Review Article

Current Trends in Ophthalmology Managing Glaucoma beyond Intraocular Pressure

Fischer J¹ and Mozaffarieh M^{1,2*}

¹University of Basel, Switzerland

²Limmat-Eye-Center, Zurich, Switzerland

***Correspondence:** Maneli Mozaffarieh, University of Basel and Limmat Eye Center, Hardturm str 133, 8005 Zurich, Switzerland, E-mail: maneli.mozaffarieh@gmail.com

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Abstract

Glaucoma is a major cause of vision loss worldwide with nearly 8 million people bilaterally blind from the disease. This number is estimated to increase over the next years. The key to preventing blindness from glaucoma is effective diagnosis and treatment. The classical glaucoma treatment focuses on IOP reduction. Increased IOP is indeed an undisputable risk factor for the development and progression of Glaucomatous Optic Neuropathy (GON). But there is mounting evidence in literature that other risk factors are involved as well. These additional factors may by themselves lead to GON or they may render the eye more sensitive to IOP. Among the most often described factors are: Flammer-syndrome, low blood pressure, increased retinal venous pressure, oxidative stress. Better knowledge of the pathogenesis has opened up additional therapeutical approaches often called non-IOP lowering treatment. Whilst most of these new avenues of treatment are still in the experimental phase, others are already used by some physicians. Non-IOP lowering treatment includes improvements of ocular blood flow, particularly blood flow regulation. This can be achieved by improving the regulation of ocular blood flow (improving auto regulation) by drugs such as carbonic anhydrase inhibitors, magnesium or calcium channel blockers. These drugs also in part decrease increased retinal venous pressure in the eyes of patients. Increased retinal venous pressure decreases perfusion pressure in the patients' eyes and thus increases the risk of glaucomatous progression. The patients' blood pressure also needs to be monitored carefully as low blood pressure, particularly nocturnal over dips or blood pressure fluctuations, increase the risk of further damage. Blood pressure can be increased by an increase in salt intake or in rare cases by treatment with fludrocortisone. Reduction of oxidative stress, especially at the level of mitochondria, also seems to be protective. This can be achieved by ginkgo or foods rich in polyphenolic flavonoids. This review describes the individual mechanisms which may be targeted by non-IOP lowering treatment.

Introduction

Since the time of van Graefe, in other words since about 1850, it is known that both increased ocular pressure and reduced blood flow contribute to glaucomatous damage. The question arises, therefore, as to why ophthalmologists focus mainly on intraocular pressure in their daily practice and pay very little attention to blood flow.

We assume the following reasons to be relevant: It is difficult to measure ocular blood flow. Ocular blood flow is difficult to understand, both from a physiological as

well as from a pathophysiological point of view. For e.g. different tissues in the eye behave very differently. In the past, researchers focused on arteriosclerosis and its risk factors as potential cause for disturbed blood flow in glaucoma. We know today, that arteriosclerosis is weakly related to GON. In contrast, vascular dysregulation in the context of Flammer-Syndrome is strongly related to GON. Most ophthalmologists, however, are not yet familiar with the Flammer-Syndrome. Therapeutical consequences of disturbed ocular blood flow have only recently been demonstrated.

The impact of ocular blood flow for glaucomatous damage is meanwhile clearly established and has been reviewed [1].

It is therefore essential for ophthalmologists to get some information about blood flow of a glaucoma patient and in particular in the context of a pathophysiological concept of GON. The reason for this has long been summarized [2-5].

Vascular dysregulation in the context of flammer-syndrome

To understand the role of blood flow in glaucoma, we have to know and understand the concept of Flammer-Syndrome.

An insufficient oxygen supply to a certain tissue can be due to a structural damage of the vessels (e.g. an atherosclerosis or thrombosis) or due to vascular dysregulation. Such a dysregulation can be local (e.g. due to a local dysfunction of the endothelial cells) or may be more or less systemic. The term vascular dysregulation syndrome in the context of glaucoma was first introduced in 1994 by J Flammer [6]. Later, a distinction was made between primary and secondary vascular dysregulation [7]. A systemic vascular dysregulation can be secondary to another disease, (Secondary Vascular Dysregulation = SVD) as for example in multiple sclerosis. The primary vascular dysregulation (PVD), however, occurs in otherwise healthy subjects. While subjects with SVD have a reduced baseline OBF, subjects with PVD have a compromised auto regulation of ocular perfusion [8]. PVD is today referred to as the Flammer-Syndrome.

Characteristics of the flammer-syndrome

The Flammer Syndrome has an inherited component. Subjects often indicate that their parents, in particular their mothers, also suffered from cold hands and other symptoms. It typically manifests itself first during puberty and declines with age. In females, the symptoms often mitigate after menopause but can increase again when patients are treated with oestrogen replacement therapy [9].

People with Flammer-Syndrome (Figure 1) have typical symptoms that differentiate them from others.

They tend to have normal or low body mass index [10], their feeling of thirst is often reduced (they drink because they know they have to drink and not so much because they are thirsty) [11], they tend to have low

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blood pressure, especially when they are young [12], they more often suffer from migraines than non-PVD subjects [13]. People with Flammer-Syndrome often show altered drug sensitivity due to differential expression of ABC transporter proteins [14]. The sensitivity for certain groups of drugs, such as calcium channel blockers and systemic beta-blockers, is increased. This means that they require lower doses of these drugs to achieve the same effects and to avoid side-effects. The sensitivity is normal or rather decreased for certain other drugs, such as pain-killers. PVD subjects have a good sense of smell and can identify smells better than others [15] (Figure 2), likely due to a differential expression of odour binding proteins.

Figure 1: Whereas people with the metabolic syndrome typically have a high body mass Index (BMI), high blood pressure (BP), diabetes mellitus (DM Typ 2) and are less active, those with the Flammer Syndrome have a low BMI, low BP, a lower chance of developing diabetes and are more active personalities. People with the Flammer Syndrome have a higher chance of developing a normal tension glaucoma (NTG), where as those with a metabolic syndrome have a higher chance of developing high tension glaucoma (HTG).

From: Mozaffarieh M & Flammer J. Ocular blood flow and glaucomatous optic neuropathy. Springer. ISBN 978-3-540-69442-7 (2009).

They have, on average, a longer sleep onset time, especially when they are cold [16]. They also have increased retinal venous pressures, as measured by means of ophthalmodynamometry [17].

Figure 2: People with Flammer-Syndrome can identify odors much better than other people do.

From: Mozaffarieh M, Hauenstein D, Schoetzau A, Konieczka K, Flammer J. Smell perception in normal tension glaucoma patients. *Mol Vis.* 2010;(16):506-10

Pathogenetic concept of GON

The observations above lead to the pathogenic concept of GON by J Flammer. Both an increased IOP as well as a decreased blood pressure and increased retinal venous pressure [18], commonly seen in people with the Flammer-Syndrome, can lead to glaucomatous damage. As a result of the increased or fluctuating IOP and blood flow regulation disturbances, there is an enhanced level of oxidative stress [19], inducing the formation of free radicals in the axons of the optic nerve head and thereby destroying various structures. This insight leads to new therapeutic avenues for glaucoma patients as described below.

Therapeutic interventions beyond lowering IOP

Low blood pressure as well as nocturnal over-dipping increases the probability of glaucomatous progression [20,21]. We can therefore assume, that an increase in blood pressure in patients with hypotension may improve prognosis. Blood pressure can be increased with an increase in salt intake [22]. In severe cases, the intake of low dosed fludrocortisone [23] (a mineralo corticoid with less side-effects than a glucocorticoid) is recommended. Vascular regulation can be improved by carbonic anhydrase inhibitors [24,25], calcium channel blockers and magnesium, a physiological calcium channel blocker [26]. Increased retinal venous pressure can also be lowered by treatment with calcium channel blockers [27,28]. Increased oxidative stress, particularly at the level of the optic nerve, can be decreased by administering ginkgo biloba and potentially by intake of nutrition rich in

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sources of polyphenolic flavonoids and anthocyanosides [29,30] (Figure 3).

Figure 3: Nutritional antioxidants can act as free radical scavengers.

From: Mozaffarieh M & Flammer J. *Ocular blood flow and glaucomatous optic neuropathy*. Springer. ISBN 978-3-540-69442-7 (2009).

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