

# Eye Health Research Review™

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Issue 1 – 2011

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## Welcome to the first issue of Eye Health Research Review.

Eye Health Research Review is a unique Australian publication bringing you some of the most important research from around the world. The Review is a summary of what we think are the most significant new papers, plus local commentary on why they are important and how they can potentially affect practice.

Selection and review of the papers has been carried out by Dr Lance Liu, who works in private practice in Preston and Glenroy, Melbourne, as well as a Glaucoma Consultant at the Royal Victorian Eye and Ear Hospital in Melbourne. The Review also provides website links to the abstracts or fully published papers so you can make your own judgements.

If you have colleagues or friends within Australia who would like to receive our publication, send us their contact email and we will include them in the next issue.

Kind Regards

**Dr Janette Tenne**

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## Stem cells make 'retina in a dish'

**Author:** Callaway E

**Summary:** Japanese scientists have created a 'retina in a dish' from a three-dimensional culture of mouse embryonic stem cells. The nutrient soup contained proteins that coaxed the stem cells to first autonomously transform into retinal cells. It also included a protein gel to prevent the cells from falling apart. The retinal cells grew over a week and formed an optic vesicle, which folded over itself over the next two days, just as it would in an embryo, to form an optic cup with two distinct cell layers and all the appropriate cells. The next step is to test whether the optic cups can sense light or transmit impulses to the mouse brain. Development of human retinal tissue from human embryonic stem cells is being investigated. If the technique can be adapted to human cells, the availability of synthetic retinal tissue could help scientists in the study of eye disease and in identifying therapies. If proved safe for transplantation, synthetic retinas could be used to replace damaged retinas.

**Comment:** First genetics, now stems cells. It is fascinating how far medical research has come. However, there are still many questions that need to be answered, like how the synthetic retina will connect to the optic nerve and blood vessels and how it will function. This is one small step in the long journey of stem cell technology.

**Reference:** Published online 6 April 2011 | Nature | doi:10.1038/news.2011.215

<http://www.nature.com/news/2011/110406/full/news.2011.215.html>

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### Appositional closure identified by ultrasound biomicroscopy in population-based primary angle-closure glaucoma suspects: the Liwan Eye Study

**Authors:** Kong X et al

**Summary:** Ultrasound biomicroscopy imaging was used to describe the characteristics of the iridocorneal angle in 117 Chinese people from the Liwan Eye Study with suspected primary angle-closure glaucoma on gonioscopy. Suspected primary angle-closure glaucoma was defined by an absence of visible posterior (usually pigmented) trabecular meshwork in two or more quadrants on static gonioscopy. Ultrasound biomicroscopy identified more iridotrabecular meshwork contact (ITC) than gonioscopy. ITC was identified in 78.6% of the superior, 40.2% of the nasal, 59.8% of the inferior, and 25.6% of the temporal quadrants. In a control group of 57 people who did not meet the criterion for suspected primary angle-closure glaucoma, these proportions were 43.9%, 15.8%, 29.8%, and 14.0%, respectively. About two thirds of the eyes with ITC were classified as high on ultrasound biomicroscopy with similar numbers for B-type and S-type ITC. Substantial increases in high ITCs were observed with Shaffer grading from 15.4% in grade 4 and 45.0% in grade 3, to 71.0% in grade 2, 70.2% in grade 1, and 86.4% in grade 0. The authors suggested careful consideration of assessment methodologies used as the reference standard in defining anatomic risk factors for glaucomatous visual loss and the need for treatment.

**Comment:** Recently, there has been a paradigm shift when examining the angle. Instead of assessing whether the angle is open, gonioscopy should now be performed to exclude angle closure (which is characterised by iridotrabecular contact). Although gonioscopy is still the gold standard when assessing the drainage angle, there are problems in its performance in clinical practice and interpretation. Iridotrabecular contact is most commonly found in dark lighting conditions and any ambient light from the room or slit lamp can constrict the pupil and "open up" an angle that is closed in the dark. This paper suggests that angle closure is probably underdiagnosed due to the subjective nature of gonioscopy. Ultrasound biomicroscopy and anterior segment OCT provides an objective assessment (and documentation) in detecting angle closure compared to gonioscopy and time will tell if they will become the gold standard.

**Reference:** IOVS June 2011;52:3970-3975  
<http://www.iovs.org/content/52/7/3970.abstract>

### Assessment of visual function in glaucoma: a report by the American Academy of Ophthalmology

**Authors:** Jampel HD et al

**Summary:** A literature review of 85 studies published from 1994 to 2010 and providing level II evidence or above was undertaken to evaluate the effectiveness of visual function tests in the diagnosis and monitoring of progression of glaucoma. Standard white-on-white automated perimetry was found to be the most commonly performed test for assessing visual field. The Swedish interactive threshold algorithm (SITA) has largely replaced full-threshold testing strategies. Frequency-doubling technology and its refinement into Matrix perimetry has been evaluated extensively in controlled clinical trials. Short-wavelength automated perimetry, now available with SITA, has also been evaluated extensively. Machine learning classifiers seem to be ready for incorporation into software to help distinguish glaucomatous from nonglaucomatous fields. Other technologies, such as multifocal visual-evoked potential and electroretinography, which were designed as objective measures of visual function, provide testing free of patient input, but issues have prevented their adoption for glaucoma management. The authors concluded that while advances in technology and analytic tools have provided more rapid and varied ways of assessing visual function in glaucoma, they have yet to produce definitive guidance on the diagnosis of glaucoma or its progression over time.

**Comment:** In glaucoma, the diagnosis and monitoring of this disease incorporates structural and functional testing of the optic nerve and nerve fibre layer. The structural assessment can be documented by cup-disc ratio, optic disc drawings, disc photography, HRT and OCT. Visual field testing (white-on-white) is currently the gold standard in monitoring the optic nerve function and its results must correlate with the appearance of the optic disc. One must remember that these studies included patients who were able to perform the visual field testing adequately. However, this may not be the case in everyday clinical practice as the results of the testing are subjective and the ability to complete the visual field test declines with the patient's age. We are still waiting for a true objective test to be developed that is better than white-on-white perimetry in terms of its accuracy of data collection and repeatability.

**Reference:** *Ophthalmology*. 2011;118(5):986-1002

[http://www.ophsource.org/periodicals/ophtha/article/S0161-6420\(11\)00282-X/abstract](http://www.ophsource.org/periodicals/ophtha/article/S0161-6420(11)00282-X/abstract)

## Eye Health Research Review

**Independent commentary by** Dr Lance Liu, who works in private practice in Preston and Glenroy, Melbourne, as well as a Glaucoma Consultant at the Royal Victorian Eye and Ear Hospital in Melbourne. Clinically, he has a special interest in cataract, glaucoma and diabetes. He also has an interest in clinical research that includes angle closure and pigment dispersion glaucoma, gonioscopy, anterior segment imaging, cataract surgery and glaucoma practice patterns on which he has published a number of papers on these topics.



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## Non-steroidal drug-induced glaucoma

**Authors:** Razeghinejad MR et al

**Summary:** Drug-induced glaucoma can be caused by many systemically administered medications. Most reported cases of non-steroidal drug-induced glaucoma are of the pupillary block closed-angle type and are preventable if the at-risk patients are recognized and treated prophylactically. Many routinely used medications with sympathomimetic or parasympatholytic properties can cause pupillary block closed angle glaucoma in individuals with narrow iridocorneal angle. The resulting acute glaucoma is generally unilateral and only rarely occurs bilaterally. Sulfa containing medications can cause bilateral non-pupillary block closed angle glaucoma in individuals with narrow or open iridocorneal angle as a result of forward movement of the iris–lens diaphragm. Open-angle glaucoma can be caused by a few medications including antineoplastics.

**Comment:** Secondary glaucomas due to systemic medications are rare. This paper shows that these medications usually produce closed-angle glaucoma which is treatable. However, it is not known whether some of these patients already had pre-existing angle closure. Although one may screen these patients to exclude angle closure before commencing these medications (by performing gonioscopy), this may not be practical.

**Reference:** Published online 3 June 2011 | *Eye* | doi:10.1038/eye.2011.128  
<http://www.nature.com/eye/journal/voop/ncurrent/full/eye2011128a.html>

## Continuous intraocular pressure monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with open angle glaucoma

**Authors:** Mansouri K et al

**Summary:** Initial clinical results with a novel wireless ocular telemetry sensor (Sensimed AG, Switzerland) for continuous intraocular pressure (IOP) monitoring in an observational cohort of 15 patients with open angle glaucoma were reported. The ocular telemetry sensor is a disposable silicone contact lens with an embedded micro-electromechanical system, which measures changes in corneal curvature induced by variations in IOP. An antenna, mounted around the eye, receives the data, which are then transmitted to a recorder. Thirteen patients completed 24-hour IOP monitoring: one patient discontinued IOP monitoring due to device intolerance, and incomplete recordings were obtained in a second patient due to technical device malfunction. In 9/13 (69%) patients, the highest signals were recorded during the nocturnal period. The ocular telemetry sensor showed good safety and functionality to monitor IOP fluctuations in patients over 24 hours. The authors believe this technology has the potential to provide previously unobtainable data on the chronobiology of IOP, possibly leading to improved care of glaucoma patients.

**Comment:** The problem with glaucoma is that the IOP we measure during the clinic may not reflect what is happening outside office hours. IOP, like blood pressure, varies over the 24 hour period. The wireless ocular telemetry sensor is one of the first devices available used to continuously monitor IOP, similar to the 24 hour ambulatory blood pressure monitoring. This small study shows that the device is tolerable and safe and one looks forward to the results of trials with larger cohorts of normals and glaucoma patients to improve our insights into diurnal IOP variation.

**Reference:** *Br J Ophthalmol* 2011;95(5):627-629  
<http://bjoo.bmj.com/content/95/5/627.abstract>

## Risk factors for visual field progression in treated glaucoma

**Authors:** De Moraes CG et al

**Summary:** A cohort of patients in the Glaucoma Progression Study were retrospectively evaluated to determine intraocular pressure (IOP)–dependent and IOP-independent risk factors for visual field progression in treated glaucoma. Data from 587 eyes in 587 patients with a mean age of 64.9 years and a mean number of 11.1 visual field examinations over a mean of 6.4 years were analysed. On univariate analysis, factors significantly associated with increased risk of visual field progression were older age (odds ratio [OR], 1.19 per decade;  $p=0.01$ ), baseline diagnosis of exfoliation syndrome (OR, 1.79;  $p=0.01$ ), decreased central corneal thickness (OR, 1.38 per 40  $\mu\text{m}$  thinner;  $p<0.01$ ), detected disc haemorrhage (OR, 2.31;  $p<0.01$ ) and presence of beta-zone parapapillary atrophy (OR, 2.17;  $p<0.01$ ). All IOP parameters (mean follow-up IOP, peak IOP, and IOP fluctuation) were associated with increased risk of visual field progression ( $p<0.01$ ). On multivariate analysis factors that still significantly correlated with an increased risk of visual field progression were peak IOP (OR, 1.13;  $p<0.01$ ), thinner central corneal thickness (OR, 1.45 per 40  $\mu\text{m}$  thinner;  $p<0.01$ ), detected disc haemorrhage (OR, 2.59;  $p<0.01$ ), and presence of beta-zone parapapillary atrophy (OR, 2.38;  $p<0.01$ ). The authors concluded that peak IOP is a better predictor of progression than mean follow-up IOP or IOP fluctuation.

**Comment:** This paper's findings are similar to those of the early manifest glaucoma trial which identifies the risk factors for progression in patients with established glaucoma. IOP, the presence of pseudoexfoliation and disc haemorrhages were the risk factors found in both studies. However, peak IOP (instead of mean or fluctuating IOP) was found to be a better predictor of progression. In the past, the focus has been on mean IOP but there has been recent evidence suggesting that fluctuating IOP is more important. Clinically, we initiate or change treatments when the IOP is high which is more likely to cause more damage to the optic nerve than when it is low.

**Reference:** *Arch Ophthalmol* 2011;129(5):562-568  
<http://archophth.ama-assn.org/cgi/content/abstract/129/5/562>

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**References:** 1. Hommer A. et al, *Eur J Ophthalmol* 2007;17(1):53-62. 2. Brandt J. et al, *J Glaucoma* 2008;17(3):211-216. 3. Feuerhake C. et al, *Curr Med Res Opin* 2009;25(4):1037-1043. PBS dispensed price \$46.82. GANFORT is a registered trademark of Allergan Inc. Allergan Australia Pty Ltd, 810 Pacific Highway, Gordon NSW 2072. ABN 85 000 612 831 AU/0135/2011



## Intraocular pressure response to selective laser trabeculoplasty in the first treated eye vs the fellow eye

**Authors:** Shazly TA et al

**Summary:** Medical records from 40 patients who underwent selective laser trabeculoplasty as primary treatment in both eyes were retrospectively reviewed to determine if the intraocular pressure (IOP) response in one eye predicts long-term response in the fellow eye. In patients with ocular hypertension, the 3-month percentage of IOP reduction in the first treated eye in response to selective laser trabeculoplasty was predictive of response in the fellow eye up to 30 months ( $r > 0.652$ ). In patients with primary open-angle glaucoma, the 3-month percentage of IOP reduction in the first treated eye in response to selective laser trabeculoplasty was predictive of response in the fellow eye up to 9 months ( $r > 0.367$ ).

**Comment:** Following selective laser trabeculoplasty in both eyes for primary treatment of ocular hypertension or primary open angle glaucoma, this paper shows that the percentage of IOP reduction of the first eye at 3 months was sustained in the fellow eye at 9 months (POAG) and 30 months (ocular hypertension). However, this paper shows the effectiveness of SLT in POAG is not long term and the patient needs to be advised that regular monitoring is needed.

**Reference:** *Arch Ophthalmol* 2011;129(6):699-702  
<http://archophth.ama-assn.org/cgi/content/abstract/129/6/699>

## Management of neovascular glaucoma with transscleral cyclophotocoagulation with diode laser alone versus combination transscleral cyclophotocoagulation with diode laser and intravitreal bevacizumab

**Authors:** Fong AW et al

**Summary:** Intravitreal bevacizumab has been increasingly used to treat neovascular diseases of the eye. This retrospective review compared the management of neovascular glaucoma in 30 patients undergoing trans-scleral cyclophotocoagulation with diode laser with or without intravitreal bevacizumab. Mean reduction in intraocular pressure was 33.5 mmHg in the 11 eyes in the trans-scleral cyclophotocoagulation group compared with 23.7 mmHg in the 20 eyes in the combination group, a difference of 9.8 mmHg (95% CI -1.5, 21.1). Hypotony occurred in three (27%) eyes in the trans-scleral cyclophotocoagulation group and two (10%) eyes in the combination group. Three eyes required enucleation. The authors concluded that trans-scleral cyclophotocoagulation alone is effective in lowering intraocular pressure in neovascular glaucoma and the addition of intravitreal bevacizumab offers no statistical advantage to treatment outcomes.

**Comment:** Bevacizumab is currently licenced used to treat colorectal cancers by binding to vascular endothelial growth factors than promote the growth of new blood vessels. Off label, it can also be used to treat macular degeneration, diabetic retinopathy and other retino-occlusive diseases. The latter diseases can lead to neovascular glaucoma by promoting abnormal blood vessel growth in the angle which becomes fibrous leading to secondary angle closure or peripheral anterior synechiae. As the visual prognosis is often poor, trans-scleral cyclophotocoagulation is used to lower the IOP. This paper shows that the addition of bevacizumab was not beneficial in lowering the IOP. Presumably, these patients probably already have established PAS and it would be interesting to see whether bevacizumab alone is effective in lowering the IOP by preventing PAS formation.

**Reference:** *Clin Experiment Ophthalmol* 2011;39(4):318-323  
<http://tinyurl.com/3emsrjk>

## Goldmann applanation tonometry and dynamic contour tonometry are not correlated with central corneal thickness in primary open angle glaucoma

**Authors:** Regev G et al

**Summary:** This study compared measurements of intraocular pressure (IOP) by Goldmann applanation tonometry and dynamic contour tonometry and assessed any correlation with central corneal thickness in 116 patients with primary open angle glaucoma participating in the Indianapolis Glaucoma Progression Study. IOP was measured by both tonometry techniques in a randomised order followed by central corneal thickness during a single study visit. IOP values obtained using both tonometry techniques showed a strong positive correlation for open angle glaucoma ( $r = 0.93$ ;  $p < 0.001$ ). Dynamic contour tonometry measured significantly higher IOP values than Goldmann applanation tonometry [18.4 (5.1) mm Hg vs 16.5 (4.5) mmHg,  $p < 0.001$ ]. Bland-Altman plots showed variable disagreement between the tonometry techniques suggesting a proportional bias. Multivariate regression analysis showed no correlation with central corneal thickness for either technique. The authors concluded that factors other than central corneal thickness may explain the tendency of dynamic contour tonometry to produce higher measures of intraocular pressure than Goldmann applanation tonometry.

**Comment:** A Goldmann Applanation Tonometer measures the IOP using a flat tonometer head that indents the cornea. The results can vary based on the central corneal thickness. Thicker corneal thicknesses result in IOP readings being higher than the true IOP and vice-versa. The measurements taken with dynamic contour tonometry use a curved tonometer head that does not alter the cornea contour. However, this paper shows no correlation with IOP measurements and the central corneal thickness. Part of the answer may lie in corneal rigidity or hysteresis which may be independent of corneal thickness.

**Reference:** *J Glaucoma* 2011;20(5):282-286  
<http://tinyurl.com/42syflu>

## Adherence with brimonidine in patients with glaucoma aware and not aware of electronic monitoring

**Authors:** Hermann MM et al

**Summary:** This prospective, observational cohort study assessed whether adherence monitoring affected patient compliance to different dosing schedules of conventional brimonidine eye drops. Thirty-seven patients with glaucoma or ocular hypertension were randomly assigned to open or masked adherence monitoring and to brimonidine twice daily (BID) or three times daily (TID). Adherence rates were above 75% in 12/36 (33%) patients, with adherence  $> 90\%$  in two of these patients. There were no significant differences between adherence rates in patients informed of the adherence monitoring compared with those who were not informed. Adherence rates were significantly lower in patients applying brimonidine three times daily compared with twice daily ( $64 \pm 12\%$  vs  $73 \pm 13\%$ ,  $p = 0.02$ ). However, the mean number of brimonidine applications per day was higher in patients randomised to three times daily dosing vs twice daily dosing ( $1.9 \pm 0.3$  vs  $1.5 \pm 0.1$ ). The median coverage was 70% with no significant difference between patients on different dosing schedules. The authors concluded that adherence to brimonidine eye drops was insufficient and was unaffected by patient knowledge of adherence monitoring.

**Comment:** This paper confirms the previous findings about drug compliance amongst patients. Patient compliance decreases the more frequent one needs to use the drops and with the number of medication bottles the patient is taking. Patient education, explanation and reinforcement as well as simplifying the drop regimen may improve compliance.

**Reference:** *Acta Ophthalmol* 2011;89(4):e300-305  
<http://onlinelibrary.wiley.com/doi/10.1111/j.1755-3768.2010.02050.x/abstract>

## Effect of cataract and its removal on signal strength and peripapillary retinal nerve fiber layer optical coherence tomography measurements

**Authors:** Mwanza JC et al

**Summary:** The effect of cataract surgery on optical coherence tomography (OCT) signal strength and peripapillary retinal nerve fiber layer (RNFL) thickness measurements was assessed in 45 patients with cataract, including 23 glaucoma patients. RNFL thickness was 9.3% higher after surgery than before surgery ( $p = 0.001$ ). Signal strength was 24.1% higher postoperatively ( $p < 0.001$ ). Patients with lower preoperative RNFL measurements had greater changes in RNFL thickness measurements after surgery ( $r = -0.63$ ,  $p < 0.001$ ). Similarly, patients with lower preoperative signal strength showed greater changes after surgery ( $r = -0.59$ ,  $p < 0.001$ ), however there were no significant changes after surgery in eyes with preoperative signal strength more than 6. The change in postoperative RNFL thickness was not significantly different between eyes with cataract only and eyes with cataract and glaucoma ( $10.9 \pm 20.8 \mu\text{m}$  vs  $7.0 \pm 14.7 \mu\text{m}$ ;  $p = 0.81$ ). The authors advised caution in interpreting OCT scans in eyes with cataract. Thinning of the peripapillary RNFL may be the result of advancing cataract rather than an indication of glaucoma progression.

**Comment:** The changes in OCT measurements following cataract surgery suggest that one must always interpret the OCT results with caution, when it comes to the diagnosis or progression of glaucoma. One must also remember to re-establish the baseline investigations after cataract surgery.

**Reference:** *J Glaucoma* 2011;20(1):37-43  
<http://tinyurl.com/3gtmnb>

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