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MINI-REVIEW

Gender Differences in Ocular Blood Flow

Doreen Schmidl[1], Leopold Schmetterer[1,2], Gerhard Garhöfer[1] and Alina Popa-Cherecheanu[3]

[1]*Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria,* [2]*Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Vienna, Austria, and* [3]*Department of Ophthalmology, Emergency University Hospital, Bucharest, Romania*

ABSTRACT

Gender medicine has been a major focus of research in recent years. The present review focuses on gender differences in the epidemiology of the most frequent ocular diseases that have been found to be associated with impaired ocular blood flow, such as age-related macular degeneration, glaucoma and diabetic retinopathy. Data have accumulated indicating that hormones have an important role in these diseases, since there are major differences in the prevalence and incidence between men and pre- and post-menopausal women. Whether this is related to vascular factors is, however, not entirely clear. Interestingly, the current knowledge about differences in ocular vascular parameters between men and women is sparse. Although little data is available, estrogen, progesterone and testosterone are most likely important regulators of blood flow in the retina and choroid, because they are key regulators of vascular tone in other organs. Estrogen seems to play a protective role since it decreases vascular resistance in large ocular vessels. Some studies indicate that hormone therapy is beneficial for ocular vascular disease in post-menopausal women. This evidence is, however, not sufficient to give any recommendation. Generally, remarkably few data are available on the role of sex hormones on ocular blood flow regulation, a topic that requires more attention in the future.

Keywords: Age-related macular degeneration, diabetic retinopathy, gender, glaucoma, ocular blood flow

INTRODUCTION

In recent years, special attention has been paid towards gender specific medicine. Women have traditionally been under-represented in clinical research, even though the prevalence for some diseases is significantly higher among them. Further, it has been shown that pharmacokinetic and pharmacodynamic profiles are different among women and men. Many drugs are, however, still mostly tested in men.[1] With this knowledge, several reviews dealing with gender differences in major research fields such as cancer, cardiovascular diseases or pharmacokinetics have been published in the recent years.[2–4]

In ophthalmic research data about sex differences are still relatively sparse. The present review focuses on gender differences in ocular blood flow. In addition, differences between males and females in major ophthalmic diseases associated with impaired ocular blood flow will be discussed, focusing on age-related macular degeneration (AMD), primary open angle glaucoma (POAG) and diabetic retinopathy (DR).

Ocular vasculature and assessment of ocular blood flow

A complete description of the vascular supply of the eye and the regulation of ocular blood flow is beyond the scope of the present review. The reader is referred to some recent review articles that focused on this topic.[5–10] Briefly, the posterior pole of the eye is nourished by two independent vascular beds. The inner retina including the retinal ganglion cells is supplied by the retinal circulation. This vascular

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Correspondence: Leopold Schmetterer, PhD, Department of Clinical Pharmacology, Medical University of Vienna, Währinger Gürtel 18-20, Vienna, Austria. Tel: +43 1404002981. Fax: +43 1404002998. E-mail: leopold.schmetterer@meduniwien.ac.at

bed lacks neural innervation proximal to the level of the lamina cribrosa. As such, control of retinal blood flow is achieved mainly by local factors such as blood gases and endothelial derived factors. Retinal blood flow is autoregulated over a wide range of perfusion pressures. The outer retina including the photoreceptors is supplied by the choroid. The vessels in the choroid receive their supply via the posterior ciliary arteries and are richly innervated. To which degree choroidal blood flow is autoregulated is still a matter of debate. In humans evidence has accumulated that the choroid shows some potential in response to both an increase and a decrease in perfusion pressure,[11–13] although this may not be called autoregulation in its strict sense, because of the neuronal component in the control of perfusion. The measurement of blood flow in humans is challenging and no currently available technique has found its way into clinical routine. With most of the techniques the time consuming measurement procedures as well as the problems in reproducibility have hampered widespread use. As such it does not come as a surprise that measurement of retinal vessel caliber is the only approach that has been used in larger scale studies, because it can be evaluated with limited technical effort and sufficient reproducibility.[14] Associations between vessel caliber changes and incident stroke,[15,16] systemic hypertension,[17] DR[18] and glaucoma[19] have been reported in the literature. A more sophisticated approach is to measure blood velocities using laser Doppler velocimetry in addition to vessel diameters. For a long time this was the only approach applicable for measurement of total retinal blood flow.[20,21] Clinical use is, however, hampered by reproducibility problems and the time-consuming measurement procedure. Other techniques such as fluorescein angiography,[22] color Doppler imaging[23] or techniques that assess the volume- or pressure-pulse[24,25] all have inherent limitations. Nowadays there is a focus on Doppler Optical Coherence Tomography and several groups have shown that total retinal blood flow can be measured with this approach.[26–32] This method carries significant potential for the future.

Even though the two vascular beds seem to be independent, it has been found that some people exhibit a collateral vessel between the choroidal and retinal circulation. One or more of these so-called cilioretinal arteries have been found to be present in 32.1% of eyes.[33] They seem to play an important role in retinal vein occlusions, since the presence of cilioretinal arteries can lead to reversion of blood flow from the retina to the choroid due to increased vascular resistance in the retinal circulation (''choroidal steal'') which leads to further ischemia of the retina.[34] In contrast, the presence of cilioretinal arteries seems to be beneficial in patients with central retinal artery occlusions (CRAO), since it can still offer blood supply from the choroidal circulation to the retina.[35] Data about specific mechanisms of blood flow regulation in cilioretinal arteries are, however, currently lacking.

The optic nerve head has a dedicated vascular supply. The pre-laminar region is supplied by the retinal circulation and consequently shares many characteristics with the retinal circulation. The post-laminar part of the optic nerve head is supplied by branches of the posterior ciliary arteries either directly or via the circle of Zinn-Haller. Using laser Doppler flowmetry[36] or laser Speckle techniques,[37] blood flow in the optic nerve head region can be assessed in arbitrary units, but absolute blood flow values cannot be measured.

Several eye diseases including ischemic optic neuropathies and vascular occlusive retinal disease are ischemic in nature. Ischemia also plays a role in DR and evidence has accumulated that alteration in blood flow is an early event in the disease process.[38–42] Evidence has also been gained that alteration in blood supply to the retina is related to AMD[40,43,44] and glaucoma (Section Vascular dysregulation in ocular diseases – general considerations).[45–48]

EPIDEMIOLOGY OF OCULAR DISEASES IN RELATION TO GENDER

For a long time, ophthalmic research has paid little attention to gender differences, since it was assumed that there is not much difference between male and female eyes. In the last few years, evidence from several population-based studies has accumulated that this might not be the case, even though some results may appear to contradict each other.

Large scale studies carried out in Europe and the United States suggest that female sex is a risk factor for AMD.[49–51] In contrast, the Beijing Eye Study found no difference between men and women regarding the 5-year incidence of AMD.[52] Some studies carried out in Asia even found a higher prevalence of AMD among men than women.[52,53] Regional differences may account for this observation including different genetic risk profiles. Additional factors may be related to food intake (soy-rich diet, which contains a high amount of phytoestrogens) as well as local differences in life expectancy between men and women as outlined in detail in the Section ''Differences in risk factors for ocular diseases and the role of hormones''.

POAG also shows differences in its frequency of occurrence between genders, but results are again inconsistent. A large meta-analysis found a higher prevalence of POAG in men, while the Blue Mountain Eye Study revealed the opposite.[54,55] Normal tension glaucoma (NTG) seems to occur more frequently in

women, and female gender has been identified as a risk factor for progression.[56] No gender difference has been found in the prevalence of ocular hypertension (OHT) between men and women.[55]

Even though some studies report a higher incidence of occludable chamber angles in women, several recent studies found no sex difference in the occurrence of angle closure glaucoma.[57–59] In contrast, several literature reviews state female sex as a risk factor for angle closure glaucoma.[60,61] The sex difference could be due to an anatomical predisposition of women to have narrower anterior chamber angles, since all studies found a significant association between lower body height and shallower anterior chamber depth, and women tend to be smaller in body height than men.[62,63]

In contrast, DR seems to occur more frequently in men, although a pooled analysis from data from the United States reported no gender difference.[64–67] Data from a large clinical register in Denmark in which patients with diabetes mellitus were followed over several years, found the risk for reaching sight-threatening DR significantly higher in men.[68] In addition, men had significantly more retinal hemorrhages at the baseline examination, higher HbA1c levels and higher systolic and diastolic blood pressure values than women. Since these are risk factors for progression of DR, it could explain the gender difference in the progression rate of DR. The authors hypothesized that the reason for this imbalanced distribution of risk factors among genders could be caused by differences in lifestyle.[68] Male sex also seems to be a risk factor for diabetes as the underlying disease in adults as well as in juveniles, at least for the western countries.[69–71] Interestingly, it is quite the opposite in countries where the population is of non-European origin, in which the prevalence of diabetes seems to be higher in women[70,72] All these findings apply for both types of diabetes mellitus, type 1 and type 2 diabetes. Again, local gender differences in dietary intake may as well influence these results.

The vasculitides are another important group of ocular diseases affecting the choroidal and/or retinal vasculature. They can occur secondary to systemic diseases, may be the consequence of infections, but may also be idiopathic or related to eye disease. Systemic diseases that can cause ocular vasculitides include rheumatic or autoimmune diseases, such as systemic lupus erythomatosus (SLE), multiple sclerosis (MS), systemic necrotizing vasculitides, sarcoidosis or Behçet's syndrome. The most common primary eye diseases associated with retinal vasculitides are intermediate uveitis and birdshot chorioretinopathy.[73]

Except for idiopathic and primary ocular vasculitides, the gender distribution of ocular vasculitides mainly depends on the incidence of the underlying disease. The autoimmune diseases SLE and MS have a significantly higher incidence in women.[74–76] However, when looking at the rate of ocular manifestations in patients with SLE, no difference in their incidence between genders is seen.[75,76] In contrast to SLE and MS, there seems to be no gender preference for polyarteritis nodosa, Wegener's granulomatosis, microscopic polyangiitis or eosinophilic granulomatosis with polyangiitis, all belonging to the group of systemic necrotizing vasculitides.[77] Whether there is a gender difference the frequency of ocular vascular complications is unknown. Sarcoidosis seems to occur more frequently in women while ocular sarcoidosis seems to affect both genders equally.[78,79] Behçet's syndrome occurs more often in males who also seem to be more prone to eye involvement.[80]

While in the industrial countries uveitis seems to occur more frequently in women, the opposite is the case in developing countries. A possible explanation for this difference could be the fact that in the developing countries, men are more likely to seek medical advice than females.[81] Also birdshot chorioretinopathy, a chronic inflammatory disease of the eye of unknown origin seems to show a slight preference for female gender, although this was not found in all studies.[82] No studies reporting on gender differences in the occurrence of idiopathic ocular vasculitides have been found in the literature.

When looking at ocular diseases associated with thromboembolic events, there is some evidence that they tend to occur more frequently in men than in women. A large longitudinal study carried out in the United States found female sex to be protective against central retinal vein occlusion (CRVO).[83] These results were, however, not confirmed by a large pooled analysis including a total of 68,751 individuals, in which no gender difference in the occurrence of CRVO as well as branch retinal vein occlusion (BRVO) was found.[84] Retinal emboli, which are a risk factor for stroke, are seen more frequently in men than in women.[85] This is also reflected in the incidence for CRAO which has been found to be higher in males.[86]

DIFFERENCES IN RISK FACTORS FOR OCULAR DISEASES AND THE ROLE OF HORMONES

As mentioned above, data on gender differences in the prevalence of ocular disease are relatively sparse and future research on this topic is required. Evidence has, however, accumulated that there are differences in the risk factors for ocular disease between men and women.

The most important risk factor for AMD is age.[87] Women tend to have a greater life expectancy than men that could well explain the higher incidence of AMD in females.[88] Obviously sex hormones could play a role as well, because AMD usually does not

occur before menopause. Results from the Blue Mountain Eye Study suggest that estrogen has a protective effect, since a longer time span from menarche to menopause was associated with a reduced risk for AMD.[49] Hormone therapy (HT) did not have a protective effect against the disease in postmenopausal women.[89–91] In the Nurses' Health Study even the opposite was the case since HT for at least three years increased the risk for early AMD, but significantly reduced the risk for neovascular AMD.[92] The Tromso Study found no association between the risk for AMD and the number of fertile years, but women who have been breast-feeding for at least six months had a lower odds ratio for the development of late AMD. The authors hypothesized that this might be an indirect effect, since breast feeding reduces the cardiovascular risk profile.[93]

Defay et al. observed a positive correlation between plasma levels of dehydroepiandrosterone sulfate (DHEAS) and the prevalence of soft drusen in women and therefore suggested further investigation on this topic.[90] More recent studies directed towards the role of DHEAS in AMD actually found an inverse correlation between AMD severity and DHEAS serum levels, while in exudative AMD no correlation was observed.[94,95] Since DHEAS is a precursor for estrogen and testosterone, studies on the role of testosterone in AMD would be of interest, but are still lacking.

Primary vascular dysregulation (PVD) syndrome has been found as a risk factor for glaucoma, especially for NTG. Common signs of PVD syndrome are cold limbs, low blood pressure, reduced feeling of thirst, altered sensitivity to drugs, low body mass index and signs of oxidative stress.[96] The prevalence of PVD syndrome is significantly higher in women than in men and seems to be associated with higher estrogen levels, since the syndrome often disappears with the onset of menopause, but can reoccur when HT is initiated.[96] One could therefore speculate that in this subgroup of patients, glaucoma onset is earlier than reported in general. Currently, no large scale studies on this topic are, however, available.

Estrogen has been found to be involved in the regulation of intraocular pressure (IOP) and therefore might play a role in glaucoma. Estrogen receptors are present in the ciliary epithelium and seem to be involved in the regulation of aqueous humor production and outflow.[97] Several studies point towards a protective effect of estrogen against glaucoma. In postmenopausal women HT significantly lowered IOP.[98,99] In the Rotterdam study, early menopause was associated with a higher prevalence of glaucoma.[100] The Blue Mountain Eye Study also found modest evidence that shorter lifetime exposure to endogenous estrogen increases the risk for development of glaucoma.[101] In addition, the risk for the onset of glaucoma was found to be significantly increased in women undergoing bilateral oophorectomy before the age of 43, and even HT afterwards did not reduce this risk.[102]

Sex hormones also seem to play a role in the progression of DR, since DR often progresses during pregnancy which is associated with higher estrogen and progesterone levels.[103,104] It has, however, been demonstrated that in women following a tight metabolic control regimen during pregnancy, there is no elevated risk for progression of DR.[105] The risk often increases again in the post-partum period since this tight regimen frequently is no longer followed.[103,105] A study on retinal pigment epithelial cell cultures found an increased production of vascular endothelial growth factor (VEGF) when exposed to a high concentration of progesterone.[106] This could give an explanation, since VEGF has been identified to be closely related to development and progression of DR.[107] In contrast, exogenous estrogen seems to have no influence on the progression of DR.[108] Studies on the role of endogenous estrogen in DR are still lacking.

High testosterone levels seem to be a risk factor for the development of DR in men.[109,110] It remains unknown whether this also applies for women. There is clear consensus that combined oral contraceptives which contain an estrogen and a progestogen increase the risk for venous thromboembolism (VTE).[111] This increased risk seems to be mainly caused by the estrogen component, since there is no or only a minimally increased risk with oral contraceptives containing progestogen only.[112] While high-dose progestogens used for emergency contraception do not seem to enhance the risk for VTE, this seems to be the case with high doses used for therapeutical indications, such as menorrhagia.[112] The risk for VTE is also elevated during pregnancy or in the postpartum period.[112] A recently published systematic review also found an increased risk for VTE in women using HT.[113] In contrast, high endogenous estrogen or testosterone levels do not seem to increase the risk for VTE in men and women not taking exogenous hormones.[114] In spite of all these findings, the overall incidence of VTE seems to be similar for both genders, although results from epidemiological studies are contradictory. Therefore, statements about gender differences in the prevalence of VTE should be given carefully, since a large epidemiological study investigating this issue that stratifies according to gender, menopausal status and the intake of hormones is still lacking.[115] Some case reports and two cohort studies also point towards an increased risk for retinal vein occlusions in women taking oral contraceptives or using HT.[116–120] In addition, oral contraceptives intake also seems to enhance the risk for retinal arterial occlusion.[121,122]

DIFFERENCES IN VASCULAR REGULATION BETWEEN WOMEN AND MEN IN HEALTH AND DISEASE

Vascular dysregulation in ocular diseases – general considerations

All of the above mentioned eye diseases have been found to be associated with impaired ocular blood flow and its regulation. In patients with AMD, retinal, choroidal and retrobulbar blood flow was significantly lower than in healthy controls.[123–125] Two studies have proven that reduced choroidal blood flow is associated with an increased risk of developing neovascular AMD.[126,127] In glaucoma evidence for reduced retinal and optic nerve head blood flow has accumulated.[128–131] Whether it is a primary factor contributing to the disease or a secondary factor related to the loss of neuronal tissue is not entirely clear. Glaucoma is, however, also associated with abnormal retinal and optic nerve head blood flow regulation.[128,132] In DR the situation appears to be complex, since both increased and decreased blood flow has been reported.[42,133–136] An early feature in DR appears to be the loss of neurovascular coupling in the retina of diabetic patients, as evidenced from abnormal flicker-induced vasodilatation.[10,42,137–140]

In diseases associated with ocular vasculitis, blood velocities have been found to be reduced.[141] A study conducted by Atcar et al. found retrobulbar blood velocities to be decreased in patients with Behçet's disease with ocular involvement during the active phase in comparison to healthy controls and patients with inactive or no uveitis.[142] In contrast, several other studies reported reduced retrobulbar blood velocities in all patients with Behçet's disease compared to healthy controls regardless whether there was ocular involvement or not.[141,143–145] An explanation for these different findings could be that retrobulbar blood velocities are reduced in patients with Behçet's syndrome with and without ocular involvement compared to healthy controls, with a more pronounced reduction in patients with ocular involvement, which might does not reach the level of significance in all studies.[145] Studies employing other techniques are, however, lacking.

Blood velocities in the central retinal artery and vein have been found to be significantly reduced in eyes with CRVO in comparison to the contralateral eye.[146–148] Likewise there is evidence that CRVO is associated with a decrease in retinal blood flow as expected, although no technique is currently available to quantify the degree of ischemia.[149–151] One study has shown that in parallel, choroidal blood flow seems to increase, which might be a compensation mechanism for this reduction in retinal blood flow.[152]

Large-scale studies have also investigated the role of changes in vascular caliber in ocular diseases. For AMD, no association between arteriolar diameter and the risk for incident AMD has been found.[153,154] The Beijing eye study reported that glaucoma seems to be associated with arteriolar narrowing, while in the Rotterdam study no association between vessel diameters and the risk for glaucoma was observed.[155,156] In the Blue Mountain Eye Study a clear relation between arteriolar narrowing and the 10 years incidence of glaucoma was reported.[19]

Increased retinal venous diameter seems to be a risk factor for the onset and progression of DR in patients with diabetes.[157,158] This is most likely related to sub-chronic inflammation in the diabetic retina.

A cross-sectional study found narrower veins over the whole retina (central retinal vein equivalent, CRVE) in patients with BRVO compared to age- and sex-matched controls.[159] It is not possible to differentiate whether this is a cause or a consequence due to the design of this study. Longitudinal studies on retinal vessel caliber and retinal vessel occlusion are currently not available.

In the eye, it is assumed that abnormal autoregulation is detrimental for the tissue as it is in the brain. As such a variety of studies focused on autoregulatory behavior during changes in perfusion pressure in different ocular conditions. Patients with neovascular AMD show an abnormally high increase in choroidal blood flow in response to an experimental increase in ocular perfusion pressure (OPP) induced by isometric exercise compared to healthy controls,[160] but other investigators did not confirm these data.[161] In glaucoma, abnormal blood flow autoregulation during an experimental increase and decrease in OPP has been observed in several studies.[45,162]

An abnormal autoregulatory behavior also seems to appear early in patients with DR.[163] This is also evidenced from an abnormal vessel diameter response in DR: Frederiksen et al. measured retinal vessel responses during isometric exercise in healthy subjects, patients with diabetes but no DR, patients with mild DR and patients with diabetic maculopathy. While in the first two groups an increase in systemic blood pressure induced retinal arteriolar contraction, the opposite was the case in patients with DR as well as in the patient group with diabetic maculopathy.[164]

Differences in ocular blood flow and its regulation between men and women

Unfortunately little is known about gender-specific differences in ocular blood flow and its regulation. A study investigating retrobulbar blood velocities in 72 women and 68 men found higher values for velocity in the ophthalmic artery and lower values for the short posterior ciliary artery in men compared to

women who were not using hormonal medication. These findings were statistically significant only in the younger age group (<40 years).[165] A study investigating choroidal blood flow in men and women also found significant differences. While age had no effect on choroidal blood flow in men, choroidal blood flow was significantly higher in women younger than 40 years compared to women older than 55 years. None of the participating women were taking oral contraceptives or using HT.[166] Also, pulsatile ocular blood flow and pulse amplitude were significantly higher in pre-menopausal women compared to age-matched males and post-menopausal women not taking HT.[167] No data about gender differences in optic nerve head blood flow are currently available.

No differences seem to exist between men and women in term of vessel calibers as shown in large population based studies, namely the Beaver Dam and the Beijing Eye Study.[155,168] One must, however, consider that in these studies participants were at least 40 years old and it cannot be excluded that younger subjects may show such gender differences. No data are currently available reporting on differences in either auto-regulatory behavior or neurovascular coupling in men or women.

THE INFLUENCE OF SEX HORMONES ON OCULAR BLOOD FLOW

As mentioned above estrogen may have protective effects against some ocular diseases. This may be related to vasoactive effects that have also been reported in other vascular beds. In a study in post-menopausal women, estrogen significantly decreased vascular resistance in the central retinal artery compared to placebo.[169] This was not the case in a study conducted by Harris-Yitzhak et al., where estrogen therapy in postmenopausal women had no effect on the central retinal artery and nasal posterior ciliary artery blood velocity, but significantly decreased vascular resistance distal to the ophthalmic artery to levels observed in premenopausal women. This suggests that maybe extrabulbar branches of the ophthalmic artery are responsible for this decrease in vascular resistance caused by estrogen.[170] In a study comparing blood velocities and resistive indices of the ophthalmic artery and the central retinal artery between pre- and postmenopausal women, significantly higher blood velocities and lower resistive indexes in premenopausal women were found. In addition, some correlations between serum estrogen and testosterone levels and retrobulbar blood flow parameters were observed. While estrogen had positive effects on ocular blood flow, the opposite was the case with testosterone.[171] In an observational study, women using HT had significantly higher retinal blood flow values compared to women who have never been taking HT.[172] Three months treatment with the selective estrogen-receptor modulator raloxifene had no effects on ocular blood flow in postmenopausal women.[173] It is, however, possible that raloxifene has an effect on ocular blood flow regulation in response to changes in OPP. Raloxifene lowers vascular tone via upregulation of the production of nitric oxide (NO) as well as through inhibition of L-type calcium channels in vascular smooth muscle cells.[174] In a study in post-menopausal women; administration of raloxifene for 30 days significantly attenuated the increase in systemic arterial resistance and elastance indices in response to isometric exercise.[175] In addition, raloxifene seems to improve endothelial function, at least in a subgroup of women with specific genotypes.[176]

Interestingly, retinal vessels have been found to be narrower in women using HT in the Beaver Dam Study.[177] The authors did, however, only assess vessel diameters at one time point in a cross sectional design. To verify the hypothesis that HT leads to retinal vasoconstriction, longitudinal studies would be needed.[177] Similar results were obtained from the data of the Blue Mountain Eye Study.[178]

Progesterone seems to have vasoconstrictive effects on ocular circulation in general. In a placebo-controlled study in postmenopausal women, 30 days treatment with progestin induced a significant increase in all Doppler indices in the central retinal and the ophthalmic artery.[179] A prospective study in premenopausal women, in which pulsatility index of the central retinal arteries was measured during all menstrual phases, also came to the conclusion that estrogen leads to vasodilatation that is antagonized by progesterone.[180] Interestingly, low progesterone levels showed a strong correlation with the presence of retinal arteriosclerosis in men. A weak correlation between retinal arteriosclerosis and low plasma levels of estrogen and testosterone was also observed.[181]

No data on the role of sex hormones in ocular blood flow auto-regulation is available. Since the vasodilatory effect of estrogen seems to be at least partially mediated via the release of NO, a role might be expected. NO seems to be involved in choroidal blood flow regulation during an experimental increase in OPP.[11] In glaucoma for instance evidence for an altered NO system has been reported.[178,182] As stated previously, the selective estrogen receptor modulator raloxifene also seems to target the NO pathway and therefore has been suggested as a therapeutic agent.[174] Sex hormones also seem to influence Endothelin-1 (ET-1) plasma levels, which is a potent vasoconstrictor that also has been implemented in the pathogenesis of glaucoma.[45,183] Higher estrogen levels have been found to be associated with lower ET-1 plasma levels, while higher testosterone levels resulted in higher ET-1 plasma levels.[183] We have previously shown that ET-A receptor blockade

alters the behavior in choroidal and optic nerve head blood flow in response to isometric exercise in healthy subjects.[12,184] Nevertheless, these are only speculations and corresponding studies are needed to enlighten these issues.

CONCLUSION

In conclusion, there is evidence that gender differences exist with regard to the incidence of ocular disease. To which degree this is related to alteration in blood flow regulation is unclear. Most likely these differences are, however, caused by sex hormones, which are assumed to be involved in ocular blood flow regulation. Indeed differences in ocular blood flow have been reported between pre-menopausal women and men. Estrogen seems to have protective effects, potentially via its vasodilator effects. HT in post-menopausal women might be protective against AMD and glaucoma, although data are not conclusive. And evidence is not sufficient to recommend HT for ocular diseases. Many questions still remain unanswered and further studies on the role of gender and hormones in ocular diseases, ocular blood flow and its regulation are eagerly awaited.

DECLARATION OF INTEREST

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