Thesis

Frequency and Laterality Predilection of Neovascular Glaucoma

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice".
Furthermore, I hereby declare that if artificial intelligence (AI) tools were used for the generation and/or correction of certain text passages in the creation of this work, such employment was conducted in compliance with ethical principles, academic integrity, and the regulations of my university. Additionally, it was ensured that this usage was transparently disclosed and appropriately attributed.

Graz, 25.08.2025 Daniel Petutschnig m.p.

Zusammenfassung

Einleitung: Das Neovaskularisationsglaukom (NVG) macht etwa 3,9% aller Glaukomfälle aus. Mit einer Prävalenz von 0,01–0,12% in Europa handelt es sich um eine seltene, jedoch potenziell zur Erblindung führende Erkrankung. Als sekundäres Glaukom geht dieser Pathologie typischerweise eine Grunderkrankung voraus. Die häufigsten davon sind die diabetische Retinopathie, der zentrale retinalvenöse Verschluss und das okuläre ischämische Syndrom. Theoretisch sollte das rechte und linke Auge in etwa gleich häufig betroffen sein. Studien zeigen jedoch eine Asymmetrie bei zerebrovaskulären Ereignissen, die möglicherweise auch Gefäßerkrankungen des Auges beeinflussen könnten. Ziel dieser Studie war es, einen möglichen Seitenunterschied im Auftreten dieser sekundären Glaukomform zu untersuchen.

Methoden: Es wurde eine retrospektive Datenanalyse unter Verwendung der hausinternen Datenbank und des Patientenverwaltungssystems der Universitäts-Augenklinik Graz durchgeführt. Es wurden alle Patientinnen und Patienten eingeschlossen, die zwischen Dezember 1996 und April 2024 mindestens einmal ambulant mit der Diagnose eines NVG vorstellig wurden. Das Hauptmerkmal der Analyse war die betroffene Seite, kategorisiert als rechts, links oder beidseitig. Zusätzlich wurden verschiedene patientenbezogene Merkmale erfasst.

Ergebnisse: Im Beobachtungszeitraum wurden insgesamt 569.537 Augen ambulant an der Universitäts-Augenklinik untersucht. Unter diesen fanden sich 648 Fälle (0,114%) mit der Diagnose neovascular glaucoma (NVG). Von den betroffenen Augen entfielen 366 (56,5%) auf das linke Auge und 282 (43,5%) auf das rechte Auge. Die statistische Auswertung ergab eine signifikant höhere Prävalenz von NVG im linken Auge ($p < 0,001$) mit einer berechneten Odds Ratio von 1,298. Eine logistische Regressionsanalyse zeigte zudem eine signifikante Assoziation zwischen dem Seitenunterschied und dem Vorliegen eines Diabetes mellitus ($OR = 1,46$; $p = 0,035$). Alle weiteren erhobenen Variablen zeigten keinen signifikanten Einfluss.

Diskussion: Signifikant häufiger war das linke Auge vom NVG betroffen als das rechte ($OR = 1.30$; $p < 0.001$). Zudem zeigte sich eine Assoziation zwischen einem linksseitigen NVG und dem Vorliegen eines Diabetes mellitus.

Abstract

Introduction: NVG accounts for approximately 3.9% of all glaucoma cases. With a prevalence of 0.01-0.12% in Europe, it is a rare but potentially blinding disease. As a secondary glaucoma, certain diseases precede the pathology, with the most common being diabetic retinopathy, central retinal vein occlusion, and ocular ischemic syndrome. In theory, the left and right eye should be affected at approximately equal rates. However, studies show an asymmetry in cerebrovascular events, which may potentially influence diseases of the ocular vessels. The aim of this study is to investigate a potential side difference in the occurrence of this secondary form of glaucoma.

Methods: A retrospective data analysis was carried out using data from the in-house database and the patient management system of the Department of Ophthalmology of the Medical University of Graz. Data were collected from all patients who had at least one outpatient visit with a diagnosis of NVG between December 1996 and April 2024. The primary characteristic analyzed was the affected side, categorized as right, left, or bilateral. In addition, several patient characteristics were collected.

Results: During the observation period, a total of 569,537 eyes were examined on an outpatient basis at the University Eye Clinic. Among these, 648 cases (0.114%) were diagnosed with NVG. Of the affected eyes, 366 (56.5%) were left eyes, and 282 (43.5%) were right eyes. Statistical analysis revealed a significantly higher prevalence of NVG in the left eye ($p < 0.001$) with a calculated odds ratio of 1.298. A logistic regression analysis revealed a significant association between the side difference and the presence of diabetes (OR = 1.46; p = 0.035). All other secondary variables surveyed showed no significant influence.

Discussion: Significantly more left eyes than right eyes were affected by NVG (OR = 1.30; $p < 0.001$). An association between left-sided NVG and diabetes was observed.

Contents

List of abbreviations

Symbols

5-FU 5-fluorouracil

A

AMD age-related macular degeneration

B

BRVO Branch Retinal Vein Occlusion

C

CRAO central retinal artery occlusion
CRVO Central Retinal Vein Occlusion

D

DME diabetic macular edema
Dpt diopters
DR diabetic retinopathy

E

EPC endoscopic CPC

G

GDD glaucoma drainage device
GFS Glaucoma filtration surgery

I

ICA iridocorneal angle
IMT intima-media thickness
IOP intraocular pressure
IPH intraplaque hemorrhage

M

MMC mitomycin C
MP-TSCPC transscleral micropulse CPC

N

NPDR Non-proliferative Diabetic Retinopathy
NVG neovascular glaucoma

O

OCT optical coherence tomography
OIS occular ischemic syndrom
OR odds ratio

P

PDGF platelet-derived growth factors
PDR Proliferative Diabetic Retinopathy
PIGF placental growth factor
PRP Panretinal Photocoagulation

R

RVO Retinal Vein Occlusion

T

TSCPC Transscleral Cyclophotocoagulation

V

VEGF vascular endothelial growth factor

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Chapter 1

Introduction

1.1 Glaucoma

Glaucoma constitutes a heterogeneous group of diseases that lead to blindness through optic nerve head damage. The main finding and often the first indication for diagnosis is elevated intraocular pressure (IOP). Due to the gradual but slow progression of vision loss and neurological compensation mechanisms for blind areas of the visual field, significant optic nerve damage may already be present upon diagnosis. In low and middle-income countries, an estimated 90% of glaucoma cases are undiagnosed. In high-income countries, it is still half of the cases. Approximately 95 million people worldwide are affected and mostly suffer from vision problems and associated limitations in daily life. Around 10 million glaucoma patients are blind in at least one eye, making glaucoma the leading global cause of irreversible blindness. While it is still not possible to reverse the vision loss caused by glaucoma, early detection and effective treatment can significantly slow down disease progression.[1][2] The greatest risk factor in the development of glaucoma is age. The majority of glaucoma patients are over 40 years old. Approximately 10% of people over 75 have open-angle glaucoma. It is noteworthy that different ethnicities have varying high risks for developing glaucoma. Among Hispanics, the likelihood of developing glaucoma is significantly higher than the global average, especially in old age. In the population of African descent, the risk is about twice as high, and the disease progression is also more severe. The relationship between blood pressure and the development of glaucoma is not fully understood. Some studies have shown an increased risk in individuals with either high or low blood

pressure. Alcohol and nicotine do not have a clear influence on the development of glaucoma. However, it has been shown that patients with open-angle glaucoma and normal IOP, known as normotensive glaucoma, are often women, particularly those with migraines or Raynaud's syndrome. In most cases, glaucoma patients have elevated IOP, which is also a risk factor.[3] Glaucomas also have a genetic component. If first-degree relatives are affected by a glaucoma diagnosis, the individual's risk increases by almost 8 times compared to the general population. Angle-closure glaucomas can often go unnoticed for a long time until there is suddenly an acute glaucoma attack. This is characterized by symptoms such as blurred vision, seeing rainbows and halos around light sources, nausea, vomiting, and even complete vision loss. The reason for this is the sudden increase in IOP. Approximately half of the patients experiencing angle-closure attacks suffer damage to the optic nerve, and the chance of experiencing permanent vision loss due to an acute glaucoma attack is 10%. Another risk factor for the development of glaucoma is myopia. Individuals with more than -3 diopters (Dpt) have a 3 times higher risk of glaucoma, and those with over -6 Dpt have an even higher risk. This is concerning as currently about 34% of the world's population suffers from myopia, with a projected increase to around 40% by 2030 and a further increase thereafter.[1][2]

1.2 Classification, Epidemiology and Etiology

1.2.1 Classification

1.2.2 Epidemiology

With 65 million people affected by open-angle glaucoma, the majority of patients have this form, while 30 million suffer from angle-closure glaucoma.

Currently, NVG accounts for about 3.9% of all cases of glaucoma. Although this represents a relatively small proportion, in these cases, the damage to the retina and associated loss of vision is often severe. Demographically, this type of glaucoma is more common in individuals over the age of 50. In the European Union, an estimated 75,000 to 113,000 people are affected by NVG, with an annual incidence of 3,800 new cases.

Approximately half of all cases of glaucoma-induced blindness can be attributed to the angle-closure type, as it often has a more severe course. Angle-closure glaucomas are most prevalent in Asia, especially among older women. Although glaucomas are strongly associated with increased IOP, half of all patients have normal intraocular pressure. Additionally, the majority of individuals with an IOP above the upper limit of 21 mmHg do not develop glaucoma within their lifetime, even without treatment. Secondary glaucomas occur when an eye disease causes a very high increase in IOP. Common causes of secondary glaucoma include uveitis, ocular trauma, and neovascularization of the anterior segment. Secondary glaucomas often lead to severe vision loss as the IOP can rise significantly in affected eyes.[1][2]

1.2.3 Etiology

Glaucomas are classified into primary, secondary, and congenital forms. Primary refers to the absence of an underlying condition that causes glaucoma. Secondary glaucomas represent an increase in IOP and subsequent optic nerve damage caused by an ocular condition. Furthermore, a distinction is made between open-angle glaucoma and angle-closure glaucoma. To differentiate between them, one must be aware of the anatomy of the anterior chamber of the eye.

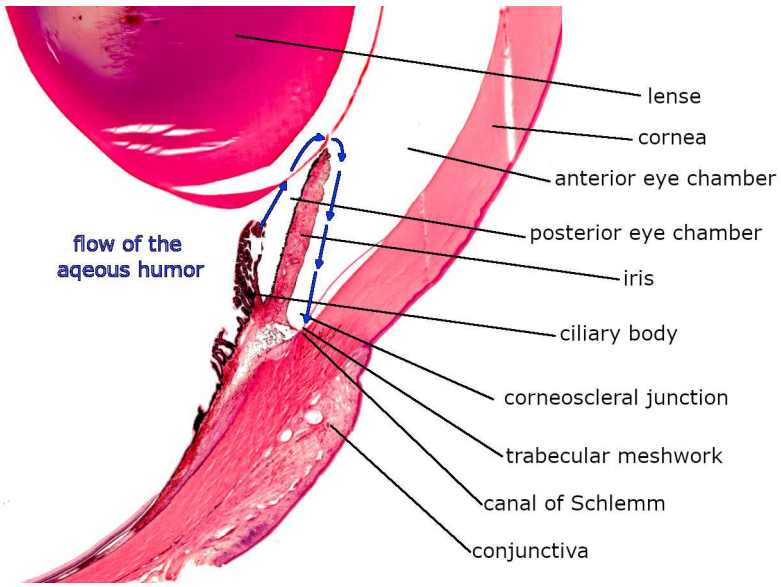

Figure 1.1: Anterior Segment of the eye, Haematoxylin-eosin stained medical facutly of the university of Basel. Autor: U.M. Spornitz

The aqueous humor produced by the ciliary body enters the anterior chamber between the iris and the pupil and flows through the iridocorneal angle into drainage channels. As the name suggests, in open-angle glaucoma, the anterior chamber angle is open, unlike in angle-closure glaucoma. However, this does not necessarily mean that the aqueous humor drainage is adequate. Reasons for that are:

An obstruction of the trabecular meshwork by accumulated material

A loss of trabecular endothelial cells

A reduction in trabecular pore density and size in the inner wall endothelium of the Schlemm canal

A loss of giant vacuoles in the inner wall endothelium of the Schlemm canal

A loss of normal phagocytic activity

Disturbance of neurologic feedback mechanism[4][5]

1.3 Neovascular Glaucoma (NVG)

1.3.1 Etiology

Neovascular Glaucoma (NVG) can arise from both ocular and systemic diseases. Common ocular ischemic causes include central retinal vein occlusion, diabetic retinopathy, carotid insufficiency or ocular ischemic syndrome, sickle cell retinopathy, radiation retinopathy, central retinal artery occlusion, retinopathy of prematurity, familial exudative vitreoretinopathy, and persistent hyperplastic primary vitreous. Inflammatory triggers include uveitis, trauma, Eales disease, retinal vasculitis, anterior segment ischemia, endophthalmitis and extraocular inflammatory vascular causes such as Giant Cell Arteritis and temporal arteritis. Retinal diseases that can lead to NVG include long-standing retinal detachment, proliferative vitreoretinopathy, Coats disease, retinoschisis, and detachment associated with intraocular tumors. Tumors can also cause NVG. These include choroidal melanoma, iris melanoma, retinoblastoma, intraocular metastases, ciliary body medulloepithelioma, vasoproliferative tumors of the retina, hyperviscosity syndromes, and myeloproliferative disorders. The three most common triggers of NVG are diabetic retinopathy (33%), central retinal vein occlusion (33%), and ocular ischemic syndrome (13%). It is worth noting that 60% of individuals with central retinal vein occlusion develop new vessels in the anterior segment of the eye within a few weeks to two years, and 40-45% of this group develop NVG within just 6-8 months. In cases of diabetic retinopathy, 65% of individuals show vessel formation

in the iris, and 20% develop NVG. Diabetics with NVG in one eye have a 33% chance of developing NVG in the other eye as well.[6][7]

1.3.2 Pathogenesis

NVG is a secondary form of glaucoma. The ingrowth of new blood vessels leads to obstruction of the iridocorneal angle (ICA). This results in inadequate drainage of aqueous humor, leading to an increase in IOP. Chronically elevated IOP can damage the optic nerve and, in the worst case, lead to blindness.[6] This form of glaucoma was first described in 1871 and has been given various names throughout history, such as congestive glaucoma, rubeotic glaucoma, and diabetic hemorrhagic glaucoma. The term neovascular glaucoma was first coined in 1906 by Coats, when histopathologically, new retinal blood vessels on the iris surface were demonstrated in a patient with Central Retinal Vein Occlusion (CRVO).[8] In 1928, Salus discovered similar blood vessel formations in a patient with diabetes. Finally, in 1963, Weiss introduced the term neovascular glaucoma to describe a condition associated with neovascularization of the iris, fibrovascular membrane in the ICA, and elevated IOP. [6]. NVG arises from the formation of new blood vessels in the iris and the anterior chamber angle. The reason for this is ischemia of the retina, which leads to the release of vasogenic substances. This creates an imbalance between pro-angiogenic substances such as vascular endothelial growth factor (VEGF), hepatocyte growth factor, insulin-like growth factor, tumor necrosis factor, inflammatory cytokines (especially IL-6), and anti-angiogenic substances such as transforming growth factor (TGF-β), thrombospondin, and somatostatin. The most important mediator, however, is VEGF, which is produced by various retinal cells such as pericytes, retinal pigment epithelium, Müller cells, ganglion cells, and especially non-pigmented ciliary epithelium. When this substance reaches the anterior chamber of the eye from the posterior eye segment, it can initiate neovascularization from the minor and major arterial rings of the iris. Furthermore, very high levels of VEGF also deteriorate the blood-retina barrier due to increased adhesion of leukocytes to the endothelial cells. In addition, TGF-β and fibroblast growth factor stimulate the proliferation of fibroblasts and the formation of fibrovascular membranes over the iris and the ICA. As a result of these mechanisms, drainage of aqueous humor is impaired, leading to an increase in IOP. In connection with retinal hypoperfusion, there is an imbalance between the IOP and the arterial perfusion pressure of the retina, leading to

a significant reduction in retinal blood flow. If not treated promptly, this can quickly lead to irreversible retinal damage and even blindness.[6]

1.3.3 Vascular endothelial growth factors (VEGF)

Vascular endothelial growth factors (VEGF) are key molecules in the initiation and guidance of neovascularization. VEGFs belong to the family of platelet-derived growth factors (PDGF). They are not only part of angiogenesis but also of vasculogenesis, which is the formation of new vessels in embryogenesis. Under physiological conditions, VEGF is responsible for embryonic vascular development and the formation of collateral vessels after trauma, in muscles after high physical exertion, or in occluded vessels. However, VEGF is also released under pathological conditions, promoting increased vascularization of growing tumors to supply them with sufficient oxygen and nutrients. Currently, six subtypes of VEGF are known: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PIGF).

VEGF-A is considered the most potent and important factor in angiogenesis. When referring to VEGF, usually VEGF-A is meant. It plays an important role in vasculogenesis and neoangiogenesis, causing cell proliferation, inhibition of apoptosis, increased vascular permeability, vasodilation, and recruitment of inflammatory cells to the injury site.

VEGF-B is already released in the early embryonic stage and plays a role in the development of the cardiovascular system and the myocardium, but is not essential for these. It is currently suspected that VEGF-B plays a role in maintaining certain cells, such as smooth muscle cells, endothelial cells, pericytes, neurons (motor neurons in the spinal cord, cortex, or retina), and cardiomyocytes.

VEGF-C is expressed in embryos to promote the growth of lymphatic vessels. An increased amount correlates with a well-developed lymphatic system, which may represent the genetic transfer of the factor as a new treatment strategy for patients with lymphedema. As an adult, VEGF-C is found in the heart, ovary, placenta, intestine, thyroid, and other tissues.

VEGF-D has similar properties to VEGF-C and is also involved in the formation of lymphatic vessels. However, its role is less significant, so genetic inactivation of the responsible gene does not show severe consequences.

VEGF-E is primarily a component of the parapoxvirus Orf, which mainly infects goats and sheep. VEGF-E, similar to VEGF-A, increases vascular permeability and also has a mitogenic effect on endothelial cells.

PIGF was first discovered in human placental tissue. There, it initiates trophoblast growth and differentiation, trophoblast invasion, and blastocyst implantation. Its effect is mainly based on synergism with VEGF-A, through which it enhances effects such as an increase in vascular permeability, cell migration, and proliferation.[9][6]

1.3.4 Treatment

The treatment of NVG comprises four key aspects:

1. Treatment of retinal ischemia in order to reduce the stimulus for neovascularization:
    a. Intravitreal anti-VEGF agents
    b. Panretinal photocoagulation
2. Treatment of the underlying systemic disease, if present, in order to improve retinal blood flow
3. Control of IOP
4. Control of inflammation (e.g. in uveitis)[6][10][7]

Type of treatment depends on disease severity. Depending on how advanced the glaucoma is, different treatment methods can be used:

Stage	Description	Ocular features	Treatment			
			PRP	Anti-VEGF	AGM	GFS
I	Preglaucoma	NVI	+	+	-	-
II	Open angle	Elevated IOP, NVA	+	+	+	+/-
III	Closed angle	Elevated IOP, NVA	+	+	+	+

Table 1.1: Therapeutic Strategies in various stages of neovascular glaucoma[7]
AGM=Anti-glaucoma medication, GFS=Glaucoma filtration surgery, IOP=Intraocular pressure, NVA=New vessels in angle, NVG=Neovascular glaucoma, VEGF=Vascular endothelial growth factor

1.3.4.1 PRP

PRP is a widely used treatment of NVG. Once retinal ischemia is present, PRP should be considered as a therapeutic option. It is not relevant whether only rubeosis iridis is

present or an advanced form of NVG with peripheral anterior synechiae. It is important that therapy is initiated without much delay. Tthe non-perfused retinal area is treated with laserphotocoagulation in one or multiple sessions. By destroying ischemic extramacular retina, the production and thus the amount of VEGF in the eye are also reduced, leading to a decrease in NV. The treated tissue scars over time and deposits pigment more strongly, leaving visible laser scars at the level of the retinal pigment layer (RPE).

PRP is generally performed at a laser-equipped slit lamp or an automated navigated peripheral laser is used. If the view of the fundus is limited, anterior retinal cryotherapy (ARC) and/or with anti-VEGF may be a better option. In severe cases, anti-VEGF therapy can be combined with PRP, and endocyclophotocoagulation.[11]

Studies have shown that PRP reduces the risk of severe vision loss by over 50%. The greatest benefit is obtained by individuals with high-risk proliferative diabetic retinopathy.

However, PRP should be performed with caution. In addition to ischemic tissue, healthy areas can also be destroyed. PRP should also not be used as a monotherapy, as this can contribute to a further increase in IOP and thus promote neovascularization of the optic nerve head.[7][12]

1.3.4.2 Anti-VEGF Therapy

In 2004, pegaptanib became the first anti-VEGF agent approved for intravitreal injection to treat neovascular age-related macular degeneration. Since then, several other agents have entered the market, including bevacizumab (Avastin), ranibizumab (Lucentis), aflibercept (Eylea), brolucizumab (Beovu) and more recently, Faricimab (Vabysmo).

Bevacizumab is a human recombinant monoclonal IgG antibody that inhibits all forms of VEGF. A retrospective study in 2017 investigated 26 eyes of 26 NVG patients who received bevacizumab therapy as part of their treatment. The medication was administered intracamerally before PRP was performed. Subsequently, during the follow-up, bevacizumab was repeatedly administered when the IOP exceeded 21 mmHg or a prominent recurrence of NVA/NVI was detected. The study showed that the IOP was significantly reduced in 22 eyes of the participants (baseline: 39.79 ± 5.33 mmHg; 1

week after: 16.5 ± 3.4 mmHg). However, in 4 other eyes, the reduction was insufficient, and surgical measures to reduce IOP were required within a week. Twelve months after the first injection, the IOP in 19 additional eyes was not adequately reduced with VEGF therapy and also required surgery.[13]

Ranibizumab is a recombinant, humanized, antigen-binding fragment of a monoclonal antibody that binds to all isoforms of VEGF and neutralizes them. In a study published in 2022, the impact of a single preoperative dose of ranibizumab was examined in 13 eyes of 11 NVG patients. The combination of Glaucoma filtration surgery (GFS) with intravitreal administration of the drug one week before the surgery significantly reduced IOP (preoperative IOP was 48.5 ± 11.76 mmHg; postoperative IOP 1 week after was 20.88 ± 4.91 mmHg; 1 month after was 19.71 ± 2.69 mmHg).[14] In a prospective, single-center, 12-month interventional case series study from 2013, 20 patients with rubeosis and NVG were injected with ranibizumab intravitreally at the beginning and monthly if necessary. The authors concluded that adjuvant therapy with ranibizumab provides an advantage in the treatment of NVG.[15]

Brolucizumab is a fragment of a humanized monoclonal single-chain Fv antibody. Brolucizumab has been shown to have a higher affinity for VEGF-A isoform than bevacizumab. Due to its smaller molecular size, it can penetrate the retina faster. In 2019, brolucizumab was approved by the Food and Drug Administration (FDA) for the treatment of neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME). A year later, it also received approval in Europe.[7][16][6]

Aflibercept is a soluble decoy receptor consisting of the core domains of human IgG1 with an estimated 100-fold higher affinity for VEGF-A than ranibizumab. Decoy receptor means that VEGF binds to aflibercept instead of its actual receptors, rendering it ineffective. A randomized, sham-controlled, double-masked, phase 3 study conducted in Japan in 2020 analyzed intravitreal aflibercept monotherapy in individuals with NVG. The study included 54 patients with anterior segment neovascularization and an IOP of over 25 mmHg. In the group receiving the actual medication, the IOP decreased on average by 9.9 mmHg, while the IOP in the control group decreased by 5 mmHg. Additionally, the treatment group showed an improvement in the degree of NVI. Aflibercept was approved by the FDA in 2011 for the treatment of neovascular (wet) AMD, in 2014 for the treatment of AMD, and in 2015 for the treatment of diabetic retinopathy in patients with DME. In 2015, Aflibercept was also approved by the

European Commission for the treatment of macular edema secondary to retinal vein occlusion, both central and branch.[17][9][**?**]

1.3.4.3 Anti-Glaucoma Medication

IOP lowering medication can be topical and systemic. The most prevalent groups of active substances are the following:

Alpha-agonists (apraclonidine, brimonidine)
Beta-blockers (timolol, betaxolol, carteolol, levobunolol,etc.)
Carbonic anhydrase inhibitors (brinzolamide, dorzolamide)
Miotics (pilocarpine,etc.)
Prostaglandins (latanoprost, bimatoprost, travoprost, etc.)
Rho-Kinase-Inhibitores (Risasudil k-115, Netarsudil AR-13503)

Prostaglandin analogs need to be administered once daily and mainly have local side effects such as hyperemia, lengthening of lashes, darkening of iris color, and periocular skin pigmentation. These are reversible and generally disappear after discontinuation of the medication. Miotics, which can worsen inflammation and promote synechial closure of the chamber angle are less effective.[7][16][18]

Another, generally well-tolerated group of drugs are beta-blockers. However, a significant portion of the medication is absorbed through passage through the nasolacrimal duct, posing a risk for systemic side effects. These include breathlessness, reduced exercise tolerance, and fall risk. These side effects particularly affect older patients. For individuals with respiratory or certain heart conditions, beta-blockers are therefore contraindicated as a topical therapy.[7][16][18]

Topical alpha-agonists and carbonic anhydrase inhibitors can also be used to lower intraocular pressure, but they are significantly less effective as they rarely reduce IOP by more than 3 mmHg.

In addition to topical carbonic anhydrase inhibitors, acute glaucoma patients can also be treated with systemic carbonic anhydrase inhibitors such as acetazolamide. However, in addition to the greater reduction in IOP, they also pose more side effects such as an increase in potassium levels. Regular blood work is therefore necessary. [19][20][7][16][18]

1.3.4.4 Surgical Treatment

1.3.4.5 Glaucoma filtration surgery (GFS)

GFS is indicated when all other treatment options have been exhausted and the IOP could not be controlled. Other indications for surgery are a closed chamber angle due to synechiae. This applies to approximately half of all eyes with NVG.

Trabeculectomy remains the gold standard for surgical treatment options with the greatest IOP-lowering effect. During the procedure, a fistula is created to connect the anterior chamber of the eye with the subconjunctival space (creating a so-called "bleb"), providing an alternative outflow for the aqueous humor into the subconjunctival space. While the procedure should ensure long-term and adequate drainage of the aqueous humor, it also bears the possibility of severe complications, such as hypotony, bleeding, scarring, inflammation, and bleb failure.[21]

A significant improvement is seen with the additional use of antimetabolites and antifibrotics such as mitomycin C (MMC) and 5-fluorouracil (5-FU). MMC is often used after performing a trabeculectomy. By inhibiting conjunctival and episcleral fibroblast proliferation, it prevents excessive scarring. Studies have shown that the success rate of trabeculectomy in combination with MMC in eyes with NVG triggered by proliferative diabetic retinopathy (DR) ranges from 62.6% to 81.2%. However, the rate of adequate outflow decreases to 51.3% after 5 years.[22][23]

It is worth noting that preoperative intravitreal administration of bevacizumab reduces the risk of postoperative hyphema in trabeculectomy with MMC and improves the surgical outcome.

Antimetabolites can also lead to complications such as postoperative hypotony, corneal toxicity, and a thinning of the wall of the filtration bleb, which creates an overdrainage of the aqueous humor and thus an increased risk of inflammation. For this reason, possible alternatives for antimetabolites and their method of inhibiting the wound healing process have been investigated in recent years. Among others, anti-VEGF agents have shown promise. VEGF is produced by endothelial cells, macrophages, fibroblasts, platelets, neutrophils, and smooth muscle cells, all of which are involved in wound healing. In addition to angiogenesis, VEGF also stimulates epithelialization and collagen deposition. Studies have also shown that patients with failed trabeculectomy have significantly higher VEGF concentrations in the aqueous humor and ocular

tissue compared to patients with adequate filtration. This phenomenon persists for approximately one year postoperatively.[6][7][24]

1.3.4.6 Glaucoma drainage devices and minimally invasive Glaucoma surgery

In the event of a failed trabeculectomy or the inability to obtain a positive postoperative outcome due to conjunctival scarring, the insertion of a glaucoma drainage device (GDD) is necessary. It is also often used as a primary procedure because it allows an adequate reduction in pressure, without the risks of a trabeculectomy.[25] A distinction is made between two main types:

1) valved or flow-restrictive implants (Ahmed glaucoma valve (AGV))
2) valveless implants (i.e. Baerveldt, Molteno, XEN, PreserFlo and Aurolab aqueous drainage implant (AADI))

In patients with NVG, valved implants are often preferred as they can adequately lower IOP in a short period of time and have a lower risk of developing ocular hypotony and iris damage. The success of valved GDD in NVG is influenced by certain factors. Age plays an important role, as younger patients have stronger wound healing and fibrous encapsulation development. Studies have shown that the preoperative use of bevacizumab does not lead to a significant difference in IOP reduction compared to the sole implantation of GDD. However, preoperative adjuvant administration of bevacizumab can improve the success rate of GDD implantation.[26][27]

Currently, the availability of scientific data comparing various surgical methods for the treatment of NVG is limited. The decision for surgery is primarily based on the patient's condition and the expertise of the surgeon. According to the literature, the difference in IOP reduction between glaucoma trabeculectomy and GDD implantation is comparable. [6][7]

1.3.4.7 Transscleral Cyclophotocoagulation (TSCPC)

Transscleral Cyclophotocoagulation (TSCPC) is a cyclodestructive procedure used for more refractory NVG once other surgical treatment options and medications have been exhausted without achieving an adequate reduction in IOP. The principle of TSCPC is to destroy the secretory epithelium of the ciliary epithelium, thereby reducing the pro-

duction of aqueous humor. The most commonly used types are transscleral micropulse CPC (MP-TSCPC) and endoscopic CPC (EPC). Both work by applying a diode laser with a wavelength of 810nm. The advantage of EPC is that, in addition to the laser system, a video camera and an illumination probe are used. This allows for better visualization of the ciliary body's response to the treatment and spares surrounding tissue. In MP-TSCPC, the laser is delivered in repetitive pulses, limiting the rate of temperature increase in the tissue and preventing coagulation necrosis and damage to adjacent tissue. Since MP-TSCPC does not represent a classic cyclodestructive procedure, it has been suggested to instead call it Micropulse Transscleral Laser Treatment (MP-TLT).[7][6][28]

1.4 Diabetic Retinopathy (DR)

1.4.1 Epidemiology

Diabetic retinopathy (DR) is the leading cause of blindness among working-age adults worldwide. The global burden of this disease is significant: Currently, there are 387 million people with diabetes mellitus (DM) worldwide, and this number is expected to rise to 592 million by 2035. Of these, 93 million suffer from diabetic retinopathy, meaning that approximately one in three individuals with diabetes mellitus is affected by this complication.

Approximately 30-40% of all diabetics suffer from diabetic retinopathy (DR). This accounts for around 100 million people worldwide, of whom approximately one-third have visual impairments and 7.6% have macular edema. Thus, DR is also one of the leading causes of visual impairment and blindness among working-age adults. Due to the continuous improvement in the early detection and treatment of DR and diabetes in general over the past few decades, the numbers of those affected are declining. This is in part due to better control of systemic risk factors and, on the other hand, due to specific ocular assessment, screening, imaging, and treatment.[29]

Within this group, 17 million people suffer from proliferative diabetic retinopathy (PDR), while 21 million have diabetic macular edema. Alarmingly, 28 million people have vision-threatening diabetic retinopathy. The prevalence of DR is widespread worldwide, showing only slight ethnic differences. The global prevalence of DR among

patients with type 1 diabetes is 77.3%, while among those with type 2 diabetes, it is 25.1%. Experts believe that changes in diet and lifestyle significantly contribute to the increasing prevalence. Additionally, earlier diagnosis of DR due to improved healthcare systems contributes to the rising prevalence figures.[30]

In Europe, approximately 3% to 4.1% of the population is affected by diabetic retinopathy. Among those over 60 years of age, prevalence is highest in France, followed by Germany. The prevalence of diabetic retinopathy among patients with type 2 diabetes varies significantly across European countries: In the United Kingdom, it is 30.3%, in Spain 26.1%, in Italy 22.2%, in Germany 21.7%, and in Portugal 16.3%.[31–36]

Regarding the different forms of diabetic retinopathy, country-specific differences are also evident. In the United Kingdom, the prevalence of nonproliferative diabetic retinopathy (NPDR) is 48%, while in Spain, it is 38,9% and in Germany 10%. The prevalence of proliferative diabetic retinopathy (PDR) is highest in the United Kingdom at 2.9%, while in Spain it is 0.56% and in Germany 0.5%. These data highlight the significant health burden that diabetic retinopathy presents both globally and in Europe, emphasizing the need for effective prevention and treatment strategies. [31–34]

1.4.2 Pathophysiology

DR is primarily driven by chronic hyperglycemia, which activates metabolic pathways such as the polyol pathway, advanced glycation end products (AGEs), protein kinase C (PKC), and hexosamine pathways, leading to retinal vascular damage.[37]

Initially, hyperglycemia causes retinal vessel dilation and altered blood flow, likely as a metabolic adaptation. However, sustained high glucose levels lead to pericyte loss, weakening capillary walls and resulting in microaneurysms, which are early clinical signs of DR.[38] Endothelial cell loss and basement membrane thickening further impair the blood-retina barrier (BRB), contributing to vascular dysfunction. Over time, capillary occlusion and ischemia trigger hypoxia-inducible factor 1 (HIF-1), leading to increased VEGF expression. VEGF disrupts vascular integrity by affecting tight junction proteins and promoting endothelial cell proliferation, exacerbating Proliferative Diabetic Retinopathy (PDR) and DME.[39] Other angiogenic factors, such as angiopoietins (Ang-1, Ang-2), also influence vascular permeability and may offer alternative therapeutic targets.[40]

Chronic inflammation is another key driver of DR. Leukostasis, characterized by excessive leukocyte adhesion to retinal vessels, damages endothelial cells and weakens the BRB. Increased expression of adhesion molecules (ICAM-1, VCAM-1, and selectins) and inflammatory cytokines (TNF-, IL-6, IL-8, IL-1) has been observed, correlating with disease severity.[41] Chemokines such as MCP-1 contribute to immune cell recruitment, further exacerbating vascular damage. Retinal glial cells, including microglia and Müller cells, amplify inflammation by releasing pro-inflammatory cytokines and VEGF.[42]

Neurodegeneration is now recognized as an early and independent process in DR. Retinal neuron apoptosis occurs soon after diabetes onset, associated with mitochondrial dysfunction, oxidative stress, and increased reactive oxygen species (ROS) production. Suppression of ROS has been shown to prevent neuronal apoptosis and visual impairment.[43] Notably, neuronal loss and retinal thinning have been detected in diabetic patients before significant microvascular alterations, highlighting the need for neuroprotective strategies in early DR management.[44, 45]

1.4.3 Diagnosis

For the diagnosis and assessment of the severity of DR, funduscopy is well suited and cost-effective. DR is generally classified into proliferative and non-proliferative. Non-proliferative DR is further divided into three severity grades: Mild: Only a few microaneurysms are present. Moderate: Characterized by an increased number of microaneurysms and dot-blot hemorrhages. Dot-blot hemorrhages are bleedings into the inner and outer plexiform layers of the retina. Additionally, hard exudates and so-called cotton-wool spots can be observed. Cotton-wool spots are white-yellowish, cotton-like lesions caused by axonal swelling in the stratum neurofibrarum. Severe: ”4-2-1-rule“: More than 20 intraretinal hemorrhages in 4 quadrants or venous beading in 2 or more quadrants or at least one quadrant with intraretinal microvascular abnormalities.

Although therapeutic intervention is generally not undertaken at this stage, emerging evidence indicates that anti-VEGF injections may reduce the severity of retinopathy and lower the risk of subsequent visual complications.

DR is considered proliferative once at least one of the following changes exists: Neovascularization involving 1/4 to 1/3 of the optic disc Any neovascularization of the optic

disc associated with vitreous or preretinal bleeding Any neovascularization elsewhere associated with vitreous or preretinal bleeding

In any form and severity of DR, macular edema can also develop. This is characterized by thickening of the macula. To determine the presence and location of the underlying fluid accumulation in or under the retina, as well as the actual thickness measurement, optical coherence tomography (OCT) is used.[46][29]

1.5 Central Retinal Vein Occlusion (CRVO)

1.5.1 Epidemiology

Retinal Vein Occlusion (RVO) is the second most common cause of retinal vascular blindness after DR. It is classified into Branch Retinal Vein Occlusion (BRVO), CRVO, and hemiretinal vein occlusion (HRVO). Among these, BRVO is the most common RVO, with a worldwide prevalence of 0.4%, followed by CRVO at 0.08%. The greatest risk factor for developing RVO is a history of RVO in the contralateral eye. Individuals who have already experienced BRVO in one eye have a 10% risk of developing any type of RVO in the second eye within 3 years. The same risk for CRVO in one eye is estimated to be 1% per year, increasing to 7% after 5 years.[47]

1.5.2 Pathophysiology

The pathophysiology of CRVO is not yet fully understood. Initially, it was assumed that CRVO is caused by the formation of a thrombus. Thrombi are formed due to imbalances in Virchow's triad, which describes changes in the vessel wall, alterations in blood flow, and changes in blood composition. The fact that comorbidities that promote thrombus formation have also been observed in patients with CRVO supports this hypothesis. These comorbidities include systemic diseases such as hypertension, diabetes, obesity, and atherosclerosis, which modify blood pressure and hemodynamics in the central retinal vein through the activation of endothelial cells, thereby inducing a prothrombotic state. Thrombus formation is regulated by a complex interaction between endothelial cells, exposed subendothelial matrix, platelets, and fibrin. Once a blood clot has formed, the anticoagulation system is activated and stops further clot

formation. Any imbalance between the procoagulation and anticoagulation systems increases the risk of thrombus formation. However, postmortem studies have shown inconsistent occurrence of thrombi in the central retinal vein in patients with CRVO. Additionally, fluorescein angiography in CRVO patients does not show complete venous occlusion but rather a reduced flow rate.[48]

1.5.3 Diagnosis

In clinical diagnostics, a distinction is made between non-ischemic and ischemic, or perfused and non-perfused CRVO. Non-ischemic CRVO is by far the more common variant, accounting for approximately 75% of cases. Patients with non-ischemic CRVO typically present with sudden unilateral visual impairment, with visual acuity usually at 0.1 decimal or better. Additionally, some patients may exhibit a mild relative afferent pupillary defect (RAPD). Fundoscopy reveals tortuous and dilated branches of the central retinal vein, dot-blot and flame-shaped hemorrhages in all quadrants of the fundus, especially in the periphery, and edema of the optic disc and macula. Cotton-wool patches may also be present. Transient peeling of the retinal vascular wall may also occur in some cases. The acute signs typically resolve within 6-12 months, but in 15% of cases, non-ischemic CRVO progresses to ischemic CRVO within 4 months, and in 34% within 3 years. Ischemic CRVO involves rapid venous obstruction leading to retinal hypoperfusion, capillary closure, and retinal hypoxia. These patients typically experience severe visual loss, with residual visual acuity usually below 0.1, and may also exhibit an afferent pupillary defect. Fundoscopy in ischemic CRVO reveals twisting and engorgement of all branches of the central retinal vein, deep blot and flame-shaped hemorrhages in the peripheral retina and posterior pole, as well as severe edema and hyperemia of the optic disc. This can lead to NVG. In non-ischemic CRVO, fluorescein angiography (FA) reveals a significant delay in arteriovenous transit time, lasting longer than 20 seconds, which may be obscured by retinal hemorrhages and vessel wall staining. Late staining along the major retinal veins is a distinctive feature seen in moderate to severe cases of CRVO. In the ischemic form, there are extensive regions of capillary non-perfusion. The presence of more than 10 disc areas of retinal capillary non-perfusion is linked to an increased risk of neovascularization. Due to its rapid development within a few months, this form is also known as 100-day glaucoma. [49][48][50]

1.6 Ocular Ischemic Syndrome (OIS)

1.6.1 Epidemiology

occular ischemic syndrom (OIS) mainly affects older individuals, with an average age of 65. Men are affected about twice as often as women, which could be due to the higher prevalence of cardiovascular disease in men. Both eyes are affected in 20% of patients. The exact incidence of OIS is not entirely clear.[51]

1.6.2 Pathophysiology

OIS is caused by reduced blood flow to the vessels supplying the eyes. Patients usually have at least 90% stenosis of the internal or common carotid artery on the affected side. In 50% of cases, the occlusion is complete. OIS is rarely caused by occlusion of the ophthalmic artery.[52] Impaired blood flow in the carotid artery leads to reduced flow in the ophthalmic artery or even to retrograde flow. The blood is often shunted into the less resistant intracranial circulation instead of the eye, which is known as the steal phenomenon. The main cause of circulatory disturbance in the carotid arteries is atherosclerosis. Other causes are dissecting aneurysm of the carotid artery, giant cell arteritis, fibrovascular dysplasia, Takayasu arteritis, aortic arch syndrome, Behçet's disease, trauma or inflammation causing stenosis of the carotid arteries among others.[51]

1.6.3 Diagnosis

One of the symptoms of OIS is vision loss in the affected eye, which affects over 90% of patients. This is triggered by acute or chronic retinal ischemia or damage to the optic nerve due to secondary glaucoma (NVG). In about two-thirds of cases, vision loss occurs gradually over several weeks, while in 1/6 of cases, vision deteriorates within a few days, and in 1/6 of cases, it deteriorates within minutes or seconds. Patients with sudden central retinal artery occlusion (CRAO) often exhibit a cherry-red spot on the fundus, indicating embolization of the central retinal artery.[53]

Approximately 10% of individuals with OIS experience transient vision loss (Amaurosis fugax), which can be attributed to CRAO or, in some cases, vasospasms. It's important to note that the majority of transient vision losses are not caused by OIS.[52]

In patients with severe carotid artery stenosis, the recovery of vision after exposure to bright light is delayed, likely due to macular ischemia.[51][54]

Around 40% of patients report pain in the affected eye or periorbital area. Typically, the pain is caused by NVG, but there are also cases with normal IOP. In these cases, the pain may be due to ocular hypoxia or dural hypoxia.[52]

Although neovascularization in the anterior eye segment is observed in 66% of cases, only 50% of patients develop increased IOP and subsequent NVG. Some patients also exhibit ocular hypotony due to ischemia of the ciliary body reducing aqueous humor production.[53][52]

In individuals with unilateral OIS, the lens of the affected eye is usually more opaque. Due to ischemia and atrophy of the pupillary sphincter muscle, the pupil is rigid and semi-dilated. Additionally, the eye responds weakly to light stimuli (RAPD).[53]

However, pathological findings in the posterior eye segment are more common. Fundoscopy reveals narrowed arteries and dilated veins, with retinal hemorrhages present in 80% of cases, predominantly in the external retinal layer or mid-periphery. These hemorrhages are generally not numerous and do not confluence, likely resulting from blood leakage and rupture of capillary microaneurysms, which are common in the macula and mid-periphery in OIS. Another manifestation of OIS is the presence of cotton-wool spots, which occur due to microinfarcts. These microinfarcts cause swelling in the nerve fibers due to interrupted axoplasmic flow. [51][55]

1.6.4 Possible side difference

Studies have shown that the risk of a cerebrovascular event, such as rupture, intraplaque hemorrhage, and stroke, is higher in the left carotid artery than in the right.[56–58]

Chaubey et al. demonstrated that cardiovascular risk factors, such as HbA1c, waist-to-hip ratio, hypertension, LDL and smoking, affect intima-media thickness (IMT) and plaque formation differently in different arterial regions. For example, a 1% increase in HbA1c was on average associated with a 0.067 mm greater increase in IMT at

the bifurcation (p=0.004). In particular, IMT was greater at the bifurcation of the common carotid artery (CCA) compared to the proximal segments, and a significant side difference was observed with a thicker IMT on the left side. These results suggest that anatomical and haemodynamic variations may contribute to asymmetric vascular remodelling.[59]

Selwaness et al. analysed asymmetries in plaque composition in a cohort of 1414 individuals without stroke. Their study confirmed that plaques in the left carotid artery were more likely to have intraplaque hemorrhage (IPH) (9.1% vs. 5.9%; P¡0.001) and fibrous tissue (45.0% vs. 38.5%; P¡0.001), while plaques in the right carotid artery were more likely to be calcified (37.4% vs. 31.6%; P¡0.001). This difference may be explained by anatomical and haemodynamic factors, such as the direct connection of the left carotid artery to the aortic arch, which exposes it to different blood flow dynamics. As unstable plaques are more prone to embolisation, their predominance in the left carotid artery could have an impact on ocular vascular disease.[60]

Larson et al. investigated asymmetries in the prevalence of IPH in the carotid arteries and their association with ischaemic strokes. Their retrospective study of 368 patients with carotid stenosis showed that ischaemic strokes occurred more frequently on the left than on the right side (55.5% versus 44.5%, p=0.03). The prevalence of diabetes mellitus was higher in patients with left-sided strokes than in patients with right-sided strokes (35.9% vs. 21.3%, p = 0.02). In addition, IPH was significantly more common in left-sided plaques (64.1% vs. 36.2%, p¡0.0001) and independently associated with left-sided strokes. Interestingly, the extent of stenosis did not differ between the two sides. These results suggest that left-sided plaques are more vulnerable despite similar luminal narrowing and may increase the risk of ipsilateral ischaemic stroke.[61]

Anatomical differences in the course of the vessels and hemodynamic factors are suspected to be the cause. This side difference could be reflected in the occurrence of OIS. The aim of this study is to figure out whether there actually is a side difference in the occurrence of NVG and if so, whether a cause can be identified.

Chapter 2

Methods and Data

2.1 Statistical Methods

This thesis is a retrospective study approved by the Ethics Committee of the Medical University of Graz under the reference number 35-505 ex 22/23.

Retrospective data from the in-house database Eyemed and the current patient management program openMedocs were analyzed. The data included all patients who had at least one outpatient visit with the diagnosis of Neovascular Glaucoma (NVG). The main focus was on the affected eye side, categorized as right, left, or bilateral.

Using the statistical software SPSS 28, a possible relationship between the eye side and the occurrence of NVG was examined using the Chi-Square test and a logistic regression model. A significance level of $\alpha = 0.05$ was chosen. The alternative hypothesis states that there is a relationship between NVG and the eye side, while the null hypothesis expresses independence between these two features.

The initial analysis involved creating the frequency distribution of the different eye sides. Subsequently, the available data of all patients was further examined, and additional patient characteristics were examined. These include:

Demographic and baseline characteristics:
- Date of initial diagnosis
- Age at diagnosis
- Spherical equivalent (in diopters)

Ophthalmological status at baseline:
- Best Corrected Visual Acuity (BCVA)
- Intraocular pressure at the time of diagnosis
- Lens status (presence of a natural or artificial lens)
- Presence of an ACI stenosis on the same side

Previous ocular surgeries:
- Retinal laser coagulation
- Trabeculectomy
- Laser iridotomy
- Vitrectomy

Glaucoma management prior to diagnosis:
- Number of locally acting glaucoma medications administered prior to diagnosis

Pre-existing conditions relevant to neovascular glaucoma:
- Diabetes mellitus
- Central Retinal Vein Occlusion (CRVO)
- Ocular Ischemic Syndrome (OIS)
- Other documented causes

2.2 Study Population

The study included all patients who presented as outpatients at the Department of Ophthalmology of the Medical University of Graz between December 1996 and April 2024. The relevant patients were those initially diagnosed with NVG in at least one visit.

2.3 Data Collection

The data of the study participants were collected from the electronic communication and hospital information network openMEDOCS of the University Hospital of Graz and the internal database Eyemed of the Department of Ophthalmology of the Medical

University of Graz using a restricted access desktop PC. Data processing was indirect and strictly pseudonymised. Only authorized personnel had access to the original data.

2.4 Literature Review

Sources from the medical online database PubMed and articles from the National Library of Medicine's (MEDLINE) were used for the literature review.

2.5 Analysis

The data were summarized in tables and imported into SPSS 28. An initial Chi-Square test was conducted to identify any potential side differences in the occurrence of NVG. The null hypothesis H0 states that there is no difference in the frequency of NVG between right and left eyes. The significance level was defined as $\alpha = 0.05$. Hypothesis H1 states that there is a statistically significant difference in the frequency of NVG between the left and right eye. In addition, the odds ratio was calculated to quantify the possible side difference. A binary logistic regression analysis was conducted to investigate risk factors for the occurrence of NVG on a specific side.

Chapter 3

Results and evaluation

3.1 Results

Variable	Diabetes	CRVO	OIS	all
Age (yr)	68.5 ± 13.2	77.8 ± 10.6	74.1 ± 10.5	72.7 ± 13.6
Female sex	126 (44.4%)	118 (50.6%)	48 (42.1%)	285 (47.6%)
Phakia	179 (54.9%)	172 (72.6%)	76 (64.4%)	402 (62%)
Ocular Surgery	220 (67.5%)	124 (52.3%)	56 (47.5%)	391 (60.3%)

Values are presented as mean ± SD for age, as number of patients (%) for sex (n = 599), and as number of eyes (%) for phakia and ocular surgery (n = 648)

Table 3.1: Baseline Characteristics

During the observation period, a total of 569,537 eyes were examined at the outpatient department of the Department of Ophthalmology of the Medical University of Graz. Among these, 648 cases (0.114%) were diagnosed with NVG. The affected eyes were distributed as follows: 366 (56.5%) left eyes and 282 (43.5%) right eyes.

The baseline characteristics of the patients with NVG, including age, sex, phakia status, and history of ocular surgery, are summarized in Table 3.1.

3.1.1 Evaluation of the Main Variable

A chi-square test was performed to assess whether NVG occurs more frequently in the left or right eye. The analysis yielded a chi-square value of 10.8827 (p = 0.00097), indicating a statistically significant difference in NVG laterality. To further quantify this difference, an odds ratio (OR) was calculated. The OR for NVG occurring in the left eye compared to the right eye was 1.30 (95% CI: 1.11–1.52), indicating that the odds of NVG were approximately 30% higher in the left eye than in the right eye.

	Totals	**NVG, N(%)**	**no NVG, N(%)**	**OR (95% CI)**	**p-value**
Left	284800	366 (0.129)	284434 (99.871)	1.298 (1.1112, 1.5162)	.000971
Right	284737	282 (0.099)	284455 (99.901)	Reference	

Table 3.2: Number of cases, Odds-Ratio (OR), Confidence Interval (CI) and p-value (based on Chi-square test)

To quantify the difference between the two sides, an OR was calculated. In prospective studies, relative risk is typically preferred to compare disease incidence. However, in retrospective study designs like this one, the OR is more commonly used. The calculated OR was 1.298, meaning that the odds of NVG occurring in the left eye were approximately 30% higher than in the right eye. Since NVG is a relatively rare condition, the OR in this context closely approximates the relative risk. It is important to note, however, that the OR compares the odds of NVG occurrence between sides:

$$LeftSide/RightSide = Odds - Ratio \rightarrow 0,0013/0,0010 = 1,298$$

$$95\% \text{ confidence interval} =$$

$$\exp\left(\ln(\text{OR}) - 1.96 \times \text{SE}[\ln(\text{OR})]\right) \text{to } \exp\left(\ln(\text{OR}) + 1.96 \times \text{SE}[\ln(\text{OR})]\right)$$

$$= 1.1112 \text{ to } 1.5162$$

It can be concluded that in the observed time period of 27 years, the chance of NVG on the left eye was 1.298 times higher than on the right eye in the investigated population.

3.1.2 Evaluation of Secondary Variables

To examine associations between underlying diseases and NVG laterality, a binary logistic regression analysis was conducted. The dependent variable was the affected eye site (left vs. right), and independent variables included underlying conditions such as diabetes, CRVO, and OIS.Diabetes was found to be significantly associated with NVG laterality (OR = 1.458, 95% CI: 1.026–2.073, p = 0.035), whereas CRVO and OIS did not demonstrate statistically significant associations.

Underlying Disease	**Absolute Frequencies (Left/Right/Totals)**	**Left Odds Ratio (95% CI)**	***p*-value**
Diabetes	199 (61%) / 127 (39%) / 326	1.458 (1.026, 2.073)	0.035
CRVO	132 (55.7%) / 105 (44.3%) / 237	1.034 (0.709, 1.510)	0.861
OIS	61 (51.7%) / 57 (48.3%) / 118	0.765 (0.498, 1.174)	0.220

Table 3.3: Combined Frequencies, Totals, and Odds Ratios for underlying Diseases

Further subgroup analysis (Table 3.4) indicated that the combination of diabetes with CRVO and/or OIS resulted in an increased prevalence of NVG in the left eye, reaching up to 83.3% in cases where all three conditions were present.

Combination of disease	Right Eye	Left Eye	Totals
Diabetes & CRVO	14 (28%)	36 (72%)	50
Diabetes & OIS	21 (42%)	29 (58%)	56
Diabetes & CRVO & OIS	1 (16.7%)	5 (83.3%)	6
CRVO & OIS	4 (30.8%)	9 (69.2%)	13

Table 3.4: Side distribution of patients with Diabetes and CRVO and/or OIS

This analysis demonstrated a statistically significant laterality in NVG occurrence, with a higher prevalence in the left eye. The findings suggest a potential association between diabetes and increased NVG risk in the left eye. Although CRVO and OIS individually did not reach statistical significance, their combination with diabetes appeared to further increase left-sided NVG prevalence. Further studies are needed to investigate potential vascular and hemodynamic mechanisms contributing to this asymmetry.

Chapter 4

Discussion

This analysis revealed a side difference in the occurrence of neovascular glaucoma. NVG appeared more frequently on the left eye among outpatients at the Department of Ophthalmology of the Medical University of Graz over a duration of 28 years. Contrary to our assumption, subgroup analysis revealed no influence of OIS on the side distribution of NVG. However, the results of this study showed a correlation between diabetes and the development of NVG in left eyes. Similar asymmetries have been reported in the context of diabetic retinopathy. Valone et al. observed an asymmetrical occurrence of the DR. A combination of PDR in one eye and non-proliferative diabetic retinopathy in the fellow eye was seen in 10.1% of the patients. However, no remarkable differences were found regarding the incidence of glaucoma.[62] Duker et al. evaluated 387 consecutive patients with PDR for asymmetry in posterior segment neovascularization and its relationship to carotid artery disease. Over the 2-year period, 20 (5.2%) of the patients manifested asymmetric PDR which was defined as the presence of PDR with high-risk characteristics in one eye, in the absence of proliferative or preproliferative changes in the fellow eye. 14 of them were left-sided and six were right-sided. Only four of those 20 patients were found to have hemodynamically significant carotid artery stenoses, with only two on the ipsilateral side of their PDR.[63] We also tried to evaluate the hemodynamic status of the patients of our study, but the data was incomplete or inaccessible. This observed laterality in the development of PDR raises the question of possible underlying systemic factors. Larson et al. reported that patients with left-sided strokes were more likely to have diabetes mellitus than those with right-sided strokes (35.9% vs. 21.3%, p = 0.02).[61] While Duker et al. primarily investigated carotid artery stenosis as a contributor to asymmetric PDR, the findings of Larson et al. suggest

that broader systemic factors, such as diabetes, could influence vascular asymmetries. Asymmetric diabetic retinopathy can have various reasons. These include inflammatory and degenerative diseases, vascular factors and previous surgeries.[64] Although we analyzed vascular causes like CRVO, OIS and carotid stenosis, we did not evaluate any previous inflammatory or degenerative conditions the patients may have had. We analyzed the number of previous surgical interventions on the respective eye but could not find any correlation regarding the occurrence of NVG. Documentation of previous ocular surgeries may have been incomplete for patients who had previous eye surgery at another clinic. Zhao et al. analyzed microvascular asymmetries in Patients with DR by optical coherence tomography. It included 258 patients who were divided into four groups: no DM, DM without DR, Non-proliferative Diabetic Retinopathy (NPDR), and PDR. The study showed a rising asymmetry with the severity of DR in terms of superficial and deep vessel density, superficial and deep perfusion density, and foveal avascular zone area, perimeter, and circularity. The side difference in the PDR group was larger than in the other 3 groups. There was also a larger asymmetry in male patients than in females, as well as a positive correlation between asymmetry and levels of Hemoglobin A1c. Even though none of the measured differences were statistically significant, the authors emphasized that asymmetry should be considered in research and clinical practice to improve the understanding of diabetic retinopathy to aid the development of better treatment strategies.[65] Jung et al. examined 90 eyes (60 patients) and found an effect of DR severity on asymmetric vessel length density and perfusion density of eye quadrants in early treatment stages. The quadrant asymmetry increased linearly with each worsening level of DR.[66]. The authors did not compare the differences between both eyes of the included patients. Given the fact that there can be different degrees of severity in the quadrants of an eye, it is reasonable to assume that there are also different degrees of DR in the two eyes of a patient. Another reason for different degrees of DR in the two eyes of patients was investigated by Kim et al. 34 of 6,963 Patients with Diabetes and a difference in axial length of at least 1 mm in each eye were examined. It was found that the progression of DR in the longer eye showed a lower rate than the one in the shorter eye.[67] There are several studies which conclude that myopia and longer axial lengths have a lower risk of DR.[68][69][70] This could mean that patients with ametropia tend to develop different degrees of DR in both eyes. The frequency of anisometropia varies between 20% for a difference of 0.5 diopters and 2-3% for 3 or more diopters.[71]. However, we could not find any studies in which an asymmetry in the lateral distribution of the difference in visual acuity was

investigated. In eyes affected by NVG, reliable refraction is often not possible because of significant retinal damage and reduced visual acuity. The majority of our patients did not have axial length measured.

This study adds to the existing evidence that diabetes can cause unequal damage to both eyes and indicates that this circumstance may also manifest as a side difference in the occurrence of neovascular glaucoma.

4.1 Limitations

Considering that 569,550 eyes were examined at the Department of Ophthalmology during the observation period and the incidence of NVG was exceptionally low, the study may be overpowered. This could mean that even minor differences are statistically significant by chance.

The study has some limitations that can influence the interpretation of the results. Firstly, not all medical histories were taken in equal detail, which leads to fluctuations in data quality. In addition, some patients only attended the clinic once, for example, because they were only in Graz temporarily; this limits the possibility of recording follow-up data. In some cases, further examinations were performed externally or not at all, and associated findings were sometimes not documented, resulting in gaps in diagnostic data. The documentation of the examinations was also occasionally inadequate. In addition, the examination standard has changed in the last 28 years, potentially impairing the comparability of the data.

4.2 Prospect

More studies with regular checks are necessary that include standard examinations such as tonometry and funduscopy, as well as more advanced examinations such as the vascular status of the eyes and carotids and ocular biometry. It is important to observe and precisely document all causes of neovascularization to obtain a true picture of how a side effect of diabetes and further NVG can occur. The better we understand the pathomechanisms behind the various pathologies that lead to neovascularization, the better we can take therapeutic action to prevent the development and consequences of NVG.

Bibliography

[1] Holden B. A., Fricke T. R., Wilson D. A., Jong M., Naidoo K. S., Sankaridurg P., Wong T. Y., Naduvilath T. J., and Resnikoff S. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*, 123(5):1036–1042, 2016. ISSN 0161-6420. doi: https://doi.org/10.1016/j.ophtha.2016.01.006. URL https://www.sciencedirect.com/science/article/pii/S0161642016000257.

[2] Glaucoma. https://eyewiki.org/Primary_vs._Secondary_Angle_Closure_Glaucoma. Accessed: 2024-01-29.

[3] Jayaram H., Kolko M., Friedman D. S., and Gazzard G. Glaucoma: now and beyond. *The Lancet*, 402(10414):1788–1801, 2023. ISSN 0140-6736. doi: https://doi.org/10.1016/S0140-6736(23)01289-8. URL https://www.sciencedirect.com/science/article/pii/S0140673623012898.

[4] Primary open-angle glaucoma. https://eyewiki.org/Primary_Open-Angle_Glaucoma. Accessed: 2024-08-20.

[5] Umezurike B. C., Akhimien M. O., Udeala O., Green U. G., Okpechi-Agbo U., and Ohaeri M. U. Primary open angle glaucoma: The pathophysiolgy, mechanisms, future diagnostic and therapeutic directions. *Ophthalmol. Res. Int. J.*, pages 1–17, June 2019.

[6] Urbonavičiūtė D., Buteikienė D., and Janulevičienė I. A review of neovascular glaucoma: Etiology, pathogenesis, diagnosis, and treatment. *Medicina*, 58(12), 2022. ISSN 1648-9144. doi: 10.3390/medicina58121870. URL https://www.mdpi.com/1648-9144/58/12/1870.

[7] Senthil S., Dada T., Das T., Kaushik S., Puthuran G. V., Philip R., Rani P. K., Rao H., Singla S., and Vijaya L. Neovascular glaucoma - a review. *Indian Journal of Ophthalmology*, 69(3), 2021.

[8] Coats G. *Further cases of thrombosis of the central vein.* J. & A. Churchill, 1906.

[9] Melincovici C. S., Boşca A. B., Şuşman S., Mărginean M., Mihu C., Istrate M., Moldovan I. M., Roman A. L., and Mihu C. M. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol*, 59(2):455–467, 2018.

[10] Kim D. I., Kim M. S., and Woo S. J. Neovascular glaucoma associated with chronic rhegmatogenous retinal detachment. *Korean J. Ophthalmol.*, 37(3):224–229, June 2023.

[11] Polat O., Inan S., Baysal Z., Yigit S., and Inan U. U. Comparison of navigated laser and conventional single-spot laser system for induced pain during panretinal photocoagulation. *Lasers Med. Sci.*, 35(3):687–693, April 2020.

[12] Paretinal photocoagulation. https://eyewiki.org/Panretinal_Photocoagulation. Accessed: 2024-01-17.

[13] Yazdani S., Hendi K., Pakravan M., Mahdavi M., and Yaseri M. Intravitreal bevacizumab for neovascular glaucoma. *J. Glaucoma*, 18(8):632–637, October 2009.

[14] Li D.-K., Zhang F., Yu J.-Q., Liu Z.-K., Wang Y., and Mu Y.-T. Clinical observation of ranibizumab combined with surgery in the treatment of neovascular glaucoma with vitreous hemorrhage. *Int. Ophthalmol.*, 42(9):2757–2763, September 2022.

[15] Lüke J., Nassar K., Lüke M., and Grisanti S. Ranibizumab as adjuvant in the treatment of rubeosis iridis and neovascular glaucoma–results from a prospective interventional case series. *Arbeitsphysiologie*, 251(10):2403–2413, October 2013.

[16] Primary open-angle glaucoma. https://eyewiki.org/Primary_Open-Angle_Glaucoma. Accessed: 2024-01-19.

[17] Inatani M., Higashide T., Matsushita K., Miki A., Ueki M., Iwamoto Y., Kobayashi M., Leal S., and VEGA Investigators . Intravitreal aflibercept in

japanese patients with neovascular glaucoma: The VEGA randomized clinical trial. *Adv. Ther.*, 38(2):1116–1129, February 2021.

[18] Lin S. Ophthalmology: case studies. *Ophthalmology*, 1:74–76, 2001.

[19] Strakhov V. V., Korsakov M. K., Fedorov V. N., Vdovichenko V. P., Shetnev A. A., Popova A. A., and Volkhin N. N. Carbonic anhydrase inhibitors for the treatment of glaucoma. , (2023(1)), February 2023.

[20] Schmickl C. N., Owens R. L., Orr J. E., Edwards B. A., and Malhotra A. Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. *BMJ Open Respir. Res.*, 7(1):e000557, April 2020.

[21] Olmos L. C. and Lee R. K. Medical and surgical treatment of neovascular glaucoma. *International ophthalmology clinics*, 51(3):27–36, 2011.

[22] Higashide T., Ohkubo S., and Sugiyama K. Long-term outcomes and prognostic factors of trabeculectomy following intraocular bevacizumab injection for neovascular glaucoma. *PLoS One*, 10(8):e0135766, 2015.

[23] Takihara Y., Inatani M., Fukushima M., Iwao K., Iwao M., and Tanihara H. Trabeculectomy with mitomycin c for neovascular glaucoma: prognostic factors for surgical failure. *American journal of ophthalmology*, 147(5):912–918, 2009.

[24] Trabeculectomy. https://eyewiki.org/Trabeculectomy. Accessed: 2024-01-20.

[25] Gedde S. J., Feuer W. J., Lim K. S., Barton K., Goyal S., Ahmed I. I., Brandt J. D., and Primary Tube Versus Trabeculectomy Study Group . Postoperative complications in the primary tube versus trabeculectomy study during 5 years of follow-up. *Ophthalmology*, 129(12):1357–1367, December 2022.

[26] Hwang H. B. and Lee N. Y. Effect of anti-vascular endothelial growth factor on the surgical outcome of neovascular glaucoma: an overview and meta-analysis. *Medicine*, 100(39):e27326, 2021.

[27] Kwon J. and Sung K. R. Effect of preoperative intravitreal bevacizumab on the surgical outcome of neovascular glaucoma at different stages. *Journal of Ophthalmology*, 2017(1):7672485, 2017.

[28] Cyclophotocoagulation. https://eyewiki.org/Cyclophotocoagulation_in_Pediatric_Glaucoma. Accessed: 2024-01-21.

[29] Hristova E., Koseva D., Zlatarova Z., and Dokova K. Diabetic retinopathy screening and registration in europe—narrative review. *Healthcare*, 9(6), 2021. ISSN 2227-9032. doi: 10.3390/healthcare9060745. URL https://www.mdpi.com/2227-9032/9/6/745.

[30] Lee R., Wong T. Y., and Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis. (Lond.)*, 2(1):17, September 2015.

[31] Yau J. W. Y., Rogers S. L., Kawasaki R., Lamoureux E. L., Kowalski J. W., Bek T., Chen S.-J., Dekker J. M., Fletcher A., Grauslund J., Haffner S., Hamman R. F., Ikram M. K., Kayama T., Klein B. E. K., Klein R., Krishnaiah S., Mayurasakorn K., O'Hare J. P., Orchard T. J., Porta M., Rema M., Roy M. S., Sharma T., Shaw J., Taylor H., Tielsch J. M., Varma R., Wang J. J., Wang N., West S., Xu L., Yasuda M., Zhang X., Mitchell P., Wong T. Y., and Meta-Analysis for Eye Disease (META-EYE) Study Group . Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care*, 35(3):556–564, March 2012.

[32] Thomas R. L., Dunstan F. D., Luzio S. D., Chowdhury S. R., North R. V., Hale S. L., Gibbins R. L., and Owens D. R. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. *British Journal of Ophthalmology*, 99(1):64–68, 2015. ISSN 0007-1161. doi: 10.1136/bjophthalmol-2013-304017. URL https://bjo.bmj.com/content/99/1/64.

[33] Raum P., Lamparter J., Ponto K. A., Peto T., Hoehn R., Schulz A., Schneider A., Wild P. S., Pfeiffer N., and Mirshahi A. Prevalence and cardiovascular associations of diabetic retinopathy and maculopathy: Results from the gutenberg health study. *PLoS One*, 10(6):e0127188, June 2015.

[34] Pedro R.-A., Ramon S.-A., Marc B.-B., Juan F.-B., and Isabel M.-M. Prevalence and relationship between diabetic retinopathy and nephropathy, and its risk factors in the North-East of spain, a population-based study. *Ophthalmic Epidemiol.*, 17(4):251–265, August 2010.

[35] Pugliese G., Solini A., Zoppini G., Fondelli C., Zerbini G., Vedovato M., Cavalot F., Lamacchia O., Buzzetti R., Morano S., Nicolucci A., Penno G., and Renal Insufficiency and Cardiovascular Events (RIACE) Study Group . High prevalence of advanced retinopathy in patients with type 2 diabetes from the renal insufficiency

and cardiovascular events (RIACE) italian multicenter study. *Diabetes Res. Clin. Pract.*, 98(2):329–337, November 2012.

[36] Dutra Medeiros M., Mesquita E., Papoila A. L., Genro V., and Raposo J. F. First diabetic retinopathy prevalence study in portugal: Retinodiab study—evaluation of the screening programme for lisbon and tagus valley region. *British Journal of Ophthalmology*, 99(10):1328–1333, 2015. ISSN 0007-1161. doi: 10.1136/bjophthalmol-2015-306727. URL https://bjo.bmj.com/content/99/10/1328.

[37] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*, 54(6):1615–1625, June 2005.

[38] Bek T. Diameter changes of retinal vessels in diabetic retinopathy. *Curr. Diab. Rep.*, 17(10), October 2017.

[39] Beltramo E. and Porta M. Pericyte loss in diabetic retinopathy: Mechanisms and consequences. *Curr. Med. Chem.*, 20(26):3218–3225, July 2013.

[40] Patel J. I., Hykin P. G., Gregor Z. J., Boulton M., and Cree I. A. Angiopoietin concentrations in diabetic retinopathy. *Br. J. Ophthalmol.*, 89(4):480–483, April 2005.

[41] Koleva-Georgieva D. N., Sivkova N. P., and Terzieva D. Serum inflammatory cytokines IL-1β, IL-6, TNF-α and VEGF have influence on the development of diabetic retinopathy. *Folia Med. (Plovdiv)*, 53(2), January 2011.

[42] Sorrentino F. S., Allkabes M., Salsini G., Bonifazzi C., and Perri P. The importance of glial cells in the homeostasis of the retinal microenvironment and their pivotal role in the course of diabetic retinopathy. *Life Sci.*, 162:54–59, October 2016.

[43] Sohn E. H., Dijk van H. W., Jiao C., Kok P. H. B., Jeong W., Demirkaya N., Garmager A., Wit F., Kucukevcilioglu M., Velthoven van M. E. J., DeVries J. H., Mullins R. F., Kuehn M. H., Schlingemann R. O., Sonka M., Verbraak F. D., and Abràmoff M. D. Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. *Proc. Natl. Acad. Sci. U. S. A.*, 113(19):E2655–64, May 2016.

[44] Sohn E. H., Dijk van H. W., Jiao C., Kok P. H. B., Jeong W., Demirkaya N., Garmager A., Wit F., Kucukevcilioglu M., Velthoven van M. E. J., DeVries J. H.,

Mullins R. F., Kuehn M. H., Schlingemann R. O., Sonka M., Verbraak F. D., and Abràmoff M. D. Retinal neurodegeneration may precede microvascular changes characteristic of diabetic retinopathy in diabetes mellitus. *Proc. Natl. Acad. Sci. U. S. A.*, 113(19):E2655–64, May 2016.

[45] Wang W. and Lo A. C. Y. Diabetic retinopathy: Pathophysiology and treatments. *International Journal of Molecular Sciences*, 19(6), 2018. ISSN 1422-0067. doi: 10.3390/ijms19061816. URL https://www.mdpi.com/1422-0067/19/6/1816.

[46] Diabetic retinopathy. https://eyewiki.org/Diabetic_Retinopathy. Accessed: 2024-01-12.

[47] Melincovici C. S., Boşca A. B., Şuşman S., Mărginean M., Mihu C., Istrate M., Moldovan I. M., Roman A. L., and Mihu C. M. Vascular endothelial growth factor (VEGF) - key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol*, 59(2):455–467, 2018.

[48] Laurance S., Marin M., and Colin Y. Red blood cells: A newly described partner in central retinal vein occlusion pathophysiology? *International Journal of Molecular Sciences*, 24(2), 2023. ISSN 1422-0067. doi: 10.3390/ijms24021072. URL https://www.mdpi.com/1422-0067/24/2/1072.

[49] Central retinal vein occlusion. https://eyewiki.org/Central_Retinal_Vein_Occlusion. Accessed: 2024-01-13.

[50] Havens S. J. and Gulati V. Neovascular glaucoma. *Dev. Ophthalmol.*, 55:196–204, 2016.

[51] Terelak-Borys B., Skonieczna K., and Grabska-Liberek I. Ocular ischemic syndrome - a systematic review. *Med Sci Monit*, 18(8):RA138–144, August 2012.

[52] Brown G. and Magargal L. The ocular ischemic syndrome: clinical, fluorescein angiographic and carotid angiographic features. *International ophthalmology*, 11: 239–251, 1988.

[53] Mendrinos E., Machinis T. G., and Pournaras C. J. Ocular ischemic syndrome. *Survey of ophthalmology*, 55(1):2–34, 2010.

[54] Brown G. C., Brown M. M., and Sharma S. The ocular ischemic syndrome. In *Retinal and Choroidal Manifestations of Selected Systemic Diseases*, pages 451–464. Springer New York, New York, NY, 2013.

[55] Cotton wool spots. https://eyewiki.org/Cotton_Wool_Spots. Accessed: 2024-08-14.

[56] Writing Group for the American Academy of Neurology, AANS/CNS Cerebrovascular Section, Society of NeuroInterventional Surgery, and the Society of Vascular & Interventional Neurology , Meyers P. M., Schumacher H. C., Alexander M. J., Derdeyn C. P., Furlan A. J., Higashida R. T., Moran C. J., Tarr R. W., Heck D. V., Hirsch J. A., Jensen M. E., Linfante I., McDougall C. G., Nesbit G. M., Rasmussen P. A., Tomsick T. A., Wechsler L. R., Wilson J. A., and Zaidat O. O. Performance and training standards for endovascular ischemic stroke treatment. *J. Neurointerv. Surg.*, 1(1):10–12, July 2009.

[57] Shao S., Shi H., Wang G., Li R., Sun Q., Yao B., Watase H., Hippe D. S., Yuan C., Zhao X., and Investigators of CARE-II study . Differences in left and right carotid plaque vulnerability in patients with bilateral carotid plaques: a CARE-II study. *Stroke Vasc. Neurol.*, 8(4):284–291, August 2023.

[58] Rodríguez Hernández S. A., Kroon A. A., Boxtel van M. P. J., Mess W. H., Lodder J., Jolles J., and Leeuw de P. W. Is there a side predilection for cerebrovascular disease? *Hypertension*, 42(1):56–60, July 2003.

[59] Chaubey S., Nitsch D., Altmann D., and Ebrahim S. Differing effect of modifiable cardiovascular risk factors on intima-media thickening and plaque formation at different sites of the arterial vasculature. *Heart*, 96(19):1579–1585, October 2010.

[60] Selwaness M., Bouwhuijsen van den Q., Onkelen van R. S., Hofman A., Franco O. H., Lugt van der A., Wentzel J. J., and Vernooij M. Atherosclerotic plaque in the left carotid artery is more vulnerable than in the right. *Stroke*, 45(11): 3226–3230, November 2014.

[61] Larson A. S., Brinjikji W., Savastano L., Scharf E., Huston J., 3rd, and Benson J. C. Left-sided carotid arteries have a higher prevalence of intraplaque hemorrhage than right-sided: An asymmetric conundrum. *Neuroradiol. J.*, 33(6):494–500, December 2020.

[62] Valone J. A. Unilateral proliferative diabetic retinopathy. *Arch. Ophthalmol.*, 99 (8):1357, August 1981.

[63] Duker J. S., Brown G. C., Bosley T. M., Colt C. A., and Reber R. Asymmetric proliferative diabetic retinopathy and carotid artery disease. *Ophthalmology*, 97 (7):869–874, July 1990.

[64] Azad R., Sinha S., and Nishant P. Asymmetric diabetic retinopathy. *Indian J. Ophthalmol.*, 69(11):3026–3034, November 2021.

[65] Zhao T., Laotaweerungsawat S., Chen Y., Liu X., Liu D., and Stewart J. M. Right versus left eye asymmetry of microvasculature in diabetes revealed by optical coherence tomography angiography. *Sci. Rep.*, 13(1):9332, June 2023.

[66] Jung J. J., Lim S. Y., Chan X., Sadda S. R., and Hoang Q. V. Correlation of diabetic disease severity to degree of quadrant asymmetry in en face OCTA metrics. *Invest. Ophthalmol. Vis. Sci.*, 63(9):12, August 2022.

[67] Kim D. Y., Song J. H., Kim Y. J., Lee J. Y., Kim J.-G., Yoon Y. H., and Joe S. G. Asymmetric diabetic retinopathy progression in patients with axial anisometropia. *Retina*, 38(9):1809–1815, September 2018.

[68] Lim L. S., Lamoureux E., Saw S. M., Tay W. T., Mitchell P., and Wong T. Y. Are myopic eyes less likely to have diabetic retinopathy? *Ophthalmology*, 117(3): 524–530, March 2010.

[69] Man R. E. K., Lamoureux E. L., Taouk Y., Xie J., Sasongko M. B., Best W. J., Noonan J. E., Kawasaki R., Wang J. J., and Luu C. D. Axial length, retinal function, and oxygen consumption: a potential mechanism for a lower risk of diabetic retinopathy in longer eyes. *Invest. Ophthalmol. Vis. Sci.*, 54(12):7691–7698, November 2013.

[70] Fu Y., Geng D., Liu H., and Che H. Myopia and/or longer axial length are protective against diabetic retinopathy: a meta-analysis. *Acta Ophthalmol.*, 94 (4):346–352, June 2016.

[71] Barrett B. T., Bradley A., and Candy T. R. The relationship between anisometropia and amblyopia. *Prog. Retin. Eye Res.*, 36:120–158, September 2013.