OULUN AMMATTIKORKEAKOULU

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SECONDARY OPEN-ANGLE GLAUCOMA – CLINICAL GUIDELINE FOR FINNISH OPTOMETRISTS

An Innovation Project

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ABSTRACT

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Background: Secondary open-angle glaucoma (SOAG) poses a unique challenge for optometrists, requiring thorough assessment and management. With current changes in the Finnish healthcare system, optometrists will play a crucial role as primary eye care providers. This role will require high levels of professional competence. The guideline provides a structured approach to help optometrists make informed decisions and offer personalized care to patients.

Purpose: This thesis aimed to create the structure for the evidence-based guidelines for Finnish optometrists on assessing and managing secondary open-angle glaucoma (SOAG). Additionally, it sought to compile a clear and comprehensive information package to support and enhance optometrists' knowledge on the subject.

Methods: This thesis was a literature review content analysis-based innovation project for the Finnish Ethical Board of Optometry (OEN). The research process was conducted as a descriptive study by analyzing the existing evidence-based literature. The comprehensive literature review was conducted mainly in spring 2023 between March and May. An electronic literature search was performed on PubMed, CINAHL, Google Scholar, and Finna databases. Clinical practice guidelines (CPGs) were also reviewed using the gray literature sources. The search was limited from the year 2010 to 2023 and only full articles and results in English or Finnish were included. The guidelines that were found and that met the inclusion criteria were further selected for the appraisal based on geographical diversity.

Results: The main result of this thesis is a recommendation of the content for the guideline for Finnish optometrists about SOAG. Based on the analysis of the literature and existing international guidelines the structure of the future national guideline was divided into three parts; patient history, assessment, and management. The assessment part contains both anterior and posterior eye examination as well as imaging/testing methods. Followed by the management where the optometrists play a role in educating the patients about the disease and providing a referral to the ophthalmologist. The second result of this thesis was a literature review providing background information about the SOAG and its subtypes.

Conclusions: In conclusion, the guideline will serve as the backbone of valued and reliable work at optometrists' practice ensuring quality patient care and providing support for professional development. Therefore a need for the guideline cannot be overstated.

Keywords: secondary open-angle glaucoma, optometry, guidelines, assessment, management

CONTENTS

1 INTRODUCTION

About 70 million people have glaucoma globally. It is the second most common reason for losing vision, causing 8% of all blindness worldwide, as estimated by the World Health Organization in 2010 (Clinical Practice Guide for the Diagnosis, Treatment and Management of Glaucoma July 2016, 2016). In Finland, approximately 85–90,000 patients are diagnosed with glaucoma. Among the Finnish elderly, age-related macular degeneration (AMD) is the leading eye condition, followed by glaucoma, causing permanent impairment of vision. (Karvonen et al., 2019.) In the near future, glaucoma will demand both economic and occupational resources from society and the field of ophthalmology.

In Finland, only an ophthalmologist has the right to diagnose and make decisions about the medical treatment of patients with glaucoma. Currently, the Finnish healthcare system is undergoing transition. The aim is to provide equal and high-quality as well as easy-to-access social and healthcare services to all citizens in Finland. On the other hand, the overload of aging people sets a challenge for healthcare professionals to answer to that demand. In the future the field of optometry, when provided with accurate and evidence-based guidelines, could reduce the burden set on the shoulders of ophthalmologists.

As part of the primary eye healthcare providers, optometrists play a pivotal role in providing eye care services. This role, which is essential in preventing possible permanent vision loss, includes early detection, assessment, and management of the ocular condition, such as secondary open-angle glaucoma. Optometrists must be confident and competent in their everyday work to assess patients with or at risk of developing glaucoma so that they can provide evidence-based management and advice within the limits of the legal rights set for Finnish optometrists.

The purpose of this thesis was to create a recommendation of an evidence-based guideline for optometrists in Finland when assessing and managing patients at risk or with secondary open-angle glaucoma. With the help of this guideline, the everyday work at the optometrist's office can be unified and the patient will be provided with the best-known care. This was an innovation project for the Finnish Ethical Board of Optometry (OEN).

2 THEORETICAL BACKGROUND

Glaucoma is a definition that comprises a versatile group of ocular disorders. Without treatment, it leads to irreversible loss of vision because of the damage it causes to the optic nerve and retinal ganglion cell axons. Glaucoma can be further subdivided into primary or secondary glaucoma and also based on the anatomy of the anterior chamber angle the division is either open-angle glaucoma (OAG) or angle closure glaucoma (ACG). This thesis concentrates only on a secondary form of open-angle glaucoma. Unlike primary open-angle glaucoma, which develops independently, in secondary OAG there is always an underlying condition that causes the development of glaucomatous optic neuropathy. These conditions can be either eye-related (e.g. inflammation, injuries, or other eye diseases) or systemic (e.g. diabetes, medications). Secondary open-angle glaucoma can be further divided into pre-trabecular, trabecular, and post-trabecular forms based on the location where the aqueous outflow is blocked. (Casson et al., 2012; Kanski & Bowling, 2016.)

The theoretical background in this thesis has been divided into three main categories, the first of which discusses the different forms of secondary open-angle glaucoma, followed by the chapters about the assessment and management of the disease.

2.1 Secondary Open-Angle Glaucoma Associated with Ocular Disease

2.1.1 Pseudoexfoliation Syndrome and Pseudoexfoliative Glaucoma

Pseudoexfoliative glaucoma (PXG) is the most common form of secondary open-angle glaucoma globally. PXG progresses from pseudoexfoliative syndrome (PXS), which is defined as a systemic genetic condition. In PXS, intraocular pressure (IOP) is elevated, but no glaucomatous optic nerve head changes or visual field defects are detected. On the contrary patients with diagnosed PXG do show glaucomatous defects on the optic nerve head and/or on the visual field in addition to elevated IOP. It is estimated that between 5 to 6 million individuals are affected by PXG and at the time of diagnosis severe glaucomatous defects are detected at least in one eye. (Holló et al., 2015.)

The pseudoexfoliative syndrome was first mentioned by Finnish ophthalmologist J. Lindberg in 1917 after observing whiteish-grey material on the pupillary border of half of his patients with chronic glaucoma (Tekin et al., 2019). The progressive formation and accumulation of the abnormal fibrino-granular extracellular material, i.e., pseudoexfoliative material (PXM), in both intraocular and extraocular tissues are characteristic of PXS. The pseudoexfoliative syndrome is rare in people under the age of 50, its prevalence increases significantly with aging. It is more common among the female gender than males. Even though PXS has been reported globally among different ethnicities it occurs more in northern Europe and especially among Scandinavians. (Kanski & Bowling, 2016; Tekin et al., 2019.) The prevalence in Finland among people over 60 years is 8% and it increases to 20% among those over 70 years (Seppänen et al., 2022). The risk of PXS developing into PXG increases cumulatively with aging, and over a five-year period the incidence of PXG requiring treatment is 15-30% but it also may be as high as 60% (Kanski & Bowling, 2016; Tekin et al., 2019).

The etiology and pathogenesis behind the PXS are partly unexplained, it is known that environmental and geographical factors as well as genetics play a pivotal role. The vast majority of patients with PXS have a genetic abnormality in a LOXL1 gene, which participates in the production of elastin. Thus, the compromised gene causes either overproduction and/or insufficient decomposition of elastin which can be detected as a chronic progressive accumulation of extracellular material, defined as PXM, in almost all parts of anterior intraocular tissues. The pathology underlying pseudoexfoliative glaucoma, in Finland, also referred to as capsular glaucoma, associated with PXS is mainly due to accumulation of the PXM. The whiteish dandruff-like material obstructs the aqueous outflow in the site of the anterior chamber angle causing the dysfunction of the trabecular meshwork, which leads to an elevation of intraocular pressure. PXM has also been found in other visceral organs, for example, lungs, heart, and kidneys, therefore PXS is defined as a systemic disorder with ocular manifestations. (Kanski & Bowling, 2016; Seppänen et al., 2022; Tekin et al., 2019.)

Since approximately 30% of PXS cases develop into PXG over a decade and the progression of glaucomatous defects occurs up to three times more rapidly than in any other form of glaucoma, it is inevitable to detect early signs and symptoms of the disease. Also, true exfoliation, which is a consequence of chronic infrared exposure, should be separated from pseudoexfoliation. PXS and PXG are usually diagnosed accidentally during a routine eye examination due to their

asymptomatic nature. At the early stage, the experienced examiner is in an important role, since the PXM accumulation can be delicate and therefore easily overlooked. Though the PXM can be found in every tissue in the anterior part of the eye, the main sites best detecting the hallmark signs are the lens, iris, cornea, and zonules. The thorough eye examination including biomicroscopy also with a dilated pupil, gonioscopy, and IOP measuring are the key aspects of recognizing the disease. (Kanski & Bowling, 2016; Seppänen et al., 2022; Tekin et al., 2019.)

The hallmark finding for PXS is the accumulation of PXM that follows a certain pattern at the anterior part of the lens surface. The pattern forms three separate zones, which can be best seen through the dilated pupil. The central zone is in the middle of the lens capsule and forms a relatively regular disk-like pattern that roughly follows the edge of the pupillary opening. The next zone is described as a clear intermediate zone and the clearness appears due to the rubbing effect of the posterior part of the iris against the anterior lens capsule during pupillary movement. At the periphery is the peripheral zone that forms the granular, flaky PXM with possibly scrolled edges. (Tekin et al., 2019.)

The changes at the iris caused by PXS are visible at the early stage of the disease and are easy to recognize. The pupillary border gets highly affected by the accumulation of PXM. The pigment loss at the iris sphincter and at the pupillary ruff is the hallmark finding at PXS. The patchy spherical thinning of the iris near the pupillary border as a consequence of pigment dispersion can be seen as a transillumination defect by using retro illumination in biomicroscopy. The liberated pigment may deposit throughout the anterior part of the eye. (Kanski & Bowling, 2016; Tekin et al., 2019.)

Scattered pigment deposits and flakes of PXM can be detected on the surface of the corneal endothelium. The accumulated pigment may form hyperpigmentation that has no specific form and is diffuse in nature, on the central part of the cornea. The Krukenberg's spindle, characteristic in pigmentary glaucoma, is rarely seen. More frequently the hyperpigmentation can be observed by gonioscopy at the anterior chamber angle and on the peripheral cornea. There the pigment deposits form one or more irregular wavy lines, termed the Sampaolesi line, located anterior to Schwalbe's line. This is an early sign of PXS. Also, the trabecular meshwork may present patchy moderate to excessive hyperpigmentation, especially located inferiorly. (Kanski & Bowling, 2016; Tekin et al., 2019.)

At the earliest, the zonules and ciliary processes are the sites that show the accumulation of PXM. This accumulation weakens the zonules and therefore increases the risk of lens instability which can lead to malpositioning of the lens especially in advanced PXS cases. Spontaneous subluxation of the lens is rare. (Kanski & Bowling, 2016; Tekin et al., 2019.)

The damage and the obstruction of the trabecular meshwork caused by PXM have been hypothesized to be the main reason for the elevation of IOP in PXS. The elevated IOP present in PXS is highly associated with the development of glaucomatous damage and therefore the development of PXG. Pseudoexfoliative glaucoma is more aggressive in nature, shows two to three times more rapid progression, and presents a poor response to management than chronic primary open angle glaucoma (POAG). The IOP levels are higher at the time of diagnosis, the diurnal fluctuation is greater and the IOP spikes are more common compared to POAG. Fortunately, not all patients with PXS and high IOP develop PXG. (Tekin et al., 2019.)

The treatment of PXG is similar to POAG. Both medical and laser treatments are shown to be equally effective but unfortunately, both treatment methods tend to lose their efficacy after some years. The medical treatment with prostaglandin analogs, β-blockers, selective α2 agonists, and topical and systemic carbonic anhydrase inhibitors, and combinations are used as the first-line therapy. Though the medical treatment shows a sufficient response in lowering the IOP at the beginning, the method loses efficacy after several years. Therefore, close monitoring and medical readjustment when needed are pivotal. Laser trabeculoplasty, especially selective laser trabeculoplasty (SLT), is commonly used in PXG. In SLT the trabecular meshwork cells are selectively targeted to enhance the outflow of the aqueous humor. The energy provided in SLT compared to other laser treatment methods is low with brief energy pulses, which does not cause a thermal effect and thus the disruptive changes to the TM. Based on the aforementioned the SLT can be safely repeated when needed to achieve better long-term efficacy. SLT should be considered as a first-line treatment, especially among the elderly, when there is poor tolerance or contraindications against medical IOP lowering treatment. (Holló et al., 2015; Tekin et al., 2019.)

2.1.2 Pigment Dispersion Syndrome and Pigmentary Glaucoma

Pigment dispersion syndrome (PDS) is the structural disorder of the iris pigment epithelium. The liberated pigment melanin granules, circulating among aqueous humor (AH), deposit on different sites and structures at the anterior part of the eye, including trabecular meshwork (TM), iridocorneal angle, corneal endothelium, iris, anterior part of the lens, and lens zonules. The accumulated pigment at the site of TM will compromise the aqueous outflow and second to that cause an elevation in IOP. The rise at the IOP level can lead to the development of pigmentary glaucoma (PG) with the signs of retinal nerve fiber layer thinning, glaucomatous optic neuropathy, and/or visual field defects. (Michelessi & Lindsley, 2016; Zeppieri, 2022.)

The prevalence of PDS and PG from all glaucoma cases all over the world is 1-1,5%. Pigment dispersion syndrome and pigmentary glaucoma are more common among Caucasians and the onset is between 30 to 45 years of age. PDS does not show specific gender predominance, but PG is more common in myopic males. The incidence of PDS is 4,8 in a hundred thousand people and approximately one-third being diagnosed with PDS develop PG. In summary, PDS, the male gender, myopia, and Caucasian inheritance are the main risk factors for PG. (Seppänen et al., 2022; Zeppieri, 2022.)

The pathophysiology behind PDS, and its conversion to pigmentary glaucoma, is due to the mechanical rubbing and friction between the posterior part of the iris and the lens zonules during the normal pupillary activity. The rubbing and friction are promoted because the eyes affected with PDS tend to have the concave mispositioned iris at the mid-periphery, also known as posterior bowing of the iris. Research has shown that individuals with PDS are often presented with a deeper anterior chamber (AC) and larger iris compared to those without PDS. The deeper width in AC can be favorable in backward bowing of the iris and therefore increase the contact between the posterior iris and anterior lens structures. The mechanism of reversed pupillary block, where the iris works as a flap valve, is another explanation for increased iridolenticular contact. In this mechanism, assisted by the blink, accommodation, and exercise, a small amount of aqueous humor is allowed to flow only in one direction from the posterior chamber (PC) to AC creating an imbalance between pressure gradience. The imbalance trappes aqueous humor into AC causing the posterior bowing of the peripheral iris, leading to pigment dispersion showers. Over time chronic IOP elevation can occur secondary to the deposition of the pigment into intertrabecular spaces and impeding the

outflow of the aqueous. (Michelessi & Lindsley, 2016; Zeppieri, 2022.) According to EGS Terminology and Guidelines for Glaucoma, TM cells are trying to balance the pigment deposition by phagocytizing the granules, which in the long term leads to apoptosis of the TM cells and hence to the IOP elevation (Spaeth, 2021).

The manifestation of PDS may be highly subtle and therefore the disease can get easily underestimated and undiagnosed at its early stage. The asymmetry of the signs of PDS between the eyes mostly occurs though the condition is known to be bilateral. The diagnosis of PDS can be challenging because the pigment dispersion is asymptomatic, and the range of clinical findings caused by pigment release can vary extremely. The hallmark signs, forming a classic triad, to be assessed in PDS are vertical deposition of the pigment on the central part of the endothelial cornea, also termed as the Krukenberg's spindle, mid-peripheral radial transillumination of the iris, and TM hyperpigmentation. (Gomez Goyeneche et al., 2015; Michelessi & Lindsley, 2016; Zeppieri, 2022.)

In the corneal endothelium, secondary to phagocytosed pigment, variation in the shape and size of the endothelial cells can occur. However, histological research has shown that the density and function of the endothelial cells do not diminish in individuals with PDS compared to controls. The Krukenberg's spindle, typically seen in PDS but not pathognomonic, also represents the phagocytosed pigment. It forms a vertical spindle-like pigment deposition both within and on the corneal endothelium, which explains not only the accumulation of the pigment granules but also the phagocytose. It is more prominent in the inferior part of the cornea. During the time of PDS, the Krukenberg's spindle may be difficult to detect because of the fact that it tends to lose the intensity of the color and size. Hormonal changes affect the development of Krukenberg's spindle. (Bustamante-Arias et al., 2021; Kanski & Bowling, 2016.)

Patients with PDS have more commonly the deeper AC and free pigment granules may float among the aqueous humor, especially at the active phase of dispersion. The deep anterior chamber favors the backward bowing of the peripheral iris and contact between the iris pigment epithelium (IPE) and the lens. The fine surface pigment granules can deposit within the iris furrows at the anterior part and also extend onto the lens. The pigment release from IPE causes radial mid-peripheral iris transillumination, best visible with retro illumination. These manifest more in eyes with light irises and are present approximately in 85% of individuals with PDS. (Kanski & Bowling, 2016; Zeppieri, 2022).

Gonioscopy reveals dense, dark brown, homogenously pigmented trabecular meshwork. The pigment line is finer without patchiness, compared to that in pseudoexfoliative syndrome and it lies both within and on the TM. It circumferences the whole TM and due to the gravity lies inferiorly. Hyperpigmentation may also be seen on or anterior to Schwalbe's line. The endothelial cells of the TM, similar to what occurs in the corneal endothelium, engulf the pigment, which eventually leads to the TM cell injury due to the overload of phagocytosed pigment granules. It has been hypothesized that the phagocytic debris compromises the trabecular structural function by clogging and destroying aqueous outflow channels, which will lead to ocular hypertension and eventually may cause a transformation to PG. (Kanski & Bowling, 2016; Spaeth, 2021; Zeppieri, 2022)

The pigment dispersion activity, the level of IOP, and the degree of glaucomatous optic neuropathy define the level of management in both PDS and PG. The course of the PDS and PG are divided into three clinically critical phases. The first phase develops in early adulthood and is mostly asymptomatic. It is triggered by pigment liberation into the anterior chamber induced by physiological factors such as exercise, excessive emotional stress, and accommodation and is therefore known as the pigment dispersion phase. During the first phase trabecular meshwork maintains its natural function and aqueous circulation does not get obstructed. The IOP levels remain at the normal range despite the moments of pigment showers when high IOP spikes occur. As time passes the TM gets hyperpigmented and loses its normal function, developing ocular hypertension with subsequent optic nerve head defects. This can be defined as the second phase of the disease progression and development from PDS to PG. Among elderly individuals, the third phase can be described when the pigment reversal sign can be referred. At this phase, the pigment gradually clears, and the TM starts to recover showing the darker mark of the pigmentary band more superiorly than inferiorly. In some cases, even the IOP may normalize and the transillumination of the iris is less visible. The glaucomatous defects that have occurred at the earlier stages are irreversible. (Bustamante-Arias et al., 2021; Zeppieri, 2022.)

The age and the stage of the disease of an individual are the determining factors when deciding whether or how the PGS and/or PG should be managed. Early PDS is usually an accidental finding during a routine eye examination and with no OHT present, will not require other procedures than regular ophthalmological follow-up. PDS with ocular hypertension (OHT) requires a thorough consideration of whether medical management is preferable compared to nonmedical monitoring. Theoretically, miotics would offer an advantage in reducing pigment liberation by blocking the

movement of the pupil, but they are not used regularly because of the poor tolerance on the ocular surface and disturbance of the vision due to the miosis. The risk for retinal tears and detachment is also greater in myopic individuals with PDS using miotics and therefore less harmful treatment is preferred. The treatment for PDS with OHT and/or PG is similar to all glaucoma management with the intention of lowering the IOP with the help of medicals, laser, or surgery. Topical glaucoma therapy is often the first-line treatment. Prostaglandins and beta-blockers have proven their effectiveness for a sufficient decrease in the IOP level and they are safe to use. (Bustamante-Arias et al., 2021; Kanski & Bowling, 2016.)

Laser therapy has become popular as a first-line treatment in glaucoma management with no exception among individuals with PG. The laser treatment can be targeted either to the iris and/or TM. In laser peripheral iridotomy (LPI), the hole is created with the use of a laser to the peripheral iris. The principle of the LPI is to equalize the pressure between the anterior and posterior chamber which also leads to the flattening of the peripheral iris and thus diminishes the pigment release due to the irido-zonular contact and friction. (Zeppieri, 2022.) According to Michelessi et al. (2016), the long-term clinical benefits of LPI show minor effectiveness and it is hypothesized that the LPI may be beneficial only in PDS at a younger age with no onset of trabecular dysfunction. Therefore, it is suggested that individuals with PDS, to be treated with LPI, should be selected with care for the fact that there is no evidence of the prevention of PDS developing into PG. (Bustamante-Arias et al., 2021.)

The trabecular meshwork, with the intention to enhance the outflow of the AH, is targeted with the use of argon laser trabeculectomy (ALT) and selective laser trabeculectomy (SLT). Younger individuals have been shown to be better respondents to ALT compared to the elderly. The reason for that may lie in the permanent tissue scarring, high energy absorption, and overload of the pigment of TM that occur over time. The use of selective laser trabeculoplasty (SLT), has come alongside the topical treatment or risen to be even more popular to be considered a first-line glaucoma treatment because of its safety and repeatability. Research has shown, that SLT is comparable with medical treatment in the efficacy of lowering the IOP. (Zeppieri, 2022) Both Bustamante-Arias et al. (2021) and Zeppieri (2022) cited in their review that the SLT in PG management showed an effective 20% lowering in IOP in 85% of the cases at one year, dropping to 14% after four years. The most common complications after treatment with SLT in PG eyes are IOP spikes and inflammation. The risk factors for post-SLT IOP spikes are highly tense

pigmentation, the use of combination IOP-lowering medication, and previous ALT. (Bustamante-Arias et al., 2021). To avoid post-operative pressure spikes careful patient selection is mandatory and the laser should be performed with low-power settings and with possible prophylactic treatment (Spaeth, 2021).

Differential diagnosis plays a pivotal role in determining accurate and individualized management. The iris transillumination and the pigment dispersion at the eye's anterior part are characteristic findings in PDS and PXS. The transillumination of the iris occurs in PXS at the pupillary border compared to the mid-periphery in PDS. The deposits in AC are whiteish, dandruff-like flakes and the pigmentation on TM is patchy in PXS in comparison to PDS where the pigmentation on TM forms a dark, solid line and the granules in the anterior part of the eye are brownish. In certain ocular conditions, such as uveitis, trauma, and post-operational inflammation, inflammatory cells, and debris can be found in AH mimicking pigment showers and causing IOP spikes and iris transillumination defects. Thorough ophthalmological examination with detailed history taking combined with additional instrumental examinations are the key components in the assessment and management of PDS and/or PG to enable the prevention of irreversible glaucomatous visual defects. (Zeppieri, 2022)

2.1.3 Inflammatory Glaucoma

Patients with uveitis have a high risk of developing glaucoma as a complication of ocular inflammation. Inflammatory glaucoma, also termed uveitic glaucoma (UG), in which the IOP elevation occurs secondary to intraocular inflammation, can be challenging diagnostically and therapeutically. The eye or eyes appear red and painful, there is a sense of photophobia and the vision is decreased. The IOP elevation may be transient and without the serious consequence of glaucomatous defects or the level of IOP may rise excessively causing more vigorous glaucomatous optic nerve head and visual field damage than in other forms of glaucoma. (Kalogeropoulos & Sung, 2018; Kanski & Bowling, 2016.)

Uveitic glaucoma is a relatively common and most devastating complication in eyes with uveitis. Approximately 20 to 25 percent of patients with uveitis will develop ocular hypertension and uveitis-induced glaucoma during the time of inflammatory disease. Frequently chronic anterior uveitis and

panuveitis are more associated with the development of uveitic glaucoma due to the direct anterior involvement of the eye, especially the pathway of aqueous outflow. In addition to the aforementioned granulomatous uveitis, compared to the non-granulomatous form, is a more common cause of uveitic glaucoma. (Rhee, 2018.)

The development of uveitic glaucoma cannot be explained in detail by one exact mechanism, it is rather a combination of multiple and mixed systemic and ocular conditions. It has been discovered that the nature of inflammation; either acute or chronic, the steroid response, and the anterior chamber angle mechanism; either open or closed, are the determinative components behind the pathophysiology. Eventually, the imbalance between the aqueous secretion and aqueous outflow is the main reason for IOP elevation in all different uveitic conditions. Although in general there is a strong connection between the elevation of IOP and the development of UG, compared to primary glaucoma where the disease progression can occur pressure-independently, the IOP may rise in intervals. There is also initially a possibility of hypotony during the incidence of acute uveitis, because of an increase in aqueous outflow compared to a decrease in secretion, due to the inflamed ciliary body. In prolonged situations also a TM becomes compromised leading to high IOP levels. (Kalogeropoulos & Sung, 2018; Sherman & Cafiero-Chin, 2019.)

In chronic uveitis, the blood-aqueous barrier becomes disrupted due to the inflammation leading to the leakage of serum proteins into the anterior chamber. The increase in the concentration of the aqueous proteins affects the trabecular meshwork by mechanically restricting the normal outflow and causing endothelial cell dysfunction. In addition to proteins, the inflammatory cells, precipitates, and other debris from the uveitic eyes among the aqueous disrupt the outflow of the aqueous by obstructing the TM and causing edema. Trabeculitis is the inflammation of the TM where inflammatory action can be detected only on the structures of the TM and other active signs of inflammation, such as flare, are absent elsewhere. All the aforementioned mechanisms affecting the normal TM function participate in the elevation of the IOP and in the development of inflammatory glaucoma in uveitic eyes. (Kalogeropoulos & Sung, 2018; Rhee, 2018; Spaeth, 2021.)

Corticosteroids are first-line medicaments used to control the inflammatory reaction of uveitis. There is a group (18-36%) of patients, steroid responders, who become affected with ocular hypertension (OHT) with at least 5 mmHg rise, due to the treatment of corticosteroids in uveitis. The corticosteroid-induced response to IOP elevation is expected to occur within 2 to 6 weeks after

starting the treatment, but supposedly it can happen at any time. The duration and the dosage strength of the corticosteroids define the impact they will have on IOP. The patients that are at great risk of being steroid responders are those who are glaucoma suspects, have a family history of glaucoma, have high myopia, are type 1 diabetics, patients with connective tissue disease, the elderly, and children younger than 10 years of age. The impairment of the conventional trabecular meshwork outflow is the eventual reason for steroid-induced OHT. It can be described in three mechanisms: the increased deposition of substances into TM, the decreased apoptosis of the substances, and by the mechanical and physical alterations in the structure of the TM. (Kalogeropoulos & Sung, 2018; Rhee, 2018.)

Acute uveitis associated with OHT and therefore a risk of developing UG is typical in Posner-Schlossman syndrome. Also, viral infections such as varicella-zoster virus (VZV) and herpes simplex virus (HSV) are common in the acute uveitis-related development of inflammatory glaucoma. (Spaeth, 2021.)

Posner-Schlossman syndrome, also known as glaucomacyclitis crisis, affects individuals between 20 to 60 years of age. It is characterized by unilaterally occurring repetitive mild cyclitis and heterochromia. Despite the mild inflammatory reaction, the IOP may rise as high as 40 to 70 mmHg during an acute active phase. The change of the prostaglandin levels in aqueous has been shown to be related to the acute elevation of IOP and it usually resolves spontaneously. In most cases the OHT is benign in nature, it has been reported that approximately 25% of the individuals develop uveitic glaucoma with glaucomatous defects. Ocular findings in Posner-Schlossman-related uveitis include keratic precipitates (KP), that are small, non-pigmented, flat, and can be detected in the inferior corneal endothelium. The iridocorneal angle appears open and some scattered deposits can be found on TM. (Kalogeropoulos & Sung, 2018.)

In *herpetic uveitis,* active iridocyclitis along with OHT are the main features in the development of uveitic glaucoma, which has been reported to be one of the most common complications in herpes infection-related uveitis. The incidence of the IOP spikes due to herpes virus-related uveitis has been reported to be 28-45% of which 10-54% may develop uveitic glaucoma. Trabeculitis, like in Posner-Schlossman syndrome, is the reason for IOP spikes. In addition, the elevation of the IOP can occur secondarily to the edema and obstruction of the TM. Herpetic uveitis is usually unilateral and acute in nature and in severe cases, hypopyon, hyphema, and fibrin formation leading to

anterior synechia are the clinical findings. The potential recurrence of herpetic uveitis and its unpredictable behavior makes the management of secondary uveitic glaucoma complex. (Kalogeropoulos & Sung, 2018.)

Chronic IOP elevation is associated with Fuchs' heterochromic iridocyclitis (Fuchs' uveitis), juvenile idiopathic arthritis, sarcoidosis, syphilis, Behcet disease, pars planitis, and sympathetic ophthalmia (Spaeth, 2021).

Fuchs' heterochromic iridocyclitis (FHI) is a chronic, idiopathic, usually unilateral, iridocyclitis with the sign of heterochromia in an iris due to stromal atrophy of the iris. It is not gender specific and the onset of the disease is around 20-40 years of age. The breakdown of the Schlemms' canal and infiltration of the inflammatory cells causing trabeculitis and rubeosis iridis is the leading cause behind the IOP elevation. The incidence of FHI-related inflammatory glaucoma varies between 13-59%. (Cusnir et al., 2020.)

The first-line management in uveitic glaucoma or uveitis-related ocular hypertension is to prevent structural intraocular alterations by controlling the underlying uveitis-induced ocular inflammation with anti-inflammatory therapy. Topical, local, or systemic corticosteroids are most commonly the treatment options to begin with and the well-managed inflammation can in many cases resolve the OHT without special glaucoma management. The inflammation's duration and chronicity define the dosage and strength of the administered treatment. Since the corticosteroids themselves have an increasing effect on IOP, especially within a group of steroid responders, finding the balance between inflammation management and potential steroid-induced hypertension could become difficult. (Kalogeropoulos & Sung, 2018; Rhee, 2018.)

Appropriate diagnosis of the underlying condition is imperative to achieve the successful management of IOP elevations. After the intraocular inflammation has been brought under control with the help of anti-inflammatory treatment the management of OHT should be considered if still needed. Topical β-blockers, if not contraindicated are considered first-line medicine to be introduced to lower the IOP in patients with inflammatory glaucoma. If β-blockers cannot be used, carbonic anhydrase inhibitors (CAIs) are used as effective agents to lower the IOP. There is controversy about what comes to the use of prostaglandin analogs (PGAs) as first-line medical treatment to decrease the IOP in uveitic glaucoma. In theory, there is a higher risk of developing

anterior uveitis, blood-aqueous barrier disruption, cystoid macular edema, and herpetic keratitis may be reactivated due to the use of PGAs. Muñoz-Negrete et al. (2015) reported in their review article that according to the data extracted from studies, PGAs can be as safe and effective to use as fixed combination treatment with β-blockers and CAIs. Especially among uveitic glaucoma patients whose uveitis is well controlled and under quiescent phase, and there has not been preexisting cystoid macular edema or previous complicated intraocular surgery. (Muñoz-Negrete et al., 2015; Sherman & Cafiero-Chin, 2019; Spaeth, 2021.)

Laser treatment can be considered when maximum topical treatment does not provide a sufficient decrease in IOP. Peripheral iridotomy is introduced as a treatment method for eyes with pupillary block caused by posterior synechiae or fibrin formation. Often there is a need for more than one iridotomy due to the failure in healing and excessive fibrin growth, or due to the highly pigmented irises. The study reported by Zhou et al. (2021) showed that selective laser trabeculoplasty (SLT) can safely be presented as a treatment option in uveitic glaucoma due to its low energy targeted to trabecular meshwork (TM). With the low energy the structural integrity of the TM is not altered, it produces less inflammation than other laser methods and it has been shown to have relatively good efficacy in lowering the IOP. Thus it is justified to use the SLT as a treatment method in circumstances where uveitic glaucoma has been rated as mild or moderate with well well-controlled stage of inflammation and the level of IOP lies between 20 to 40 mmHg. Argon laser trabeculoplasty (ALT) should be avoided among patients with uveitic glaucoma due to the risk of aggravating inflammation, failure in controlling the IOP, and causing permanent damage to the structure of TM. (Muñoz-Negrete et al., 2015; Sherman & Cafiero-Chin, 2019; Zhou et al., 2021.)

2.1.4 Neovascular Glaucoma

Neovascular glaucoma (NVG) is vision-threatening secondary glaucoma, characterized by neovascularization over the iris, proliferation of the fibrovascular membrane that covers the anterior chamber angle, and IOP elevation. The term, NVG, was presented for the first time by Weiss et al., in 1963, before that the disease was referred to as rubeotic glaucoma, diabetic hemorrhagic glaucoma, and congestive glaucoma. It is a potentially severe blinding form of glaucoma, where the visual acuity of hand movements and light perception is not uncommon. The course of NVG development can be divided into three stages: pre-glaucoma, secondary open-angle glaucoma,

and secondary angle-closure glaucoma. The pre-glaucoma can be further subdivided into pre-rubeosis and rubeosis iridis phases. (Rodrigues et al., 2016; Urbonavičiūtė et al., 2022.)

Though NVG is rare, the prevalence in the population reaches only 0,01-0.12%, which contributes to significant visual loss and morbidity. The incidence of NVG in all secondary glaucoma is 9-14.7% and of all cases of glaucoma 3,9%. Neovascular glaucoma can be caused by several systemic and ocular disorders but in 75% of the cases, one of the following ophthalmological conditions has the major role – proliferative diabetic retinopathy (PDR) (33%), ischemic central retinal vein occlusion (CRVO) (33%), the ocular ischemic syndrome (OIS) (13%), and the central retinal artery obstruction. The incidence of NVG is not particularly gender-specific, only with a slightly higher prevalence of men and it more often affects the elderly. (Dumbrăveanu et al., 2021; Rodrigues et al., 2016; Senthil et al., 2021; Urbonavičiūtė et al., 2022.)

Retinal ischemia is known to be associated with the development of NVG. In most of cases, up to 60%, ischemic CRVO is behind the NVG. The neovascularization at the anterior part of the eye typically develops in 3 months after the onset of vein occlusion, but the time frame of a few weeks up to 2 has been documented. It is usually unilateral. Nonischemic CRVO does not participate in the development of NVG unless there is an association of PDR or OIS. In diabetic eyes, the new vessels of the iris (NVI) are an advanced manifestation that occurs especially in the proliferative phase of the retinopathy. The key factors of NVI development are poor glycemic balance and untreated advanced posterior segment ischemia. Potentially 20% of diabetic eyes with NVI will progress into NVG. The progression may occur after 12 months of the incidence of neovascularization of the iris. The PDR-related NVI and NVG are often bilateral, there is one of the third risk of creating NVG in the contralateral eye when having it in the fellow eye. In ocular ischemic syndrome (OIS), the entire globe can possibly suffer from ischemia due to the reduced blood flow to the eyeball. Especially the ischemic condition of the anterior part of the eye in OIS is responsible for the growth of NVI. (Dumbrăveanu et al., 2021; Kanski & Bowling, 2016; Senthil et al., 2021; Urbonavičiūtė et al., 2022.)

The pathogenesis behind the uncontrolled IOP elevation in NVG is related to the growth of new blood vessels in the iris and in the anterior chamber angle due to the severe ischemic condition on the retina. The ischemic retina leads to the production of vasogenic substances, and the imbalance between these angiogenic and anti-angiogenic substances is what stimulates neovascularization.

Vascular endothelial growth factors (VEGFs), hepatocyte growth factor, insulin-like growth factor, tumor necrosis factor, and inflammatory cytokines (especially IL-6) are the common angiogenic factors. The common anti-angiogenic factors that are known are transforming growth factor-beta (TGF-β), thrombospondin, pigment epithelium-derived factor, and somatostatin. Multiple retinal cells: such as Müller cells, retinal pigment epithelium, pericytes, and ganglion cells, as well as the non-pigmented ciliary epithelium, participate in the release of VEGF, which is a major factor playing a pivotal role in neovascularization. Excessive amounts of VEGF release due to the ischemic conditions induce the vaso-permeability and endothelial cell migration which in addition increases the leucocyte adhesion to the endothelium and causing eventually the failure of the blood-retinal barrier. The fibroblast proliferation and the formation of fibrovascular membrane over the iris and anterior chamber angle are induced by the stimulation of TGF-β. The formation of new leaky vessels and the membrane with proliferated myofibroblasts explained above, are responsible for the obstruction of aqueous outflow through the trabecular meshwork, resulting in the secondary open-angle phase of NVG. Eventually, the contraction of the fibrovascular membrane will cause the severe and devastating synechial angle-closure phase of the NVG with extremely high elevation of the IOP. (Senthil et al., 2021; Urbonavičiūtė et al., 2022.)

Symptoms in NVG vary from none, especially in the early stages, to chronically red, painful, and photophobic eyes with decreased vision. The IOP level may be normal and the elevation of IOP can be gradual at the early asymptomatic phase, especially in young individuals with adequate corneal endothelial cell function. However, at the advanced stage of the disease, the IOP level exceeds to the extreme. The glaucomatous optic nerve damage may already be present at the time of diagnosis depending on the level of IOP and the duration. The early assessment of symptoms and clinical findings as well as the proper management of the NVG is in a crucial role in the prognosis of the visual impairment of the NVG. (Rodrigues et al., 2016; Urbonavičiūtė et al., 2022.)

Iris new vessels, on slit-lamp examination, are the first visible clinical signs of NVG. The pupillary zone is the common site to be first affected and neovascularization of angle (NVA) can occur simultaneously. Only seldom will the development of NVA occur alone. In contrast to normal blood vessels of the iris, which are radial and derive from the circular ciliary band and ciliary trunk, the new vessels of the iris (NVI) are chaotically arranged, thin, and tortuous on the iris surface. At the early stage, the abnormal NVI can be easily missed if not carefully looked for, because they are thin or appear as small tufts of blood vessels. Therefore, at the early stage, even to detect the pre-

rubeosis phase, fluorescein angiography (FA) would be a preferable addition for assessment compared to slit-lamp examination alone. FA will detect the leakage of the neovessels before they are clinically detected in slit-lamp biomicroscopy and thus improve the early diagnosis. Gonioscopy is an essential tool not only to visualize the NVI but also the only way to recognize neovascularization at the iridocorneal angle (NVA). These neovessels appear as thin, branching vessels that cover the structures of the angle. (Dumbrăveanu et al., 2022; Senthil et al., 2021.)

As a result of connective tissue proliferation, there is another severe clinical finding, fibrovascular membrane, that can be detected in NVG. In gonioscopy, the membrane may be difficult to visualize due to its transparency which leads to diagnostic difficulties. The anterior chamber angle appears to be open though it may be partially or totally closed. Especially at the later phase of the NVG the fibrovascular membrane tends to contract causing the peripheral anterior synechia and the angle closure. At this stage, the IOP usually rises acutely reaching levels up to 40 to 60 mmHg or even more. (Dumbrăveanu et al., 2021.)

To achieve the proper management of NVG it is important to conduct an accurate differential diagnosis since several other ocular conditions mimic the disease. Compared to dark eyes in light-colored eyes the prominent iris vessels are more visible and should not be misdiagnosed as NVI. The flare, inflammatory cells, and hemorrhage in the anterior chamber can be confused with uveitis. Acute angle-closure glaucoma mimics the NVG best. In both conditions, the patient experiences severe pain, elevated IOP, and dilated circumciliary blood vessels that can be mixed with the rubeosis iridis, or it could be impossible to evaluate the iris vessels due to the IOP-related corneal edema. In the case of edematous cornea, examining the fundus and iridocorneal angle of the fellow eye to detect signs of hypoxia or ischemia, will be helpful in either diagnosing or ruling out the NVG. (Dumbrăveanu et al., 2021; Senthil et al., 2021.)

The main principle in the treatment of NVG is to reduce the stimulus of neovascularization caused by retinal ischemia. This can be achieved by pan-retinal photocoagulation (PRP) or by intravitreal anti-VEGF agent injections. With PRP the goal is to increase the oxygen supply to the retinal areas that are not ischemic by reducing the retinal areas that suffer from ischemia, which in turn also reduces the secretion of VEGF and therefore restrains neovascularization. The anti-VEGF agents, that are used when the PRP is not possible for example due to the cloudy media, have been shown to provide effective and rapid reduction of neovessels at the anterior segment of the eye leading to

lowering of IOP. Although the anti-VEGF therapy is effective it only provides a temporary sufficiency that lasts about 1-1.5 months, therefore the combination therapy with PRP is suggested whenever it is possible. Also, anterior retinal cryotherapy can be performed when adequate PRP is not possible due to the blurry view of the fundus, and it can as well be combined with anti-VEGF therapy when needed. (Senthil et al., 2021; Urbonavičiūtė et al., 2022.)

The second principle is to treat the underlying systemic condition to balance the blood circulation to the retina and the other structures of the eye (Dumbrăveanu et al., 2022). Both topical and systemic antiglaucoma medication is required to manage the elevated IOP, but surgical intervention is often needed to achieve the desired level of IOP. The aqueous production lowering medication, such as carbonic anhydrase inhibitors (both topical and oral), beta-blockers, and alpha-2 agonists are beneficial in lowering the IOP. Prostaglandin analogs are effective in IOP reduction, but they are used only if the aforementioned other medications do not show sufficient efficiency, because of their tendency to promote inflammation. Miotics are contraindicated for the same reason as prostaglandin analogs, they increase inflammation and also affect anterior chamber angle closure. Topical corticosteroids should be used as a supportive medication to reduce inflammation when observed and to reduce vascular permeability and the growth of neovessels. Cycloplegic medications are used to reduce acute severe pain. Surgical intervention is needed approximately in 50% of the cases with NVG due to insufficient IOP control despite the maximum pharmacological treatment. (Senthil et al., 2021; Urbonavičiūtė et al., 2022.) Because of the nature of this thesis, the surgical procedures will not be described in detail.

2.2 Secondary Open-Angle Glaucoma Due to Ocular Trauma

Ocular trauma, especially if associated with glaucoma, is a significant cause of blindness globally. Secondary to the damage of intraocular tissues due to blunt or penetrating ocular trauma, bleeding, inflammation, and chemical injury the IOP level may become elevated and difficult to control. Both blunt and penetrating ocular trauma can be further subdivided into closed and open-globe injuries. The development mechanism of traumatic glaucoma varies with the nature of the underlying injury and therefore a careful examination must be performed to provide accurate management. The IOP elevation may occur after a very long time from the initial injury and a thorough history-taking to identify the possible underlying trauma is always pivotal. (Razeghinejad et al., 2020; Rhee, 2018.)

The anterior part of the eye, i.e., cornea, sclera, and anterior chamber, get easily affected by both blunt and penetrating trauma leading to either closed or open globe injury. In a closed globe injury, the eye wall does not get fully penetrated whereas in an open globe injury, there is full-thickness damage involving either cornea, limbus, sclera, or all the mentioned structures. The pathology behind traumatic glaucoma depends on the extent and amount of ocular tissues that get damaged in the injury. Post-traumatic glaucoma can occur due to direct damage or due to the inflammatory scarring of the trabecular meshwork. Also, inflammatory debris, lens particles, hyphema-related red blood cells, or prolonged vitreous hemorrhage could compromise the aqueous outflow and lead to the development of traumatic glaucoma. (Osman, 2015.)

Trauma-related bleeding into the anterior chamber (AC) or to the vitreous cavity may cause the IOP elevation and development of glaucoma. The blood accumulation in the anterior chamber is called hyphema and it can be categorized by the extent it fills the AC. The micro hyphema is the smallest amount that can be detected only with a slit lamp as single non layering blood cells in the aqueous whereas grade I to IV hyphemas are layered and visible also without the slit lamp. Grade I hyphema fills up to 33% of the AC, grade II up to 50%, grade III over 50%, and the whole anterior chamber in grade IV. Grade IV hyphemas are often referred to as 8-ball or blackball hyphemas due to the presentation. Young active men are compared to women more commonly affected by trauma-related hyphemas. The reason for injury in men tends to be occupational or sports-related whereas women tend to get ocular traumas at an older age and mostly due to falls. The extent of a hyphema can be used to predict the visual outcome, the bigger the grade of the AC fill the worse the prognosis of the vision and post-traumatic complications. (Kanski & Bowling, 2016; Osman, 2015; Razeghinejad et al., 2020; Rhee, 2018.)

The majority, up to 66% of the incidences where the blood arises to the AC is a consequence of a direct, forceful blow to the orbit. The anteroposterior forces along with the equatorial elongation may cause the rupture of the iris and ciliary body blood vessels and lead to bleeding. Vision loss is rarely caused by the hyphema alone but the associated complications such as IOP elevation, rebleeding, corneal blood staining, and optic nerve atrophy can cause ocular morbidity. The IOP elevation in the case of post-traumatic hyphema results from the compromised aqueous outflow due to the obstruction of trabecular meshwork by the red blood cells, inflammatory cells, and debris. Also, the clots in the AC participate in the IOP elevation by causing a pupillary block that leads to the impairment of aqueous circulation. The incidence of IOP elevation correlates with the extent of

hyphema. Half of the patients with grade IV hyphema with secondary bleeding may develop elevated IOP and secondary traumatic glaucoma. Rebleeding which may occur up to 35% of the hyphema patients within 3-7 days after the initial trauma, is often more severe than the hyphema at the time of injury. (Kanski & Bowling, 2016; Osman, 2015; Razeghinejad et al., 2020; Rhee, 2018.)

Patients with traumatic hyphema should be examined thoroughly to be determined the nature and timing of the trauma. The thorough examination will allow for evaluation of the likelihood of additional injuries and proper management. The patients may be asymptomatic, or they may suffer from pain and photophobia along with impaired vision. IOP elevation-related nausea and vomiting may also occur. Clinical findings are presented in slit lamp examination as single red blood cells circulating among the aqueous humor alone or in combination with layered hyphema in the anterior chamber. Corneal blood staining can be clinically evaluated when there is elevated IOP present secondary to extensive and prolonged hyphema. Gonioscopy should be postponed to the time when the risk of rebleeding is no longer present, i.e., 3-4 weeks after the initial trauma. The AC may show residual blood or angle recession, or it may appear undamaged. (Rhee, 2018.)

In the case of traumatic hyphema, supportive therapy is the first-line management. A strict bed rest is not needed, but during the sleep and rest the head elevation is suggested and some activity restrictions are instructed. It promotes the hyphema to be layered inferiorly in the anterior chamber which on the other hand allows the visual axis to be cleared of blood more rapidly. Hypotensive medications such as beta-blockers and/or carbonic anhydrase inhibitors (CAI) both topical and systemic are used to control the elevated IOP. CAI should be avoided, if possible, in patients with sickle cell hemoglobinopathies because of their role in promoting the sickling of the red blood cells by increasing the pH of the aqueous and causing hemoconcentration. Prostaglandins and miotics should also be avoided due to their tendency to advance the inflammatory process. Topical steroids are used to control inflammation and also because they reduce the risk of rebleeding. (Kanski & Bowling, 2016; Razeghinejad et al., 2020; Rhee, 2018.)

Angle recession can occur after blunt or penetrating trauma to the anterior section of the eye. Histologically angle recession can be described as a tear between the circular and longitudinal muscle layer in the ciliary body. Clinical findings in gonioscopy include a widened ciliary body band, a prominent scleral spur, and a greyish-white membrane that covers the iridocorneal angle. It is

important to examine the eye with great accuracy since the findings of angle recession may be subtle and cyclodialysis can mimic it. Only 7-9% of eyes with angle recession develop into traumatic glaucoma in a period of 10 years, however, 71-100% of eyes with traumatic hyphema are observed to have angle recession. The IOP elevation can be explained to develop rather secondary to the damage of the trabecular meshwork or due to a possible extension of a Descement-like membrane from the cornea over the TM than to angle recession itself. However, the risk of glaucoma is directly related to the extent of angle recession. Eyes, that have damage larger than 180 degrees have an incidence of developing angle recession-related glaucoma as high as up to 10% and it usually occurs as late-onset glaucoma, i.e., months or years after the initial injury. Recession damage larger than 270 degrees may lead to the earlier onset of traumatic glaucoma. It has been hypothesized that in angle recession-related glaucoma the injury may only be the triggering factor to the other existing glaucoma predisposing factors, as the risk of glaucoma in the contralateral eye is up to 50%. (Kanski & Bowling, 2016; Razeghinejad et al., 2020; Rhee, 2018.)

Patients at risk of developing angle recession-related glaucoma, especially ones that have damage larger than 180 degrees, are in need of annual long-term follow-up examinations. Medical treatment is the first-line approach in managing the angel recession-related traumatic glaucoma. Common secondary open-angle glaucoma medications are usually used to lower the IOP, and they may show sufficiency but often the elevated IOP stays at an unsatisfying level and is hard to control. Miotics should be avoided since they can worsen the angle recession by decreasing the aqueous outflow and due to the fact that they increase vascular permeability. In an acute phase, this can lead to a fibrin clot formation which may predispose the posterior synechiae and secluded pupil. Prostaglandins are also contraindicated at the acute phase but can be used after the exclusion and/or resolution of the inflammation. Laser trabeculoplasty has not shown effective benefits in decreasing the IOP in the case of angle recession glaucoma. According to Razeghinejad et al. (2020) in their major review, argon laser trabeculoplasty led to failure in controlling the IOP within three months in 7 patients out of 11. Surgical procedure is often required to control the IOP in patients affected with traumatic angle recession glaucoma. (Razeghinejad et al., 2020; Rhee, 2018.)

Trabecular meshwork can get affected by trauma in multiple ways and mechanical trauma can occur without angle recession. Trabecular pigmentation is usually associated with pigmentary and pseudoexfoliative glaucoma, but it can also be related to the development of traumatic glaucoma

after a closed globe injury. The trabecular meshwork gets blocked by the liberated pigment and also by the endothelial cells that are involved in phagocytizing the released pigment particles. Visible lacerations can also be present after the trauma in the trabecular meshwork. These lacerations can at first cause the improvement in aqueous outflow by incorrectly mimicking the function of surgical treatment such as trabeculectomy and first lead to the decrease of the IOP in the affected eye. (Razeghinejad et al., 2020.)

The trauma can affect the eye in several ways and therefore the mechanism behind the IOP elevation in traumatic glaucoma can vary. The key component in the management of trauma-related glaucoma is to accurately identify the underlying cause of the IOP elevation. The early glaucomatous changes should be taken rapidly into consideration, especially among the high-risk patients, such are the ones with high age, the ones with poor vision at the time of trauma, the ones that have suffered perforating rather than penetrating trauma, and the ones that have suffered lens injury, presence of vitreous hemorrhage and/or presence of intraocular foreign body. In the majority of cases the topical glaucoma treatment can provide a satisfactory result in lowering the IOP and if it fails the surgical treatment will usually provide the eligible result. Despite the heterogenous nature of the trauma, the visual outcome is often good if the IOP is treated properly and there is no significant irreversible anatomical damage occurred. (Osman, 2015; Razeghinejad et al., 2020.)

2.3 Iatrogenic Secondary Open-Angle Glaucoma

2.3.1 Glaucoma Due to Corticosteroid Treatment

Steroid-induced ocular hypertension (SIOH) or glaucoma (SIG) develops due to the use of corticosteroids which are commonly used as anti-inflammatory drugs to control both ocular and systemic inflammatory conditions. In SIOH the intraocular pressure is elevated with no glaucomatous defects present at the affected eye, but the condition may develop into SIG when additional glaucomatous optic neuropathy is detected. The definition of steroid responsiveness to ocular pressure has been proposed in many different variations over the years, but the IOP elevation with more than 10 mmHg increase over the baseline with clinical significance has been the most widely accepted definition. The person whose IOP gets easily affected by the use of corticosteroids is defined as a “steroid responder”. (Roberti et al., 2020.)

According to Roberti et al. (2020), different ex vivo and in vivo studies with both human donor eyes and eyes of many different species have shown that the pathophysiology in corticosteroid-related hypertension and glaucoma is related to compromised trabecular meshwork. The corticosteroids can directly affect the beams of the TM and juxtacanalicular tissue by thickening them, and also the intertrabecular spaces may get diminished due to the increased amount of extracellular matrix and activated TM cells related to corticosteroid use. All above leads to the increased resistance of the aqueous outflow followed by the elevation of IOP. (Roberti et al., 2020.)

The majority (61-63%) of the population with normal ocular history are nonresponders to the corticosteroids, presenting only IOP elevation less than 5 mmHg. The moderate IOP increase between the values 6 to 15 mmHg affects 33% of the normal population and only 4-6% of the normal population is highly responsive with the IOP elevation more than 15 mmHg. However, 46 to 92% of patients diagnosed with primary open-angle glaucoma can potentially get harmful IOP elevation due to the use of topical steroids. Therefore, the prevalence of steroid-induced glaucoma among all the other forms of secondary glaucoma is not clear. The IOP rise in both healthy individuals with no glaucomatous defects and in steroid responders who also have glaucomatous defects will occur within a time period of 2 to 6 weeks after initiating the administration of topical steroids, but it is not rare occurring at any time. (Spaeth, 2021.) If the trabecular meshwork has not suffered irreversible damage during the steroid administration the IOP will be reversed back to baseline level approximately in two weeks after the discontinuation of the medicine (Roberti et al., 2020).

It is not clearly explained why there are individual differences in the risk of manifesting steroid-induced ocular hypertension and glaucoma. One possible explanation could be in the different expression of the two glucocorticoid receptors, GRα and GRβ, that are mediating the clinical and cellular reactions of the glucocorticoids. Also, mutations in GR gene transcription and/or in DNA bindings along with environmental factors can influence the steroid response and thereby to the susceptibility to steroid-induced glaucoma. The elderly are at a higher risk of developing SIOH and SIG after the administration of topical steroids. However, Roberti et al. (2020) point out in their review that few studies have shown that uveitic patients aged under 30 and treated with intravitreal implants of sustained-release steroids show a risk factor of IOP elevation 10 mmHg or greater. In children, the possible exaggerated response to steroid use can be explained by the structural and functional immaturity of the TM and the IOP elevation with possible glaucomatous defects that are

more severe at presentation and have an earlier onset than in adults. Patients diagnosed with primary open-angle glaucoma (POAG) and the ones that have a first-degree relative with POAG are at a higher risk of presenting steroid-induced hypertension and/or glaucoma. High myopia, angle recession glaucoma, type I diabetes, and connective tissue disease have also been shown in studies to be risk factors of response to steroids and possible development of SIG. (Roberti et al., 2020.)

Corticosteroids can be administered by exogenous routes, which are topical, intraocular, periocular, oral, intravenous, inhaled, nasal, and transcutaneous routes. All these routes can more or less affect IOP elevation and at development of SIG. Very rarely SIG develops due to the excess production of glucocorticoids from endogenous routes due to some particular endocrine diseases. The chemical structure of the steroid which defines the strength of the steroid, frequency and duration of administration, and the dose along with the route of administration play a pivotal role in defining the risk of IOP elevation and the development of steroid-induced glaucoma. (Roberti et al., 2020; Spaeth, 2021.)

Topical steroids are commonly used to treat several ocular conditions and also after different surgical and laser procedures to control and prevent postoperative complications. Topical steroids tend to induce ocular hypertension and glaucoma more commonly than systemic steroids. In recent years the medical industry has developed topical steroids that are safer to use compared to older ones because they do not have the same elevation affection on IOP. The older corticosteroids such as for example dexamethasone (DEX) and prednisolone tend to affect the IOP ten times more frequently in a range of 6 mmHg to 22 mmHg compared to the newer corticosteroids such as loteprednol etabonate, difluprednate, or rimexolone. The hypertensive effect of the corticosteroid drops has been found to last up to 18 months after termination of the use of the steroids therefore the possible IOP-lowering medication should not be discontinued earlier. (Roberti et al., 2020.)

Intravitreal injections along with the sustained-release intravitreal implants represent the intraocular route of administration of the corticosteroids. The intraocular administration of corticosteroids has become very popular in medicine during the last decade because of the effectiveness it has shown in the treatment of several retinal and choroidal diseases. However, secondary steroid-induced ocular hypertension or glaucoma has become a considerable problem in patients treated with this route of administration. In intravitreal injections, the dosage of the corticosteroid can be easily

targeted to the intended site, and it allows rapid delivery and volume of the medicine. DEX and triamcinolone acetonide (TA) are the most commonly used corticosteroids for intravitreal injections. According to the studies that were conducted on the injections with TA the IOP reached its peak values in 2-16 weeks after the injection, remained elevated for 1-9 months, and reached the pre-injection values in 4-9 months. The injections administered with DEX showed an earlier increase in IOP (within one day) and also quicker regression to pre-treatment values (one month). (Roberti et al., 2020.)

Though the treatment of corticosteroids with intravitreal injections are effective, it often needs to be repeated which leads to the increased risk of possible serious ocular complication. To reduce the risk, biodegradable and nonbiodegradable sustained-release intravitreal implants have been developed. FA, which is nonbiodegradable and must be surgically removed, and DEX, which is biodegradable are the two sustained-release implants available. The DEX sustained-release implants are better tolerated in terms of IOP elevation compared to the ones with FA. The IOP elevation caused due to the use of DEX implants is usually better controlled with the IOP-lowering medications and the elevation is more transient. Whereas ocular hypertension or glaucoma caused by the use of FA implants varies from an incidence of 11% in a real-world clinical practice setting up to 79 % in patients with uveitis. With FA the IOP elevation commonly occurs 2-4 weeks after implantation and has the peak value within 24-28 weeks, the IOP returns back to its baseline after 9-12 months. Though the majority of patients treated with FA implants required the IOP lowering medication, the diagnosis of secondary glaucoma due to the use of corticosteroids was reported less frequently (0% -10.2%). In a large study that was conducted on the patients treated with DEX implants the occurrence of IOP elevation was reported in 26,5% of patients and the steroid responders had a greater risk to be affected. Generally, little over half of the patients (51%) had ocular hypertension detected after 2 months of DEX implantation. Approximately 33% of the study subjects were forced to use the hypotensive medication after DEX implantation to lower the elevated IOP and 54% of patients already on glaucoma medication had an escalation on current treatment. (Roberti et al., 2020.)

Corticosteroids can also be administered via the periocular route. The subconjunctival space, the sub-Tenon space, the orbital floor alongside the globe via a transcutaneous or trans-conjunctival injection, or the retrobulbar space are all considered as periocular routes. While using the subconjunctival and anterior sub-Tenon space for administration the steroids enter the eye

anteriorly via the cornea and the tear film and the higher concentration of the medicine have a bigger effect in the anterior chamber. Posteriorly while using the peribulbar and retrobulbar routes along with posterior sub-Tenon space the corticosteroids enter the eye via the sclera and have a higher affection within the retina and vitreous. The sub-Tenon space is the most commonly used of all the periocular routes and is also associated with the highest risk of causing IOP elevation or steroid-induced glaucoma. The anterior part of the sub-Tenon space administration has been shown to induce a bigger elevation on IOP compared to the posterior sub-Tenon space. This may be due to the fact that the anterior chamber angle is located near the injection site of the anterior sub-Tenon space. The IOP elevation caused by corticosteroid administration via the sub-Tenon space has been reported to vary from 2 weeks up to 5 months, reaching the baseline within 10 months after discontinuing the administration of the steroids. Young age, myopia, higher baseline IOP, the number of injections needed with concomitant intravitreal injections along with the strength and dose of corticosteroids are all risk factors for IOP elevation in a periocular corticosteroid treatment. IOP monitoring is mandatory during the periocular corticosteroid administration, especially on patients who are known to be steroid responders and those who are already on glaucoma medication. (Roberti et al., 2020.)

Corticosteroids, especially in several chronic inflammatory diseases, are also administered via systemic routes such as oral tablets, nasal sprays, pulmonary inhalation, dermatological ointments and creams, and intravenous pulse therapy. The relationship between developing ocular hypertension or steroid-induced glaucoma while administering corticosteroids via systemic routes has been reported according to many studies to be conflicting. Though many studies show that the systemic intake of corticosteroids is relatively safe the patients should still be monitored closely because the IOP may rise months to years after initiating the treatment. The baseline IOP should be measured before starting the corticosteroid treatment and a 1-month measurement along with 3 months follow-up are suggested. The systemic intake of corticosteroids induces a risk of IOP elevation, especially in long-term use along with high dosages of the medicine and additional use of topical steroids. Especially patients who are steroid responders and have a history of first-degree relative with glaucoma are at a higher risk of developing OH and/or SIG due to systemic use of corticosteroids. (Roberti et al., 2020.)

The medical management of SIG is no different from the one that is used for patients with primary open-angle glaucoma. All topical and systemic IOP-lowering medications alone or in combinations

can be used. However, it is important to remember that prostaglandin analogs are contraindicated in patients who have developed high IOP after the use of corticosteroids to control ocular inflammations since prostaglandins are known to induce uveitis. Laser trabeculoplasty (both ALT and SLT) can be considered as an option in IOP lowering treatment. Despite the medical and/or laser treatment 1-5% of the SIG patients need to undergo surgery to achieve a sufficiently low IOP level. The ocular hypertension induced by the use of corticosteroids is often reversible therefore, if possible, the steroid treatment should be discontinued or replaced with a weaker steroid if discontinuation cannot be introduced due to the underlying condition. The IOP usually reverts to its normal baseline level within 2-4 weeks after interruption of the steroid therapy, especially if the medicine has not been used for longer than a year. The IOP increase is more persistent if corticosteroids have been in use for 18 months or longer. The impact of corticosteroids cannot be underestimated in an increase of IOP and possible development of SIG and therefore the strict follow-up plan should be mandatory for patients under steroid therapy to prevent irreversible glaucomatous damage. The pretreatment IOP level should be measured and after initiating the therapy the frequency of measurements is dependent on the route of steroid management. Evidence has been obtained that topical steroid treatment increases the IOP within hours and days compared to systemically administered treatment which can affect the IOP level increasingly after years. (Roberti et al., 2020.)

2.3.2 Glaucoma Due to Ocular Surgery

Ocular surgery can be considered as one possible cause behind the development of secondary open-angle glaucoma. The risk factors behind developing secondary glaucoma after surgery are intraocular hemorrhage, inflammatory reaction, lens material, pigmentary loss from uveal tissue, and trauma. The resistance of normal trabecular outflow causes the elevation at the IOP level. The causes that are behind the outflow decrease of the trabecular meshwork are inflammatory debris, viscoelastic material, vitreous in the anterior chamber after cataract surgery, lens particles, and prostaglandin release. The pathology behind these are explained in detail in chapters 2.1 and 2.2. Fortunately, the elevation of the IOP is usually transient. (Spaeth, 2021.)

Pars plana vitrectomy (PPV) is a common surgical procedure that aims to remove vitreous gel. The procedure is done for several different reasons including macular puckers and holes, retinal

detachment, diabetic retinopathy, and trauma. Vitreous removal and replacement with different substances that include for example gas, and silicon oil can cause a significant increase in IOP both acutely and chronically, leading to the possible development of different forms of secondary glaucoma. The IOP increase can be explained by the following mechanisms hyperfilling of the vitreous replacement substances, aqueous misdirection, zonular weakness, lens diaphragm sifting, ciliary body edema, damage of the trabecular meshwork, neovascular stimulations, and vortex vein damage are the most frequent causes to mention. (Rossi & Ripandelli, 2020; Spaeth, 2021.)

The early onset of post-operative IOP elevation after PPV is mainly due to the migration of the overfilled silicon oil into the anterior chamber which results in obstruction of the trabecular meshwork (TM). Intermediate and late onset of IOP elevation may occur when emulsified silicon oil obstructs and partially phagocytized silicon oil debris accumulates into TM. The trabecular meshwork may get permanent structural damage when the contact with silicon oil is prolonged. (Rossi & Ripandelli, 2020; Spaeth, 2021.)

The treatment of secondary open-angle glaucoma related to ocular surgery follows the same management path as any other form of the same condition. The topical and systemic IOP medication is introduced as first-line treatment as well as anti-inflammatory treatment if needed. (Spaeth, 2021.)

2.4 Assessment of Secondary Open-Angle Glaucoma

2.4.1 Risk Factors

In glaucoma diagnostics, it is essential to detect and recognize high-risk patients at an early stage to be able to optimize the management of the disease and thereby prevent irreversible damage to the optic nerve and nerve fiber layer (Seppänen et al., 2022). Risk factors can be subdivided into non-modifiable; age, ethnic origin, family history, thin central corneal thickness, refractive error, and modifiable; elevated intra-ocular pressure, medications, and associated conditions (Lee & Mackey, 2022). There are also several characteristic risk factors (Table 1) associated with certain types of secondary open-angle glaucoma that are explained in more detail in the chapters 2.1, 2.2, and 2.3.

Age. Age is known to be one of the main risk factors in the development of both primary and secondary open-angle glaucoma. Older age increases the prevalence of glaucoma by doubling the risk every ten years (Seppänen et al., 2022.)

Ethnic origin. Individuals from African backgrounds are at the highest risk of developing open-angle glaucoma and the disease tends to be more aggressive in nature compared to individuals with Caucasian ethnicity (Seppänen et al., 2022).

Family history. Having a family history of glaucoma especially a first-degree relative diagnosed with the condition is an important and considerable risk factor (Lee & Mackey, 2022). The risk of developing glaucoma is three times higher in patients with family history compared to those without (Seppänen et al., 2022). The prevalence of glaucoma in first-degree family members has shown according to several population-based studies to be up to nine times higher in comparison to controls without the family history. In addition, they have a 22% risk of developing glaucoma during their lifetime while the risk at normal controls is 2.3%. (Lee & Mackey, 2022; Mcmonnies, 2017.)

Thin central corneal thickness. Thinner central corneal thickness is highly associated with the risk of ocular hypertension conversing to glaucoma. The model pooled from both The Ocular Hypertension Study (OHTS) and the European Glaucoma Prevention Study (EGPS) shows that the risk doubles within 5 years. Therefore central corneal thickness (CCT) is considered an important parameter when assessing potential glaucoma patients. There are several different factors including ethnicity, age, genetics, the subtype of glaucoma, and glaucoma treatment which will affect the CCT and should be considered when interpreting the level of IOP of the glaucoma suspects and patients. Belovay et al. (2018) pointed out in their review article that pseudoexfoliation syndrome and pseudoexfoliation glaucoma patients have been reported to have either thinner or similar CCT to normal controls. Studies that have included patients with pigment dispersion syndrome have not been able to show the difference in CCT compared with primary open-angle glaucoma or normal eyes, due to the small cohort. (Belovay & Goldberg, 2018.)

Refractive error (myopia). The prevalence of myopia worldwide is estimated to rise from 34% to 50% by the year 2050. Studies have shown that the one dioptre decrease to myopic direction in a refractive error increases the risk of glaucoma by 20%. The connection between the myopia and the risk of glaucoma can possibly be explained by the structure of the myopic eye. In the myopic

eye, the optic nerve and the surrounding tissues are structurally in weaker condition due to longer axial length compared to the emmetropic eye. Thus, exposing the retinal ganglion cells to greater mechanical damage. Myopic patients are at higher risk of developing pigmentary glaucoma. (Lee & Mackey, 2022.)

Elevated intraocular pressure. Intraocular pressure (IOP) is a result of a balance between the aqueous humor formation and the resistance of an outflow. Normal intraocular pressure typically falls within a range of 10-21 mmHg (millimeters of mercury), and any IOP above the level of 21 mmHg is considered to be elevated. In glaucoma onset and progression, the elevated IOP plays a strong role, and it remains the only clinically modifiable risk factor to slow the progression. According to two large studies in the field of glaucoma, OHTS (Ocular Hypertension Treatment Study) and EMGT (The Early Manifest Glaucoma Trial), the 1mmgH increase above the reference value will increase the relative risk for glaucoma development by 10% and patients with newly diagnosed glaucoma will have an 11% risk of progression. (Da Silva & Lira, 2022; MacIver et al., 2019; Spaeth, 2021.)

TABLE 1. Risk factors in Primary Open-Angle Glaucoma (POAG) and Secondary Open-Angle Glaucoma (SOAG).

Risk Factors	POAG	SOAG
Age	x	x
Corticosteroids		x
Ethnic Origin	African	Caucasian, Scandinavian
Elevated IOP	x	x
Exfoliation Syndrome		x
Family History	x	x
Myopia	x	x
Pigment Dispersion Syndrome		x
Surgery		x
Systemic Disease/Virus Related Uveitis		x
Systemic and Ocular Disorder		x

Risk Factors	POAG	SOAG
Thin CCT	x	Pseudoexfoliation Glaucoma
Trauma		x

2.4.2 Comprehensive Eye Examination

A comprehensive eye examination consists of an overall evaluation of the eyes**. Patient and family health history** plays a pivotal role when gathering background information about the patient. Andersson, S. (2022) has published a patient history questionnaire as part of her Master's studies and more detailed information about the subject can be found in her thesis. According to Andersson (2022), more detailed information should be gathered during the history taking than we are used to at the moment in Finland. The following aspects should be highlighted more; interviewing in more detail about the history of current illness and symptoms, the history and current status of general health, and the social history. (Andersson, 2022.)

Although **Visual acuity** and **best-corrected refraction** are essential parts of the comprehensive eye examination, the existence of glaucoma or the progression of the disease cannot be made based on these factors. Glaucoma does not affect central vision or cause a decrease in visual acuity before its late and severe stages. Therefore preliminary tests such as peripheral vision tested by an automated field analyzer, color vision, and pupil reactions to the light will provide with more accurate information about the current function and health of the eyes. (Richman et al., 2010; Seppänen et al., 2022.)

2.4.3 Intraocular Pressure Measurement

This chapter will discuss the importance of tonometry in assessing and managing patients with a history or with a suspicion of SOAG. The equipment mostly used in optometry stores will be pointed out, but the technique of the measurement and all different types of tonometry devices available on the market are out of the scope of this thesis and therefore will not be included in this chapter.

The performance of IOP measurement can be divided into three methods; transpalpebral measurement, tonometry, and manometry, of which the transpalpebral method gives the less

accurate result. Manometry being a true invasive measurement will result in the most accurate IOP readings while external tonometry with certain biases (Table 2) will give an estimation of a precise IOP. There are four principles in tonometry, that are applanation, rebound, indentation, and contour matching. Applanation tonometry is further subdivided into contact and non-contact tonometry. This chapter will concentrate on Goldmann applanation tonometry as contact tonometry and i-Care tonometry as rebound tonometry. (Da Silva & Lira, 2022.)

TABLE 2. The IOP error is caused by different corneal statuses when measuring with Goldmann applanation tonometry (Adapted from Spaeth, 2021, 55).

Cornea Status	Incorrectly Low IOP	Incorrectly High IOP
Thin Central Cornea	**x**	
Thick Central Cornea		**x**
Refractive Surgery Performed	**x**	
Epithelial Oedema	**x**	
Excessive Tear Film	**x**	
Insufficient Tear Film		**x**

Intraocular pressure has diurnal fluctuation. The studies have found that the IOP follows the circadian rhythm with peak value occurring during the night time and early morning and the minimum value settles somewhere between morning time and early afternoon. Though the 24-hour follow-up is difficult and not cost-effective to arrange, the longer follow-up during office hours compared to a single measurement will provide more information about the risk of onset and the progression of the disease. (MacIver et al., 2019; Noya-Padin et al., 2023.)

Goldmann applanation tonometry (GAT) is currently the golden standard method of IOP measurement used in a clinical setting to which the reliability of other methods is compared. It is a fixed-area contact tonometer, meaning that the force needed to flatten a certain fixed area of the corneal surface is measured. As seen in (Table 1) a few parameters can affect the accuracy of the measurement of IOP, of which the central corneal thickness is one of the most significant factors. The GAT has been designed to give the most precise readings when the thickness of the cornea

is on its average measurement of 520 microns. Also, a significant astigmatism can give less reliable IOP measurements. **iCare rebound tonometry** has shown reliable results compared to GAT at the normal IOP range. However, the accuracy of iCare diminishes at high levels of IOP, and the readings given are overestimated. (Da Silva & Lira, 2022; MacIver et al., 2017; Suman et al., 2014.)

2.4.4 Gonioscopy

Gonioscopy is one of the most important components when examining patients having or suspected of having glaucoma. It is considered a golden standard method to evaluate the structure and function of the iridocorneal angle also known as the anterior chamber angle (ACA). This paragraph will not go into details about the technique of the procedure because it is nowadays considered as a part of education in Finland. Gonioscopy is a highly specialized technique that is performed with the help of a slit lamp along with the use of a special gonioscopy lens and demands high competence. According to Phu et al. (2019) and their retrospective investigation conducted at the Centre for Eye Health Glaucoma Management Clinic (University of New South Wales, Sydney, New South Wales, Australia), they were able to show that optometrists achieved fair to moderate agreement between general ophthalmologists in terms of accurate assessment of the ACA structures. To become an experienced professional in this subjective examination, gonioscopy requires a long learning curve. Unfortunately, gonioscopy is an examination that remains often omitted in an eye examination performed by optometrists because of its time-consuming and demanding nature. Despite the new additional objective techniques introduced to complement the evaluation of ACA, such as anterior segment ultrasound biomicroscopy, Scheimpflug imaging, and anterior segment optical coherence tomography (AS-OCT), the gonioscopy remains the only method giving the total *in vivo* view of the iridocorneal angle and trabecular meshwork. (MacIver et al., 2019; Phu et al., 2019; Riva et al., 2020.)

Gonioscopy is essential to differentiate the open angle from the closed angle and to recognize the other pathological conditions that are characteristic of secondary open-angle glaucoma such as pigment dispersion syndrome, pseudoexfoliation syndrome, angle recession, and anterior segment dysgenesis. The documentation of an anterior chamber angle openness or closure is a subjective methodology that utilizes the different established grading systems, and the Schaffer system is the most used one. This system estimates the angular width based on anatomic structures seen, giving

a numerical grade from 0-4. (Shinoj et al., 2016.) The following structures from the posterior perspective to the anterior can be visualized; ciliary body (CB), scleral spur (SS), trabecular meshwork (TM), and Schwalbes' line (SL). Commonly the gonioscopic grades 0 and 1 are considered closed angle when at least in two quadrants there is no visibility of the pigmented TM or other posteriorly situated structures. Grade 2 is borderline with only Schwalbes' line and TM to be seen, and the angle is considered to be open in grades 3 and 4. In grade 3 the structures from SS posteriorly to SL anteriorly are visualized and in grade 4 all the ACA structures can be seen. (Phu et al., 2019; Riva et al., 2020; Shinoj et al., 2016.)

The ciliary body (CB) is the most posterior part of the iridocorneal angle to be visualized when performing gonioscopy and as mentioned above it marks a wide-open angle. It shows at the site of the iris root as a brownish-grey band, and it manifests in deeper angles and less-pigmented irises. When proceeding anteriorly the next structure to be seen is the scleral spur (SS) which appears as a white line located between the CB and the pigmented trabecular meshwork (TM). Trabecular meshwork, which can be further divided into the posterior pigmented and anterior non-pigmented TM, is found anterior to the SS. The pigmented part forms two-thirds of the whole TM and is considered as the functional uveal part of the TM filtering agueous humor to the underlying canal of Schlemm. Anterior non-pigmented, non-functional corneoscleral TM appears light and even bluish-grey because of the less-pigmented nature compared to the posterior TM.(MacIver et al., 2019.)

The Schwalbe line (SL) is the most anterior structure of the iridocorneal angle. It is a peripheral part of the Descement membrane and appears as an opaque but fine line covered with various amounts of pigmentation. A pigmented SL, also known as the Sampaolesi line, can refer to the presence of exfoliation and pigment dispersion leading to a risk of developing secondary glaucoma. The iridocorneal angle is at risk of closure when the SL is the only visible structure in the gonioscopy. (MacIver et al., 2019.)

Since having a degree of invasiveness, performing gonioscopy requires topical anesthetics in both eyes along with lubricant gel, so as not to appear as a bothersome procedure for the patient. Limbal anterior chamber depth (LACD) assessment is the non-invasive method using a slit-beam of a biomicroscope to determine the openness of the ACA. This is also known as the Van Herick technique. Park et al. (2011) came into conclusion in their comparative study that there is a good

consistency between gonioscopy and Van Herick technique especially in narrow angles. In Van Herick technique, the depth of a peripheral anterior chamber is compared to the thickness of the cornea over the central portion of the light beam, and it is reported in a fraction. Van Herick established a four-point grading system, where the grade 1 angle (LACD is less than ¼ of the thickness of the cornea) is at a high risk of angle closure. In grade 2 the LACD equals ¼ of the thickness of the cornea, and according to Van Herrick, all eyes having grade 2 or less require gonioscopy for a thorough evaluation of the ACA. (Jindal A et al., 2020; Park et al., 2011; Seppänen et al., 2022.)

2.4.5 Optic Nerve Head Assessment

The appearance of the optic nerve head (ONH) is a predictive factor in the diagnosis and progression of glaucoma. According to the OHTS 40% of the retinal ganglion cells, which axons form the rim, can be destroyed before the damage appears as a loss in a visual field (VF). Therefore, it is essential to perform a careful and systematic assessment of the ONH. The **size**, by which is meant the overall size of the optic disk and the correlation between the width of the rim and the size of the cup, varies significantly among the population. Along with the aforementioned, the refractive error and race bring their own characteristics into the parameters of ONH. (MacIver et al., 2019; Spaeth, 2021.)

In a healthy eye, the optic disc is slightly vertically oval. The mean vertical diameter being approximately 1.92mm whereas the average of the mean horizontal diameter of the optic disc is 1.76mm. The neuroretinal rim appears at its widest and thickest in the inferior sector. Followed by the superior and then the nasal and temporal sectors. ISNT-rule can be used as a tool in an assessment of the optic nerve head, meaning that a vertically elongated cup should raise suspicion of rim loss and therefore presence of possible glaucomatous optic neuropathy. Glaucoma specific early signs of structural optic nerve head changes are excavation or diffuse impairment of rim tissue. Superiorly and inferiorly appearing focal notches are also glaucoma related findings that can be predictive of a rapid visual field loss, especially in fixation. Focal changes are easier to localize than diffuse ones, but the latter is more common. The ISNT rule is best implemented in medium-sized discs, whereas in large discs the rim is distributed more evenly and appears relatively narrow and therefore can be misinterpreted as glaucoma suspicious. With small discs,

there is a risk of overlooking the glaucomatous changes because there is no evident cupping, and the rim appears relatively wide. (MacIver et al., 2019; Spaeth, 2021.)

The optic nerve head can be clinically divided into five prominent rings, which start from the center: the cup, the rim, the scleral ring, central zone beta, and peripheral zone alpha **parapapillary atrophy** (PPA). The PPA in the alpha zone is found to a large extent in healthy eyes. It is typically located in the temporal horizontal sector of the optic nerve head, followed by inferio-temporal and superio-temporal regions and it appears due to irregular pigmentary change in the retinal pigment epithelium (RPE). On the contrary PPA in zone beta is rare in healthy eyes. The PPA in zone beta is due to the total loss of the RPE and choriocapillaris next to the ONH, causing increased visibility to the large choroid vessels and the sclera. Though the PPA in the beta zone is common in myopic eyes, it is age-related and there are controversies about the association with glaucoma. Despite aforementioned the studies have shown that the PPA in beta zones exists more frequently in glaucomatous eyes. The defect of the beta zone in glaucomatous eyes is more extensive in width compared to non-glaucomatous eyes and appears more often infero-temporally following the superio-temporal quadrant. More often the progression of the PPA in the beta zone is diagnostically more useful than the presence of atrophy itself. (Banc & Bianchi Marzoli, 2022; MacIver et al., 2017.)

Studies have shown that there is a strong association between **optic disc hemorrhages** and glaucoma. The disc hemorrhages can be present now and then in glaucomatous eyes, especially in those that are at the early or moderate stage. Despite the association with glaucoma the IOP, mechanical disruption, or the vascular factors alone cannot explain the birth mechanisms of the disc haemorrhages, which makes it a complex phenomenon. Hemorrhages can be considered as a single, strongest hallmark of the higher risk of the progression of the established glaucoma. It is though not shown weather the hemorrhage is the factor for progression or the result of progression. It is generally thought that when the hemorrhage is present, it indicates that glaucoma is in an active stage. Typically, the hemorrhage, which is feathery and flame-shaped, is located at the inferior part of the optic disc crossing the ONH margins. It is not excluded that it can be found at the superior part of the optic disc or intrapapillary at the level of lamina cribrosa, where the hemorrhage appears as blot-shaped. Clinically via slit lamp microscopy, the hemorrhages are difficult to detect and therefore often overlooked. Careful assessment with the help of photography,

when possible, gives the best result for documenting the condition. (MacIver et al., 2019; Spaeth, 2021.)

2.4.6 Nerve Fiber Layer Assessment

Retinal nerve fiber layer (RNFL) loss is one of the earliest signs of glaucomatous defect and it precedes the observable visual field defects by up to several years. Unfortunately, the RNFL loss is not easy to visualize on clinical slit lamp assessment of the eye, and even a dark pigmented fundus and clear media do not bring ease. To get the defect to be visible on ophthalmoscopy more than half of the RNFL thickness must be lost. In a healthy and normal eye, the nerve bundles that enter the optic nerve head will show relatively bright striation inferiorly and superiorly. The striation is less prominent adjacent to the nasal and temporal sectors of the ONH. (MacIver et al., 2019.)

Glaucomatous RNFL defects can be either diffuse or local. In diffuse thinning the striation appears more opaque compared to the one in a healthy eye and the visibility of the edges of parapapillary retinal vessels is improved. The edges will appear clear and sharp against the matt background of the fundus. Asymmetry, between eyes and between inferior and superior poles, is typical for diffuse thinning. Often age in general affects the RNFL by causing a diffuse loss in visibility, making the detection of glaucomatous diffuse changes extremely challenging. (MacIver et al., 2019; Spaeth, 2021.)

Focal defects are easier to localize and detect. They appear as a wedge or smaller slit-shaped defects with total loss of the brightness and density of the striation. The width of the defect is at least the size of a major retinal vessel, and it tends to widen following the arcuate pattern of the ONH. Typically, the wedge defects appear at the inferior-temporal and/or superior-temporal quadrants of the ONH and they represent the active phase of glaucomatous damage often along with disc hemorrhages and neuroretinal rim notching. It is extremely important to pay attention to the widening and deepening of the wedge defects because it predicts the progression of glaucoma. (MacIver et al., 2019; Spaeth, 2021.)

The best way to assess the RNFL clinically with slit lamp microscopy is to use red-free illumination combined with low magnification. Also, the narrow and short beam of the white bright light with high

magnification can be used for assessing the RNFL. The evaluation should be made around the ONH approximately from the distance of two disc diameters from the margin of the optic disc. (Spaeth, 2021.)

2.4.7 Visual Field Assessment

Visual field (VF) testing in glaucoma is considered as a gold standard assessment method when diagnosing and also monitoring both the progression of the disease and the effectiveness of the treatment. Damage to the retinal nerve fibre layer and glaucomatous changes in the optic nerve head cause defects in the visual field that are characteristic of the disease. Although the aforementioned structural changes are what define glaucoma, the damage in the visual field is what impacts the functional vision of the glaucoma patient most. Therefore it is essential to perform a reliable automated visual field assessment to the patient with the suspicion of glaucoma to help the diagnosis and to set a baseline for the regular follow-up examinations. (Heijl et al., 2012; MacIver et al., 2017.)

Glaucomatous field defects follow the recognizable pattern. At an early stage of glaucoma the initial defect commonly appears in a paracentral area of the visual field or as nasal step and/or arcuate scotoma. The most central part of the visual field usually remains intact and is affected not until the severe stage of the disease. (Heijl et al., 2012; MacIver et al., 2017.)

Standard automated perimetry (SAP) uses white static stimuli on a white background and is recommended as a standard perimetry in glaucoma assessment and management. It is an objective tool which provides numerical results and progression analysis reports with computer-aided interpretation. The most commonly used SAP static perimeters are Octopus perimeter and Humphrey Field Analyzer perimeter and for the former, the Dynamic strategy is mostly recommended to be used to detect glaucomatous changes and for the latter SITA (Swedish Interactive Threshold Algorithm) Standard or SITA Fast strategies are often used. (Spaeth, 2021.)

For clinician to be able to determine the diagnosis and/or the progression of VF reliable repetitive examinations are essential. To gain reliable results the examinator plays a pivotal role in providing accurate and clear instructions for the patient on how to perform from examination. It has been

proven that the reliability of the exams will improve along with the experience and the learning curve. There are also indices developed for the SAP programs to evaluate the reliability of the examination. These are false negatives (FNs), false positives (FPs) and fixation losses (FLs). The patient who has a high rate of false positives is called “trigger happy” since he/she respondes more often to the stimuli than there has been an actual ones. In this situation the result of a visual field may appear too good indicating either false stability or false progression. The test is automatically considered unreliable if the rate of FPs is 15% or greater. The FNs are considered as a indication to express the patients ability to focus on an examination since the rate of FNs increases when the reactions to the stimuli are unlogical. The small and dim stimulus is seen and answered while the bigger and brighter stimulus from the same location is not seen and answered. The high rate of FLs indicate that either the gaze of the patient has not been stable and focused or the placement of the blind spot is incorrect. The Octopus perimeter also has the Reliability Factor (RF) which summarizes all the FPs and FNs and is expressed as a percentage to all the positive and negative catch trials presented. (MacIver et al., 2017; Spaeth, 2021)

2.4.8 Imaging and Testing in Glaucoma Assessment

Diagnosis and management of glaucoma is based on assessment of the structure and function of the optic nerve head (ONH) and retinal nerve fiber layer (RNFL). Objective tools, such as automated visual field (AVF) perimetry, optical coherence tomography (OCT), and fundus photography, are additional and extremely helpful in diagnosing and managing glaucoma. In Finland, these devices are not common in every optical store, but the prevalence has been increasing in recent years. The more accessible these devices get among optometrists the more knowledge of how to use them they will have to perform these additional examinations before referring to the ophthalmologist.

If imaging tools are not available it is suggested that some form of documentation should be done to help the further assessment and follow-up. The visual field should be evaluated and estimated by performing the confrontation field. The best way to document the optic nerve head without the imaging tools is to make as accurate a drawing as possible. (Spaeth, 2021.)

OCT and fundus photography devices are currently the most common tools accessible in optometry stores. OCT is a patient-friendly, non-invasive, easily repeatable, and generally accepted examination in the assessment and management of glaucoma. It gives the possibility to evaluate the structure of the optic nerve head (ONH), retinal nerve fibre layer (RNFL), and ganglion cell layer. Quantitative results from the patient are compared to the normative database. Algorithms developed to analyze the results are device-dependent and therefore progression comparison should not be made between the results from different devices. However, comparison images alone should not be directly relied on without critical analysis and examination of the overall data. An analysis report in the red sector does not automatically indicate diagnosable glaucoma and the green sector does not confirm that there is no glaucoma. The development of these objective assessment devices has not removed the fact that subjective evaluation of ONH and RNFL through biomicroscopy is still the most important factor in glaucoma diagnosis and fundus photography of ONH and RNFL are needed for documentation. (MacIver et al., 2017; Seppänen et al., 2022; Spaeth, 2021.)

2.5 Glaucoma Management Information and Quality of Life

2.5.1 Medical Treatment

For several decades topical medical treatment has been the first-line treatment method to lower the intraocular pressure for most patients with glaucoma. The goal is to lower the IOP from the baseline at the time of the diagnosis and/or the detection of the progression of the disease. The target pressure is set individually and it should be achieved with the fewest medications and the least side effects possible. Prostaglandin analogs, topical carbonic anhydrase inhibitors, beta-blockers, and alpha agonists are the products of an evolvement of pharmacotherapy in the field of glaucoma over the past decades. These medications are shown to have more effectiveness in lowering the IOP while providing a better safety profile compared to the older systemic and topical treatments. Schuster et al. (2020) point out in their literature review that a network of meta-analyses has shown that the prostaglandin analogs lower the IOP to the greatest extent, followed by beta blockers, alpha agonists, and carbonic anhydrase inhibitors. The majority of glaucoma patients will start the treatment with one medicine administered at a time and based on the efficacy the second or even the third medicine is added. The combination drops are used to minimize the number of

different drops to be administered which contributes to improving compliance with the treatment and reduces the side effects caused by preservatives. (Schuster et al., 2020; Seppänen et al., 2022; Wagner et al., 2022.)

Prostaglandin analogs are the most common medicines introduced to start the treatment of glaucoma because these are well tolerated, have minimal side effects, and are administered only once per day, in the evening. The effectiveness of lowering the IOP with prostaglandin analogs is in the range of 25-35%. The mechanism of this medicine is to improve the uveoscleral and trabecular outflow and thereby lower the IOP. The side effects that are most common with the use of prostaglandin analogs are an extensive growth of eyelashes, conjunctival hyperemia, increased pigmentation of the periorbital skin and the iris, and the reduction of the periorbital fat. If the target pressure is not achieved with the initial PGA medicine it should be first changed to another PGA before adding the combination medicine. (Schuster et al., 2020; Wagner et al., 2022.)

Topical beta blockers are a good alternative to be used as a single medicine if PGAs are not tolerated. The effectiveness in the reduction of the IOP is approximately 20-25%. These are usually administered twice per day and the mechanism of lowering the IOP relies on decreasing the production of the aqueous humor. There are several contraindications to be considered when prescribing beta blockers. These are asthma, diabetes, chronic obstructive pulmonary disease, and cardiovascular disease. (Schuster et al., 2020; Seppänen et al., 2022; Wagner et al., 2022.)

2.5.2 Laser Treatment

Laser treatment, especially selective laser trabeculoplasty (SLT) has become a successful first-line treatment alongside topical medical treatment for newly diagnosed open-angle glaucoma and ocular hypertension. This chapter will not go into detail about SLT as a procedure, because in Finland only ophthalmologists are entitled to decide the need and perform the treatment. Instead, the chapter will focus on reviewing the pros and cons of the treatment to increase the awareness of the optometrists about the subject when managing the patients. Also, other invasive treatment options, such as glaucoma surgery, are not included because of the scope of this thesis and the legal restrictions that guide the work of Finnish optometrists.

Previously laser treatments have been a last resort before the surgical intervention to lower IOP after the medical treatment has lost effectiveness or there has been challenges to achieve the target pressure with the maximum medication provided. In SLT the aqueous outflow is improved by targeting the pigmented cells of TM with a quick and low-energy laser. Compared to the older treatments SLT is less damaging to the structure of TM and can therefore be repeated. The Laser in Glaucoma and Ocular Hypertension (LIGHT) trial (2019) showed that patients with a new diagnosis of open-angle glaucoma and/or ocular hypertension can be safely and effectively treated with SLT as a first-line treatment. The main outcome of the trial was that after 3 years 74.2% of patients treated with SLT were in no need of additional topical treatment to maintain the target IOP. With no need for topical treatment the systemic and ocular side effects, the risk of progression of the disease caused by poor patient adherence, and the risk of failure in later ocular surgery because of long-term use of topical medications can all be avoided. This is a major factor in improving the health-related quality of life. (Gazzard et al., 2019; Seppänen et al., 2022.)

The second outcome of the trial made by Gazzard et al. (2019) was the cost-effectiveness of SLT compared to medical treatment. Patients introduced with SLT as first-line treatment had lower overall costs, including ophthalmological visits, medical costs, and ocular surgeries needed compared with peers treated only with IOP-lowering medicine. Despite the positive outcome of the SLT as a first-line treatment and drop-free everyday life for the majority of the patients, healthcare providers must explain carefully to patients that a drop-free life does not mean disease-free life and regular follow-ups are still mandatory. (Gazzard et al., 2019.)Over the years SLT will lose its effectiveness by approximately 8% per year and despite the possibility of repeating the procedure, after seven years only 20% of patients will carry on without additional topical treatment (Seppänen et al., 2022).

2.5.3 Glaucoma and Quality of Life

The National Eye Institute has developed a questionnaire that evaluates the vision-related quality of life (VRQoL). The questionnaire consists of vision-related questions that chart the health status of ocular diseases, including glaucoma. Vision-related problems for near and far, limitations in the visual field, driving difficulties, vision-related mental health issues, social functioning, and dependency are subjects that are evaluated. It has been known for a long time and has also been

taught to patients that glaucoma is a “silent thief” that affects vision at its severe and late stages. Therefore preserving the visual field and with that the visual function of the glaucoma patients is mandatory to save the VRQoL from deteriorating. (Nishida et al., 2023.)

The loss of the visual field among glaucoma patients has been described as a loss of the peripheral field, traditionally this can be understood as the loss of vision from the outer edges of the visual field when seeing binocularly. Therefore the public guides of the visual field loss for glaucoma patients have been illustrated as “tunnel vision” which deteriorates over time along with the progression of the disease. By teaching this to the general public the wrong perception of glaucomatous symptoms in the visual field may be created. The peripheral field in glaucoma describes the field of one eye which means that the narrowing can occur also from the nasal side of the periphery. This linguistic mispredention can cause a situation where early glaucomatous symptoms in the visual field can be overestimated and ignored as not being caused by glaucoma. (Gagrani et al., 2022; Hu et al., 2014.)

Hu et al. (2014) researched in their study the symptoms of early glaucoma. The aim was to improve understanding of how glaucoma affects vision from the patients’ perspective. As a result of their study, the most common symptoms described among patients with early glaucoma were blurry vision, need for more light, and glare. In the study of Gagrani et al. (2022) the iPad app was developed allowing glaucoma patients to map out how they experience their visual field. Also in this study, the different stages of blurriness and/or missing objects were described and not a single patient mapped the vision as blackness in the visual field. The absence of blackness can be explained with the mechanism of “filling in” where the visual system can construct a filling to the voids in the visual field based on the surrounding information. Providing patients with the awareness of these vision-related symptoms will possibly lead to the earlier detection and management of glaucoma. Early Detection of the disease on the other hand may help to sustain or improve the VRQoL by preserving the visual function in everyday life. (Gagrani et al., 2022; Hu et al., 2014.)

Compliance with glaucoma medication is generally poor. The smallest amount of medication and application times per day to achieve the desired target pressure are suggested for the treatment of glaucoma. Combination drops are preferred when the single medication is not enough to lower the IOP. Two bottles of combination drops are the recommended maximum for glaucoma medication.

If there is a need to apply the third bottle of medication it is suggested to consider other pressure-lowering treatment options, for example, selective laser trabeculoplasty. (Seppänen et al., 2022.) Also, the study made by Nishida et al. (2023), showed that already early-stage glaucoma patients reported lower VRQoL. Though there is no evidence of objective visual field defects in early-stage glaucoma the instillation and the amount of different IOP lowering medications introduced can cause an experience of an impairment of the quality of life. (Nishida et al., 2023.)

3 THE PURPOSE, OBJECTIVES, AND TASKS OF THE RESEARCH AND DEVELOPMENT WORK AND THE DIFFERENT STAGES

3.1 Purpose of the Study Project

The purpose of this thesis was to provide a thorough, easy-to-understand theoretical background about secondary open-angle glaucoma along with a general framework of evidence-based recommendations to be utilized when creating the guidelines for Finnish optometrists about the assessment and management of patients with secondary open-angle glaucoma. This was an innovation project for, and in cooperation with, the Finnish Ethical Board of Optometry.

3.2 Statement of the Research Question

The framework of the CLIP model was used when conducting the research question. This model is useful in qualitative and mixed-method studies, especially when the purpose of the study is to examine particular services or professions. (Wildridge & Bell, 2002.)

C (client group)	= adult patients with secondary open-angle glaucoma
L (location)	= Finland/ optometry stores
I (improvement/innovation/information)	= assessment/ guidelines/ key components
P (professionals)	= optometrists

What key components should be considered when conducting guidelines for Finnish optometrists about the assessment and management of patients and/or suspects with secondary open-angle glaucoma?

3.3 Summary Description of the Experimental Design

This thesis was conducted as a literature review content analysis-based innovation project to provide suggestions for the Finnish Ethical Board of Optometry to be utilized when creating a guideline for the assessment and management of secondary open-angle glaucoma for Finnish

optometrists. The future guideline is targeted to serve optometrists working at the optical store since colleagues in the hospital environment are most likely working under the supervision of ophthalmologists along with the care processes and guidelines of the hospital. The idea was to provide evidence-based recommendations for the guideline, which will help to unify the assessment made and the best-known management given in the optometrist´s everyday work. This innovation project included three phases. The first phase was to gather and analyze current guidelines about the topic. The second phase was to conduct a thorough literature review about secondary open-angle glaucoma based on the content of selected existing guidelines. The third and last phase was to develop evidence-based recommendations to be used as a guideline when assessing and managing patients with secondary open-angle glaucoma. The project took place between spring 2023 and spring 2024.

3.4 Study Objectives

The first objective was to search national and international guidelines and analyze those selected by using the qualitative approach of content analysis and select the most relevant aspects as key elements.

A thorough literature review of the subject of secondary open-angle glaucoma was conducted as a second objective of this thesis to obtain an evidence-based theoretical background.

The third and last objective was to conduct a framework of recommendations to be utilized to create evidence-based clinical guidelines on the subject for Finnish optometrists by adopting the information received from the two objectives above.

4 IMPLEMENTATION OF RESEARCH AND DEVELOPMENT WORK

4.1 Methodology

4.1.1 The Literature Search and Selection

To identify topics relevant to the thesis subject the search for clinical practice guidelines (CPGs) was made by using the electronic literature search and grey literature sources. In addition, a comprehensive literature review for the theoretical background was conducted mainly in spring 2023 between March and May. An electronic literature search was performed on databases PubMed, CINAHL, Google Scholar, and Finna. The search was limited from year 2010 to 2023 and only full articles and results in English or Finnish were included. The guidelines that were found and that met the inclusion criteria were further selected for the appraisal based on the geographical location to get as wide an overview as possible.

The first search was mainly concentrated on clinical practice guidelines. The search terms were “secondary open-angle glaucoma” AND “guidelines” OR “sekundääriglaukooma” AND “hoitosuositukset”. It was quickly noticed that there was a limitation since no specific guidelines were found that were considering specifically and exclusively secondary open-angle glaucoma. The search was expanded to include glaucoma in general and was generated with the following MeSH terms: glaucoma (OR “exfoliation syndrome” OR “exfoliative syndrome” OR pseudoexfoliati* OR pseudo-exfoliati*) AND guidelines (OR “guidelines as topic” OR “practice guidelines as topic” OR “evidence-based practice” OR “evidence-based medicine” OR guideline* OR evidence-based OR “treatment recommendation” AND optometry (OR “ophthalmology” OR “eye care” OR eyecare OR “vision care” OR visioncare OR ophthalmolog*

From the guidelines detected the European Glaucoma Society Guidelines for Glaucoma, 5th Edition was selected as a baseline for the structure of the theoretical background of this thesis. Search terms were used individually based on the specific subtype of the secondary open-angle glaucoma, and were for example “pseudoexfoliation syndrome”, “pseudoexfoliation glaucoma”, “pigmentdispersion syndrome”, “pigmentdispersion glaucoma”, “pigmentary glaucoma”, “uveitic

glaucoma", "neovascular glaucoma", "iatrogenic glaucoma", "secondary open-angle glaucoma AND trauma", "secondary open-angle glaucoma AND ocular disease", "sekundääriglaukooma", "eksfoliaatiosyndrooma", "eksfoliaatioglaukooma", "pigmenttidispersiosyndrooma", "pigmenttidispersioglaukooma" AND (prevalence OR epidemiology OR ethiology). The search results were first viewed by title and the ones that met the inclusion criteria were further analyzed by the abstract. Based on the narrative nature of the literature review, the studies that were relevant to the subject were chosen.

4.1.2 Reliability of the Research Development Work

This innovation project study was conducted by only one author. This may contribute to the unreliability of the research, as no other perspective is available on the interpretation of the results and decision-making. In addition, the author's previous professional experience and skills, or lack thereof, may lead to guided decision-making. The clinical practice guidelines should be made by a working group consisting of several professionals, which would contribute to ensuring more perspectives on the topic and thus increase the reliability of the project. To achieve more reliability in this project, two content supervisors were involved throughout the work. Their contribution was to ensure the correctness of the content of the work. In addition, Oulu University of Applied Sciences' information specialist and her professional skills were utilized in the literature search to obtain as comprehensive material as possible. The finalized guidelines of this thesis project are not put into practice as such, but the OEN that commissioned the work verifies the content and utilizes the guidelines of the completed project as such or modified to suit the intended use. With this expertise evaluation, the reliability of the project will be improved.

4.1.3 Ethicality of the Research Development Work

This thesis is conducted by following the guidelines of the Oulu University of Applied Sciences and the Finnish National Board on Research Integrity (TENK). The basic principles of research integrity which are, reliability, honesty, respect, and accountability, are followed throughout the implementation of this thesis. Separate permission from the Institutional Review Board (IRB) was not needed as human participants were not involved in this research project.

4.1.4 Evaluation of the Research Development Work

The end product of this thesis was a content of recommendations that can after expertise evaluation be further developed into guidelines for Finnish optometrists about the assessment and management of secondary-open angle glaucoma. The work was ordered from Oulu University of Applied Sciences as a Master Thesis project by the Finnish Ethical Board of Optometry (OEN). The OEN has unanimously concluded that the field of optometry requires uniform guidelines for the use of Finnish optometrists that are in line with Nordic and international best-care practices. However, the content for guidelines developed during this thesis project will not be submitted into use as such, but the OEN owns the decision-making power regarding the status of the guidelines and the further use of the content of the final theses. The supervision of the thesis work was carried out by the two supervisors of the Oulu University of Applied Sciences and the OEN omitted themselves from the development phase of this project. Feedback from peer students or collegial supervision was not part of this thesis either.

From the very early stage of this project, it was realized that the scope of the thesis subject is very specific yet enormous, and detailed planning plays an important role in good and transparent implementation. The preliminary literature search gave no results in secondary open-angle glaucoma as a single subject. Therefore it was decided that the best approach in the literature search would be to evaluate the different secondary glaucoma subtypes separately. The author's lack of academic competence and experience was a limiting factor in the systematic implementation of this thesis project and made the development work very time-consuming and intermittently hard to process. Fortunately, the scheduled online meetings and collaboration when needed with the supervisors and their encouragement gave an enormous willpower and belief to finish this project.

4.2 Specific Aim 1, Literature Search of the Subject Secondary Open-Angle Glaucoma and Selection of Existing Guidelines

4.2.1 Methods

The first specific aim of this study was to search and select the literature and the existing national and international guidelines about the subject assessment and management of secondary open-angle glaucoma. The guidelines were selected based on overall geographical coverage.

TABLE 3. Geographical coverage of the existing guidelines found for the thesis.

Guideline	US	Europe	UK	Canada	Australia
European Glaucoma Society Terminology and Guidelines for Glaucoma.		X			
American Optometric Association (AOA), Care of the Patient with Open Angle Glaucoma.	X				
Hyvä optometristin tutkimuskäytäntö -ohjeistus.		X			
Screening, Diagnosis, and Management of Open Angle Glaucoma, Evidence-Based Guideline for Canadian Optometrists				X	

Guideline	US	Europe	UK	Canada	Australia
Glaucoma: diagnosis and management NICE guideline.			X		
Healthcare Improvement Scotland, SIGN 144, Glaucoma referral and discharge. A national clinical guideline.			X		
Clinical Practice Guide for the Diagnosis, Treatment and Management of Glaucoma.					X

4.2.2 Results

The following guidelines were selected to be analyzed in more detail and utilized to determine the key components to be used when conducting the suggestions for evidence-based guidelines for Finnish optometrists as a development project made within this study.

- European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th Edition (Spaeth, 2021)

- American Optometric Association (AOA), Care of the Patient with Open Angle Glaucoma. (Fingeret et al., 2010)

- Hyvä optometristin tutkimuskäytäntö -ohjeistus. The Finnish Ethical Board of Optometry (OEN) (*Hyvä Optometristin Tutkimuskäytäntö-Ohjeistus*, 2018)

- Screening, Diagnosis, and Management of Open Angle Glaucoma, Evidence-Based Guideline for Canadian Optometrists. (MacIver et al., 2019)

- Glaucoma: diagnosis and management NICE guideline(*Glaucoma: Diagnosis and Management NICE Guideline*, 2017)

- Healthcare Improvement Scotland, SIGN 144, Glaucoma referral and discharge. A national clinical guideline. (*SIGN 144 • Glaucoma Referral and Safe Discharge*, n.d.)

- Clinical Practice Guide for the Diagnosis, Treatment and Management of Glaucoma July 2016 (*Clinical Practice Guide for the Diagnosis, Treatment and Management of Glaucoma July 2016*, 2016)

4.3 Specific Aim 2, Content Analysis of the Literature and Existing Guidelines to Confirm Key Components

4.3.1 Methods

The second aim was to conduct a comprehensive and easy-to-internalize theoretical background about the subject based on a content analysis of the existing guidelines and a literature review of the subject. The European Glaucoma Society Guidelines for Glaucoma, 5th Edition was chosen to be the baseline when determining the structure for the theoretical background. Because of the wide scope of the topic, the best approach to achieve thorough evidence was to search every subtype of secondary open-angle glaucoma separately. The key components were built up from selected guidelines by careful coding of the relevant elements (Table 4). Repetitive elements were further gathered to relevant recommendations. Recommendations were divided to guide the assessment and management of secondary open-angle glaucoma separately.

TABLE 4. Content analysis of existing guidelines

Guidelines	EGS	AOA	NÄE	CAO	NICE	SIGN
Patient History and Risk Factors	Y	Y	Y	Y	Y	Y
Eyelids	N	Y	Y	N	N	N
Pupil Reactions	N	Y	Y	N	N	Y
Visual Acuity	N	Y	Y	Y	Y	Y
IOP	Y	Y	Y	Y	Y	Y
CCT	Y	Y	N	Y	Y	Y
Anterior Segment Examination						
Anterior Chamber	Y	Y	Y	Y	Y	Y
Iridocorneal Angle	Y	Y	Y	Y	Y	Y
Conioscopy	Y	Y	N	Y	Y	Y
Van Herick	Y	N	Y	Y	Y	Y
Cornea	N	Y	Y	Y	Y	N
Iris	Y	Y	Y	Y	Y	Y
Lens	N	Y	Y	N	Y	N
Posterior Segment Examination						
Vitreous	N	Y	Y	N	Y	N
ONH	Y	Y	Y	Y	Y	Y
Symmetry	Y	Y	N	Y	N	N
C/D Ratio	Y	Y	N	Y	N	Y
Neuro-Retinal RIM	Y	Y	N	Y	N	Y
Peripapillary Area	Y	Y	N	Y	N	N
Disc Haemorrhages	Y	Y	N	Y	N	Y
Macular Area	N	Y	Y	Y	Y	N
Peripheral Retina	N	Y	N	N	Y	N
Visual Field / OCT / Photography	Y	Y	Y	Y	Y	Y

EGS=European Glaucoma Society, **AOA**=American Optometric Association, **NÄE**=Näkeminen ja silmäterveys NÄE ry, **CAO**=Canadian Association of Optometrists, **NICE**=National Institute for Health and Care Excellence, **SIGN**= Scottish Intercollegiate Guidelines Network, **CCT**=central corneal thickness, **IOP**= intraocular pressure, **ONH**=optic nerve head, **Y**=yes, mentioned **N**=not mentioned.

4.3.2 Results

The result of the coding is explained in Figure 2 and all the components of the structure composed from literature are discussed separately in theoretical background.

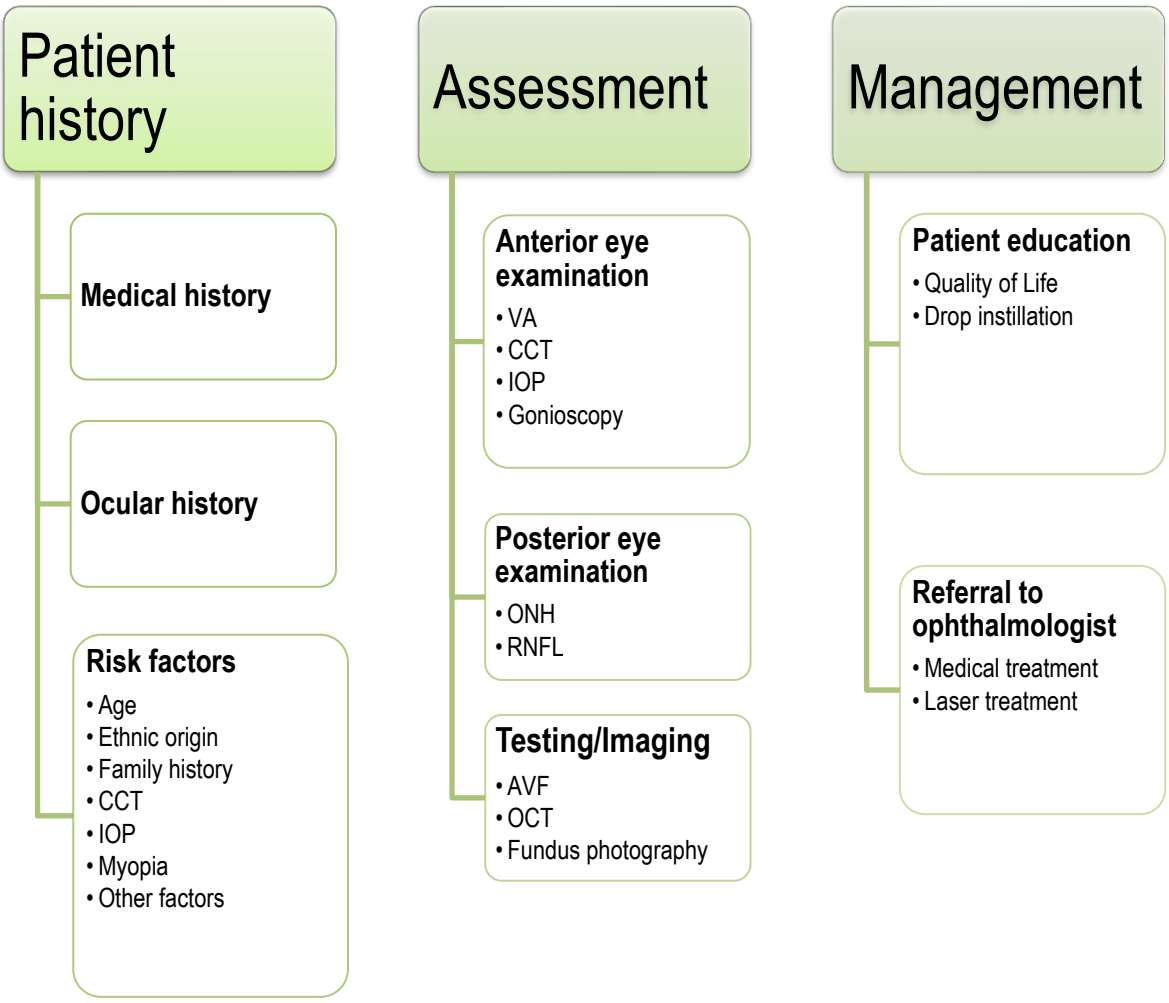

FIGURE 2. Main elements, sub-elements, and key components identified from literature review. AVF=automated visual field perimetry, CCT=central corneal thickness, IOP=intraocular pressure, OCT=opticl coherence tomography, ONH=optic nerve head, RNFL=retinal nerve fiber layer, VA=visual acuity.

4.4 Specific Aim 3, Determining Content for The Clinical Guidelines for Finnish Optometrists about The Subject Secondary Open-Angle Glaucoma

4.4.1 Methods

The third aim was to establish recommendations, based on content analysis results of the existing guidelines and evidence-based literature, to be used to create the clinical guidelines for Finnish optometrists about the assessment and management of secondary open-angle glaucoma. The current law considering the limitations of the work of Finnish optometrists has been noticed when conducting the content for future guidelines.

4.4.2 Results

Patient history

- Medical history
    - High risk medications
    - Diabetes
    - Hypertension or hypotension
    - Peripheral vasospasm
    - Sleep apnea
- Ocular history
    - Blunt ocular trauma
    - Hyphema
- Risk factors
    - Age
    - Ethnic origin
    - Family history
    - Myopia

Assessment

- Vision / Visual acuity
  - Accelerated deterioration of vision → Pseudoexfoliation syndrome/pseudoexfoliation glaucoma
- Anterior eye examination
  - Cornea
    - Pigment deposits on corneal endothelium (Krukenberg's Spindle) → Pigmentary glaucoma
  - Iris
    - Exfoliative, dandruff-like material on pupil margin → Pseudoexfoliation syndrome/pseudoexfoliation glaucoma
    - Iris transillumination defects → Pigmentary glaucoma
    - Neovascularization within the anterior segment of the iris → Neovascular glaucoma
  - Anterior chamber
    - Depth / Van Herick method
    - Pigment deposits
    - AC inflammation → Inflammatory/uveitic glaucoma
    - Hyphema → Traumatic glaucoma
  - Anterior chamber/ iridocorneal angle
    - Gonioscopy
      - Homogenous pigmentation of TM (trabecular meshwork) → Pigmentary glaucoma
      - Exfoliative, dandruff-like material on TM → Pseudoexfoliation syndrome/pseudoexfoliation glaucoma
      - Angle recession → Traumatic glaucoma
      - Neovascularization over the iridocorneal angle → Neovascular glaucoma
  - IOP
    - Goldmann applanation tonometry is the golden standard
    - Excessive elevation of IOP → Inflammatory/uveitic glaucoma

        - IOP spike after use of topical/systemic steroids → Steroid-induced glaucoma
    - Lense
        - Pseudoexfoliative material on anterior lens capsule → Pseudoexfoliation syndrome/pseudoexfoliation glaucoma
        - Premature cataract after blunt trauma → Traumatic glaucoma
- Posterior eye examination
    - Retina
        - Retinal ischemia → Neovascular glaucoma
    - Optic nerve head
        - Size / CD-ratio
            - Enlarged cup-disc ratio, especially vertically
            - Asymmetric cup-disk ratio >0.2
        - Optic disc hemorrhages
            - Flame-shaped hemorrhages crossing the disc margin
            - Blot hemorrages on disc
        - Para papillary atrophy
            - Zone-beta PPA
        - Nerve fibre layer
            - Defects in the inferior and superior nerve bundles.
- Standard Automated Perimetry (SAP)
    - The gold standard for assessment of the visual field (VF)
        - Humphrey perimeter (SITA Standard and SITA Fast)
        - Octopus perimeter (Dynamic Strategy)
        - Goldmann perimeter (suitable for the advanced stage of the disease)
    - VF defects characteristic of glaucoma
        - Paracentral scotoma
        - Nasal step
        - Arcuate scotoma
    - Perimetry should be performed at least once per year
        - Greater level of VF loss at the time of diagnosis → Pseudoexfoliation Glaucoma

        - More rapid VF loss → Pseudoexfoliation Glaucoma
- Optical Coherence Tomography (OCT)
- Fundus Photography

Management

- Patient education
    - Quality of life
    - Drop instillation
        - Patient information about the technique of instillation and the importance of the regularity
- Referral to ophthalmologist
    - Medical treatment
        - Prostaglandin analogues as first-line medicine
    - Laser treatment
        - SLT-trabeculoplasty

5 DISCUSSION

Optometry, as a specialized branch of healthcare, plays an important role in maintaining and enhancing visual health. Optometrists, as important primary eye care providers, are entrusted with the responsibility of assessing and managing a range of ocular conditions. To ensure optimal patient care and safety and maintain professional standards, adherence to well-established guidelines is crucial in the practice of optometry. Currently, there are no existing guidelines to be utilized for Finnish optometrists that consider secondary open-angle glaucoma or any type of glaucoma. Current Care -guideline (Käypä hoito -suositus) for ophthalmologists exists in Finland and has been updated in spring 2023 but it can not be used as such in the daily work of Finnish optometrists because of the laws and legislations that obligate optometrists in Finland.

Referring to the above, the importance of developing the evidence-based guideline for optometrists in Finland about the assessment and management of secondary open-angle glaucoma is inevitable. The guideline will serve as a roadmap to shape and support optometrists' work, emphasizing their role in ensuring the high-quality and consistent care to be delivered and promoting continuous professional development. By following established protocols, optometrists ensure that each patient receives appropriate and standardized diagnostic procedures, such as visual acuity assessments, refractive error measurements, and comprehensive eye examinations. One of the key reasons these guidelines are essential in the field of optometry is their contribution to guaranteeing the delivery of high-quality patient care. With the help of established guidelines, it is easier to make informed clinical decisions and further referrals when it comes to recognizing certain complicated ocular conditions such for example secondary open-angle glaucoma, and provide both effective and consistent management plans.

Consistency is a cornerstone of effective healthcare delivery, and guidelines are essential in promoting uniformity within the optometric profession. The standardized recommendations presented in these guidelines will help to create a common language and approach among optometrists, regardless of their geographic location or practice setting. This consistency is crucial not only for enhancing the profession's credibility but also for ensuring patient safety and satisfaction.

Guidelines provide a framework for optometrists to follow, reducing variability in clinical assessment and management approaches. This uniformity is particularly vital in conditions such as secondary open-angle glaucoma where standardized assessment criteria and management regimens can significantly impact patient outcomes. This thesis outlined that it is important to achieve cooperation tools across the borders of other healthcare fields since in secondary open-angle glaucoma other medical conditions affect ocular health. It is widely known that glaucoma as a disease is challenging to diagnose even among professionals who have been in the field for a long time. Secondary open-angle glaucoma adds more challenge to the assessment, requiring great clinical skills in identifying the underlying conditions and risk factors. Differential diagnosis plays a significant role when assessing patients suspected of having secondary glaucoma, which is why uniform guidelines enhance the safety of the diagnostic process. By following these guidelines, optometrists contribute to a collective effort to establish a standardized quality of care, strengthening the profession's reputation and achieving trust among patients.

In Finland, the work of optometrists is operated in a highly regulated environment. There are laws and regulations, such as the law on healthcare professionals (559/1994) and regulation on healthcare professionals, that guide everyday work. At the moment of writing this thesis, the Finnish government has decided to reform the regulation on health care professionals (564/1994) by removing its 16§. This allows some time in the future for optometrists to independently assess the eyes and to prescribe eyeglasses for children under the age of eight, for a person who has previously had eye surgery, for a person whose visual acuity will not become normal with the best-prescribed eyeglasses, and for person who has been diagnosed with eye condition. In light of these future changes that will demand appropriate skill levels, the development of guidelines will have an important value. These guidelines will ensure uniformity in assessment and management, ensuring that the standard of care provided by optometrists is consistently upheld. Following these guidelines is not only a matter of professional ethics but also a legal obligation. By developing guidelines for Finnish optometrists and incorporating these into their daily practice, optometrists not only reduce legal risks but also demonstrate their commitment to providing care that aligns with the highest professional standards.

Guidelines in optometry extend beyond clinical recommendations to involve the crucial aspect of patient education. Optometrists must communicate effectively with their patients, ensuring they understand their diagnoses and treatment options, and potential risks when they do not commit to

the management of their ocular condition. The goal of the guidelines developed is to provide a structured framework for patient education, offering optometrists a roadmap for discussing the conditions, treatment possibilities, and preventive measures. This standardized approach enhances patient comprehension and empowers individuals to make informed decisions about their eye health.

The field of optometry is dynamic, with ongoing advancements in technology, diagnostics, and treatment modalities. Optometrists in Finland are required to update continuously their education to achieve the current best-known knowledge. Guidelines will play an instrumental role in facilitating continuous professional development (CPD) for optometrists. Regular updates to guidelines incorporate the latest evidence-based practices, ensuring that optometrists stay abreast of emerging trends and evolving standards of care. This commitment to ongoing learning not only benefits individual practitioners but also contributes to the overall advancement of the optometric profession.

This thesis had some limitations. Because of the large scope of the subject, the literature review was performed by each subtype of secondary open-angle glaucoma on its own. This way the author was able to collect the best knowledge about the whole subject of secondary open-angle glaucoma and decide the structure of the thesis which will best serve the objectives of this project. This type of literature gathering provided an enormous amount of data, which led to the fact that the systematic approach and selection of literature was very time-consuming. The lack of academic knowledge and confidence of the author was a major limiting factor of this thesis. Based on the aforementioned the narrative approach was selected as a literature review. It allows one to approach the subject more descriptively and the aim is to conduct an overall picture of existing literature. The weakness of the narrative review is that it is random in nature and subjective in its search for information. (Vilkka Hanna, 2023.)

Guidelines developed in this thesis were not tested or implemented into the practice during this project. Therefore there has not been feedback available from the end users to have the possibility to further develop and finalize the guidelines. A recommendation for future study would be the testing phase in practice among Finnish optometrists. Also, the study about the current skills and knowledge among optometrists assessing and managing secondary open-angle glaucoma would give essential information to further develop the content of preexisting guidelines. Not forgetting

that the feedback collected from optometrists in the field could also identify gaps and needs in current education and help to develop it to meet the needs.

6 CONCLUSIONS

In conclusion, the importance of guidelines in the work of optometrists cannot be overstated. The guidelines will serve as the backbone of reputable and reliable work at optometric practice ensuring quality patient care and supporting continuous professional development. Optometrists must recognize the significance of incorporating guidelines into their daily routines, viewing them not as constraints but as invaluable tools that elevate the standard of care, instill confidence in patients, and contribute to the ongoing advancement of the field.

As the field of eye care continues to evolve, optometrists must remain committed to embracing and implementing guidelines that uphold the highest standards of professionalism and excellence. This is extremely topical at the moment of this thesis writing since the future will hold changes in the everyday work of Finnish optometrists. The main purpose of this thesis was to compile a comprehensive information package on open-angle glaucoma and thus increase optometrists' knowledge of the subject. The guidelines will serve not so much as a strict framework but as a guideline when an optometrist encounters a patient or a suspect of secondary open-angle glaucoma.

7 TIMETABLE AND BUDGET

This project was started at the beginning of the year 2022 with the selection of the topic. The first year was spent planning and ideating the implementation of the thesis. During this planning phase, the main goal was to get familiar with the existing literature. The preliminary literature search was conducted in March 2023. The writing of the theoretical background of the theses began in April 2023. The writing phase continued until September 2023 after which the project was put on hiatus. It was picked up again at the end of February 2024 and was finalized during the spring term 2024. The time spent on the thesis project is explained in more detail in Table 4.

TABLE 5. The timetable of the progress of the thesis project.

Time	Assignment
Spring 2022	Topic selection and confirmation with supervisors Planning and ideating the implementation of the thesis
February 2023	First content management meeting with supervisors
March 2023	Definition of the study question and objectives Preliminary literature search of the topic Literature reading and analyzing Thesis writing (theoretical background)
April 2023	Content management meeting with supervisors Thesis writing (theoretical background)
May 2023	Librarian meeting Secondary literature search of the topic Thesis writing (theoretical background)

Time	Assignment
June 2023 – September 2023	Thesis writing (implementation of the thesis) Content management meeting with supervisors
February 2024 – May 2024	Revision search of the literature Conducting the guideline Thesis writing (results, discussion, conclusion)
May 2024 – October 2024	Finalizing the thesis

This thesis was produced as a part of the Clinical Optometry studies in the Master´s Degree in Health Care program. Therefore, there are no financial costs needed to finalize this project.

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APPENDIX

Declaration of Use of the Artificial Intelligence

I have used ChatGPT, an artificial intelligence program, to change the language of the content of my thesis: I first wrote the text myself but used an artificial intelligence-based correction program to edit the language (sentence structure, word choices, and grammar correction).

I have used artificial intelligence in my work in the Discussion section.

I am aware that I am fully responsible for the entire content of my thesis (correspondence of text contents and references), including parts modified with artificial intelligence. I accept responsibility for possible violations of ethical guidelines.