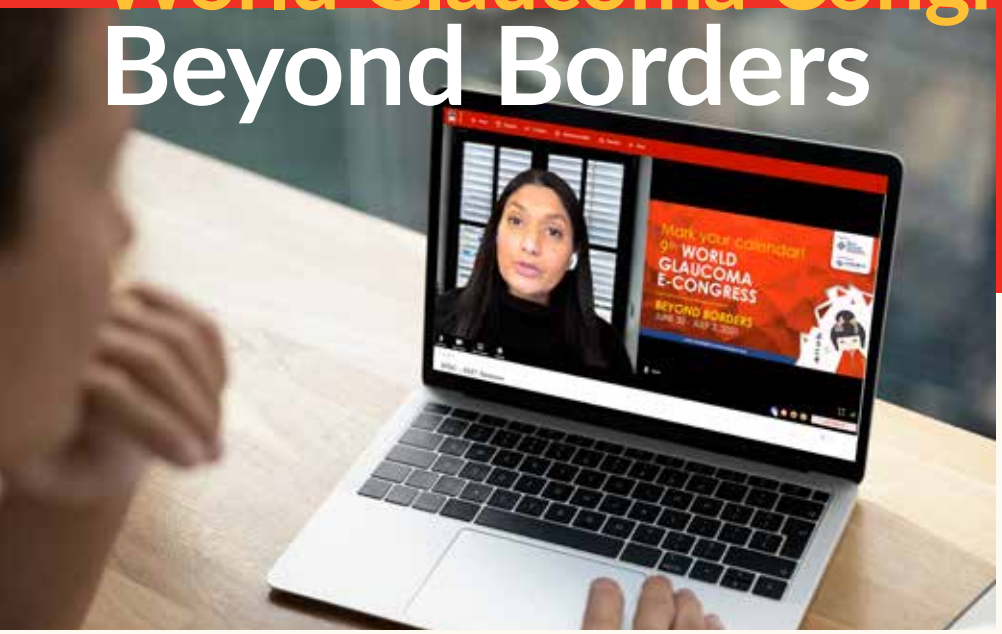
World Glaucoma Congress 2021

Beyond Borders



WRITER Dr Nathan Kerr

The 9th World Glaucoma Congress (WGC) was held online this year and delivered an experience that truly went beyond borders. Hosted virtually by the Japan Glaucoma Society, the congress provided stimulating educational exchanges, scientific news, and best practice updates in glaucoma care. Topics covered basic science and genetics of glaucoma, the latest developments in medical and surgical management of the disease and more. This year's congress was attended by 2,800 delegates from over 100 countries and disseminated evidence-based, scientific knowledge to help support the care of people with glaucoma. In this article, Dr Nathan Kerr shares some of the highlights from WGC 2021.

UNRAVELLING THE PATHOGENESIS OF GLAUCOMA

The Presidential Symposium provided new insights into the pathogenesis of normal tension glaucoma, a type of glaucoma that occurs where the untreated intraocular pressure (IOP) is consistently measured within normal limits. This condition is more prevalent in certain Asian populations, particularly so in Japan, the virtual host country.

Professor Jost Jonas, Chairman of the Department of Ophthalmology of Medical Faculty Mannheim at Heidelberg University in Germany, discussed the latest research examining translaminar pressure differences and ocular blood flow in normal tension glaucoma. Prof Jonas highlighted the morphological differences between glaucoma and vascular optic neuropathies. Other than in giant cell arteritis, thinning of the neuroretinal rim is unique to glaucoma and is not seen in vascular optic neuropathies. Similarly, in glaucoma there is enlargement of the parapapillary beta-zone. In areas of beta-zone parapapillary atrophy, retinal pigment epithelium and photoreceptors are absent and choroidal vessels with underlying sclera are visible. These clear morphological differences suggest that normal tension glaucoma is not purely a problem of impaired vascular perfusion. Rather, patients with normal tension glaucoma may have low orbital cerebrospinal fluid (CSF) pressure, which provides counter-pressure to IOP, leading to an increased translaminar pressure gradient. Prof Jonas quoted a landmark study by Ren et al showing that patients with normal tension glaucoma have lower CSF pressure, measured by lumbar puncture, than both people without glaucoma and patients with primary open angle glaucoma (POAG). This study examined 43 patients with open-angle glaucoma (14 with normal IOP, and 29 with an elevated IOP) and

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71 subjects without glaucoma. Lumbar CSF pressure was significantly ($P<0.001$) lower in the normal IOP glaucoma group (9.5 ± 2.2 mmHg) than in the high IOP glaucoma group (11.7 ± 2.7 mmHg) or the control group (12.9 ± 1.9 mmHg). Further supporting an association between CSF pressure and glaucoma, patients with lower CSF pressure and a higher translaminar pressure gradient tended to have worse glaucoma.

Professor Ki Ho Park, Professor of Ophthalmology at the Seoul National University College of Medicine, discussed the systemic and ocular risk factors for normal tension glaucoma. Interestingly, he reports that Helicobacter pylori (H. pylori) infection may increase the risk of normal tension glaucoma. H. pylori is a type of bacteria that lives in the digestive track that can cause chronic inflammation, gastric ulcers, and even gastric cancer in some individuals. Prof Park's group found that patients with normal tension glaucoma were more likely to have positive serology for H. pylori-specific immunoglobulin G antibodies than healthy controls. In a retrospective study of 100 patients with normal tension glaucoma and 88 controls, there were statistically significant differences in serology between the two

groups, with normal tension glaucoma patients being 2.05 times more likely to have positive H. pylori serology (P = 0.02). It is speculated that H. pylori infection may lead to breakdown of the blood-brain barrier and the release of proinflammatory cytokines, resulting in oxidative stress, apoptosis, and optic nerve head damage. Prof Park suggests that disc haemorrhages and parapapillary atrophy may be clinical indicators of breakdown of the blood-brain barrier. As both beta-zone parapapillary atrophy and disc haemorrhage are known risk factors for glaucomatous progression, they are important signs for optometrists and ophthalmologists to pay careful attention to in patients with glaucoma.

THE HUNT FOR NEW MODIFIABLE RISK FACTORS FOR GLAUCOMA

Currently, the only modifiable risk factor for glaucoma is IOP. However, many researchers are examining whether factors such as diet, air pollution, physical activity, systemic medication, and sleep affect one's risk of glaucoma.

Diet and Lifestyle

Professor Louis Pasquale, from the New York Eye and Ear Infirmary of Mount Sinai, presented research from his group showing that dietary intake of nitrates from leafy green vegetables was associated with a lower risk of glaucoma. Participants in the prospective Nurses' Health Study (63,893 subjects) and the Health Professionals Follow-up Study (41,094 subjects) were followed-up every two years. Eligible participants were 40-years or older, free of glaucoma at enrolment, and reported the results of eye examinations. Researchers found that a greater intake of dietary nitrate and green leafy vegetables was associated with a 20 to 30% lower risk of glaucoma. The association was particularly strong for glaucoma with early paracentral visual field loss, a subtype of glaucoma linked to dysfunction in blood flow autoregulation. It is believed that dietary nitrates are converted to nitrites in the blood, resulting in nitric oxide production, a potent regulator of blood flow.

Professor Paul Foster, Professor of Ophthalmic Epidemiology and Glaucoma Studies at University College London Institute of Ophthalmology, has been studying the relationship between glaucoma and air pollution. Air pollution has been linked to neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, and there is now increasing evidence to suggest a possible association with glaucoma. In the Chennai Glaucoma Study, the rate of open-angle glaucoma in urban participants was twice that of rural participants (3.5% versus 1.6%; P = 0.001) despite no difference in age between the two groups. Professor Foster's group examined data from 111,370 UK Biobank participants, who underwent eye tests from 2006 to 2010 at assessment centres across Britain. Participants were asked whether they had glaucoma and underwent ocular testing to measure IOP and macular ganglion cell-inner plexiform layer thickness on optical coherence tomography (OCT). Eye data was linked to air pollution measures for participants' home addresses, with the researchers focusing on fine particulate matter (equal or less than 2.5 micrometres in diameter or PM2.5). It was found that participants in areas with higher PM2.5 concentration were 6% more likely to report a diagnosis of glaucoma. Higher PM2.5 concentrations were also associated with thinner ganglion cell layer thickness and this association was independent of IOP, suggesting the relationship may occur through a non-pressure-dependent mechanism, possibly neurotoxic and/or vascular effects.

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Physical activity can prevent and protect against many different diseases. Professor Pradeep Ramulu, Professor of Ophthalmology at Johns Hopkins Wilmer Eye Institute, presented his research examining the relationship between glaucoma and physical activity. In a longitudinal, observational study, participants wore accelerometers for one week to define average steps per day, minutes of moderate-to-vigorous activity, and minutes of non-sedentary activity. All available visual field measurements before and after physical activity assessment were retrospectively analysed to measure rates of visual field loss. Professor Ramulu found that increased walking, greater time spent doing moderate-to-vigorous physical activity, and more time spent in non-sedentary activity was associated with slower rates of visual field loss in a treated population of patients with glaucoma. Professor Ramulu also cited a study by Williams et al that examined the relationship between glaucoma and physical activity in male runners. Williams analysed data from 29,854 male runners who were followed prospectively for 7.7 years. It was found that the risk of glaucoma decreased 5% per kilometre-per-day run, suggesting that vigorous physical activity may reduce glaucoma risk. Exercise has been shown to result in many physiological changes that could potentially explain these observations. In mice, Professor Jonathan Crowston's research group showed that exercise has a protective effect mediated through the action of brain-derived neurotrophic factor (BDNF). There is also evidence in humans that BDNF is released with exercise and that patients with glaucoma release lower levels of BDNF compared to controls. It is therefore suggested that optometrists and ophthalmologists recommend exercise to their patients with glaucoma but that this should be offered in conjunction, not as an alternative, to IOP-lowering therapy.

Systemic Medications

A thorough medical history is essential as many patients with glaucoma may be taking systemic medications that could affect their glaucoma. Dr Anthony Khawaja, a senior research associate at University College London Institute of Ophthalmology and Consultant Ophthalmic Surgeon at Moorfields Eye Hospital, summarised the findings of a recent review he co-authored on systemic medications that may modulate the risk of glaucoma. Several classes of systemic medications are known to, or suspected to, modulate glaucoma risk, either through their direct effects on IOP or via mechanisms independent of IOP. It is well known that exposure to corticosteroids causes increased resistance of aqueous outflow through the trabecular meshwork due to the accumulation of undigestible glycosaminoglycans in the trabecular meshwork. In their review, they note that steroid-induced ocular hypertension has been linked to a range of drug delivery routes, including oral or intravenous, inhaled or intranasal, topical eye drops, topical cutaneous ointments, periocular injection, and intraocular corticosteroids. Approximately one quarter to one third of patients develop elevated IOP from corticosteroid use, with 5% classified as 'high responders' defined as an IOP increase >15 mmHg and IOP measurements >31 mmHg. Dr Khawaja notes there are also medications that may decrease the risk of open-angle glaucoma, including systemic beta-blockers, metformin, statins, and selective serotonin reuptake inhibitors. However, apart from systemic beta-blockers, the magnitude and mechanism of risk reduction needs further study. Lastly, patients should be

warned about the risk of angle closure with sulfonamide, anticholinergic, and certain antidepressant medication.

Sleep Behaviour

Professor David Mackey, from the University of Western Australia, discussed the link between glaucoma and obstructive sleep apnoea (OSA). OSA is a common sleep-related breathing disorder where patients have repeated episodes of partial or complete obstruction of the upper airway. Symptoms include snoring and daytime sleepiness. OSA results in physiologic changes including intermittent oxygen desaturation and associated oxidative stress, surges in blood pressure, sympathetic nervous system activation, systemic inflammatory responses, and large fluctuations in thoracic pressure swings. The condition is strongly associated with hypertension, myocardial infarction, and stroke. Professor Mackey presented the results of a cross-sectional cohort study conducted in Australia. Eight hundred forty-eight adults, aged 19 to 22 years, underwent an ophthalmic examination that included OCT imaging of the optic disc and measurements of IOP, axial length, and refractive error. Participants then underwent an overnight polysomnography study that obtained measurements of apnoea-hypopnea index (AHI) – a measure of OSA. They found that OSA was associated with preclinical thinning of the peripapillary retinal nerve fibre layer in young adults. This suggests that individuals with OSA may be at an increased risk of glaucoma.

SELECTIVE LASER TRABECULOPLASTY AS FIRST-LINE TREATMENT

Professor Gus Gazzard, Professor of Glaucoma Studies at University College London Institute of Ophthalmology and Director of the Glaucoma Service at Moorfields Eye Hospital, presented the results of the LiGHT study for which he was the Principal Investigator. Professor Gazzard pointed out that while the standard first-line treatment for open-angle glaucoma and ocular hypertension was historically with eye drops, adherence with therapy is low, and drops require multiple hospital visits for monitoring and treatment adjustment. Long-term and multiple topical medications are associated with numerous ocular and systemic side-effects and are a risk factor for later surgical failure. Selective laser trabeculoplasty (SLT) reduces IOP by increasing aqueous outflow through the trabecular meshwork with a simple, painless outpatient laser procedure, minimal recovery time, and good safety profile. The LiGHT study was an observer-masked, randomised controlled trial of treatment-naive patients with open angle glaucoma or ocular hypertension. Patients were randomly allocated to initial SLT or to eye drops. Professor Gazzard reported that compared to eye drops, patients treated with SLT were more likely to be within target IOP at more visits (93%) than in the eye drop group (91%). At 36 months, 74% of patients in the SLT group required no glaucoma eye drops while only 3% of the drop-first group were on zero medications at 36 months. Importantly, patients treated with SLT showed better control of their disease, with a reduced risk of glaucoma progression and significantly reduced need for invasive glaucoma surgery. In the group treated with eye drops first, 11 patients required trabeculectomy within three years, while not a single patient treated with SLT required surgery. Based on these results, Professor Gazzard recommends that SLT should be offered as a first-line treatment for open angle glaucoma and ocular hypertension.

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NEW DRUGS AND TREATMENTS

Professor Makoto Aihara, Professor of Ophthalmology at the University of Tokyo, discussed new drug therapies and noted that these help address an unmet need for medications that are safer, with more potent IOP-lowering. Professor Aihara covered two novel therapeutic advances: EP2 agonists and Rho-kinase (ROCK) inhibitors. These medications are not available in Australia.

Omidenepag isopropyl (OMDI) is a once daily novel EP2 agonist anti-glaucoma drug approved in Japan, Korea, and Taiwan. OMDI is a selective EP2 receptor agonist with a non-prostaglandin structure and has a mechanism of action different from that of FP receptor agonists (FPAs). OMDI increases aqueous humour outflow via both uveoscleral and trabecular pathways. The efficacy and safety of this medication has been evaluated in the AYAME study, a phase three, randomised, investigator-masked, active-controlled, parallel-group, multicentre study which compared the efficacy and safety of OMDI 0.002% with latanoprost 0.005% for four weeks in Japanese subjects with POAG or ocular hypertension (OHT). Overall, OMDI 0.002% was non-inferior to latanoprost 0.005% in reducing IOP in patients with OHT or POAG and was well tolerated. The most frequently reported treatment-related ocular adverse event (OMDI vs latanoprost) was conjunctival hyperaemia (23/94 patients [24.5%] vs. 10/96 patients [10.4%]).

Professor Aihara then discussed a new once daily ROCK inhibitor – Netarsudil 0.02%. ROCK inhibitors directly improve trabecular outflow by causing episcleral venous distension and thus lowering episcleral venous pressure, loosening endothelial cell adhesions in Schlemm canal, inhibiting extracellular matrix production, and changing the cytoskeleton of trabecular meshwork cells. Ripasudil is approved in Japan for glaucoma or ocular hypertension when other treatments are ineffective or cannot be administered. Its long-term safety and efficacy are being examined in a post-marketing surveillance study – the ROCK-J study. This study found that Ripasudil was safe and effective in patients with glaucoma or OHT during routine care. Side effects occurred in 626 patients (18.6%); the most common being conjunctival hyperaemia and blepharitis.

Dr Paul Singh, President of The Eye Centers of Racine and Kenosha in Wisconsin USA, talked about how new medication delivery systems may help overcome some of the limitations of eye drop therapy including adherence, side effects, and cost. Bimatoprost SR, tradenamed Durysta, is a sustained-release, biodegradable implant for the treatment of open-angle glaucoma or OHT and is designed to lower IOP for at least four months while freeing patients from daily eye drop regimens. However, in the clinical trials, 25% of patients had two years of efficacy from a single dose. The insertion is performed at the slit lamp, similar to an IOP check. This implant provides 24-hour release of preservative-free bimatoprost, directly to the target tissues. Compared to eye therapy, tissue levels of the medication are higher in the target tissues such as the trabecular meshwork/ciliary body, and lower in other tissues such as the conjunctiva. This helps reduce side effects like hyperaemia, which can be problematic with topical eye drops, especially for newer classes of medications. In the phase 1/2 APOLLO study, 36% of subjects had one year of control and 26% had two years of IOP control without additional therapy

from a single implant. In the ARTEMIS study, 86% of patients had IOP control for 360 days after three planned treatments. The implant delivers IOP reduction at least as good as topical eye drops, but with much lower rates of side effects such as red eyes, eye pain, light sensitivity, and blurred vision. The Durysta is approved for use in the United States and is in clinical trials at selected sites in Australia.

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ADVANCES IN GLAUCOMA SURGERY

The introduction of minimally invasive glaucoma surgery (MIGS) has seen the move toward procedures that provide efficacy in lowering IOP, and are much less invasive than traditional glaucoma surgeries. With more people having MIGS procedures to manage their glaucoma without daily eye drops, it is important to ensure these procedures are not only effective but also safe, especially with regards to corneal health. In the healthy eye, aqueous drains over 360° through the conventional outflow pathway. Aqueous exits the anterior chamber by passing through the trabecular meshwork and into Schlemm canal. From there, aqueous flows through collector channels into the episcleral venous system. Stent-based procedures and conventional surgeries bypass or create new routes for aqueous outflow. It has been suggested that these artificial routes for aqueous outflow cause preferential flow that could damage the corneal endothelium. Additionally, postoperative inflammation, such as that caused by tissue-destructive procedures like goniotomy, may also damage the cornea. One of the few MIGS procedures to improve aqueous outflow over 360° is the iTrack ab-interno canaloplasty system. The iTrack microcatheter is passed 360° around Schlemm canal before sterile viscoelastic is injected to dilate the canal and distal collector channels. This implant-free, non-destructive procedure helps re-establish natural aqueous flow while preserving the angle and conjunctiva.

Drs Lubeck and Noecker, from the United States, presented a one-year evaluation of endothelial cell density loss following iTrack ab-interno canal-based surgery. This was a prospective, multi-centre registry study of patients in the United States of America, Europe, and Australia who underwent iTrack ab-interno canaloplasty combined with cataract surgery. At 12 months, the mean change in endothelial cell density, following iTrack canal-based surgery combined with cataract surgery, was just -3.2% (standard deviation [SD] 9.0%). The authors compared this with the endothelial cell loss in the control groups of the FDA pivotal trials for Hydrus and iStent, which were -10.0 (SD 11.0%) and -12.3% (SD 12.7%) respectively. Drs Lubeck and Noecker concluded that iTrack has some of the lowest rates of endothelial cell loss, similar to cataract surgery alone. This is especially important for younger patients who do not have cataract and for those with endothelial cell disease such as Fuchs' dystrophy or previous corneal grafts.

For patients with glaucoma refractory to glaucoma eye drops, the XEN is a minimally invasive device that drains aqueous from the anterior chamber to the subconjunctival space. Placed ab interno via a single clear corneal incision, it is not necessary to dissect and suture the conjunctiva. This minimises surgical trauma and operating time while eliminating the risk of suture-related complications and bleb leak, which helps provide patients with a comfortable eye following surgery and a rapid return of clear vision. I presented data from our study on XEN at the World Glaucoma Congress. Our study examined primary needling, an optional procedure performed at the time of XEN surgery to ensure the stent is free and mobile. The procedure is designed to ensure a low and diffuse bleb with minimal subconjunctival resistance. We found that where this optional procedure was performed routinely, the need for post-operative needling reduced to just 3.9%, compared to 25.7% with the conventional surgical technique. At 12 months, the median IOP was 11.0mmHg (IQR, 9.0-14.0). Additionally, patients who received the optional procedure required fewer post-operative clinic visits (seven vs. nine visits over 12 months; P = 0.043). We concluded that this simple surgical modification preserves the benefits of an ab interno technique while reducing the need for postoperative needling and the number of clinic visits required.

CONCLUSION

The World Glaucoma Congress brought together thousands of eye care providers from around the world to share insights and best practises with the goal of delivering the best possible eye care for each person with glaucoma, and eliminating blindness and visual disability from glaucoma worldwide.

Dr Nathan Kerr is a glaucoma specialist in Melbourne, Australia. Dr Kerr completed a prestigious glaucoma fellowship at Moorfields Eye Hospital in London, the first specialist eye hospital in the world, where he trained under Professors Gus Gazzard and Keith Barton. Dr Kerr manages all stages of glaucoma, from early diagnosis through to the most complex cases. He specialises in minimally invasive glaucoma surgery (MIGS), both combined with cataract surgery or standalone, and is one of only a handful of surgeons to be fellowship-trained in all currently available procedures including iStent, iTrack, Hydrus, XEN, and PreserFlo. Dr Kerr has been invited to teach MIGS and conventional trabeculectomy and tube surgery internationally. Dr Kerr serves as a Glaucoma Section Editor for *Clinical and Experimental Ophthalmology* and is a Principal Investigator in Glaucoma at the Centre for Eye Research Australia. He is currently an investigator for the Durysta (bimatoprost implant) trial. Dr Kerr is a consultant ophthalmologist at the Royal Victorian Eye and Ear Hospital and consults privately at Eye Surgery Associates in East Melbourne, Doncaster, and Vermont South. Visit doctorkerr.com.au.

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