While macrophages play positive roles in tissue repair they may contribute to diabetic retinopathy as chronic mediators of inflammation (Duh 2009). It is believed that leukocyte recruitment increases under certain conditions such as atherosclerosis, hypercholesteremia and diabetes (Hammes and Porta 2010). Elevated expression of ICAM-1 has been shown in the blood vessels of diabetic patients and animals and soluble VCAM-1 has been detected in the serum of persons with type 1 diabetes (Hammes and Porta 2010; Miyamoto et al. 1999). The results of increased cell adhesion of leukocytes to retinal capillary endothelial cells can be correlated with leukostasis, capillary occlusion, blood-retinal barrier disruption, increased retinal edema, endothelial cell injury and death (Hammes and Porta 2010).

McCrohon et al. using a co-culture of monocytes and HUVEC found that dihydrotesterone (DHT) increases the level of VCAM-1 in HUVEC and that this results in an increase of adhesion of these cells to monocytes. This effect was blocked by the AR blocker hydroxyflutamide (McCrohon et al. 1999). In a similar experiment, Death et al. found that DHT increased expression of VCAM-1 in male human endothelial cells through a mechanism involving NF-κB that was blocked by hydroxyflutamide (Death et al. 2004). Others have shown DHT and testosterone can inhibit VCAM-1 and ICAM-1, but Mukherjee et al. demonstrated that VCAM-1 inhibition in HUVECs can be reversed by an aromatase inhibitor, demonstrating that the apparent VCAM-1 inhibition by testosterone was caused by the aromatase conversion of testosterone to estrogen (Mukherjee et al. 2002; Villablanca et al. 2010).

As one might expect, estrogen inhibits the expression of ICAM-1 and VCAM-1 in the vascular endothelium during inflammation (Cid et al. 1994; Simoncini et al. 1999; Villablanca et al. 2010). Interestingly this inhibition was blocked by the ER antagonist ICI 182,780, but the selective estrogen receptor modulator (SERM) tamoxifen had no inhibitory effects (Simoncini et al. 1999). It is believed VCAM-1 inhibition occurs through ERβ. While progesterone at supra-physiological levels inhibits expression of VCAM-1, another progestin, medroxyprogesterone acetate (MPA) does not. When tested with HUVECs at normal physiological concentrations progesterone has no effect on ICAM-1 or VCAM-1 expression. When estrogen and progesterone are used concurrently progesterone increases the estrogen inhibition of ICAM-1 and VCAM-1 in human iliac artery at supra-physiological levels (Villablanca et al. 2010).

Proliferation of endothelial cells can be viewed as a positive or negative factor. It can be positive as a vessel repair mechanism, or negative as in tube vessel formation such as occurs in proliferative diabetic retinopathy or rheumatoid arthritis. In conditions such as atherosclerosis and diabetic retinopathy an intact endothelium is important due to its role in providing "an antithrombotic and anticoagulant surface" (Vazquez et al. 1999). Gender differences have been found to exist with endothelial cell proliferation. Liu et al. found testosterone, when used at nanomolar concentrations, increased the proliferation of male rat vascular endothelial cells (VEC), but had no effect on the proliferation of female VEC. Nanomolar E2 increased the increased proliferation of both male and female VEC. Vazquez found that progesterone had an inhibitory effect on endothelial cell proliferation acting through PR in WT mice (Vazquez et al. 1999). Espinosa-Heidmann studied 9 month old female mice (middle aged) with either: 1) a sham operation, 2) an ovariectomy with empty pellets, or 3) an ovariectomy with an E2 pellet. After choroidal thermal burns they found that female ovariectomized mice with E2 supplementation had a larger area of neovascularization compared to either sham operated female mice, ovariectomized female mice, or male mice implanted with an estrogen pellet. They hypothesized that the E2 "in the absence of other ovarian hormones, paradoxically increased the severity of choroidal neovascularization (CNV) in middle aged female mice" (Espinosa-Heidmann et al. 2005). Tanemura et al., using the fact that pre-menopausal women are more susceptible to choroidal neovascularization than men, found greater neovascularization using laser-induced photocoagulation in female rats than in male rats. They found that E2 and photocoagulation increased the expression of ERβ and VEGFR-2 and found no change in the expression of ERα mRNA at any time after photocoagulation. Using a culture of HUVEC to measure cell proliferation of transfected endothelial cells they found a significant increase in

cell number in those overexpressing ERβ, but no change in cell number in cells overexpressing ERα (Tanemura et al. 2004).

5.2 Basement membrane

New blood vessel growth is complex involving breakdown of a vessel wall, endothelial cell migration, proliferation, tube formation and formation of a new basement membrane (Folkman 1995). Extracellular matrix proteins work as a scaffold whereby cell migration, proliferation and capillary formation can occur. Basic fibroblast growth factor (FGF-2) is a potent extracellular cytokine which functions in these stages of neovascularization. FGF-2 is unique in that it lacks a sequence to allow its release from then endothelial cell where it is manufactured. Albuquerque et al. found that FGF-2 release into the cell media is enhanced when estrogen is present in a cell culture of human coronary artery endothelial cells and that this enhancement can be blocked by the ER blocker ICI 182,780. Furthermore, they found this enhancement was inhibited by inhibition of protein kinase C, indicating that estrogen does not necessarily result directly in the production of more FGF-2, but that it may function with cell matrix proteins to enhance the release of FGF-2 (Albuquerque et al. 1998). Extracellular matrix proteases which are regulated post-translationally also play an important role in basement membrane remodeling. As an example, tPA and uPA are plasminogen activators which are inhibited by the plasminogen activator inhibitor (PAI-1). When endothelial cells are quiescent, such as when they are confluent, estrogen functions to increase PAI-1 production and reduces production of tPA and uPA, decreasing protease activity. When cells are activated such as in angiogenesis, estrogen decreases PAI-1 production and consequently increases tPA and uPA production thus accelerating protease activity (Rubanyi and Kauffman 1998).

5.3 Pericytes

Pericytes are derived from the same pluripotent mural precursor cells as vascular smooth muscle cells (Hammes and Porta 2010). They appear to play a role in supporting the microcirculation against hydrostatic pressure and also function to sustain vessel stability through physical and chemical signaling with vessel endothelial cells (Hall 2006). It is believed pericyte loss is the first damage occurring with hyperglycemia (Hammes 2005; Vidro et al. 2008). Brignardello et al. using bovine retinal capillary pericytes found that DHEA, a precursor to both testosterone and estrogen, reduced pericyte loss resulting from high glucose as a result of its antioxidant properties. They report that this effect was not produced through either AR or ER (Brignardello et al. 1998). In a study of rabbits fed a high-fat diet, which has been known to increase oxidative stress, Aragno et al. found that DHEA restored the rabbits oxidative balance. This supports Brignardello's hypothesis that the protective cellular effect of DHEA is through its antioxidant properties (Aragno et al. 2009). Nanomolar concentrations of DHT and E2 had no effect on pericyte loss as a result of high glucose (Brignardello et al. 1998).

6. Hormone receptors in the retina

Sex hormones and sex hormone receptors are present in the retina from an early stage. Many areas of the brain and retina develop in a sexually dimorphic manner during prenatal,

perinatal and postnatal development. Salyer et al. using Long-Evans rats found that prenatally and early postnatally in normal rats males had thicker retinas than females. This increased thickness was reduced using flutamide, an androgen inhibitor, but not significantly so compared to normal males or testosterone-treated males, indicating that the process was not entirely mediated through AR. Females at this life-stage had undetectable testosterone levels, but when these females were treated with testosterone their retinal thickness did not differ significantly from normal or testosterone-treated males. To help rule out the conversion of testosterone to estrogen Salyer et al. using immunocytochemistry found no aromatase present in the neuroretina at this stage of development, but they did find quantities of it in the retinal pigment epithelium (RPE) (Salyer et al. 2001). Interestingly, Kobayashi et al. found evidence of 17β-hydroxysteroid dehydrogenase type IV in the RPE of chick embryo eye. 17β-hydroxysteroid dehydrogenase type IV is an enzyme which converts E2 to less reactive estrone (Kobayashi et al. 1997). It has been proposed its function is to protect the embryonic eye against excessive amounts of E2 (Gupta et al. 2005). Messenger RNAs of AR have been found in adult rat retina and uvea, rabbit retina and choroid and human RPE (Rocha et al. 2000; Wickham et al. 2000). In addition, Rocha et al. found the mRNA for 5α reductase, which translates the enzyme which converts testosterone to the more active DHT in the RPE (Rocha et al. 2000). Prabhu et al. found AR protein in all layers of rat retina except the ganglion and outer nuclear layers (Prabhu et al. 2010). However, in an interesting comparison of transformed rat cell lines from brain capillary endothelial cells and retinal capillary endothelial cells, Ohtsuki et al. found dominant expression of AR in the brain capillary cells, but not the retinal capillary cells. DHT acting through AR, in brain capillary endothelial cells (but not the retinal capillary endothelial cells), up-regulated the mRNA for organic anion transporter 3 (OAT3) a protein which is found in blood brain barrier (Ohtsuki et al. 2005).

ERs are nuclear receptors but may be also be located either in the cytoplasm or in the cell plasma membrane (Marquez and Pietras 2001; Simoncini et al. 2000). As discussed, ER has been found in the vascular endothelium of organs other than the gonads including the retina (Gupta et al. 2005; Ogueta et al. 1999; Suzuma et al. 1999). The ligand for either ERα or ERβ can be a form of estrogen or a selective estrogen receptor modulator (SERM). ERα has been mapped to the long arm of chromosome 6 and the ERβ has been mapped to band q22-24 of chromosome 14 (Enmark and Gustafsson 1999). ERα and ERβ are highly conserved with >95% homology for the DNA-binding domain. The two ERs differ functionally in how they are regulated. The β-receptor lacks ligand–independent transcriptional activity as compared to ERα, meaning when the ligand-dependent carboxy area of ERβ is blocked from its ligand, it retains very little activity (Manni and Verderame 2002).

The ligand-independent area of ERα usually displays only weak activity; however in certain cell types it can exhibit strong independent activity (Berry et al. 1990). A pre-requisite for transcriptional activity of the estrogen receptors are their compatibilities with certain co-activators (Shibata et al. 1997); thus, differences in the composition of the highly variable (Enmark and Gustafsson 1999) amino area of ERα and ERβ results in differences in intrinsic activity related to differences in affinity for their co-activators (Webb et al. 1998). It should also be noted there is significant variability between ERα and ERβ in their ligand-binding domains, ≈50% variability(Enmark and Gustafsson 1999). These differences suggest it may be possible to create pharmaceuticals which could activate one but not the other.

Prior to activation with estrogen, ERα and ERβ are held in the nucleus attached to a molecular chaperone such as heat shock protein 90 (HSP90) (Webb et al. 1998). Estrogen combines with estrogen receptors to create either homo- or hetero-dimers (Cowley et al. 1997; Osborne et al. 2000; Pettersson et al. 1997). These dimers combine with appropriate coactivators and bind to estrogen response elements (ERE) on the DNA which consist of an inverted repeat of two half-sites with the consensus motif AGGTCA spaced by 3 base pairs. ERα has been detected in pre-menopausal human female retinas (descending amounts 35 years>49 years>74 years) and in human male retinas. Interestingly, Ogueta et al. found the amount of ERα in males was intermediate between the levels found in 49 to 74 year old females. They localized ERα in the retina to the nuclei of the outer and inner nuclear layers, the outer plexiform layer (horizontal and bipolar cells), the nuclei of the ganglion cell layer and the RPE (Ogueta et al. 1999). ERβ has been localized to the RPE and also to neovascular tissue evolving from the choroid in both males and females in a manner which is dependent on estrogen concentration (Giddabasappa et al. 2010; Gupta et al. 2005; Marin-Castano et al. 2003).

7. Effects of sex hormones on individual steps in retinopathy

Due to prevailing evidences of the roles of sex hormones and sex hormone receptors in the development and maintenance of retina, Gupta et al. commented that "it is likely that sex-based incidences of retinal disorders may be regulated by estrogens (Gupta et al. 2005). We suggest androgens and progesterone also play a role.

7.1 Vascular cell maintenance

It is well established that the incidence and progression of retinopathy is related to the control of systemic factors such as blood pressure and blood glucose management (The Diabetes Control and Complications Trial Group 1993; UK Prospective Diabetes Study Group 1998). Furthermore lipid levels and waist-hip ratio have been correlated with the progression to proliferative retinopathy (Dorchy et al. 2002; Porta et al. 2001). As discussed above, blood pressure, lipid levels and waist-hip ratio have all been linked to the effects of sex hormones.

At the cellular level there are factors in the response of retinal capillary endothelial cells, pericytes and basement membrane that are often at least partially under the control of sex hormones. Leukostasis is positively influenced by the expression of ICAM and VCAM-1 with androgens and estrogens modulating expression of these attachment proteins. The upregulation of these proteins by DHT has been blocked by the androgen receptor blocker hydroxyflutamide (McCrohon et al. 1999). Estrogens inhibited ICAM and VCAM-1 expression (Cid et al. 1994; Simoncini et al. 1999; Villablanca et al. 2010). Progestins seemed to inhibit VCAM-1 expression while medroxyprogesterone did not. Progesterone used concurrently with estrogen further enhances the estrogen inhibition of ICAM-1 and VCAM-1 (Villablanca et al. 2010).

Androgens have been found to increase vascular endothelial cell proliferation in males. E2 has been found to increase endothelial cell proliferation in both males and females and progesterone has a negative effect on this proliferation. Thus sex hormones can play an important role in vascular repair (Liu et al. 2002). However it can also be a negative in

conditions such as the progression of proliferative diabetic retinopathy. Remodeling of the basement membrane is an important element in the development of neovascularization. E2 plays a role in the control of the extracellular cytokines FGF-2 and PAI-1 which maintain some control over this process (Albuquerque et al. 1998; Rubanyi and Kauffman 1998). It is well known that pericyte and endothelial cell communication plays an important role in the health of retinal capillaries (Hall 2006). It is also well known that pericyte loss is one of the first damaging effects of hyperglycemia. The fact that sex hormones can work to protect pericytes further links the role of sex hormones to the cell responses to diabetes. Furthermore, as discussed previously, sex hormones and their cognate receptors are well known to populate the retina of humans.

7.2 Angiogenesis

Vascular endothelial growth factor (VEGF) is well known as a controller of angiogenesis (Aiello et al. 1994; Folkman 1971).

Suzuma et al. used bovine retinal microvascular endothelial cells and Mueller et al. used human primary and Ishikawa uterine cells to show an increase in VEGF linked to E2 exposure (Mueller et al. 2000; Suzuma et al. 1999). Kazi et al. have demonstrated in rat uterine luminal cells that E2 required the P13K/AKT pathway to increase VEGF gene expression (Kazi et al. 2009). Grigsby et al. using a primate cell line of rhesus monkey retinal endothelial cells (RhREC) showed a decrease in VEGF levels with E2 exposure, which only partially recovered with the concurrent use of tamoxifen and raloxifene (Grigsby et al. 2011).

Pigment epithelium-derived factor (PEDF) is a 50-kDa glycoprotein secreted by the RPE (Tombran-Tink et al. 1991; Tombran-Tink and Johnson 1989). It has been shown to be the most important inhibitor of angiogenesis in mammalian eyes, strongly suggesting that decreased levels of it play an important role in angiogenic eye diseases such as proliferative diabetic retinopathy (Dawson et al. 1999; Takenaka et al. 2005). Gao et al., using Brown Norway rats, found PEDF levels to be inversely related to VEGF levels. The latter was inversely linked to retinal oxygen concentrations in a balance controlling angiogenesis (Gao et al. 2001). Cheung et al. found in human ovarian and surface epithelial cells that ER is an important upstream regulator of PEDF. They further found that E2 reduced PEDF levels, and that this reduction could be modulated by the introduction of the ER antagonist, ICI 182,780 (Cheung et al. 2006). In normoxic conditions Grigsby et al. found that, in response to E2, PEDF levels were reduced in RhREC cells. Furthermore, this reduction in response to E2 could be mitigated by concurrent exposure to tamoxifen or raloxifene, but the relative change in PEDF and in VEGF did not exactly correspond to cell growth patterns indicating that additional factors are involved in E2-induced proliferation of RhREC (Grigsby et al. 2011).

8. Conclusions

There is ample evidence that sex hormones do play a role in the development and progression of diabetic retinopathy in humans. For clinicians, there is evidence the attainment of puberty and especially pregnancy should raise the level of suspicion of the presence or progression of retinopathy.

Androgens and androgen blockers could possibly have mixed results in treating or preventing retinopathy. Androgens can raise blood pressure, have negative results on blood lipids, and increase levels of ICAM and VCAM-1. Low levels of androgens are linked with metabolic syndrome in males and can negatively affect lipid levels, blood glucose, blood pressure and increase hip-waist ratio. However, DHEA, a testosterone precursor, has been shown to be effective in protecting pericytes against the effects of high glucose (Brignardello et al. 1998).

It is believed high glucose levels can induce oxidative stress through several mechanisms (Brownlee 2001; Cunha-Vaz 2011 Du et al. 2000). Nishikawa et al. found superoxides may be generated in either complex I or complex III of the mitochondria, especially as a result of hyperglycemia (Nishikawa et al. 2000). The toxicity of glucose and consequent vascular damage has been postulated to occur through four supposedly dissimilar mechanisms: 1) activation of protein kinase C, 2) aldose reductase activation, 3) advanced glycation endproduct formation (AGE) and 4) the hexosamine pathway. What has been described as the "unifying hypothesis" is that reactive oxygen species formation is the upstream event that occurs in each of these mechanisms (Brownlee 2001; Cunha-Vaz 2011). Giddabasappa et al. have recently described their work on ARPE-19 cells in which they find that ERβ protects these cells from oxidative damage by protecting the mitochondria and up-regulating ERβ and antioxidant genes (Giddabasappa et al. 2010).

Similar to the "timing hypothesis" 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. 2005; Grigsby et al. 2011; Suzuma et al. 1999).

Since selective estrogen receptor modulators (SERM) can stimulate or depress estrogen effects depending on the type of ER or co-activators present in a particular cell, a SERM, or a co-activator blocker might be designed to suppress only that ER found in the retinal microvascular endothelial cell environment or to reduce leukostasis by inhibiting ICAM or VCAM-1 (Smith and O'Malley 2004). Their actions can be either non-genomic or genomic. Tamoxifen has been approved by the US-FDA for reducing the incidence of breast cancer in women at high risk for developing the disease, and in the treatment of metastatic breast cancer (Tamoxifen 2007). It has been used for over 30 years to treat estrogen-sensitive breast cancer. Raloxifene (Evista©) was originally approved for the treatment and prevention of post-menopausal bone loss and, more recently, for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis as well as in postmenopausal women at high risk for invasive breast cancer (Tamoxifen 2007). Both tamoxifen and raloxifene inhibit cell proliferation in breast tissue, but only raloxifene inhibits cell proliferation in the uterus; in fact, tamoxifen has been linked to an increase in uterine cancer (Cuzick et al. 2002). The use of tamoxifen has also been linked to cataract formation (Zhang et al. 1994). Grigsby et al. are the first to demonstrate that raloxifene is as effective as tamoxifen in reducing the E2-induced proliferation in a primate retinal endothelial cell line. Results from this cell study on tamoxifen and raloxifene inhibition of E2-induced cell proliferations

suggest that tamoxifen and raloxifene have similar potency to block estrogen mediated retinal angiogenesis (Grigsby et al. 2011).

Much is yet to be learned about the role sex hormones play in the development and progression of diabetic retinopathy. It appears that any treatment of diabetic retinopathy using sex hormones, or their blockers, may not be a "one size fits all" treatment, but may vary according to the life stage, level of retinopathy and the gender of an individual. 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.

9. Abbreviations

ACE, angiotension converting enzyme; AGE, advanced glycation end-products; AR, androgen receptor; Akt, serine/threonine protein kinase; CNV, choroidal neovascularization; COX, cyclooxygenase; CVD, cardiovascular disease; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; DIEP, Diabetes in Early Pregnancy Study; E, estrogens; E2, 17β-estradiol; EDRF, endothelium-derived relaxing factor; ETDRS, Early Treatment of Diabetic Retinopathy Study; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; ERE, estrogen-response element; ERK, extracellular signal-regulated kinases; FGF, fibroblast growth factor; HAM, hypoandrogen metabolic syndrome; HDL, high-density lipoprotein; HLA, human leukocyte antigen; HRT, hormone replacement therapy; HSP, heat-shock protein; HUVEC, human umbilical endothelial cells; IDDM, insulin-dependent diabetes mellitus, type 1; ICAM, inter-cellular adhesion molecule; LDL, low-density lipoprotein; LH, luteinizing hormone; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MPA, medroxyprogesterone; NFκ-β, nuclear factor κβ; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drugs; OAT, organic anion transporter; PAI, plasminogen activator inhibitor; PEDF, pigment epithelium-derived factor; PG, progesterones; PI3K, phosphoinositide 3 kinase; POS, polycystic ovary syndrome; PRA, progesterone receptor A; PRB, progesterone receptor B; RAGE, advanced glycation end-product receptor; RPE, retinal pigment epithelium; SERM, selective estrogen receptor modulator; tPA, tissue plasminogen activator; uPA urokinases plasminogen activator; VCAM, vascular cell adhesion molecule; VEC, vascular endothelial cells; VEGF, vascular endothelial growth factor, VEGFR, vascular endothelial growth factor receptor; VSM, vascular smooth muscle; WESDR, Wisconsin Epidemiological Study of Diabetic Retinopathy; WT, wild-type.

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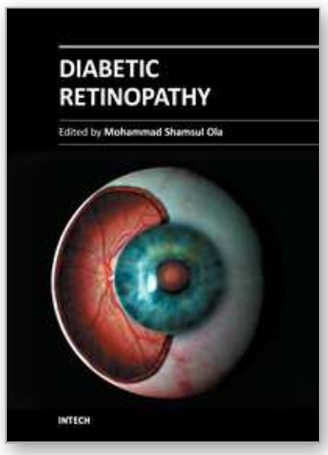

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The aim of this book is to provide a comprehensive overview of current concepts in pathogenesis, diagnosis and treatments of diabetic retinopathy. It provides a collection of topics written by excellent authors, covering discussions on advances in understanding of pathophysiology, immunological factors and emerging concepts, relating to clinical aspects and treatment strategies. The contents of the book will not only provide a resource for our knowledge but also improve diagnosis and treatment options for those patients who suffer vision loss due to diabetic retinopathy.

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Phone: +385 (51) 770 447
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