Chapter

Introductory Chapter: Glaucoma Beyond 2020

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1. Introduction

Glaucoma is an optic neuropathy and possibly the most common optic neuropathy seen in the clinical care of general eye care physicians [1, 2]. Glaucomatous optic neuropathy has distinct structural changes visible on the optic nerve head. Thus, it has become a hallmark of the disease, making the optic nerve head a biomarker for evaluation. Although the optic nerve head and retinal nerve fiber changes are visible through dilated fundus evaluation, the objectivity, repeatability, and micron-level resolution provided by imaging technology have been extremely welcome in the last few decades. Imaging devices have become pivotal to glaucoma evaluation and follow-up care. The natural course of history has led to multimodal devices becoming a standard that can serve multiple functions in the clinical care of various anterior-segment and posterior-segment diseases, including glaucoma.

2. Diagnostic advances in glaucoma

The cause of open-angle glaucoma still eludes us; however, we know numerous risk factors are related to glaucoma, like age, race, intraocular pressure, and perfusion pressure, to name a few [1, 2]. Of all the risk factors associated with glaucoma, intraocular pressure is the modifiable risk factor that all treatment and management modalities focus on; intraocular pressure is the most critical risk factor [3–5]. Tonometry is used routinely in all eye examinations, and various forms exist, with the Goldmann applanation tonometer being the "gold standard" in clinical practice. Various ocular, systemic, patient, and examiner-related issues influence the outcome of intraocular pressure measurements [3, 4, 6]. The Goldmann applanation tonometer is far free of errors, yet it remains the "gold standard" because it is the most commonly used device in the clinics [3]. The main inaccuracies in the Goldmann applanation tonometer measurements are due to the variations in biomechanical properties of the cornea, particularly the central corneal thickness, which varies significantly in humans [3–6]. Numerous attempts have been made to create correction equations that adjust the Goldmann applanation tonometer measured IOP measurements to account for the corneal biomechanics [6]. These correction factors or equations lead to further errors and are unsuitable for individual patient care. At best, using multiparameter equations, we can get the IOP adjusted in a population and obtain IOP values that will decrease the effect of corneal biomechanics in clinical studies [6].

The world glaucoma consensus series in 2007 declared that the Ocular Response Analyzer and the Dynamic Contour Tonometer are better at measuring intraocular

pressure when compared to the intraocular pressure measured using the Goldmann applanation tonometer [7]. These devices are less influenced due to corneal parameters. Yet these devices are not standard of care in clinical practice. There is a real need for home tonometry and to democratize intraocular pressure measurements [8]. Accurate intraocular pressure measurements are highly dependent on the eye care providers' equipment and skill. There is a need for IOP to be measured by nurses and nurse practitioners, and primary care physicians. It will be ideal if technician-independent automated devices capable of measuring IOP are housed in supermarkets, pharmacies, or other community locations. Having tonometers available to the public could provide access to IOP measurements away from eye care providers' offices, and aid the issue of underdiagnosis of the disease. Access to these automated testing options can and also potentially offer between-office visits IOP measurements for patients already on treatment for the disease. In the same spirit of obtaining multiple measurements of IOP, there is a need for at-home IOP monitoring. The iCare home tonometer is FDA-cleared for measurements of IOP at home, and has been shown to have clinical utility, however, is still an expensive device and not always affordable [9]. Contact lens devices like the Triggerfish have shown some clinical utility and gained some traction. But the accuracy in identifying nocturnal acrophase is less than ideal and probably identifiable in 60–65% of the patients. Although the benefits of home tonometry are intuitive, the exact socioeconomic benefits of these remain to be ascertained [10].

Imaging devices have become a mainstay in any clinic, and optical coherence tomography (OCT) has revolutionized eye care. These devices have undergone a lot of transition since their introduction in early 1990s. Today multimodal devices that image and measure anterior- and posterior-segment of the eye and perform ophthalmic photography are commonplace [11]. More recently, due to high scan capture rate (70–120 K scans per second), these devices have been able to provide superficial and deep vasculature measurements. These are clinically valuable measures, and their use as a diagnostic or prognostic indicator is increasing [12, 13]. At-home testing using OCT is a close reality in the retina space, and once the model is successful, its glaucoma implementation is a possible logical extension [14]. We will need to see if the at-home monitoring of glaucoma using OCT enhances detection of progression of glaucoma.

Similarly, the visual field devices have seen some software upgrades with more tests concentrating on the macular region in addition to the damage seen in the peripheral fields [15, 16]. Devices like Octopus Perimeter have had G-protocol in glaucoma for a while and provide clinically meaningful information that could enhance our understanding of structure and function correlation [17]. Visual fields have seen some fundamental transformations in recent years. From large devices that perform one function, the virtual reality perimeters provide the comfort of patients performing tests independently in a waiting room [18–20]. Additionally, the device allows coupling with a few entrance tests like pupillary testing, visual acuity testing, color vision, and multi-modality testing helps in having greater functionality. These tests have been compared to the Humphrey Visual Field Analyzer [18–20]. Early results indicate that these can have an excellent correlation to Humphrey Visual Fields, but as expected, their agreement is less than ideal [18–20]. We are only experiencing the tip of the iceberg when evaluating the potential of virtual reality testing technology. A lot more innovation is yet to come; perhaps at-home monitoring of visual function in glaucoma would be the next phase in developing this technology.

3. Advances in medical management

In the last few years, we have seen a flurry of updates in the medical management of glaucoma, with new medications like latanoprostene bunod and rhokinase inhibitors getting approved [21]. These new drugs based on new mechanisms of action or working on multiple modes of action like uveoscleral pathway, trabecular meshwork, or lowering episcleral venous pressure and lowering intraocular pressure have provided physicians with a greater armamentarium in managing glaucoma. Further, the last decade also saw the approval of the first prostaglandin fixed-combination agent in USA [21]. The approval of fixed-combination agents with the prostaglandin group of drugs was long overdue as various fixed-combination agents are available in other countries and have been used successfully. More recently, it is particularly exciting to see the approval of EP2 receptor agents, specifically prostaglandin agents, in USA [22]. Omidenepag isopropyl 0.002% was approved in Japan in 2018 [23]. Given that Omidenepag isopropyl is an EP2 receptor prodrug instead of the FP receptor prostaglandin, one could expect that specific side effects affecting FP receptor class agents may be less in this new EP-receptor drug [24]. Early indicators show that the new EP2 receptor prodrug will likely not have or show decreased changes to iris pigmentation and prostaglandin-related periorbitopathy [24].

The issues of patient adherence and compliance to the medications and instructions of physicians hinder the use of medications for any chronic disease. The management of glaucoma is no exception to this. Glaucoma medications usually come in multi-dose units and require preservatives to prevent contamination and the growth of microorganisms. When used chronically, these preserved medications can lead to an iatrogenic dry eye syndrome [25]. To alleviate this problem, preservative-free options are available. To further improve comfort for the patient, implantable devices that can dissolve over time and provide continuous medication to the eye are available. A bimatoprost intracameral implant was recently approved [26]. It was realized that multiple injections could lead to decreased endothelial cell count and corneal decompensation [26]. Thus, it was approved for only one-time application and provided reasonable control in IOP for 15 weeks [26].

Similarly, the Travoprost Implantable devices are under investigation. The iDose Travoprost implant is titanium travoprost-eluting intracameral delivery system [27]. Its phase 2 studies have shown 8.0–8.5 mmHg (32–33%) reduction in IOP depending on whether a fast or slow system was used. The phase 3 results are not yet published but are expected this year [27]. The intracameral implants and delivery systems will likely immediately decrease the patient-related compliance and persistence issues in glaucoma but, in the long-term will help improve the dry eye and anterior-segment issues that affect patients on topical medications. A final but perhaps most important benefit will improve the quality of life in patients with glaucoma.

4. New frontiers in glaucoma

Neuroprotection has been a holy grail that still eludes us [28]. One of the most extensive clinical trials in ophthalmology was the Memantine Eye Study which explored the efficacy of oral memantine as a neuroprotective agent in open-angle glaucoma at risk for progression. The study failed to meet its endpoint, and daily treatment with memantine over 48 months did not prevent glaucomatous progression [29]. Some

drugs and agents have the potential as neuroprotective agents. For example, brimonidine has shown early indications as neuroprotective agent but has not advanced to clinical trials or successful outcomes [28]. There is indeed a need for treatments that could be used as a standalone or adjunctive therapy to IOP-lowering modalities, given that patients progress despite successful IOP lowering. To this accord, nutritional supplements potentially have a role to play as an adjunctive therapy [30]. The nutritional agents that are explored are antioxidants or agents that could increase blood flow to the optic nerve that could be beneficial as an IOP-independent mechanism/technique to aid the survival of retinal ganglion cells. Recent evidence substantiates that sustained oxidative stress and compromised antioxidant defenses are critical drivers in the onset of glaucomatous neurodegeneration. Overwhelming oxidative injury is likely attributed to compounding mitochondrial dysfunction that worsens with age-related processes, causing the aberrant formation of free radical species. Thus, a compromised systemic antioxidant capacity exacerbates further oxidative insult in glaucoma, leading to apoptosis, neuroinflammation, and subsequent tissue injury. These mechanisms have been tested in laboratory and small-scale studies but need further evaluation with large-scale randomized controlled clinical trials [30].

Selective laser trabeculoplasty has enjoyed second-line therapy status for a while and was occasionally used as a first-line agent. More recently, the LIGHT trials propelled it as a solid first-line option and have shown that it can provide good IOP lowering in a substantial group of participants [31]. Over 50% of the participants obtained and maintained their requisite IOP levels with one 360-degree treatment, and around 74% maintained target IOP levels with two treatments [31]. It would not be surprising if the results of this study were to be a paradigm shift in managing patients with glaucoma. Given the excellent success rate of the Selective Laser Trabeculoplasty, it is very appropriate that the Transscleral Selective Laser Trabeculoplasty that does not need gonioscopy will be highly welcome and should aid in lowering variability between physicians and reduce complications post-SLT [32].

It will be ideal if all glaucoma management is achievable by IOP-lowering agents or laser procedures, however, given the complexity and heterogeneity of the disease it is unlikely to be true even with the best of the medications and technology. Surgical interventions remain a mainstay when robust IOP lowering is desired. Trabeculectomy is necessary for patients for whom very low IOPs are desired, there are substantial post-operative risks. Further, the success of trabeculectomy depends on the skill of the operating surgeon and requires advanced sub-specialty training in ophthalmology. The Minimally Invasive Glaucoma Surgery (MIGS) fulfills the role of surgical intervention that may be coupled with or without cataract extraction and does not cause a substantial increase in risk greater than that of the cataract extraction itself [33–35]. With these tenets, numerous MIGS devices that target various routes of outflow have been introduced. These have seen tremendous success in decreasing the IOP successfully and reducing the dependence on IOP-lowering medications post-surgery. In the field of MIGS we indeed expect a lot of advances.

Glaucoma is known for a long time, and it is fair to take stock of the current situation and ask "Where are we now"? One way is to compare glaucoma with other known chronic diseases. One of the chronic diseases that glaucoma often gets compared to is diabetes. The comparison is fair as both diseases require regular monitoring and continuous treatment, no cure is known for the diseases, but they both can be kept under control with appropriate monitoring and medications. To this accord, diabetes management has always been a little ahead of glaucoma management. Patients with diabetes have had options of at-home monitoring, continuous glucose monitoring,

insulin pumps available long before such options were available for glaucoma. With the numerous changes that we are seeing in both the diagnostic and treatment, glaucoma management beyond the year 2020 is looking particularly attractive. With the new treatment options for medications and surgical modalities being launched regularly, we are perhaps entering a Golden age of glaucoma. We should not celebrate or rejoice prematurely. A lot will be needed before these new modalities become a standard of care. But perhaps paraphrasing the words of Winston Churchill best expresses the current sentiment, "this is not the beginning, this is not the end, but it is perhaps the end of the beginning".

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