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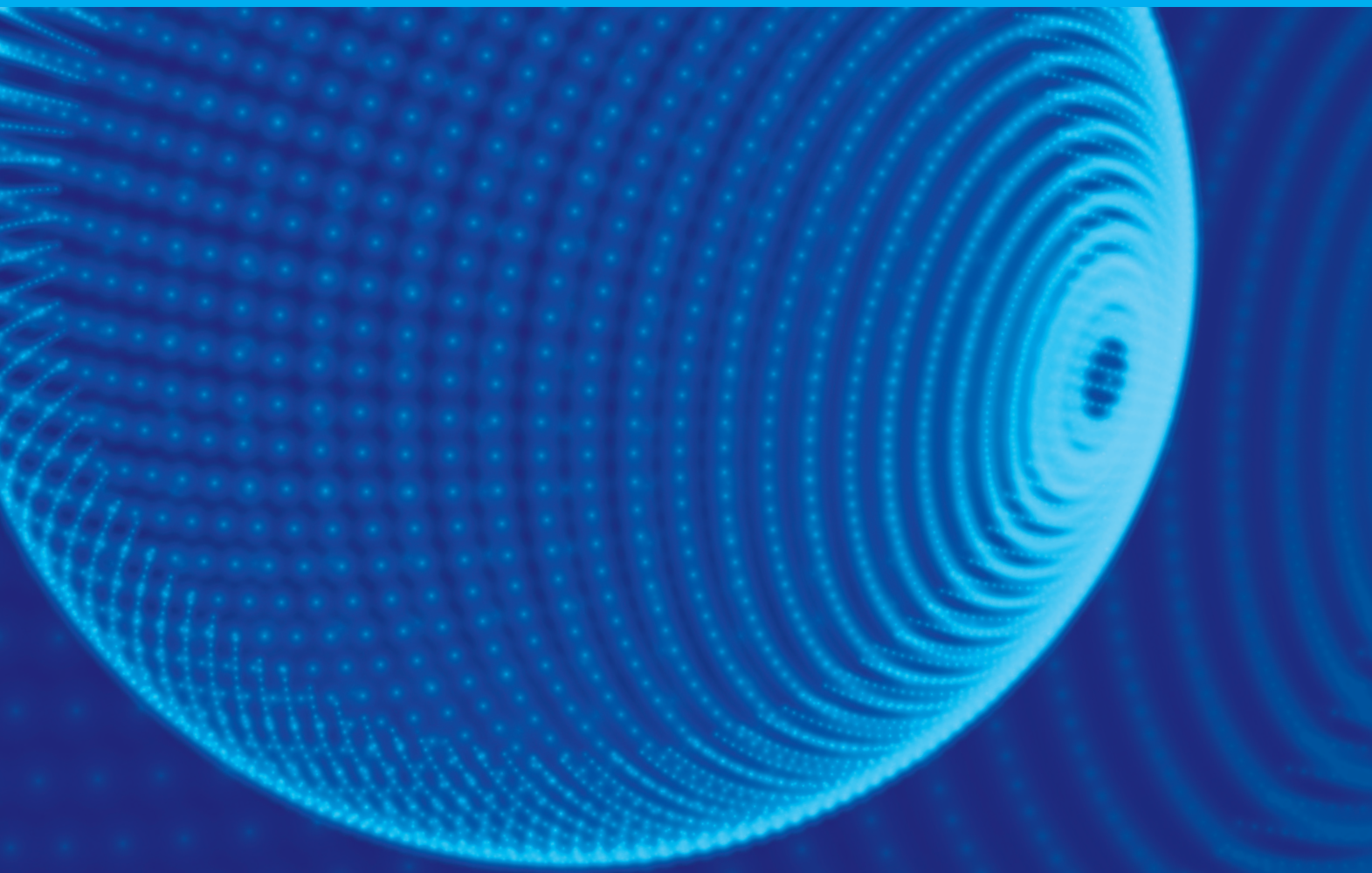

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CONGRESS ABSTRACTS

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Manchester, UK | 23-25 June 2016

FREE PAPER SESSIONS

INTRAVITREAL RANIBIZUMAB FOR DIABETIC MACULAR OEDEMA - A RETROSPECTIVE REVIEW OF 12 MONTH FOLLOW UP DATA AT THE MANCHESTER ROYAL EYE HOSPITAL (MREH), UK

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Design: Retrospective analysis of clinical data.
Purpose: Ranibizumab was approved in the UK for the treatment of Diabetic Macular Oedema (DMO) by the National Institute of Health and Care Excellence (NICE). This retrospective analysis aimed to evaluate key clinical outcomes at a large regional eye unit.
Methods: Data were extracted from the Medisoft electronic patient record system at MREH. An initial search was conducted to include all eyes receiving Ranibizumab for DMO between July 2013 and April 2014. Eyes treated with any intravitreal agent in the 3 months preceding July 2013 were excluded, and each eye was analysed individually.
Results: Fiftynine cases were identified, 9 were excluded having had Bevacizumab and 4 were excluded having had Ranibizumab in the preceding 3 months. Two patients did not attend follow up appointments beyond 1 and 3 months each and 1 patient chose not to have any injections after 6 months due to sterile endophthalmitis. Fourtysix eyes of 32 patients were analysed up to 6 months, and 45 eyes up to 12 months. Patients had a mean age of 57.7 years (SD 15.1). The mean starting visual acuity was 54.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The change in mean visual acuity at 6 months to 61.8 ETDRS letters was not significant ($p = 0.019$) but at 12 months was 64.2 ETDRS letters which was significant ($p<0.01$). The mean starting Optical Coherence Tomography (OCT) Central Retinal Thickness (CRT) was 481.4 µm. The mean at 6 months was 341.7 µm, and at 12 months was 350.8 µm, and the reduction at both time intervals were statistically significant ($p<0.01$). Thirtyeight of 46 patients gained or at least did not lose vision at 6 months, and 39 of 45 patients at 12 months. Seven of 46 patients gained 3 or more lines in vision at 6 months, 9 of 45 at 12 months.
Conclusions: In keeping with comparisons of clinical practice to prospective randomized-control trials, the visual gains were less but still encouraging.

REAL-WORLD OUTCOMES WITH RANIBIZUMAB TREATMENT IN DIABETIC MACULAR OEDEMA PATIENTS WITH POOR BASELINE VISUAL ACUITY: 1-YEAR RESULTS FROM THE LUMINOUS™ STUDY

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Design: LUMINOUS™ (NCT01318941) is an ongoing, 5-year, global, multicentre, observational, open-label study designed to evaluate the safety, efficacy, treatment patterns, and health-related quality of life outcomes associated with Ranibizumab 0.5 mg treatment in routine clinical practice.
Purpose: To report baseline characteristics of 4427 patients with diabetic macular oedema (DMO) enrolled before March 2015 and efficacy and safety results of 1828 DMO patients enrolled before March 2014 who had the potential for 1-year follow-up, from the third interim analysis of LUMINOUS™.
Methods: Consenting adult (≥18 years) DMO patients, who were treatment-naïve (T1) or previously treated with Ranibizumab (T2) or other ocular treatments (T3), were treated according to the local product label. Data were analysed by prior treatment status of the primary treated eye.
Results: Baseline characteristics were: mean age, 64.0 years; male, 57.2%; Caucasian, 73.9%; mean HbA1c, 62.7 mmol/mol. For T1, T2, and T3, baseline visual acuity (VA) was 53.9, 59.1, and 55.6 letters, and central retinal thickness (CRT) was 414.8, 370.4, and 430.1 µm, respectively. At 1 year, in T1, T2, and T3, the mean VA improved by 4.4, 1.9, and 4.6 letters, accompanied by a reduction in mean CRT of 57.7, 34.0, and 92.9 µm, respectively. The VA improvements in T1 were similar to T3 at 1 year but with a lower mean number of injections (T1, 3.7; T3, 4.7) and visits (T1, 6.4; T3, 8.4). In treatment-naïve patients at 1 year, VA outcomes stratified by baseline VA of <23, ≥23 to <39, ≥39 to <60, ≥60 to <74, and ≥74 letters were 11.8, 15.0, 6.2, 1.7, and -2.4 letters, with a mean of 2.3, 2.8, 3.7, 4.1, and 4.0 injections, respectively. The rate of ocular and non-ocular serious adverse events reported was 0.38% and 4.86%, respectively.
Conclusions: Prior Ranibizumab-treated patients showed higher VA and lower CRT at baseline versus treatment-naïve patients. VA improved over one year irrespective of previous treatment status. Ranibizumab 0.5 mg showed substantial improvements in VA in treatment-naïve patients with low baseline VA in a real-world scenario.

PROGNOSTIC FACTORS IN THE TREATMENT OF DIABETIC MACULAR OEDEMA (DMO) USING AFLIBERCEPT, RANIBIZUMAB AND BEVACIZUMAB (DRCR.NET PROTOCOL T)

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**The source of the data is the DRCR.net, but the analyses, content and conclusions presented herein are solely the responsibility of the authors (OPTIMA study group) and have not been reviewed or approved by DRCR.net.*

Design: Post hoc analysis of the DRCR.net protocol T study.
Purpose: Anti-VEGF therapy has been established as the gold standard in the treatment of diabetic macular oedema (DMO) achieving improvement in best corrected visual acuity (BCVA) and central retinal thickness (CRT). The DRCR.net protocol T study analysis has concluded that treatment outcome at year 1 depends on baseline BCVA. Our aim is therefore optimized treatment outcomes and disease management by identification of other prognostic features and substance characteristics. Advanced analyses of optical coherence tomography (OCT) images using computational methods allows to deduct prognostic factors.
Methods: Post-hoc analyses were conducted in randomized trial data from 629 individuals with central DMO and BCVA from 78-24 ETDRS letter scores (letters), randomized 1:1:1 to receive Aflibercept (2.0 mg), Ranibizumab (0.3 mg) or Bevacizumab (1.25 mg) in a per-protocol PRN regimen. Automated spectral-domain OCT image analysis was used for quantification of CRT in the central mm of the macula and volume of intraretinal cystoid fluid (IRC) and subretinal fluid (SRF) within the central 3 mm at baseline, weeks 4, 8, 12 and 24. Predictive computerized modelling was used for ranking of predictive features for BCVA.
Results: In the overall group baseline CRT and baseline IRC volume showed a moderate correlation with BCVA at baseline, while SRF had no relevant impact on baseline BCVA and no prognostic value for BCVA outcomes at week 52. The IRC volume at week 4 (after the first injection) was already predictive of BCVA outcomes at week 52 with a mean difference of +4.6 letters, whereas persistent IRC were a poor prognostic factor. Aflibercept was most efficient in reducing IRC volumes from week 24 which translated into superior BCVA gains. The impact of morphological predictive features was of highest value in the group with baseline BCVA <69 letters.
Conclusions: From treatment initiation, IRC volume appears to be the most relevant morphologic prognostic factor determining BCVA gains. An anti-VEGF substance having an effect on rapid IRC reduction enhances the benefit. Automated algorithms and computational modelling offer promising tools to identify predictive factors.

NURSE-LED EYE SCREENING IN A SPECIALIST DIABETES CLINIC IS COST-EFFECTIVE AND HAS SHOWN A REDUCTION IN VISUAL IMPAIRMENT AND BLINDNESS

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Design: A retrospective observational controlled study with data from an eye care database.
Purpose: To investigate if supervised specialist nurses trained to grade photographic fundus images of diabetic eye disease demonstrate similar outcomes to those seen with ophthalmologist screening.
Methods: A shortage of ophthalmologists has led to collaboration between a large diabetes clinic, with 5800 patients, and a Department of Ophthalmology to develop a special training programme for nurses to ensure timely diagnosis and care in order to prevent severe diabetic eye disease. Nurses are trained to read retinal images. They can both make a provisional assessment of any diabetic retinopathy changes, and perform the final grading and determination of patient´s eye status. The programme consist of 90 study hours, including bedside supervision, literature study, structured case assessment, 10 lectures in diabetic eye disease, and reading 100 retinal images. Before certifying the nurse to grade retinal images independently, the nurse passes an oral test and a multiple choice test. Nurses enter the findings in an intelligent database which supports the nurses in making the right diagnosis, retinopathy level and screening interval suggestions. The quality of the final assessment is controlled in regular multidisciplinary audits where images are assessed and compared with the ophthalmologist as judge.
Results: Specially trained nurses are able to grade 100% of the images and results shows that they are able to make the final determination in more than 85% of the images. 15% of the retinal images require further investigation or treatment by ophthalmologist. The amount of severe adverse eye outcomes has been reduced by a factor of 5 during the period where the screening model has been active.
Conclusions: The screening model is implemented across twelve clinics as reading centres for retinal images, with nurses reading more than 15.000 images/year. The reading centre has no geographical boundaries, and has recently included a Clinic abroad in our telemedicine healthcare set-up. The running cost each year of the reading centre is approximately 65.000 EUR.

RETINOPATHY IN CHILDREN WITH DIABETES: WHEN SHOULD THEY BE SCREENED?

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Design: Retrospective cohort analysis.
Purpose: Current advice in the UK is to commence screening for diabetic retinopathy with digital retinal photography at twelve years of age. We report on the relationships between age at diagnosis of diabetes, age at diabetic eye screening and severity of Diabetic Retinopathy (DR) in children diagnosed with diabetes before age of 12.
Methods: Data were extracted from 6 UK screening programmes. Time from diagnosis of diabetes to first screening and age at diagnosis were calculated. Survival analysis was used to examine disease progression.
Results: Data were available for 2125 children screened for the first time at age 12 or 13 and diagnosed with diabetes before the age of 13. The proportion with any retinopathy decreased monotonically from 20% in those diagnosed at age of 2 years or below to 8% in those diagnosed at 12 ($p<0.0001$). The proportion with mild non-proliferative retinopathy in both eyes decreased from 11% in those diagnosed at 2 or below and 2% those diagnosed at 12. Only 3 children (aged 8, 10 and 11 respectively at time of diagnosis of diabetes) had images graded with referable retinopathy and of these 2 had non-referable DR at all subsequent screenings. Of 1703 children with subsequent images 25 were graded with referable DR over a mean follow-up of 3 years, incidence rate of 5 per 1,000 per year. Those with longer duration of diabetes at age 12 were at higher risk of progression to referable DR with hazard ratio of 1.3 per year (95% CI 1.18 to 1.50).
Conclusions: Although the rate of retinopathy in children below the age of 13 at first screening in the UK is significantly higher in those diagnosed with diabetes in early childhood, the rate is low and few children progress to referable DR. In this large cohort there is no evidence to suggest that earlier screening or more frequent screening is needed in this age group.

MICRO-COSTING DIABETIC EYE SCREENING: ESTIMATION OF PERSONAL EXPENSE, ATTENDANCE AND HEALTH CARE RESOURCE USE

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Design: Micro-costing study with collection and analysis of primary and secondary data on resource use and costs.
Purpose: To estimate the cost of screening within the NHS Diabetic Eye Screening Programme from a health service and societal perspective. Findings will inform future cost-effectiveness analyses of screening programmes for diabetic retinopathy.
Methods: Data were collected from multiple sources for people with diabetes in Liverpool, UK. Within the ISDR trial, 874 participants self-completed a bespoke questionnaire at baseline screening attendance, collecting information on travel, duration and personal expenses associated with the visit. A time study was conducted for 104 screening attendances to capture associated staff costs. Data for over 50,000 screening appointments since 2013 were used to elicit attendance rates and grading activity. Additional resource use estimates, including overheads, were obtained from screening programme staff.
Results: Per visit, people spent on average 90 minutes attending, with 32 minutes of help from a friend, relative or carer. The mean travel cost associated with screening was £2.50. 18% of people took time off work to attend, and 7% received assistance from someone who took time off work. The productivity loss associated with this time was on average £5 per visit across the population. The duration of screening attendance, dilatation and photography was consistent. Dilatation took on average 4 minutes with 85% 6 minutes or less. Photography took on average 3 minutes, with 93% 5 minutes or less. Attendance was 64%.
Conclusions: The primary source of inefficiency in diabetic eye screening is non-attendance. Patients who do not attend (36%) represent a substantial opportunity cost to the health service. Costs associated with personal expense and productivity losses are small, but these must be included when evaluating screening programmes with large eligible populations and major budget impacts. An additional cost of £7.50 per visit equates to a societal burden of around £20 million in the UK.

PROVIDING THE INTERNATIONAL TEST AND TRAINING (ITAT) FOR QUALITY ASSURANCE AND TRAINING SUPPORT FOR RETINOPATHY SCREENING THROUGH 'SEEING IS BELIEVING' PROJECTS

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Design: Monthly on-line self-testing and eLearning in a number of nations and locations, with periodic face-to-face training support.
Purpose: Help improve knowledge, skills and confidence assessing diabetic retinopathy from screening images.
Methods: On-line iTAT system presents 20 cases each month for assessment of features of retinopathy, scored against previously 'ground-truthed' grading. 'Seeing is Believing' pilot project funding provided iTAT access and periodic training support over an 18-month period ending August 2015 for three countries: Bangladesh (2 locations, 18 users), Botswana (4 locations, 18 users) and Indonesia (3 locations, 29 users). 'Preparing to scale' extension funding for 18 further months from December 2015 will enable continued and expanded support for these locations with extension to Zambia, Uganda and Malawi (2 locations each) and one extra site in Indonesia. Extension funding will also support essential telecoms and computer hardware plus staff qualification where required. Concurrently, iTAT has been translated into

Mandarin Chinese and Spanish with Bahasa Indonesian and other languages to follow.
Results: Participation: Bangladesh users participated regularly, with an average of 14 users per month completing the on-line set over the 12-month period it was available. One user in Indonesia completed 8 sets of the 11 available sets and four others attempted but did not complete one or more monthly sets. Lack of available and protected time was the main reported reason for non-activity. Three Botswanan users attempted sets but lack of available or protected time, little access to computers and very poor internet access precluded meaningful participation. Performance: Bangladesh users achieved high overall agreement on the test sets, scoring mean 80% (range 57 to 100%). Indonesian users achieved mean 70% agreement (range 55 to 82%). These are comparable with most users in the UK. Performance in Botswana was not measurable.
Conclusions: High participation and performance in some locations but lack of protected time, very poor computer- and internet-access has limited involvement by many. These issues are planned to be addressed as much as possible during the extension phase of the project.

VISION RELATED QUALITY OF LIFE IN PATIENTS WITH TYPE 2 DIABETES IN THE EUROCONDOR TRIAL

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Design: EUROCONDOR is a project funded by the European Commission's Seventh Framework Programme (Grant Agreement N. 278040) to test an innovative strategy to prevent diabetic retinopathy (DR) by locally administering the neurotrophic agents somatostatin and brimonidine. A 2-year randomized controlled trial was carried out in 11 centres across Europe.
Purpose: To evaluate Vision Related Quality of Life (VRQL) at baseline in the patients enrolled in the trial.
Methods: Four-hundred-forty-nine patients with Type 2 Diabetes Mellitus (T2DM) of ≥5 years known duration, aged 45-75 were enrolled. They had either no DR (ETDRS level <20) or mild DR (ETDRS 20-35). VRQL was measured by the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25) translated and validated in the 7 languages of the countries involved. The items explore 12 subscales: General Health and General Vision, Ocular Pain, Difficulty with Near Activities, Difficulty with Distance Activities, Vision Specific Social Functioning, Vision Specific Mental Health, Vision Specific Role Difficulties, Vision Specific Dependency, Driving Difficulties, Difficulty with Colour Vision, Peripheral Vision. Subscales are converted to scores between 0 and 100, higher scores indicating better VRQL.
Results: The patients (153 women and 296 men) were 62.8 ± 6.7 years old and had 11.0 ± 5.7 years disease duration. DR was absent in 194 patients and mild in 255. Those without DR were older (64.3 ± 6.4 vs 61.7 ± 6.8; p = 0.0001) and had shorter duration of T2DM (9.9 ± 5.2 vs 11.9 ± 6.0; p = 0.0001). Patients with and without DR did not differ by gender, Best Corrected Visual Acuity (BCVA) (85.7 ± 5.4 vs 86.4 ± 4.8; n.s.) or any of the NEI VFQ-25 subscales, except Vision Specific Mental Health (88.8 ± 11.5 vs 86.4 ± 12.0; p = 0.0042) and Vision Specific Role Difficulties (89.8 ± 18.6 vs 93.3 ± 15.4; p = 0.017). Dichotomizing retinal thickness by GLC, those with thinner retinae (n = 36) had, despite similar BCVA, lower scores for Difficulty with Colour Vision (94.3 ± 15.0 vs 98.3 ± 7.5; p = 0.0384) and Peripheral Vision (89.6 ± 19.2 vs 95.7 ± 11.4; p = 0.0179).
Conclusions: Patients in the EUROCONDOR trial had fairly high scores for VRQL, possibly reflecting no visual impairment in absent/mild DR. However, the NEI VFQ-25 questionnaire may be able to detect subtle changes in the patients' perception of their visual function.

OSCILLATORY POTENTIAL: A MORE SENSITIVE MARKER FOR DIABETIC MACULOPATHY PROGRESSION?

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Design: Single-centre, prospective, cohort study.
Purpose: To determine longitudinal changes in macular function in the presence of varying severities of diabetic maculopathy.
Methods: Treatment naïve patients with diabetes mellitus (DM) were recruited prospectively into a study of diabetic maculopathy [n = 89]. Of them 61 were invited for longitudinal follow up at 6 months and 12 months. Patients were divided into three groups: i) DM but no retinopathy [n = 5 and n = 4 at 6 and 12 months respectively]; ii) early diabetic maculopathy but no features of clinically significant macular oedema (CSMO) [n = 16 and n = 13]; iii) sight-threatening maculopathy (defined as the presence of CSMO and/or ischaemic maculopathy [n = 19 and n = 14]. All subjects underwent best corrected visual acuity (BCVA), FA, multifocal electroretinography (mfERG), oscillatory potentials (OP), microperimetry (MP) and assessment for systemic risk factors. Statistical analysis was performed on SPSS version 22 using paired *T*-Tests and Wilcoxon test.
Results: There was no statistically significant difference in BCVA at either 6 or 12 months (p = 0.48 and 0.50 respectively). OP implicit time was significantly increased at both 6 months and 12 months (p = 0.01 and <0.01 respectively). Subanalysis revealed that the group with sight threatening maculopathy developed a greater mean prolongation in implicit time as compared to the early maculopathy group (2.1 ms vs 0.7 ms at 6 months and 5.9 ms vs 1.1 ms at 12 months). OP sum amplitude decreased statistically significantly at 12 months (-6.2 μV, p = 0.03) but not at 6 months (-6.9 μV, p = 0.14). Mean mfERG central ring amplitude was reduced but non-significantly at 6 months (-0.9 nV/deg^2, p >0.50) and at 12 months (-5.0 nV/deg^2, p = 0.15). MfERG implicit time was relatively unchanged at either time point. Microperimetry sensitivity increased at both 6 months (0.6 dB, p = 0.02) and 12 months (1.7 dB, p<0.01).
Conclusions: Neural macular function appears to decrease longitudinally with oscillatory potentials appearing to be the most sensitive test. This tool may offer a more sensitive method of monitoring macular function prior to the development of visual loss.

MEDIATORS BETWEEN REACTIVE GLIOSIS AND VASCULAR LEAKAGE IN DIABETIC RETINOPATHY: A PROTEOMIC APPROACH USING HUMAN RETINAS

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Design: Experimental study.
Purpose: Retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy (DR). Reactive gliosis (also named glial activation) is a main feature of neurodegeneration and could be identified by glial acidic fibrillar protein (GFAP) overexpression in Müller cells. The effect of glial activation on early microvascular impairment remains to be elucidated. To shed light on this issue we have used a proteomic analysis approach aimed at identifying potential mediators of vascular leakage associated with glial activation.
Methods: For this purpose, human retinal samples were obtained from 5 non-diabetic donors, and 10 type 2 diabetic donors without (n = 5; group A) or with (n = 5; group B) reactive gliosis. Diabetic donors did not present microcirculatory abnormalities in the ophthalmoscopic examinations performed during the two years before death. Retinal lysates from each group were pooled and run on an SDS-PAGE gel. Bands were excised and analysed sequentially by LC/MS using an Orbitrap Mass Spectrometer.

Results: A total of 307 proteins were upregulated and 373 were downregulated in Group B in comparison with Group A. Notably, retinas with reactive gliosis (group B) presented a significant increase of biological markers of vascular leakage, such a as serum albumin and immunoglobulins, thus indicating the presence of early microvascular damage. Among the proteins upregulated in group B it should be noted the abundance of inflammatory mediators (TNF-alpha receptor, Complement C4 factor, ICAM-1), and carbonic anhidrase. Among the downregulated proteins, several isoforms of the sodium/potassium transporting ATPase subunit and Complement factor H (CFH: the soluble inhibitor of the alternative pathway of complement) were identified.
Conclusions: In conclusion, by means of a proteomic analyses several candidates that could play a relevant role in the link between reactive gliosis and vascular leakage have been identified. In addition, our results suggest new pathogenic pathways involved in the early microvascular impairment mediated by neurodegeneration.

PLVAP REGULATES ANGIOGENESIS THROUGH VEGFR2

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Design: Gene knockdown and overexpression in functional *in vitro* models of angiogenesis.
Purpose: Plasmalemma vesicle associated protein (PLVAP), a protein involved in vascular permeability in diabetic retinopathy was recently shown to be also essential for angiogenesis *in vivo* in the oxygen induced retinopathy model. To further investigate the molecular mechanisms underlying PLVAP-dependent angiogenesis, we studied the effect of PLVAP knockdown or overexpression in a variety of functional *in vitro* models relevant for angiogenesis.
Methods: For PLVAP knockdown, lentiviral pLKO.1 constructs were used expressing mouse or human short hairpin (sh)RNA. Control cells were transduced with non-targeting shRNA constructs. In overexpression studies, ORF expression pReceiver-Lv105 construct, GFP expressing and empty pReceiver-Lv105 vector were used. Knockdown and overexpression of PLVAP was investigated in the aortic ring model, in the spheroid-based sprouting model, in a novel tip cell model and in migration assays. In addition VEGFR2 mRNA and protein levels were determined after PLVAP manipulation by real-time quantitative PCR, FACS analysis and immunocytochemistry.
Results: Inhibition of PLVAP reduced endothelial cell sprouting in the aortic ring model and in spheroids, reduced the number of tip cells and cell migration. On the other hand, overexpression of PLVAP resulted in increased sprouting in the spheroid model and increased cell migration. Overexpression also enhanced the number of tip cells and these cells showed excessive formation of filopodia, a characteristic of tip cells. PLVAP silencing resulted in reduced VEGFR2 protein levels, but not mRNA levels, whereas PLVAP overexpression caused an increase in VEGFR2 protein.
Conclusions: Our findings indicate that PLVAP is an essential endothelial cell-specific regulatory cofactor for VEGFR2 signalling in angiogenesis.

MODULATION OF MICROGLIA POLARIZATION DYNAMICS BY A SP2-IMINOSUGAR DERIVATIVE DURING DIABETIC RETINOPHATY IN DB/DB MICE

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Design: Retinal diseases linked to inflammation, including diabetic retinopathy (DR), are often accompanied by macrophage/microglia cell activation. However, the dynamics between M1 (pro-inflammatory) and M2 (anti-inflammatory) microglia polarization stages during DR progression has not been investigated and might be therapeutically useful. Iminosugar glycosyl hydrolase inhibitors have a strong potential in therapies for cancer, viral infections, tuberculosis, diabetes and glycosphingolipid storage disorders. However, their potential anti-inflammatory effects in the context of neuroinflammation associated to DR have not been reported.
Purpose: We have evaluated microglia-mediated effects of the bicyclic nojirimycin derivative (1R)-1-dodecylsulfinyl-5N, 6O-oxomethylidenenojirimycin (R-DS-ONJ) in Bv2 microglia cell line and retinal explants from db/db mice.
Methods: We analysed the inflammatory signalling pathways and the M1/M2 polarization profile in Bv.2 cells treated with LPS (200 ng/ml) in the absence or presence of R-DS-ONJ or M2 anti-inflammatory cytokines (Il4/IL13) as a positive control. Retinal explants from db/db mice treated with R-DS-ONJ were used to measure the expression of pro- and anti-inflammatory markers by western-blot and immunofluorescence.
Results: Treatment of Bv.2 microglial cells with lipopolysaccharide (LPS) in the presence of R-DS-ONJ or IL4/IL13 as a positive trigger of the M2 response, prevented the activation of inflammation-linked stress kinases (JNK and p38 MAPK) and the degradation of IκBα. As a consequence, this compound decreased the expression of pro-inflammatory markers (M1). Treatment of retinal explants from db/db mice with R-DS-ONJ increased arginase-1 expression (M2 response) and reduced reactive gliosis, monitored by GFAP immunostaining.
Conclusions: Our results have shown that targeting neuroinflammation with R-DS-ONJ switches microglia towards a M2 polarization state and this approach might be a therapeutic strategy to prevent the deterioration of visual function in DR.

DIFFERENT MIRNA PATTERNS IN EXTRACELLULAR VESICLES FROM DIABETIC AND HEALTHY SUBJECTS

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Design: We demonstrated that extracellular vesicles (EV) derived from mesenchymal stem cells (MSC) cultured in high glucose and/or hypoxia are able to enter the pericytes, causing their detachment from substrate and migration, and stimulating angiogenesis *in vitro*. In fact, they downregulate miR-126 leading to increased expression of angiogenic molecules (VEGF and HIF-1α). Our present hypothesis is that circulating EV in diabetes may influence small vessel homeostasis, and that identification of molecular differences in EV from healthy controls and diabetic subjects, with/without microvascular complications, could represent a predictive option for diagnostic purposes.
Purpose: The aim of this study was the molecular characterization and comparative analysis of EV derived from healthy and diabetic subjects and their influence on pericyte detachment and angiogenesis.
Methods: EV were extracted from plasma samples of 3 diabetic patients with microvascular complications (nephropathy and retinopathy) (DM) and 3 healthy age-matched controls (noDM). EV expression of surface molecules was measured by FACS. microRNA (miRNA) content was evaluated by Taqman Human MicroRNA Array, which allows detection of 377 different miRNAs. Human retinal pericyte (HRP) detachment was evaluated after 4 and 24 hr exposition to EV obtained from MSC, DM and noDM plasma.
Results: FACS analysis of surface molecules showed no significant changes between DM and noDM. We found differences between the two groups in six miRNAs: 4 of them, which have anti-angiogenic properties (miR-150, miR-155, miR-342-3p, let-7-g), were decreased, while 2 of them with a pro-angiogenic function (miR-17 and miR-106a) were increased in DM vs noDM ($p<0.05$). EV from DM patients induced HRP detachment (-19.6% after 4 hrs, -31.4% after 24 hr exposure, $p<0.05$), similarly to EV derived from MSC in diabetic-like conditions, while noDM-EV had no effect.
Conclusions: These observations suggest that diabetic patients may have different EV patterns in comparison with healthy subjects. In particular, an imbalance between miRNAs with pro- and anti-angiogenic functions could lead to abnormal microvessel proliferation, and consequently result in proliferative diabetic retinopathy. Further studies on this subject could potentially provide a useful therapeutic tool for the treatment of various types of vessel abnormalities.

TARGETING STAT3 FOR THE TREATMENT OF PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Signal transducer and activator of transcription 3 (STAT3) plays an important role in inflammation and angiogenesis. Previous studies have shown that STAT3 is involved in the pathogenesis of Diabetic Retinopathy in models of type-1 diabetes and that ocular fluid from proliferative diabetic retinopathy (PDR) patients contains high levels of IL-6 (a key activator of STAT3). We hypothesize that inhibition of STAT3 may ameliorate pathologic neo-vascular growth in PDR.
Purpose: To investigate the therapeutic potential of pharmacological inhibition of STAT3 in retinal pathologic neo-vascularization.
Methods: The effect of STAT3 inhibition on pathologic retinal neovascularization was tested in the murine model of oxygen-induced retinopathy (OIR). New-born C57BL6/J mouse pups (n ≥5 per group) were exposed to 75% O2 from post-natal day 7 (P7) to P12. Mice were then treated from P13 to P16 by daily intraperitoneal injection of a STAT3 inhibitor (LLL12, 5 mg/kg) or vehicle (1% DMSO in PBS). The expression of phosphorylated STAT3 (pSTAT3) in the retinas was examined by Western blotting at different time-points (P12 to P22). At P17 eyes were collected and the extent of retinal neo-vascularization/vaso-obliteration examined in retinal flat-mounts by dual staining of isolectin-B4 and collagen IV. Retinal thickness was assessed in haematoxylin and eosin stained cross-sections. Retinal function was assessed by electroretinography (ERG) and retinal thickness by SD-OCT at P90.
Results: The expression of pSTAT3 was significantly increased in OIR eyes from P16 to P22. LLL12 treatment significantly decreased neo-vascular tufts area in OIR mice (6% ± 1.2%; p<0.001) compared to vehicle treated (12% ± 0.5%) and non-injected controls (15.5% ± 1.5%) at P17. This was accompanied by a significant preservation of retinal thickness in LLL12-treated mice (90.1 ± 2.3 µm; vehicle 74.5 ± 2 µm; non-injected 76.7 ± 3.1 µm; p<0.01). LLL12 treatment significantly improved retinal function (scotopic a-wave and b-wave amplitudes, p<0.001) and retinal thickness (p<0.05) by P90.
Conclusions: Our results suggest that STAT3 activation may contribute to pathologic neo-vascular growth in the murine model of OIR. STAT3 may be a therapeutic target for retinal neovascular disorders such as PDR.

STUDY OF SAFETY AND EFFECTIVENESS OF AN AUTOMATED DIABETIC RETINOPATHY SCREENING SYSTEM ON A LARGE SET OF CONSECUTIVE PATIENT VISITS

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Design: We compute screening sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) of EyeArt version 2.0 DR screening software on a large set of 59,005 consecutive patient visits/encounters obtained from the EyePACS DR telescreening program. EyeArt automatically analyses multiple colour fundus images captured during a patient visit/encounter for DR and provides a "refer" screening recommendation for patients indicating (i) moderate non-proliferative DR (NPDR) or higher on the International Clinical Diabetic Retinopathy (ICDR) severity scale and/or (ii) presence of surrogate markers for clinically significant macular oedema (CSME) defined to be hard exudates within one disc of the macula.
Purpose: To evaluate the safety and efficacy of EyeArt v2.0 for automated DR screening.
Methods: A total of 59,005 consecutive patient encounters (totalling 469,953 images captured between January 2014 and February 2015) were obtained from the EyePACS database without any patient identification data, each with 1-22 images including external eye images. The DR severity on the ICDR scale and indication of surrogate markers for CSME provided by EyePACS graders was the reference standard. Prevalence of encounters with moderate NPDR or higher or with surrogate markers for CSME was 20.3% and prevalence of encounters with potentially treatable DR (severe NPDR or proliferative DR) was 5.3%.
EyeArt analysed these images and produced a "refer" and a "no refer" screening recommendation for each patient. Encounters with fewer than two gradable retinal images were automatically flagged as non-screenable, given a "refer" recommendation, and included in the performance analysis.
Results: EyeArt's screening sensitivity was 91.0% (95% CI: 90.5%-91.6%) and specificity was 90.8% (95% CI: 90.5%-91.0%). This corresponds to 15,232 "refer" recommendations (including 725 encounters flagged by EyeArt as non-screenable) and 1072 false negatives out of which 95.0% had moderate NPDR and did not meet the general treatment criteria. The AUROC was 0.959 (95% CI: 0.957-0.961) and sensitivity for referring potentially treatable DR was 98.3%.
Conclusions: EyeArt v2.0 achieves high sensitivity for detecting both referable DR and for potentially treatable DR at a high specificity making it both safe and effective for automated DR screening.

AUTOMATED MICROANEURYSM COUNTS IN THE REGION TEMPORAL TO THE FOVEA ASSOCIATED WITH THE SEVERITY OF DIABETIC RETINOPATHY.

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Design: Cross-sectional study.
Purpose: Microaneurysm (MA) counts have been shown to be predictive for the severity and progression of diabetic retinopathy using manual grading of fluorescein images and retinal photographs. However manual microaneurysm counting is not practical in routine clinical practice. We examined the count and location of microaneurysm in retinal images obtained as part of our regional screening programme using an automated retinopathy detection system.
Methods: Retinal images and grading of 16282 patients who attended the Grampian retinal screening programme between 2005 and 2008 were obtained and pseudononymised by the Grampian data management team. To assess the position of microaneurysms, we divided the retina into four quadrants centred at the fovea and the horizontal axis running through the foveal centre and centre of the optic disc. The relative position of each automatically detected microaneurysm was calculated by the automated retinal image analysis.
Results: 9140 (56.1%) patients were male, 12298 (77.4%) had type 2 diabetes, 10904 (67.0) were ever smokers. In the right eye there were significant correlations (Spearman's correlation) between the severity of retinopathy and total microaneurysm count (Correlation coefficient: 0.59, P value <0.0001), MA in the supratemporal quadrant (0.58, <0.001), the infratemporal quadrant (0.54, <0.001), supra nasal (0.23, <0.001), infranasal (0.2, <0.001). Similar correlations were noted in the left eye.
Conclusions: There was a stronger correlation between microaneursyms in the region temporal to the fovea (than those present nasally) and the presence of severe diabetic retinopathy. Further exploration is required to assess whether regional variations in microaneurysm formation predict progression of diabetic retinopathy.

AUTOMATIC DETECTION OF FOVEA AND OPTIC DISC USING DEEP NEURAL NETWORKS

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Design: This is a software development and evaluation study involving colour fundus images of the retina from people with diabetes.
Purpose: To investigate the feasibility of deep learning techniques to simultaneously detect the centres of the fovea and the optic disc (OD) from colour fundus images.
Methods: 1200 macula-centred digital colour fundus photographs from the publically available MESSIDOR dataset were used. The centres of the fovea and the OD in each image were marked up by expert graders (DGP and SL) as ground truth. 975 images and their annotated locations of the foveal and OD centres were used to train convolutional neural networks (CNNs) and the rest 225 images were used to evaluate the performance of the trained CNNs. In the pre-processing step, the intensity of each image was scaled between

[0, 1] and the centres locations were scaled between [-1, 1]. The proposed CNNs comprises multiple convolution layers, max pooling layers, fully connected layers, dropout layers and output layer. Following the literature, an automatically detected foveal (resp. OD) centre is considered to be correct if the distance between it and the annotated foveal (resp. OD) centre is less than 0.5 OD diameter (ODD). The ODD was estimated by dividing the distance between the annotated foveal centre and the OD centre by 2.5).
Results: The accuracy is 95.1% for the detection of the foveal centre while 96.0% for the detection of the OD centre. The mean ± standard deviation (std) distance of the detected foveal centre from the annotated foveal centre is 0.151 ± 0.225 ODD. The distance of the detected OD centre from the annotated OD centre is 0.146 ± 0.139 ODD.
Conclusions: The proposed CNNs approach showed very promising results for simultaneously automated detection of the centres of the fovea and OD. Further optimisations on CNNs are underway for its introduction into general clinic practice.

ULTRA-WIDE FIELD SWEPT-SOURCE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY (UWF SS OCT-A) IN DIABETIC RETINOPATHY

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Design: Serial case report.
Purpose: To describe the Ultra Wide-field Swept-Source Optical Coherence Tomography Angiography (SS OCT-A) (UWF SS OCT-A) features of Diabetic Retinopathy (DR).
Methods: Serial case report. Description of DR features in patients undergoing routine examination. Eighty six eyes (43 consecutive patients) underwent full ophthalmological evaluation, 45° (CFPh) and Optos California® Ultra Wide-field Colour Fundus Photography (UWF CFPh) and SS OCT-A with both Topcon DRI OCT-1 Atlantis® and Topcon DRI OCT Triton® of the posterior pole and the mid peripheral retina. When clinically necessary, Ultra Wide field Optos California® Fluorescein Fundus Angiography (UWF FFA) was performed. Individual SS OCT-A images were montaged to create an UWF SS OCT-A image. Two independent reviewers compared images as follows: CFPh vs UWF SS OCT-A, UWF CFPh vs UWF SS OCT-A, and UWF FFA vs UWF SS OCT-A.
Results: Diabetic Macula Oedema (DMO), posterior pole and mid-peripheral retinal non-perfusion and Neovascularization of the Disc (NVD) and elsewhere (NVE) were identified on UWF SS OCT-A with 100% inter-reviewer agreement. Microvascular lesions observed on CFPh and UWF CFPh were also observed on UWF SS OCT-A in 86/86 eyes. An enlarged Foveal Avascular Zone (eFAZ) was observed on both UWF FFA and UWF SS OCT-A in 36/36 eyes. Microvascular lesions, DMO, NVD and NVE were observed on UWF FFA and UWF SS OCT-A in 28/28 eyes. Within the central 100°, there was good correlation between sensitivity of both UWF FFA and UWF SS OCT-A in detecting NVE in 9/10 eyes.
Conclusions: UWF SS OCT-A is a sensitive and non-invasive imaging technique that can offer additional spatial information regarding the localization and the morphology of the vascular lesions in DR, not only within the posterior pole but also up to the mid-periphery.

COMPARISON OF DIABETIC RETINOPATHY CLASSIFICATION USING FLUORESCEIN ANGIOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

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Design: Observational Cross-sectional Study.
Purpose: To analyse and compare the classification of eyes with Diabetic Retinopathy (DR) using Fluorescein Angiography (FA) and Optical Coherence Tomography Angiography (OCTA), with either AngioPlex or AngioVue.
Methods: Twenty nine eyes eyes from 15 diabetic subjects underwent FA, colour fundus photography (CFP) and OCTA, 3 × 3 mm scan, using two different devices (Zeiss AngioPlex and Optovue OCTA system). ETDRS DR levels were obtained from CFP. From OCTA the superficial retinal vascular layer (SRL) were depicted as an enface image and exported as image file. For FA, 20° images from field 2 of the initial stage of the procedure were also exported. Two independent graders classified the FA using the ETDRS Report 11, and a similar evaluation was performed for OCT-A. Foveal avascular zone (FAZ) was also measured using an image processing program (ImageJ) and the free hand selection tool.
Results: The mean age of the diabetic patients was 66.1 ± 7.8 years (range 52-76) and 34.5% were females. The FAZ size varied widely (from 0.146 to 0.670 mm^2 for Zeiss AngioPlex, from 0.113 to 0.816 mm^2 for AngioVue OCTA system and from 0.092 to 0.741 mm^2 for FA). Outline of FAZ, capillary loss, arteriolar abnormalities and capillary dilatation showed a higher percentage of ungradable features using FA in comparison with both OCTA devices. Gradable images for outline of FAZ in central subfield (CSF) were 70.0% with FA, 86.2% with AngioPlex, and 75.9% with AngioVue (FA vs AngioPlex p = 0.006; FA vs AngioVue p = 0.100). For capillary loss, gradable images in the inner ring were 56.9% with FA, 69.8% with AngioPlex, and 64.7% with AngioVue (FA vs AngioPlex p = 0.169; FA vs AngioVue p = 0.732).
Conclusions: Examination of the retinal superficial capillary net with OCTA allows better discrimination of the CSF and parafoveal macular microvasculature than FA, especially for FAZ rupture and capillary loss, without the need of intravenous injection of fluorescein. In addition, FA shows a higher number of ungradable features. The OCT-A can replace with advantage the FA as a non-invasive and more sensitive procedure for detailed morphological evaluation of retinal vascular changes.

OCT PREDICTORS FOR BCVA RESPONSE TO INTRAVITREAL ANTI-VEGF TREATMENT IN EYES WITH DIABETIC MACULAR OEDEMA

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Design: Prospective, observational study.
Purpose: To determine OCT morphological characteristics that can predict the response to anti-VEGF treatment of Diabetic Macular Oedema (DMO).
Methods: Seventy-one patients with DMO were enrolled in the CHARTRES study (NCT01947881-CHARTRES) following accepted clinical practice, and 67 completed the study. All patients received monthly intravitreal injections of anti-VEGF Lucentis in the first 3 months. All underwent BCVA measurements (ETDRS protocol) and SD-OCT (Cirrus HD-OCT5000) at baseline, months 1, 2, 3 and 6 and Colour Fundus Photography and Fluorescein Angiography at baseline, months 3 and 6. The treatment response was characterized in groups according to BCVA letters increase: Good Responders (improvement of ≥10 letters), Moderate Responders (improvement between 5 letters and 10 letters) and Poor Responders (improvement of <5 letters or loss of letters). SD-OCT images were analysed and graded by an independent Reading Centre to obtain a morphological characterization of DMO before and after treatment. Central Retinal Thickness (CRT), extension of Disorganization of Retinal Inner Layers (DRIL), size of intraretinal cystoid spaces and extension of disruption of External Limitant Membrane (ELM), Ellipsoid Zone (EZ) and Retinal Pigment Epithelium (RPE), were quantified in the 1 mm area centred on the fovea.
Results: Twenty-six patients (38.80%) were identified as Good Responders, 19 (28.35%) as Moderate Responders and 22 (32.83%) as Poor Responders. No significant differences regarding BCVA and central retinal thickness (CRT) were found at baseline between the 3 groups (p = 0.176 and p = 0.573 respectively). Higher values of DRIL area and disruption of external retinal layers at baseline, especially EZ and ELM layers, were significantly correlated with a poor response to treatment ((0.12; CI:0.02-0.59; P = 0.009) (0.24; CI:0.07-0.86; P = 0.029) and (0.21; CI:0.04-1.20; P = 0.079, respectively)). A poor response to treatment was also correlated with the presence of larger cystoid spaces in the 1 mm centred on fovea (80.95% of larger cysts in poor responders vs 46.15% in good responders).

Conclusions: Higher values of DRIL area and disruption of external retinal layers, especially damage of the EZ and ELM are good predictors for BCVA response to anti-VEGF therapy in DMO.

AUTOMATED ANALYSIS OF RETINAL EXTRACELLULAR SPACE USING OPTICAL COHERENCE TOMOGRAPHY. A NON-INVASIVE INDIRECT IDENTIFICATION OF THE SITES OF ALTERATIONS OF THE BLOOD-RETINAL BARRIER

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Design: Optical Coherence Tomography (OCT) automated retinal extracellular space assessment of eyes/patients with mild non-proliferative diabetic retinopathy, without or with different degrees of macular oedema, and comparison to information obtained from fluorescein angiography (FA) images.
Purpose: Monitoring Blood-Retinal Barrier (BRB) alterations is presently performed invasively by fluorescein angiography. We demonstrate the use of a new non-invasive OCT based method for localization and quantification of increases in retinal extracellular space indicating BRB breakdown, herein designated as OCT-Leakage.
Methods: OCT-Leakage maps are based on the distribution of OCT low optical reflectivity (LOR) sites. These maps are generated for the full A-Scan and for the different retinal layers after semi-automated segmentation of the OCT data volume. To compare LOR area ratios with retinal layer thickness we examined 25 eyes from 21 healthy volunteers (m ± sd: 60.6 ± 5.4; 49-75 [years]) and 48 eyes from 48 diabetic patients (m ± sd: 61.2 ± 8.1; 43-82 [years]) gathered by Coimbra Centre in the context of the NCT01145599 trial. Comparison between OCT-Leakage maps and FA images was performed on 24 eyes from 17 diabetics patients (m ± sd: 64.8 ± 7.9; 52-77 [years]) gathered in the context of the NCT02391558 trial.
Results: Increases in central subfield retinal thickness in diabetic eyes were located mainly in the INL and OPL. These increases correlated well with the changes in LOR ratios for the INL ($r = 0.8$, $p<0.01$) and for the OPL ($r = 0.6$, $p<0.01$). The OCT-Leakage maps identified well the sites of fluorescein leakage on FA. Furthermore, the location of the increases in extracellular space identified by the LOR ratios could be seen in different retinal layers in different eyes, indicating the location of the increase of the extracellular space resulting from BRB breakdown.
Conclusions: The method here described is able to complement OCT-Microangiography localizing and quantifying non-invasively the sites of leakage, i.e., alteration of the BRB. FA may now be used only when a direct focal laser treatment of the BRB alteration is an option considered by the clinician.

GLUCOSE METABOLISM STATUS IS ASSOCIATED WITH CHANGES IN MACULAR THICKNESS

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Design: Cross-sectional population-based cohort study.
Purpose: Macular thinning may be an early sign of diabetic retinopathy. We therefore evaluated to what extent macular thickness differed between individuals with prediabetes (preDM2) and individuals with type 2 diabetes (DM2) without cysts compared with individuals with a normal glucose metabolism (NGM).
Methods: Using SD-OCT we measured macular thickness in five ETDRS subfields in 2385 participants (mean age 59 ± 8 years, 50% men, 1397 NGM, 357 preDM2, 631 DM2).
Results: After adjustment for age, sex, and spherical equivalent, individuals with preDM2 showed a significant decrease in pericentral superior macular thickness compared with individuals with NGM (-3.34 ± 1.28 µm, $P<0.01$). In individuals with DM2 without cysts, the four pericentral quadrants were significantly thinner compared with individuals with NGM (range: -5.42 ± 1.04 µm to -5.91 ± 1.03 µm, $P<0.001$). There was a significant linear trend of pericentral macular thinning with severity of glucose metabolism status ($P<0.001$).
Conclusions: This study demonstrates that the pericentral macular thickness decreases with worsening of glucose metabolism. This may reflect early neurodegenerative changes.

POSTER SESSION

CAPSULOTOMY INDUCED RETINAL DEGENERATION IN INS2-AKITA MICE IS PROTECTED BY WNT INHIBITION

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Design: Cataract surgery increases the risk of developing diabetic retinopathy (DR) and can exacerbate the progression of any underlying DR which can lead to significant detrimental changes to the neural retina. However, the mechanism by which this occurs remains to be elucidated. The Wnt/βcatenin pathway has previously been implicated in the pathogenesis of DR and inflammation.
Purpose: Investigate whether neutralizing Wnt has therapeutic potential for DR mediated worsening of capsulotomy.
Methods: Male heterozygous Ins2Akita mice (2 months of hyperglycaemia) and age-matched non-diabetic siblings were used in the study. Capsulotomy was performed in the anterior lens capsule, followed by an intracameral injection of either Mab2F1 antibody (a specific blocker of the canonical Wnt LRP6 receptor) or mouse IgG at the time of surgery. Twenty days after surgery, mice received an intravitreal injection of the respective treatments. Forty days following surgery, retinal function was assessed by electroretinography (ERG), immune cell activation and neuronal retinal damage by immunohistochemistry (IHC). Unoperated eyes from age-matched Ins2Akita and non-diabetic siblings served as full control groups.
Results: Wnt neutralizing Mab2F1 antibody, but not IgG control, resulted in a significant reduction in the number of infiltrating immune cells together with significant neuroprotection in capsulotomy eyes in both diabetic and non-diabetic retinas. This was evidenced by a marked improvement of ERG response (both a- and b-waves) and a significant preservation of synaptic structures at the OPL, photoreceptor outer segment integrity, and increased amacrine and retinal ganglion cell density in Mab2F1 treated mice compared to control IgG treated mice.
Conclusions: Wnt inhibition by Mab2F1 antibody following capsulotomy resulted in decreased retinal inflammation and significant neuroprotection in the diabetic retina and non-diabetic siblings. Our results suggest that blocking Wnt/βcatenin pathway may be a novel approach to protect diabetic retinas following cataract surgery.

PLVAP IS REQUIRED FOR ANGIOGENESIS *IN VIVO*

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Design: The mouse oxygen induced retinopathy model was used in combination with gene silencing to investigate the role of PLVAP in ocular angiogenesis.
Purpose: Plasmalemma vesicle associated protein (PLVAP) is an endothelial cell-specific structural component of caveolae and fenestrae that is highly upregulated in angiogenic environments such as in tumours and proliferative diabetic retinopathy. PLVAP was shown to be essential for increased vascular permeability and loss of the blood-retinal barrier. We hypothesized that PLVAP may also be essential in physiological or pathological angiogenesis.
Methods: From postnatal day 7 (P7), C57BL/6 mice were exposed to 75% oxygen for 5 days. At P12, pups were divided randomly into 3 groups, anesthetized and injected intraocularly using a 34 G Hamilton needle with 1 µl of 50 µM Plvap small interfering RNA (siRNA) or control siRNA, or remained untreated. Next, pups were returned to room air. At P17, eyes were collected and retinas isolated. Knockdown of Plvap mRNA expression was verified by PCR. The vasculature was stained with isolectin B4 in retinal wholemounts and vascular, neovascular and avascular areas where quantified. Three independent experiments were performed. n≥8 for each experimental group.

Results: Eyes injected with siRNA against Plvap showed a significantly reduced vascularized area, as compared to eyes injected with non-targeting siRNA and untreated eyes. The neovascular areas with extraretinal vascular tufts were also significantly decreased in these retinas and larger avascular areas around the optic nerve were observed. The silencing efficiency of intraocularly-injected siRNA was confirmed at the mRNA level at P15 and P17 and at the protein level at P17.
Conclusions: PLVAP is involved in physiological and pathological angiogenesis in the retina *in vivo*.

THE DEVELOPMENT OF THE BLOOD-RETINAL BARRIER AS AN INVERSE MODEL OF BLOOD-RETINAL BARRIER LOSS IN DISEASES OF THE RETINA

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Design: Formation of the retinal vasculature and the blood-retinal barrier (BRB) were followed during postnatal development in mouse pups.
Purpose: In a wide range of human ocular diseases, visual loss is caused by breakdown of the blood-retinal barrier (BRB) and subsequent macular oedema. The endothelial-specific protein plasmalemma vesicle associated protein (PLVAP) is expressed in the retinal vessels during development, but is absent in intact barrier endothelium. However, PLVAP is present under pathological conditions and we recently showed that PLVAP is actively involved in BRB loss. Here, we investigated the molecular and cellular postnatal development of the BRB in mice by assessing gene and protein expression of PLVAP and BRB-specific components. A better understanding of these mechanisms is crucial in future efforts to develop alternative treatment strategies for macular oedema.
Methods: Gene expression levels of BRB-specific genes was measured in retinas of mouse pups at ages P3, P5, P7, P9, P11, P13, P15, P17 and P25 with real-time quantitative PCR in isolated retinal vessels. In retinal whole mounts and retinal tissue sections retinal protein expression of selected BRB components and perivascular cell types like astrocytes and pericytes was determined.
Results: We found that Plvap mRNA levels in the retinal vasculature decreased during development with very low expression from P11 onward and these mRNA data were confirmed on the protein level in retinal whole mounts. On the other hand, the tight junction genes occludin and claudin-5 increased over time during development, peaking around P15 for claudin-5 and P17 for occludin. Expression levels of VEGF-receptors VEGFR2 and neuropilin-2, a co-receptor of VEGFR2, decreased quickly over time, whereas VEGFR1 and VEGFR3 increased during BRB development.
Conclusions: In the current study, we have used a mouse model to study the developmental formation of the BRB in great detail. The knowledge that we gained with this study not only helps in the understanding of the molecular and cellular mechanisms of the formation of the BRB, but may also provide important information on possible mechanisms involved in BRB breakdown.

EARLY CORNEAL CELLULAR AND NERVE FIBRE PATHOLOGY IN YOUNG PATIENTS WITH TYPE 1 DIABETES MELLITUS IDENTIFIED USING CORNEAL CONFOCAL MICROSCOPY

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Design: Cross-sectional, observational study.
Purpose: The aim of this study was to quantify epithelial, stromal and endothelial cell density and subbasal nerve morphology in young patients with type 1 diabetes mellitus with and without diabetic retinopathy.
Methods: Twentyeight young patients (mean age: 22.86 ± 9.05 years) with type 1 diabetes, with (n = 18) and without (n = 10) retinopathy and 17 age-matched healthy control subjects (mean age: 26.53 ± 2.43 years) underwent corneal confocal microscopy (CCM).
Results: We found significantly lower epithelial (P<0.0001), and endothelial (P = 0.001) cell densities and higher keratocyte cell density (P = 0.024) in patients with type 1 diabetes compared to controls. Significantly lower corneal nerve fibre density (P = 0.004), nerve branch density (P = 0.004), total nerve branch density (P = 0.04) and nerve fibre length (P = 0.001) and greater nerve fibre width (P = 0.04) were observed in patients with type 1 diabetes compared to control subjects. Significantly lower epithelial (P<0.001), and endothelial (P = 0.02) cell densities, nerve branch density (P = 0.02) and nerve fibre length (P = 0.04) and significantly lower keratocyte cell density (P = 0.02) were found in type 1 diabetes patients without retinopathy compared to control subjects.
Conclusions: Corneal confocal microscopy identifies corneal cellular and small nerve fibre pathology in young patients with type 1 diabetes without retinopathy which increases in severity in those with retinopathy. CCM appears to have considerable utility as an imaging biomarker for early subclinical pathology in young patients with type 1 diabetes mellitus.

INHIBITION OF PROTEIN TYROSINE PHOSPHATASE 1B PROTECTS AGAINST INFLAMMATION-INDUCED GLIOSIS IN THE RETINA

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Design: Insulin like growth factor-I receptor (IGF-IR) signalling mediates retinal growth and survival and its failure may contribute to aggravate diabetic retinopathy (DR). Protein tyrosine phosphatase 1B (PTP1B) negatively modulates IGF-IR signalling but its involvement in inflammation during DR remains unknown.
Purpose: Our goal was to study the role of PTP1B in retinal neuroinflammation associated to DR.
Methods: Ex vivo assays were performed with retinas from 10-week-old C57/BL6 mice, db/+ and db/db mice. Animals were killed by cervical dislocation and eyes were enucleated. The lens, anterior segment, vitreous body, retinal pigment epithelium, and sclera were removed and the retina was cultured in R16 medium (provided by Dr. P.A. Ekstrom, Lund University, Sweden) with no additional serum. Retinas from C57/BL6 mice were stimulated with cytokines (TNFα, IL6 and IL1β; 20 ng/ml each) and/or PTP1B inhibitor (3-(3,5-Dibromo-4-hydroxy-benzoyl)-2-ethyl-benzofuran-6-sulfonicacid-(4-(thiazol-2-ylsulfamyl)-phenyl)-amide). Retinas from db/db mice were treated with the PTP1B inhibitor. Western blot, quantitative RT-PCR and immunofluorescence were used to analyse retinal explants.
Results: Treatment with cytokines (TNFα, IL6 and IL1β) for 24 h increased GFAP expression in mouse retinal explants and this response was ameliorated by co-treatment with a PTP1B inhibitor (10 μM). PTP1B mRNA and protein levels were significantly increased in retinal explants from db/db mice. Treatment of retinal explants from db/db mice with the PTP1B inhibitor for 24 h reduced GFAP immunostaining.
Conclusions: PTP1B is elevated in a pro-inflammatory context in the retina. Targeting PTP1B might be useful for reducing neuroinflammation associated to DR.

EXPLORING THE PATHOBIOLOGY OF DIABETIC MACULAR OEDEMA BY POST-MORTEM IMMUNOHISTOCHEMISTRY

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Design: Clinicopathological study.
Purpose: The majority of pathological knowledge about diabetic macular oedema (DMO) has been gained from animal models and much of it still awaits confirmation in humans. Here we aimed to test whether mechanisms and pathobiological changes established in animals also apply to human DMO.
Methods: We performed a clinicopathological study on a postmortem retina sample from a 70-year-old type 1 diabetic DMO patient. To match clinical and

histological data (stains on the wholemount and serial sections) the distribution of vessels was used and compared to control tissue. Immunohistochemistry was used to interpret cells of the neurovascular unit and transmission electron microscopy of selected vessels was performed.
Results: The wholemount revealed the retinal vasculature with typical DR changes, including microaneurysms and ghost vessels. This relates to the clinical data and structural stains, which demonstrated the presence of both cystoid oedema and focal leakage from microaneurysms. Therefore, potential contributors to leakage were assessed. Surprisingly, disruption of tight junctions was not identified. However, a strong downregulation of PDGFR-beta was found, although EM only showed a partial loss of pericytes. This suggested pericyte signalling dysfunction which may contribute to vascular leakage and eventual pericyte loss. Moreover, we also found that Müller cells downregulate Aquaporin-4 in perivascular end-feet, which might contribute to impaired retinal fluid balance.
Conclusions: Our findings suggest that both vascular leakage and impaired fluid balance can be part of DMO pathobiology. In Aquaporin-4 and PDGFR-beta, we identified two novel histological biomarkers for dysfunctional processes seen in human DMO. These may precede permanent, structural changes and therefore provide a potential target for DMO treatment.

THE RELEVANCE OF SERUM APOLIPOPROTEIN B, APOLIPOPROTEIN A1 AND THEIR RATIO TO THE SEVERITY OF DIABETIC RETINOPATHY IN TYPE 1 DIABETES MELLITUS

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Design: Controlled cross-sectional clinical study.
Purpose: To determine the differences of apoA1, apoB and the apoB – to-apoA1 ratio (apoB/apoA1) between "fast progressive proliferative diabetic retinopathy" (FPPDR) and control diabetic patients groups.
Methods: A total of 60 patients with type 1 diabetes mellitus (DM) were enrolled in this study. 25 patients were determined as "fast progressive proliferative diabetic retinopathy" (FPPDR) cases, when proliferative diabetic retinopathy (PDR) occurred faster than 15 years after DM onset and 35 diabetic patients were defined as control group. The serum levels of apoA1, apoB and its ratio were compared.
Results: Age and glycated haemoglobin A1c% (HbA1c%) did not differ between FPPDR and control group (38.76 ± 10.7 vs. 34.6 ± 9.5 years, p = 0.119); (8.6 ± 1.7 vs.8.5 ± 1.5%, p = 0.931), while DM duration was statistically significant longer in FPPDR group (23.44 ± 8.1 vs. 19.34 ± 7.4 years, p = 0.049). The apoB and apoB/apoA1 ratio levels were significantly increased in FPPDR than in control group (0.982 ± 0.28 vs. 0.828 ± 0.19 g/L, p = 0.024); (0.593 ± 0.17 vs. 0.471 ± 0.13 g/L, p = 0.003). The apoA1 levels did not differ between groups (p = 0.089). After adjustment for DM duration the apoB/apoA1 ratio >0.54 was associated with FPPDR (odds ratio 5.57 [95% CI 2.05-20.1], p = 0.004).
Conclusions: The apoB/apoA1 ratio may contribute as a prognostic marker of FPPDR in patients with type 1 DM. High apoB B and apoB/apoA1 values may be related to FPPDR development.

DIABETIC RETINOPATHY AFTER INITIATING CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (INSULIN PUMP)

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Design: Audit of diabetic retinopathy before and within 12 months after starting continuous subcutaneous insulin infusion pump.
Purpose: To assess worsening of diabetic retinopathy.
Methods: Diabetic retinopathy (DR) in 38 patients (11 M, 27 F, mean age 38 yrs) recently transferred to continuous subcutaneous insulin therapy was assessed. HbA1c mmol/mol was measured within 12 months before and after fitting the pump. Patients were grouped according to changes in HbA1c mmol/mol (decreased ≥10, no change ± 9.9, and increased ≥10). DR screening by digital photography, using disc and macula-centred views, were graded according to the English national scheme. Deterioration was defined as no retinopathy to background retinopathy or worse, or the development of new maculopathy. Improvement defined as background retinopathy to no retinopathy, or resolution of maculopathy. Mean screening intervals pre-pump were 5.8 months and post-pump 6.3 months.
Results: Overall HbA1c mmol/mol improved (64.2 ± SD 13 vs 61.5 ± 11.8, p = 0.076), and by ≥10 mmol/mol in 10 (26%) patients. Retinopathy status was unchanged in 23 patients (61%) and improved in 8 patients (21%). In 7 patients (18%) whose retinopathy grade worsened, 5 progressed from no DR to background and 2 patients developed early maculopathy in one eye. Insignificant worsening of retinopathy occurred in a greater proportion of patients whose diabetic control improved or was essentially unchanged. (p = 0.38).
Conclusions: Despite awareness of the risks, significant improvement of glycaemic control occurred on initiation of pump therapy in 26% of patients with a non-significant worsening of retinopathy grade. Maculopathy developed in two patients in whom glycaemic control was unchanged. Current advice to avoid rapid improvement of glycaemic control remains appropriate, and our results suggest retinal screening within 6 months of starting an insulin pump is a clinically safe recommendation.

RISK FACTORS FOR DIABETIC RETINOPATHY IN TYPE 1 DIABETES MELLITUS PATIENTS WITH POOR GLYCEMIC CONTROL

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Design: Retrospective cohort study.
Purpose: To investigate risk factors for the development and progression of diabetic retinopathy (DR) in type 1 Diabetes Mellitus (T1DM) patients with poor glycaemic control.
Methods: We conducted a retrospective cohort study among 288 DM1 patients with poor glycaemic control (defined as HbA1c level ≥53 mmol/mol). Subjects with DR (n = 200) were compared to subjects without DR (n = 88). A variety of variables were analysed: age, gender, median HbA1c, HbA1c variability (defined as coefficient of variation of five separate measurements), duration of diabetes, age of onset of T1DM, mean arterial blood pressure (MAP), body mass index (BMI), glomerular filtration rate, albuminuria, lipid profile, visual acuity, history of cigarette smoking and family history of T1DM or T2DM. We used multivariable binary logistic regression models to analyse the data and accuracy of prediction was determined through a Receiver Operating Characteristic (ROC)-curve. The association between these variables and the progression of DR into Vision Threatening DR (VTDR) was determined using Cox regression analyses.
Results: Median HbA1c (OR 1.024 [1.002-1.046], p = 0.029), HbA1c variability (OR 1.087 [1.012-1.167], p = 0.029), MAP (OR 1.063 [1.030-1.097], p<0.001) and BMI (OR 1.009 [1.014-1.190], p = 0.021) were independently associated with the development of DR. The ROC-curve showed an area under the curve of 0.711. Median HbA1c (HR 1.033 [1.021-1.046], p<0.001) was associated with progression of DR to VTDR.
Conclusions: Median HbA1c, HbA1c variability, MAP and BMI were associated with the development of DR in T1DM patients with poor glycaemic control. Median HbA1c was associated with progression of DR. The discriminative ability of the prediction model was 71.1%. Further research is warranted to identify other risk factors.

QUALITY OF LIFE IN PATIENTS WITH DIABETIC MACULAR OEDEMA AND MODERATE TO SEVERE VISION LOSS TREATED WITH RANIBIZUMAB IN CLINICAL PRACTICE

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Design: Observational, prospective, non-comparative, case series study.
Purpose: To evaluate the effect of intravitreal Ranibizumab for diabetic macular oedema (DMO) on patients' Vision Related Quality Of Life (VR-QOL) and

to investigate associations between changes in the QL and changes in visual acuity following anti-VEGF treatment for DMO in patients with low vision.
Methods: The study is a prospective, non-comparative, observational, case series study. Eligible patients self-administered the 14-item VF questionnaire (previously validated for this purpose) prior to treatment and after 6 months of the first intravitreal injection. Visual acuity of the study eye and central macular thickness (CMT) were measured. Binocular Visual acuity and its correlation with the QL was also evaluated.
Results: Eighty five patients with DMO and low vision were eligible for the study and included. The mean age of the study population was 70.89 years. 53% were women. All were type 2 diabetic patients. Visual acuity improved in 75,3% of patients with treatment, 20% remained stable and 4,7% worsened. There was an important reduction in CMT ($p<0.05$) after treatment. Scale scores after treatment improved in 67% of the patients. Near vision, distance vision, and the capability for driving were significantly improved following anti-VEGF treatment. A moderate correlation was found with BCVA binocular vision at six months and the improvement in the VF 14 in patients with low vision ($r = 0.55$, $p<0.01$). The correlation with CMT was low ($r = -0.28$, $p<0.01$). The mean number of intravitreal injection was 3,70 ± 0,91. There were no safety concerns.
Conclusions: Intravitreal anti-VEGF treatment for DMO in patients with moderate/severe vision loss has a beneficial effect on patients' subjective perception of visual function in clinical practice. The use of vision function questionnaires in clinical practice appears to provide a more comprehensive overview of the benefits of treatment.

10 YEAR OBSERVATIONAL STUDY OF PATIENT RELATED OUTCOMES DURING EXPANSION TO FULL POPULATION COVERAGE OF A SYSTEMATIC DIABETES EYE CARE PROGRAMME - THE LIVERPOOL DIABETIC EYE STUDY

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Design: Observational cohort study.
Purpose: Data on incidence and prevalence of diabetic retinopathy is largely from studies performed in the 1980s, since when important changes in treatment and diagnosis have occurred. We aim to estimate long term changes in patient related outcomes of sight threatening retinopathy and treatment rates in a current systematic diabetic retinopathy detection and management programme.
Methods: Data from established digital photographic screening and primary and secondary care systems were combined in a purpose built observational cohort repository and investigated in the context of a population based epidemiological study. Individuals were identified in a whole population disease register maintained as part of routine care. The local ethics committee approved an opt-out approach to consent. Effects of increasing population size and changing clinical practice were examined.
Results: The screening programme increased as follows: 2006-10,322, 2012-15,789, 2014-16,585. Annual incidence of STDR remained stable over the 9 years: mean 2.28% (range 1.87-2.59). The cohort dataset contained follow-up data on treatment for 19,070 people with diabetes (100,070 person years) between 2007 and 2015. Annual proportions of people undergoing laser remained stable at 2.15% (range 1.46-2.46). Numbers of laser procedures rose from under 2 per person prior to 2012 to around 3 from 2012. Numbers of intravitreal injections increased rapidly in later years to an estimated 840 procedures in 2015. Numbers of vitrectomies stayed low at below 1%.
Conclusions: Over a 10-year period coinciding with an expansion of screening, annual incidence of STDR remained consistent. Intravitreal injection rates increased substantially in line with introduction of anti-VEGF therapy into clinical practice but there was also a moderate increase in numbers of laser procedures. Vitrectomy rates stayed low.
These data give important information on rates of STDR and treatments in population based management.

VALIDATION OF AN ALGORITHM TO PREDICT THE RISK OF SIGHT THREATENING RETINOPATHY IN A MULTI-ETHNIC PATIENT GROUP TREATED IN A SECONDARY CARE SETTING

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Design: A retrospective cohort study.
Purpose: Validation of a screening risk algorithm in secondary care setting
Methods: Data of 888 persons with T2DM, treated a single hospital in the Netherlands were used for this study. Using the Icelandic model, STR risk and an accompanying screening interval ranging from 6 to 60 months were calculated for each person based on gender, diabetes duration, HbA1c, systolic blood pressure and presence of retinopathy. In patients who developed STR during follow-up, we checked whether STR occurred before or after the model-recommended time of screening. Outcomes of omitted fundus photographs according to the model and potentially missed cases of STR were checked.
Results: The persons in this study had a Caucasian (n = 403 (45.4%)), Hindustan-Surinam (n = 178 (20.0%)), Negroid (n = 33 (3.7%)), unknown (n = 246 (27.7%), or other background (n = 18 (3.2%)). During the average follow-up duration of 40.1 months, 47 patients (5.3%) developed STR, of which 15 (31.9%) in the Hindustan-Surinam group. In 7 patients (15.2%) STR had developed before the recommended date of screening. Of these 7 patients, 4 patients (57.1%) had a Caucasian background, 1 patient (14.3%) had a Hindustan-Surinam background and 2 patients (28.6%) had an unknown ethnic background.
Conclusions: The model was less accurate in a multi-ethnic population of T2DM patients treated in secondary care. We speculate that this lower accuracy may be due to the secondary care setting and that there is room for improvement of the current model.

CAN WE ADOPT A PRAGMATIC APPROACH TO ARTERIAL EMBOLUS REFERRALS FROM THE DIABETIC EYE SCREENING PROGRAMME?

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Design: A retrospective review of 33 cases referred as retinal artery embolus from the Diabetic Eye Screening Programme to a single eye clinic in London over a one-year period in 2014-15 was carried out.
Purpose: The primary aim of the NHS diabetic eye screening programme is to reduce the risk of sight loss among people with diabetes by prompt identification and effective treatment of sight-threatening retinopathy. Additional ocular pathology which is identified on screening images is referred on to the hospital eye service according to local protocols as non-diabetic retinopathy. Currently, no nationally agreed referral standards for non-diabetic retinopathy exist.
Methods: The electronic and paper medical records were reviewed to confirm the diagnosis of arterial embolus, assess the time course from referral to being seen in the eye clinic, and evaluate subsequent management of these cases.
Results: None of these patients had any referable diabetic retinopathy pathology. The average time for patients to be seen in clinic from referral was 49 days (range 7-166 days).
The embolus was only documented as visible in one third of the patients on their visit to the eye clinic, with the remainder being documented as having a normal eye examination. Eight patients (27%) were referred directly to the transient ischaemic attack (TIA) clinic. Only twenty-one patients (70%) had specific correspondence to the general practitioner advising cardiovascular investigations.
Conclusions: There is no ophthalmic treatment for retinal arterial emboli. Instead, investigations for potential cardiovascular and cerebrovascular complications in these high-risk patients must be carried out as there have been studies showing nearly half the cases of death in patients with diabetes is from cardiovascular causes. Referring these patients to the eye clinic introduces undue delay in their risk factors being addressed and potential treatment being started. We propose a direct referral of these cases from

screening to the local transient ischaemic attack clinic nationally, which we implemented successfully in our hospital.

FACTORS DETERMINING PATIENT UPTAKE OF DIABETIC RETINOPATHY SCREENING IN OXFORDSHIRE

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Design: Audit.
Purpose: Diabetic eye disease is an important microvascular complication that may lead to visual loss without treatment. Non-attendance at diabetic eye screening is a major risk factor for sight threatening diabetic eye problems. We investigate parameters which influence uptake at the GP level.
Methods: Analyses used data from patient management software from one screening programme. Uptake of screening was examined by gender, age group and modality of screening (mobile unit versus optometrist practice). Patient uptake at each of 79 individual GP practices was determined. The total proportion of patients screened as a function of time from initial invitation up to one year was determined for patient groups stratified by gender, age group, screening modality, town and GP practice. A telephone survey of high street optometrists provided information on appointment availability.
Results: Uptake of screening was 82% during the study period, higher for men than for women ($p<0.001$) and lowest in the youngest patients. Uptake was higher for those invited to a GP location than for those invited for screening at an optometrist ($p = 0.006$). Unexplained heterogeneity in uptake occurred between GP practices. Our survey of optometrist practices indicated heterogeneity in availability and flexibility of DR screening appointments.
Conclusions: DR screening services do not achieve high uptake amongst the younger or very old patients. Uptake rates are lower for those invited to optometrists. Variation in uptake between GP practices suggests that practice level factors may have an important role in determining rates of attendance. Further work is needed to determine the extent to which this variance can be accounted for by modifiable practice level factors that may be amenable to intervention.

EVALUATION OF CLINICAL AND TREATMENT OUTCOMES OF PATIENTS REFERRED FROM THE NHS DIABETIC EYE SCREENING PROGRAMME

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Design: Retrospective analysis of electronic patient records of patients referred to the medical retina service over an 18-month period.
Purpose: To assess the clinical and treatment outcomes of patients referred from the DESP by the seniority of the assessor in Hospital eye services.
Methods: Retrospective analysis of electronic patient records of patients referred to the medical retina service over an 18-month period. Data regarding patient demographics, diabetic retinopathy and maculopathy severity, visual acuity, treatment outcome, and seniority of assessor were collected.
Results: 315 patients were included. Inter-rater agreement (kappa) between screening-grades and clinicians was moderate in maculopathy ($k = 0.415$, 95%CI = 0.324 to 0.507), and poor in retinopathy ($k = 0.304$, 95%CI = 0.191 to 0.417). 24 patients (7.6%) received treatment after initial assessment; 7 (2.2%) received pan-retinal laser, 7 (2.2%) macular laser, and 10 (3.2%) intravitreal therapy. 103 patients (32%) were seen by consultant-grade clinicians. The seniority of clinician had no impact on treatment outcomes ($p = 0.112$), but there was a significant difference in follow-up interval ($p = 0.0003$). Non-consultant grade clinicians were more likely to review patients in <3 months (71.4%) compared consultants 15.7%.
Conclusions: The interval of follow-up for patients referred from DESP was greater when senior clinicians assessed patients. Additional training of junior clinicians may help improve clinic capacity in the medical retinal service.

CHARACTERISTICS AND OUTCOME OF REFERABLE DIABETIC MACULOPATHY

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Design: A retrospective analysis of the characteristics and outcomes of the eyes of patients with referable diabetic maculopathy and the associated control of their diabetes.
Purpose: The aim was to determine whether the characteristics and outcome of referable maculopathy from an English Screening programme differed if associated with pre-proliferative diabetic retinopathy compared with background diabetic retinopathy.
Methods: Referral data from digital retinal screening were extracted from the screening programme database and outcomes were recorded over the study period of 18 months in the Hospital Eye Service and the results of their HbA1c tests.
Results: A total of 665 patients were referred to the diabetic retinopathy service from a screening programme between 1st October 2012 and 30th April 2014. 423 attended for the first time with a screening diagnosis of maculopathy (without proliferative disease).
Of the 422 patients referred with maculopathy who attended their appointment, 320 had signs of background DR and 102 (24.2%) had significant pre-proliferative disease (R2) in one or both eyes. Of the 320 with maculopathy that had signs of background DR, 21 (6.6%) required treatment (intravitreal injections or laser treatment). Of the 102 with maculopathy that had signs of preproliferative DR, 19 (18.6%) required treatment. Chi2 for the difference between the two groups in requiring treatment $X2 (1) = 11.753$, $p<0.05$. The average HbA1c in the R2 group was 76.6 mmol/mol compared with 68.9 mmol/mol who did not. A two-sample test is performed on the transformed HbA1c data. Patients referred with diabetic maculopathy who also have significant pre-proliferative disease in either eye tend to have significantly higher HbA1c values ($p<0.05$). The average OCT central retinal thickness in patients with significant pre-proliferative disease in either was 318 µm compared with 290 µm in those who do not, which was a significant difference $p<0.05$.
Conclusions: Patients with significant pre-proliferative disease in either eye are significantly more likely to require interventional treatment, they had significantly higher HbA1c values and central retinal thick thickness measurements than those without.

THE CHARACTERISTICS OF PATIENTS REFERRED BY AN ENGLISH DIABETIC EYE SCREENING PROGRAMME

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Design: A retrospective analysis of the characteristics and demographics of patients referred with diabetic retinopathy by an English Diabetic Eye Screening Programme.
Purpose: The aim was to determine the characteristics of patients with referable diabetic retinopathy referred by an English Diabetic Eye screening programme.
Methods: Referral data from digital retinal screening were extracted from the screening programme database over the study period of 18 months.
Results: A total of 665 patients were referred to the diabetic retinopathy service from a screening programme between 1st October 2012 and 30th April 2014, 62% were male and 38% female. 85% were white British, 15% other ethnic groups (predominantly Asian Pakistani). There was no significant difference in gender distribution between the White British patients and the other ethnicities. The overall mean age at presentation was 57.9 years. 51% in the white British group were 60 or under, compared with 61% in other ethnicities. The mean age in the white British group was 58.4, compared with 55.2 in other ethnicities, which was statistically significant $p<0.005$. The average overall index of multiple deprivation was 31.2. The average for the UK is

21.7. The average IMD of the white British Ethnic Group was 29.9 compared with 38.6 for the other ethnicities. This was statistically significant p<0.005. There was no statistical difference in average HbA1c or mean cholesterol between the different ethnic groups.
Conclusions: Patients referred were predominantly male white British, with gender profile being similar across ethnic groups. Patients from other ethnic groups were referred younger and lived in areas of higher deprivation.

THE CHARACTERISTICS OF PATIENTS WHO DO NOT ATTEND THEIR HOSPITAL EYE CLINIC APPOINTMENT FOLLOWING REFERRAL WITH DIABETIC RETINOPATHY

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Design: A retrospective analysis of the characteristics of patients referred with diabetic retinopathy who did not attend their hospital appointment following referral.
Purpose: The purpose was to determine the characteristics of patients who do not attend their hospital eye service appointment following the detection of referable diabetic retinopathy by an English Diabetic Eye screening programme.
Methods: Referral data from digital retinal screening were extracted from the screening programme database over the study period of 18 months.
Results: A total of 665 patients were referred to the diabetic retinopathy service from a screening programme between 1st October 2012 and 30th April 2014. Of these, 16% of patients did not to attend their clinic appointment, 18% of females failed to attend their appointment compared with 15.5% of males which was not statistically significant (p = 0.537), 15% of white British did not attend their appointment, while 22% of those from other ethnicities did. This difference was not statistically significant p = 0.156. The mean age of those who attended there was 59.3 years compared with 50.7 years who did not. This was statistically significant p<0.05. The average distance from the patient's place of residence from the receiving hospital was 5.92 miles for patients who did attend compared with 5.69 miles who did not, which was not statistically significant p = 0.331.The average index of multiple deprivation for the patient's was 30.7 for those who did attend and 33.7 for those who did not, which was almost statistically significant p = 0.06. The average HbA1c was 71 mmol/mol in patients who did attend compared with 78 mmol/mol who did not, which was statistically significant p<0.012. Higher HbA1c levels were correlated with non-clinic attendance p<0.05.
Conclusions: Patients who did not attend their eye clinic appointment had worse control of their diabetes, were younger and tended to live in areas of higher deprivation, although distance travelled to the hospital was not a factor. Attendees and non-attendees had similar ethnicity and gender.

PREDICTIVE VALUE OF RETINAL VENOUS LOOPS IN THE SCREENING FOR PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Cross-sectional study.
Purpose: The clinical importance of retinal venous loops in diabetic retinopathy (DR) is debatable, and it is no longer a referable feature of DR in the National Health Service Diabetic Eye Screening Programme in the UK. In this study we examined the association between retinal venous loops and the presence as well as the location of proliferative diabetic retinopathy (PDR).
Methods: We included 22 eyes of 16 patients identified with retinal venous loops. Patients were referred to the Department of Ophthalmology, Odense University Hospital, Denmark, from practicing ophthalmologists or from a local screening clinic for DR. None of the patients had previously been diagnosed with PDR. All patients were examined by Optos ultra-wide field fundus fluorescein angiography (UWF-FFA) (Optomap, Optos PLC., Dunfermline, Scotland, UK).
Results: This study population consisted of five women and 11 men, 11 with type 1 diabetes and five with type 2. Mean age and duration of diabetes was 48.6 years and 22.8 years and mean HbA1c was 62.3 mmol/mol. PDR was found in nine of the 22 eyes with retinal venous loops (40.9%). In six of the nine eyes with PDR, the neovascularization was found in the same quadrant as the venous loop (66.6%), and all nine had coinciding locations to the same hemisphere. In three of nine cases with PDR (33.3%) the neovascularization was located outside the 75° range of the seven standard Early Treatment Diabetic Retinopathy Study (ETDRS) fields.
Conclusions: Retinal venous loops were associated with PDR in forty per cent of cases with a large consistency between the locations of the two lesions. One in three patients with PDR would not have been diagnosed according to the ETDRS seven field standard photos.

PREVALENCE OF DIABETIC RETINOPATHY IN CHILDREN AND YOUNG PERSONS WITH TYPE 1 DIABETES WITHIN THE DIABETIC RETINOPATHY SCREENING SERVICE FOR WALES (DRSSW)

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Design: Cross-sectional retrospective analysis.
Purpose: The aim of this study was to determine the prevalence of DR in children and young persons (CYP) with type 1 diabetes (T1DM) aged 12-18 years undergoing screening by the National community based diabetic retinopathy (DR) screening programme in Wales (DRSSW).
Methods: Data on persons with T1DM aged between 12-18 years at first screening between 2003 and 2013 were analysed (n = 1,770). The DRSSW employs standardised quality assured image capture and grading protocols. Referable DR includes preproliferative DR (PPDR), proliferative DR (PDR) and exudative maculopathy, further assessed by hospital based ophthalmologists.
Results: The prevalence of any DR at first screening was 17.4% (308), consisting of 13.32% (237) minimal background DR (BDR), 3.73% (66) moderate BDR, and 0.3% (5) referable DR (RDR). Of those with RDR 1 person was found to have PPDR, 4 had maculopathy and none had PDR. The youngest with RDR was aged 14 years. 11.9% presented with BDR aged 12-13 years. Adjusting for gender and duration of diabetes those aged 14-16 years and ≥17 years were 2.8 fold and 2.9 fold respectively more likely to develop DR compared to those aged ≤13 years.
Conclusions: Almost 20% of CYP with T1DM aged between 12-18 years had evidence of DR at first screening with only 0.3% having RDR. However, the secondary aim of detecting DR is to allow for modifications to be made to diabetes management to avoid the development of RDR. The data suggests that screening for DR should not be extended beyond the age of 12 years without further evidence to the contrary.

HEALTH-RELATED QUALITY OF LIFE OF PEOPLE ATTENDING SCREENING FOR DIABETIC RETINOPATHY WITHIN A TRIAL SETTING

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Design: Health-related quality of life questionnaire study.
Purpose: To estimate generic health-related quality of life for a cross-section of attenders within the UK screening programme for sight threatening diabetic retinopathy (DR), in order to inform calculation of quality-adjusted life years for model-based economic evaluation.
Methods: A sample of 874 people were administered EQ-5D-5L and HUI3 questionnaires across 7 screening centres in Liverpool, UK as part of the Individualised Screening for Diabetic Retinopathy (ISDR) study of risk-based variable interval screening. Index scores were estimated based on UK population

values. Data were matched with screening outcome (R0M0) data collected routinely by the screening programme, in order to estimate quality of life values by disease state.
Results: A total of 840 (96%) participants fully completed the EQ-5D-5L and 738 (84%) the HUI3. The mean EQ-5D-5L index score was 0.777, compared with 0.707 for the HUI3. Individuals whose subsequent screening outcome was R1 (background retinopathy) in at least one eye had a lower health-related quality of life on average than individuals with R0 (no retinopathy) for both the EQ-5D-5L (0.762 vs 0.776) and HUI3 (0.660 vs 0.713). For the HUI3 index score, this difference was statistically significant (p = 0.03). The distribution of responses for the vision domain of the HUI3 were similar for R0 and R1 groups. Median self-assessed health from the EQ-5D visual analogue scale (0-100) was similar across groups, at 80 for the sample.
Conclusions: The HUI3 is recognised as being more sensitive to sight problems, but there may be a loss in data quality due to poorer completion. Previous model-based economic evaluations of screening for DR have treated screen-negative populations as homogeneous in terms of their health-related quality of life. This work challenges that assumption. Assuming the groups are homogeneous may lead to inaccurate cost-effectiveness estimates.

WHEN DOES RETINOPATHY HAVE AN IMPACT ON VISUAL ACUITY?

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Design: Retrospective analysis of routinely collected screening data.
Purpose: To investigate the relationship between diabetic retinopathy (DR) grade and age with visual acuity (VA).
Methods: Data were from one programme of the English NHS Diabetic Eye Screening Programme on all patients screened between 2005 and 2012. Up to eight screening episodes per patient were included. Retinopathy was graded as R0- no retinopathy, R1- background, R2- pre-proliferative and R3- proliferative retinopathy. Diabetic maculopathy was graded as M0 - no maculopathy or M1 - maculopathy present. Generalised linear models were used to assess the contribution of age and retinopathy grade to visual acuity as measured by LogMAR score.
Results: Data were analysed from 16,551 patients, 56.6% men, age at screening 67 (58, 75) years (median (25th, 75th centile). Time since diagnosis of diabetes at time of screening episode was 6 (3 to 11) years. Data was analysed by eye, thus two eyes for each of up to 8 screening episodes, maximum of 16 eyes per person, n = 142,608. VA increased with patients' age from 0 (0.00, 0.06) in those under 45 to 0.14 (0.06 to 0.24) in those aged 75 and above. VA was 0.06 (0.0, 0.14) in R0M0, 0.06 (0.00, 0.14) in R1M0, 0.08 (0.02, 0.16) in R2M0, 0.12 (0.4, 0.24) in R3M0, 0.14 (0.02, 0.34) in R1M1, 0.14 (0.04, 0.34) in R2M1 and 0.28 (0.08, 0.52) in R3M1. Analysis of variance showed that the effects of age and DR grade were highly significant (both $p<0.0001$), however using the Ryan-Einot-Gabriel-Welsch Multiple Range Test R0M0, R1M0, R2M0 were not significantly different from each other (mean VA 0.117, 0.105, 0.125 respectively), mean VA for eyes graded R3M0 was 0.219, R1M1 and R2M1 were not significantly different (mean VA 0.243 and 0.243), mean VA for eyes graded R3M1 was 0.400.
Conclusions: Patients may remain symptomless with no visual loss with background or pre-proliferative DR unless the macula is affected.

FIRST DIABETIC EYE SCREENING PROGRAM IN MOLDOVA - 2 YEARS RESULTS

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Design: Prospective study.
Purpose: This study evaluated the incidence of diabetic retinopathy (DR) and diabetic macular oedema in known diabetic patients in Moldova using digital retinal imaging.
Methods: The screening program involved 7582 type 1 and 2 diabetes patients examined in 2013-2015 in 2 diabetic eye clinics in Chisinau and Orhei. Digital fundus images were obtained using Topcon 3D OCT 2000 FA Plus and Topcon 3D OCT 1000 retinal cameras. The severity of DR was assessed using the ETDRS scale. The predominant duration of diabetes among the patients was 10-15 years. A total of 7051 (93%) patients had type 2 diabetes and 530 (7%) patients had type 1 diabetes.
Results: Evaluation of the 45° colour fundus photos showed that 3488 patients (46%) did not have DR, 2578 (34%) had non-proliferative DR and 1516 patients (20%) had proliferative DR. In proliferative DR vitreous haemorrhage was present at least in one eye in 73% of cases, iris rubeosis in 16%, NVD - 85%, NVE - 54%, preretinal haemorrhage - 18%, retinal detachment - 11% of cases. DR was associated with diabetic macular oedema in 87% of cases.
Conclusions: The level of DR is very high with high prevalence of sight threatening forms of proliferative DR and diabetic macular oedema. Thus implementation of regular screening program is highly recommended in Moldova.

THE RISK OF CLINICAL HARM DUE TO DELAYED FOLLOW-UP IN PATIENTS WITH SIGHT THREATENING DIABETIC RETINOPATHY

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Design: Retrospective clinical notes review of 250 patients with sight threatening retinopathy (STDR) and in care of hospital eye services (HES) with a delay in clinic follow-up of greater than 12 months.
Purpose: To assess the risk and level of clinical harm in patients diagnosed with STDR and delayed hospital initiated follow-up of greater than 12 months.
Methods: Patients with confirmed delays of greater than 12 months in receiving follow-up appointments were identified. Patients who were in care of ophthalmology for non-diabetic retinopathy (non-DR) disease, in care of other providers, moved out of area or recurrent non-attenders were excluded. Clinical harm was defined as (a) loss of three or more lines of LogMAR visual acuity due to diabetic retinopathy (b) progression to active R3 disease and (c) CVI registration due to diabetic retinopathy. The level of clinical harm was classified as severe, moderate or mild depending on the degree of residual disability. The entire patient pathway including the pre and post 'gap' period and subsequent management was assessed by a retinal Consultant and the patients grouped into harm and no harm categories. Those in the harm category were assessed for the level of harm.
Results: Of the total study cohort 5.6% patients were in the harm category. Half of these patients suffered severe harm due to progression to proliferative diabetic retinopathy. One patient was registered sight impaired. The main cause for delayed follow-up was shortage of clinic capacity.
Conclusions: Lack of capacity in HES is a current problem in ophthalmology. The British Ophthalmological Surveillance Unit (BOSU) are collecting data on patients coming to harm due to hospital initiated delayed follow up appointments. Our study in patients with STDR has shown that there is a 5.6% risk of sight loss in this patient group.

BUILDING A DYNAMIC FUNCTIONAL CLINICAL DATA WAREHOUSE (CDW) FOR PERSONALISED HEALTH CARE - LESSONS FROM THE INDIVIDUALISED SCREENING FOR DIABETIC RETINOPATHY (ISDR) STUDY

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Design: Technology development.
Purpose: To develop a robust CDW with functionality within the clinical environment to support personalised care pathways for diabetic retinopathy and to report methodology and key processes involved.
Methods: The ISDR CDW imported routinely collected NHS data from 5 external sources. Data comprised: primary care (EMIS Web); secondary care - photographic screening (OptoMize), screening outcome (Cis Orion and Diabolos), and hospital patient management (iPM).

Results: We developed a CDW capable of linking and validating primary and secondary care data from multiple sources, importing and exporting data extracts and generating outputs on demand. The CDW holds data from 2009 on 22,533 patients generating 9.08 × 10^10 fields. Data were cleaned and validated using MATLAB and imported/exported using SQL Server Integration Services (SSIS) over the secure NHS network. These systems enabled automated and secure data exchange between the CDW and the input and output platforms.
The challenges encountered during CDW development included working in a multidisciplinary public sector environment (clinicians, technical staff and external data providers), understanding the complexity of multiple datasets with minimal documentation and inconsistent data quality. Applying the Structured System Analysis and Design Methodology (SSADM) addressed knowledge gaps within the study team and helped recognition of data sources. Detailed schemas were introduced for each data import/export process. Consistent and extensive communication with clinicians and key external contacts were crucial. Feedback to data processors, sanity checks, outlier handling protocols and imputation addressed data quality inconsistencies.
Conclusions: Large scale routinely collected NHS data can be successfully collated and linked across different organisations and platforms to form a dynamic CDW. The commissioning of public sector IT systems should include full documentation. Our approach is generalizable and applicable for future clinical care and research in complex chronic diseases and provides a basis for the implementation of personalised health care.

QUALITY ASSURANCE IN DIABETIC RETINAL SCREENING IN SOUTH AFRICA: A BASELINE AND FOLLOW-UP STUDY

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Design: Observational study.
Purpose: To perform external quality assurance (EQA) on graders registered in the Ophthalmological Society of South Africa (OSSA) DR screening programme. The study hope to establish a proof of concept for this form of QA in this setting.
Methods: Graders registered on the South African Diabetic Register website were invited to participate in the study. The Scottish EQA software system was used to enable on-line grading of 100 retinal photographs. Expert UK National Health Service graders provided the consensus expert grading for the image set. The baseline study was completed in January 2014. A follow-up study in a subgroup of those that took part in 2014 was completed in December 2015.
Results: Two hundred and sixty-one participants completed the baseline EQA process, including nine ophthalmologists, 243 optometrists, and nine other graders. A wide range of outcomes were demonstrated, with a mean sensitivity of 0.905 (range 0.286-1.000) and mean specificity of 0.507 (0.000-0.935). The mean diagnostic odds ratio was calculated to be 12.3 (range 0.147-148.2). 32 of the original participants completed the follow-up. The results showed a reduction in sensitivity for these 32 participants from 0.949 in the first test to 0.908 in the second but a significant improvement in specificity from 0.505 to 0.666 ($p<.05$). Accordingly there was a significant improvement in the mean diagnostic odds ratio from 38.3 to 132.6 ($p<.05$).
Conclusions: This is the first quality assurance study conducted with SA healthcare professionals. The outcomes are of interest to all stakeholders dealing with the diabetes epidemic, particularly in countries working to develop their healthcare provision. The disparity in grader performance indicates room for improvement. The results suggest that most graders are performing safely, but with a high number of inappropriate referrals. The follow-up study in a small subgroup generally indicated some improvement with screeners becoming significantly more specific at the cost of a small reduction in sensitivity.

VISUAL OUTCOMES IN PATIENTS ATTENDING THE SURVEILLANCE AND SLIT LAMP CLINIC (SLB) OF THE TOWER HAMLETS DIABETIC EYE SCREENING PROGRAMME

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Design: Service Audit.
Purpose: To assess if patients attending the Surveillance and the Slitlamp (SLB) clinics are clinically safe in terms of attending the appropriate clinic, receiving follow-up appointments within the required timeframe and in terms of visual and grading outcomes.
Methods: All patients invited for Surveillance and SLB clinics between 1st April 2014 and 31st August 2014 were included, this visit was denoted as Visit 0, the reference visit. Electronic patient and imaging records were then retrieved from the screening software, OPTOMIZE, for Previous Visit (Visit -1) and Follow up Visit (Visit +1). For each visit the type of clinic attended, patient demographics, visual acuity, diabetic retinopathy (DR) grade, referral outcome and attendance at clinic was recorded. All patient who did not attend or cancelled Visit 0 were excluded from the current analysis as reference visit must have been attended for the current analysis to be meaningful.
Results: Altogether, 257 patients attended Surveillance and 146 attended SLB clinics, representing 49.5% and 44.9% of patients invited, respectively. Of all patients, 18 eyes progressed to referable maculopathy and 6 to proliferative DR by Visit 0. Non-DR referrals consisted the largest group, of the 72 patients referred the most common reasons were cataracts, vein occlusions and age related macular degeneration. Those patients who did not attend, 60% had a 2nd appointment <14 weeks in Surveillance and 78% for SLB. All patients were in the appropriate clinic at Visit0. No patient lost sight during the study period, other than one who did not agree to the cataract surgery offered (but had no DR) and another one with a new retinal vein occlusion at Visit 1.
Conclusions: The patients attending the Surveillance and the SLB clinics were safe in all studied outcomes, however, there was a high DNA rate, putting a lot of pressure on services. Optimisation of clinic scheduling and further studies on how to enable more patients to attend their screening are essential.

COMPARING HEALTH PROFESSIONALS' AND PATIENT PERSPECTIVES OF INDIVIDUALISED SCREENING INTERVALS FOR DIABETIC RETINOPATHY SCREENING

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Design: In-depth qualitative study.
Purpose: There is increasing interest in developing variable interval protocols in screening for sight threating diabetic retinopathy. However the acceptability of a change from annual intervals has not been well evaluated. We used in-depth qualitative methods to make a detailed, contextualized comparison of patient and health professionals' perspectives of introducing personalised risk-based screening intervals.
Methods: Qualitative in-depth semi-structured interviews following a grounded theory method were conducted with 16 health professionals involved in the delivery of services for People With Diabetes (PWD) and eye screening. An additional 5 professionals participated through questionnaire. Interviews explored the screening process, diabetes care, and views on individualised variable screening intervals. These data were compared with data from 34 semi-structured interviews with PWD who attend for retinopathy screening who were recruited through primary care providers. Both samples were recruited through purposive sampling strategies.
Results: Both PWD and health professionals presented a broad range of perspectives. However, some common themes emerged which can be used to guide the development of future eye screening services. These include: 1) Eye screening is not integrated into diabetes care, 2) Resource sustainability of

annual screening, 3) Safety concerns, particularly surrounding extended intervals, 4) Loss of annual reassurance, 5) Conflicting health behaviour messages, 6) Potential impact on DNA rates and for patients who DNA, and 7) Quality and management of data required to manage individualised screening.
Conclusions: Initial analysis of data suggests that, overall, health professionals and patients share similar views regarding individualised eye screening intervals. However, within each of the samples there is considerable variability in these perspectives. These interviews have highlighted a range of issues which should be considered in weighing up the introduction of risk based and extended eye screening intervals.

ADDED VALUE OF AN AUTOMATED ANALYSIS SYSTEM IN THE CONTEXT OF DIABETIC RETINOPATHY SCREENING

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Design: Analysis of 2015 data from patients attending the ongoing Diabetic Retinopathy (DR) Screening Program in the Central Region of Portugal. Patient visits consist of non-mydriatic photographs aiming at detecting vision-threatening disease in diabetics not yet treated for DR.
Purpose: To evaluate the added value of the Retmarker (Retmarker SA, Coimbra, Portugal), an automated analysis solution incorporated in the Coimbra Ophthalmology Reading Centre (CORC) daily activities for the DR screening program.
Methods: The images from this DR screening program are sent to CORC where Retmarker makes a first automated analysis and sends for human grading all patients that a) do not obey to the imaging protocol; b) are flagged by the photographer; c) are classified as positives by Retmarker; d) are picked up due to quality control measures. All the remaining patients do not require human grading and are accounted as "burden reduction", i.e. the added value from using the automated system. Detailed performance indicators are also automatically produced which allows for fast corrective actions when deviations are identified.
Results: In the period under analysis, approximately one year, data was collected from 19535 patients. Retmarker sensitivity was 91,50% (6 cases of macular oedema were not detected partly due to the presence of cataract; there were no false negatives for proliferative retinopathy). Retmarker specificity was 70,44%. Burden reduction amounted to 48,22%.
Conclusions: Our Reading Centre has been using automated analysis technology in the grading activities for DR screening. Automated analysis of the images using the Retmarker appears to be a safe solution and introduces a burden reduction of around half of the patients screened. It has the potential to safely reduce the human burden associated with the grading of diabetic patients undergoing periodic examinations.

AUTOMATED DETECTION OF DIABETIC RETINOPATHY IN THREE EUROPEAN POPULATIONS

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Design: Epidemiology retrospective cohort.
Purpose: The International Diabetes Federation (IDF) estimates that in 2035 a total of 592 million people are living with diabetes mellitus (DM). This increase in DM patients implies an increase in patients with diabetic retinopathy (DR). Currently recommendations advise DM patients to be DR screened yearly. With the increase in DM numbers this would be a struggle for services to keep up with current recommendations. There is a need for new reliable tools for keeping high standards on screening services. Automated grading software may support the screening services by lowering numbers of patients needed to be seen by human graders. The current study aimed to compare the Daphne software's ability to detect DR compared to human grading carried out on three different European populations at the Moorfields Eye Hospital Reading Centre.
Methods: Three European study groups, from Lithuania, Italy and Germany were invited to participate sharing their study images. These were analysed by human graders for presence of DR and by the Daphne software to make a comparison between the two. Primary investigation was sensitivity, specificity, positive predictive value and negative predictive value of the Daphne versus the human grader as reference standard.
Results: A total of 2805 participants were enrolled from three study sites. The number of ungradable patients by the software was 128. The sensitivity of the Daphne software was in all three studies above 93%, specificity was above 80%, positive predictive value was above 28% and the negative predictive value not below 98.8% in any of the studies. The Daphne software did not miss any vision-threatening DR.
Conclusions: The need for a reliable (semi-)automated DR screening service is growing with the increases in DM patients to meet recommended yearly DR screening. The Daphne software proved to meet the UK standards of sensitivity above 80% in all three study samples. The software still needs further testing and development before being incorporated into DR screening services.

HYPERREFLECTIVE RETINAL SPOTS IN DIABETIC EYES: THE VALIDATION APPROACH

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Design: A retrospective study.
Purpose: To evaluate and validate hyperreflective retinal spots (HRS) in diabetics (with and without macular oedema: DMO vs no DMO) on linear B scans and corresponding en-face imaging obtained using spectral domain OCT (SD OCT).
Methods: A retrospective detailed evaluation of OCT images of 38 eyes/subjects (19 diabetics without DMO and 19 with DMO) was performed. A population of normal 19 subjects/eyes served as controls. On B scan SD OCT, the following characteristics of HRS were evaluated: location (inner retina: IR or outer retina: OR); size (<30 μ or >30 μ); reflectivity (similar to retinal nerve fibre layer: RNFL or to retinal pigment epithelium: RPE); presence/absence of back-shadowing. On en-face SD OCT: absence of vessel or any other lesion; presence of vessel or microaneurysm; presence of hard exudates (confirmed on fundus colour photo) were recorded. All gradings, were performed twice by two graders in a masked fashion.
Results: HRS size <30 μ, reflectivity similar to RNFL, absence of back-shadowing and location in both IR and OR (the last one mainly in DMO patients), were associated with absence of vessels or any other lesion on en-face imaging ($p = 0.0001$, for each evaluation). Size >30 μ, reflectivity similar to RPE, presence of back-shadowing and location in the OR were all associated with the presence of hard exudates on en-face image, ($p<0.0001$, for each evaluation). Multiple logistic regression analysis showed that HRS presence in the IR ($p<0.0001$), size >30 μ ($p = 0.0075$), reflectivity similar to RNFL ($p = 0.02$) and presence of back-shadowing ($p<0.0001$) are directly associated with the presence of microaneurysms on en-face imaging. Intra-grader and inter-grader repeatability were excellent for all evaluations, for both B scans and en-face images.
Conclusions: HRS can be easily evaluated on OCT images in normals and diabetics, even with DMO. HRS with specific characteristics may have different origin, including a pure inflammatory one. This data may help to better understand the pathophysiology of HRS in diabetic eyes, to address a tailored treatment.

DIABETIC MACULAR OEDEMA WITH SUBFOVEAL NEURORETINAL DETACHMENT: SPECIFIC MORPHOLOGIC AND FUNCTIONAL ENTITY

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Design: Cross-sectional, comparative case series.
Purpose: To assess specific morphologic and functional characteristics in diabetic macular oedema (DMO) with subfoveal neuroretinal detachment (SND+) vs DMO without SND (SND-).
Methods: Seventy two patients (72 eyes) with naive centre-involving DMO were divided in: 22 eyes SND+ and 50 eyes SND-. All patients had good quality fundus colour photo, spectral-domain (SD)-OCT, best corrected visual acuity (BCVA) and microperimetry recorded on the same day. Following parameters were evaluated on SD-OCT: central retinal thickness (CRT); choroidal thickness (CT); and on linear B-scan at 0°: nasal and temporal retinal thickness at 500 µm and 1500 µm from the fovea; total number of hyperreflective spots (HRS) counted in the area of 3000 µm centred on the fovea and presence of SND. Retinal sensitivity was evaluated within 4° and 12°. All measurements were performed by 2 masked graders, independently.
Results: There was no significant difference in HbA1c and systemic hypertension in eyes with SND+ vs SND-. CRT was significantly higher in SND+ (576 + 174.4 µm), vs (499.5 + 116.7 µm) in SND-, (p = 0.03). CT was significantly higher in SND+ (238.4 + 52.2 µm) vs SND- group, (206.5 + 57.4 µm), p = 0.03. Temporal retinal thickness at 1500 µm was significantly higher in SND+ (500.9 + 130.7 µm) vs SND- (430.3 + 117.5 µm), p = 0.03. Mean number of HRS was 82.5 + 24.2 in SND+, vs 79.7 + 22.8 in SND-, p = 0.64. Mean BCVA was 55.8 + 12.4 ETDRS letters in SND+, vs 59 + 13.8 in SND- group, p = 0.34. Retinal sensitivity within 4° was 4.5 + 4.4dB in SND+, vs 10 + 4.4dB in SND- group, p = 0.002. Retinal sensitivity within 12° was 5 + 0.6dB in SND+ vs 12.8 + 3.9dB in SND- group, p = 0.015.
Conclusions: Diabetic macular oedema with SND is a specific entity of DMO with different hypothesis about its pathophysiology. Glycaemia and hypertension do not seem relevant systemic factors. DMO with SND shows greater CRT, temporal retinal thickness and choroidal thickness vs SND-. DMO with SND shows greater functional impairment in terms of central retinal sensitivity reduction vs DMO without SND. This data may help in better morphologic and functional characterization of DMO with SND.

VITREOUS SEGMENTATION OF OCULAR COHERENCE TOMOGRAPHY ANGIOGRAPHY OF THE POSTERIOR POLE AND MID-PERIPHERY IN DIABETIC RETINOPATHY

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Design: Case series analysis.
Purpose: OCTA is a non-invasive technique which can visualise pathological vascular structures. Vitreous segmentation in OCTA is necessary for the visualization of new vessels in the superficial retinal layer or in the depth of the vitreous cavity.
We describe the vitreoretinal segmentation of posterior pole and mid periphery with two standardised semi-automated segmentation systems.
Methods: Case series analysis of 86 eyes (43 consecutive patients) which underwent Ultra-High Speed Swept Source OCTA routine examination.
Results: DRI OCT-1 Atlantis SS-OCTA prototype can segment the vitreous after flattening the retina at the ILM plane and then analyse a segment of variable width as needed. That allows the segmentation of the superficial retinal layer in association with the outer vitreous cavity, or of vitreous segments of various depths. DRI OCT Triton SS-OCTA offers a semi-automated segmentation. The user has to adjust the lower segmentation band in a retinal layer as IPL/INL or ILM. The upper band can be adjusted to the desired depth of study, generating a vitreoretinal or an outer vitreous segmentation accordingly. Standardized vitreoretinal segmentation has been achieved in 85/86 eyes.
Conclusions: OCTA is an effective non-invasive imaging technique that can offer additional spatial and morphological information of vascular lesions in DR ranging from the retinal layers to the vitreous cavity. Manual segmentation may be needed to improve the quality of images from mid-extreme periphery as the software sensibility to recognise the outer retinal layers reduces.

DYNAMIC FUNCTIONALITY AND STATIC CHANGES OF RETINAL VESSELS IN EYES WITH DIABETIC MACULAR OEDEMA

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Design: Cohort Study.
Purpose: To investigate the differences between diabetic patients with macular oedema (DMO) and diabetic patients without DMO on dynamic and static retinal vessel functionality by Dynamic Vessel Analyzer (DVA, Imedos, Jena, Germany).
Methods: Diabetic patients with and without DMO presenting between April 2015 and October 2015 were enrolled in the study. All patients underwent a complete ophthalmic evaluation, including optical coherence tomography and dynamic and static retinal vessel analysis by means of DVA. Diabetic patients were compared with age and sex matched control subjects.
Results: A total of 45 eyes of 45 subjects (15 eyes for each group) were included in the analysis. In DMO patients (15 eyes), dynamic analysis showed a mean arterial and venous dilation of +1.9% ± 2 and +3.1% ± 1.6 respectively, significantly different from RD patients without DMO (Dilation artery of +2% ± 2.7 [P = 0.015], dilation vein of +3.9% ± 5 [P = 0.05]) and significantly different from those of healthy control subjects (+4% ± 1.4, p = 0.01 and +5% ± 2.8, p = 0.015 respectively). Mean central retinal artery (CRAE) of DMO patients was 164 ± 15, significantly different from RD patients without DMO (186 ± 18 MU, p = 0.002). CRAE was 195 ± 20 MU in healthy control subjects, significantly different from CRAE of DMO patients, but non-significantly different from RD patients without DMO.
Conclusions: Dynamic analysis in both patients with and without DMO showed a decrease of retinal vascular dilation during flicker stimulation compared to control subjects. A significant reduction of arterial vessels could be demonstrated in DMO patients compared to RD patients without DMO and controls.

IMPACT OF INTRAVITREAL RANIBIZUMAB ON VESSEL FUNCTIONALITY IN PATIENTS WITH DIABETIC MACULAR OEDEMA

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Design: Cohort study.
Purpose: To investigate the short-term effects of intravitreal Ranibizumab on retinal vessel functionality in patients with diabetic macular oedema (DMO) by Dynamic Vessel Analyzer (DVA, Imedos, Jena, Germany).
Methods: Patients presenting with DMO between April 2015 and October 2015 were enrolled in the study. All patients underwent a complete ophthalmic evaluation, including optical coherence tomography and dynamic and static retinal vessel analysis, using the DVA before (baseline) and 1 week after administration of intravitreal Ranibizumab.
Results: A total of 15 eyes of 15 subjects were included in the analysis. Dynamic analysis showed a significant decrease of mean arterial dilation from +1.9% ± 2 at baseline to +0.7% ± 1 at 1 week (p = 0.05) and a trend decrease of mean venous dilation from +3.1% ± 1.6 at baseline to +2.6% ± 2.3 at 1 week (p = 0.37). Static analysis showed no significant differences from baseline to 1 week in DMO patients.
Conclusions: Using DVA in patients with DMO, dynamic analysis showed a significant decrease of mean arterial dilation from baseline to 1 week.

METHODS FOR QUANTIFICATION OF RETINAL MICROVASCULAR DENSITY IN CIRRUS ANGIOPLEX OCT ANGIOGRAPHY (OCTA) IMAGES

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Design: Prospective observational study.
Purpose: To measure the microvascular density using different algorithms in normal eyes and eyes with diabetic retinopathy (DR) imaged using Cirrus AngioPlex.
Methods: This was a prospective imaging study using a prototype CIRRUS 5000 AngioPlexy system (www.clinicaltrials.gov NCT02391558). Subjects with DR were imaged with OCTA and fundus photography. ETDRS grade was determined from the fundus image, and HbA1c and duration of diabetes were recorded. Normal eyes were recruited from AIBILI staff and patient companions. Both eyes of each subject were imaged using a 3 × 3 mm OCTA scan. Superficial Retinal Layer images were exported as bitmaps and processed with two algorithms to generate density maps, one based on the area of vessels as observed (area density), and one based on a map with vessels of one pixel width (length density). Vessel density was averaged over the full 3 mm × 3 mm area. A separate region growing algorithm was used to determine the size of the foveal avascular zone (FAZ). A comparison to basic normal limits was done to determine if parameters could be used to separate normal eyes from DR.
Results: Vascular density and FAZ results from 47 eyes from 27 subjects with mean age of 65 (SD 8) with DR and from 32 healthy eyes from 17 subjects with mean age of 50 (SD 14) were imaged. The sensitivity to DR is higher for length density (60%) when compared with area density (26%) or FAZ area (17%), if the 95th percentile of the normal eyes is used as a threshold, indicating that length density is best at differentiating normal eyes from DR eyes. There is a wide range of vascular density observed within each ETDRS grade level, suggesting that capillary closure may provide relevant information regarding progression in individual DR patients. This study did not detect a correlation between vascular density or FAZ and HbA1c or duration of diabetes.
Conclusions: OCT Angiography performed with Cirrus AngioPlex and using a length density algorithm provides a metric to monitor capillary closure in the parafoveal region.

MORPHO-FUNCTIONAL EVALUATION OF DIABETIC EYES WITHOUT DIABETIC RETINOPATHY

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Design: Prospective study.
Purpose: Our aim was to study retinal function in type 2 diabetic patients without diabetic retinopathy (DR).
Methods: Twelve consecutive type 2 diabetic patients with no signs of DR and 12 healthy controls underwent a comprehensive ophthalmologic examination, including spectral-domain optical coherence tomography (SD-OCT), a retinal sensitivity map with customized grid of 45 Goldmann III stimuli covering the central 12° microperimetry (MP-1 microperimeter Nidek Technologies, Padova, Italy) and multifocal electroretinography (mfERG, RE-TI scan multifocal system, Roland Consult, Brandenburg, Germany). The first-order mfERG responses, namely the P1 and N1 amplitudes, were analysed. Results were analysed by means of Student's *t* test (SPSS, vers.20).
Results: Twenty-four eyes of type 2 diabetic patients (7 males, 5 females, mean age of 61.8 ± 5.7) and 24 eyes of 12 healthy controls (8 males, 4 females, mean age of 62.7 ± 5.1) were included for analysis. Mean central foveal thickness (CFT) was 245.4 ± 29 µm and 224.5 ± 12 µm, in diabetic eyes and healthy controls, respectively (p = 0.007). Mean retinal sensitivity on microperimetry was 17.98 ± 1.58 dB and 19 ± 0.46 dB, in diabetic eyes and healthy controls, respectively (p = 0.01). mfERG showed normal amplitude of waves N1-P1 with a normal implicit time in both groups: the mean amplitude of N1 in the three central rings was -0.54 ± 0.41, -0.29 ± 0.20, -0.25 ± 0.10 and -0.53 ± 0.1, -0.28 ± 0.06, -0.23 ± 0.06 in diabetic eyes and healthy controls, respectively (p = 0.2, p = 0.6, p = 0.5); the mean amplitude of P1 in the three central rings was 0.70 ± 0.31, 0.43 ± 0.24, 0.28 ± 0.15 and 0.75 ± 0.19, 0.39 ± 0.08, 0.26 ± 0.06 in diabetic eyes and healthy controls, respectively (p = 0.4, p = 0.5, p = 0.8).
Conclusions: Type 2 diabetic patients with no signs of DR present significantly thickened CFT and reduced sensitivity on microperimetry, but similar mfERG findings compared to healthy controls.

RETINAL VASCULAR FRACTAL DIMENSION AS A POTENTIAL MARKER OF TREATMENT OUTCOME IN PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Six months prospective, interventional clinical study.
Purpose: The retinal vascular fractal dimension (FD) is a non-invasive marker of retinal vascular geometry. The purpose of the study was to evaluate FD as a preoperative biomarker for disease activity 6 month after panretinal photocoagulation (PRP) in patients with proliferative diabetic retinopathy (PDR).
Methods: Forty eyes from 38 newly diagnosed patients with PDR were included and followed for 6 months. All patients received standard PRP treatment by a navigated laser (NAVILAS®; OD-OS GmbH, Berlin, Germany) at baseline, with additional treatment at month 3 and 6, if necessary. Widefield fundus fluorescein angiography (WF-FFA) (Optomap; Optos PLC., Dunfermline, Scotland, UK) was performed for diagnosis at baseline and for disease activity assessment at month 3 and 6. Based on this, patients were categorized with progressing (group 1, n = 18) or stabilized (group 2, n = 22) disease. FD was measured at baseline and month 6 by a trained grader using the Fractal Analyzer (Singapore Institute Vessel Assessment-Fractal image analysis software, Singapore) and a standardized grading-protocol.
Results: At baseline, mean age and duration of diabetes were 52 ± 14 years and 21 ± 11 years, respectively, and 75% were male. HbA1c was 68 ± 16 mmol/mol, and the mean blood pressure was 183/84 mmHg. Groups 1 and 2 did not differ according to the mean number of laser spots (1581 vs. 1573, p = 0.84) or the total laser energy delivered (13.67 joule vs. 13.35 joule, p = 0.20). Patients in groups 1 and 2 did not differ in FD at baseline (1.4044 vs. 1.4063, p = 0.89), month 6 (1.4017 vs. 1.4023, p = 0.87) or by the difference from baseline to month 6 (-0.0027 vs. -0.0040, p = 0.66). Likewise, in both groups, there was no intra-patient difference in FD from baseline to month 6 (group 1 p = 0.71, group 2 p = 0.62).
Conclusions: In our cohort, retinal vascular fractal dimension does not seem to be a valid marker for prediction of activity in patients with proliferative diabetic retinopathy 6 months after panretinal photocoagulation.

ASSESSMENT OF FOVEAL AVASCULAR ZONE IN DIABETIC RETINOPATHY BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY AND CORRELATION ANALYSIS WITH PERIPHERAL PERFUSION INDEX

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Design: Prospective observational study.
Purpose: To investigate the foveal avascular zone (FAZ) by Optical Coherence Tomography Angiography in patients affected by diabetic retinopathy (DR) and its correlation with peripheral perfusion index.
Methods: Patients presenting with treatment naive mild to moderate non-proliferative (NP)DR between October and December 2015 were included. All patients underwent a complete ophthalmological evaluation including ultra wide-field fluorescein angiography (UWF FA; California, Optos, PLC, Scotland) and optical coherence tomography angiography (OCT-A) (ANGIOPLEX, Cirrus HD-OCT model 5000, Carl Zeiss Meditec, Inc., Dublin, USA).
A correlation analysis (Pearson test) between peripheral perfusion index and FAZ size was performed.
Results: Five eyes of 4 consecutive patients (3 males, 1 female, mean age 69.2 ± 4.0 years) were enrolled in this study. DR was graded as mild in 3 eyes

and as moderate in 2 eyes. FAZ size was 0.269 ± 0.07 mm² and peripheral perfusion index was 26.4 ± 0.09%. No significant correlation between FAZ and peripheral perfusion index was found (r = 0.36, P = 0.5516).
Conclusions: In this small series of mild to moderate NPDR eyes, peripheral retinal perfusion as evaluated by UWF FA was not correlated to FAZ size as evaluated by OCT-A.

ULTRA WIDE-FIELD FUNDUS FLUORESCEIN ANGIOGRAPHY-GUIDED PASCAL LASER TARGETED RETINAL PHOTOCOAGULATION AS A FIRST TREATMENT OPTION FOR THE MANAGEMENT OF PROLIFERATIVE AND EXUDATIVE VASCULAR RETINAL DISORDERS

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Design: Retrospective case review.
Purpose: Panretinal photocoagulation (PRP) remains the standard therapy for proliferative diabetic retinopathy (PDR). However, there is no standardized treatment for exudative Coats' disease (CD). We aimed to assess whether Targeted Retinal Photocoagulation (TRP) can be effective and safe as a First Treatment Option for the management of retinal ischemia in PDR and stage 3 CD.
Methods: Patients with treatment-naïve PDR (n = 10) underwent Optos® Ultra Wide-Field Fluorescein Angiography (UWF-FFA) -guided single-session TRP with 20-ms-Pascal 532-nm laser (up to 2,500 laser spots, spacing: 0.75 spot-width). Follow-up for 12 weeks included assessment of average central retinal thickness (CRT) on optical coherence tomography, PDR regression on Optos® UWF-FFA, ETDRS best-corrected visual acuity (BCVA) and Mean Deviation (MD) on visual fields (VF).
Patients with stage 3 CD (n = 8) underwent Optos® and RetCam® UWF-AF-guided TRP with binocular indirect argon laser combined with transscleral drainage of subretinal fluid (TDSF) and intravitreal injection of 1.25 mg Bevacizumab. Patients were followed-up for up to 60 months: BCVA, number of retreatments and recurrence of the detachment were recorded.
Results: At 12 weeks' visit, we observed a reduction in PDR grade in 70% of patients (partial regression in 60% and complete regression in 10%), significant reduction in mean CRT (9.6 µm; SD 10.8; p = 0.021) and improvement in MD on VF (mean +0.70 dB; p = 0.07). BCVA remained stable. No ocular complications were noted. Patients with stage 3 CD presented with complete retinal reattachment and neither recurrent subretinal fluid nor evidence of disease progression at the last follow-up visit.
Conclusions: Targeted Retinal Photocoagulation seems to be safe and effective as a First Treatment Option for PDR and as an adjunct to TDSF and intravitreal anti-VEGF injection for the management of exudative RD in stage 3 CD. It is a non-ischaemic retina and peripheral vision-sparing treatment technique that can be supplemented with additional laser treatment, as necessary.

BARELY VISIBLE YELLOW PASCAL® LASER WITH OR WITHOUT ENDPOINT MANAGEMENT® IN TREATING PROLIFERATIVE DIABETIC RETINOPATHY AND DIABETIC MACULAR OEDEMA: SAFETY AND EFFICACY STUDY

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Design: Retrospective case review.
Purpose: Assess the safety and efficacy of 577 nm yellow wavelength Pascal® laser (YW-PL) with and without EndPoint Management® (EpM®) in the treatment of Proliferative Diabetic Retinopathy (PDR) and/or Diabetic Macular Oedema and establish optimum treatment parameters.
Methods: Sixty-one laser procedures performed in 49 patients (June 2013 - September 2014). Patients were categorised into 3 treatment groups: 1. Single-session Pan-retinal Photocoagulation (PRP); 2. Macular Focal or Grid; 3. Single-session PRP with Macular Grid. All procedures: 577 nm YW-PL with or without EpM®, inter-spot spacing of 0.75-1.0 spot-size and exposure times 20 ms outside the posterior pole (PP) and 10 ms within the macula. All patients underwent best-corrected visual acuity (BCVA), PP- and ultra wide-field (UWF-) Fundus Autofluorescence (FAF) and Fourier-Domain Optical Coherence Tomography (FD-OCT) with average central retinal thickness (CRT) assessment.
Results: Nineteen Females (38.77%) and 30 males (61.22%). Mean age of 60.4 years (SD: ± 12.1). In group 1 (n = 21), EpM® ranging between 50% and 70% was used in 30.7% of patients. In group 2 (n = 26), EpM® ranging between 40% and 70% was used in 69.7% of patients. In group 3 (n = 3), EpM® set at 50% was used in 33% of patients. The following mean powers were used: group 1: 367 mW ± 76.96 mW; group 2: 148.18 ± 48.61 mW; group 3: for macular grid- 146.6 mW, outside the PP- 275 mW. Complete regression of new vessels was achieved in all followed up group 1 patients (n = 17/21). CRT diminished (group 2 and 3) or remained unchanged (group 1 and 2). BCVA stabilized (group1) or improved (group 2 and 3). Laser spots were barely or non-visible on biomicroscopy. However, PP- and UWF-FAF confirmed their presence in all cases. No laser treatment-associated adverse events were reported.
Conclusions: Barely visible 577 nm YW-PL with or without EpM® seems to be safe and effective. PP and UWF-FAF allow the post-treatment identification and documentation of treated areas. Higher number of treatment spots with an inter-spot spacing of 0.75 to 1.00 spot-width does not seem to cause adverse events.

OUTCOMES OF INTRAVITREAL ANTI-VEGF THERAPY IN EYES WITH BOTH NEOVASCULAR AGE- RELATED MACULAR DEGENERATION AND DIABETIC RETINOPATHY

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Design: Observational cohort study.
Purpose: To investigate the outcomes of intravitreal anti-vascular endothelial growth factor (VEGF) therapy in eyes with both neovascular age-related macular degeneration (AMD) and diabetic retinopathy (DR).
Methods: Patients from 4 high-volume referral centers who presented with neovascular AMD and DR, and received intravitreal anti-VEGF therapy, were included. Data retrieved from medical records and multi-modal imaging were analysed.
Results: Forty-one eyes of 38 patients (21 male, 17 female; mean age 78 ± 8 years) were enrolled. Median follow up was 28 ± 19 [12-72] months with a mean of 9.2 ± 7.4 intravitreal anti-VEGF injections per eye were administrated. Best-corrected visual acuity (BCVA) was 0.5 ± 0.3 LogMAR; it improved significantly at 1 year (0.3 ± 0.3 LogMAR; p = 0.02) and returned to baseline values at last follow up visit (0.6 ± 0.4 LogMAR; p = 0.26). Mean central macular thickness (CMT) significantly decreased from 408 ± 150 µm to 328 ± 104 µm at one year (p = 0.021) and to 335 ± 127 µm at last follow up visit (p = 0.032). The baseline severity of DR was graded as mild non proliferative diabetic retinopathy (NPDR) in 21 (51%) eyes, moderate NPDR in 15 (36%), severe NPDR in 3 (7%) and inactive proliferative diabetic retinopathy in 2 (5%). At last follow-up visit, 1 eye graded as moderate NPDR improved to mild, 1 eye graded as severe NPDR improved to mild and 1 eye graded as severe NPDR was inactivated due to panretinal photocoagulation.
Conclusions: Outcomes analysis of intravitreal anti-VEGF therapy for eyes with both neovascular AMD and DR showed stabilization of BCVA and reduction of CMT, along with stable or improved DR throughout follow-up.

SHORT TERM OUTCOMES OF INTRAVITREAL AFLIBERCEPT ON INTRAOCULAR PRESSURE

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Design: Retrospective clinical study.
Purpose: The aim of this study was to investigate the effect of intravitreal injection of Aflibercept on intraocular pressure (IOP).
Methods: This prospective study included a total of 25 eyes of 25 patients treated with intravitreal injection of Aflibercept as treatment for diabetic macular oedema, active choroidal neovascularization or central retinal vein occlusion. None of the cases had medical histories of any kind of glaucoma or increased IOP. IOP was measured by Goldmann applanation tonometry before the intravitreal injection and at 1st hour, 1st day and 7th day after the procedure. IOP elevation was defined as IOP ≥21 mm Hg and/or a change from baseline of ≥5 mm Hg recorded at least on two or more measurements on the same visit.
Results: The mean age of 12 males and 13 females was 66.4 ± 2.8 years (ranging from 51-80 years). The most common reason for injection of Aflibercept was neovascular age-related macular degeneration (64%), followed by central retinal vein occlusion (24%) and diabetic macular oedema (12%). No serious ocular/systemic complication was observed after intravitreal injections. Mean preoperative IOP was 15.8 ± 5.4 mm Hg and postoperative IOP values were 19.7 ± 8.4 mm Hg (at 1st hour), 14.2 ± 6.8 mm Hg (at 1st day) and 15.2 ± 4.9 mm Hg (at 7th day). The IOP variation was not statistically significant between pre- and postoperative measurements (P>0.05).
Conclusions: Intravitreal injection of Aflibercept did not alter the IOP and seems to be safe. Routine prophylactic use of anti-glaucoma medication is not recommended. Further prospective studies with a greater sample size may lead to a better understanding of IOP changes after intravitreal Aflibercept injections.

NONRESPONDERS IN A GROUP OF UNSELECTED DIABETES PATIENTS TREATED WITH RANIBIZUMAB FOR DIABETIC MACULAR OEDEMA

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Design: Retrospective chart review.
Purpose: To evaluate nine months outcomes of visual acuity and central retinal thickness and percentage of apparent non-responders in patients with diabetic macular oedema (DMO) treated with a variable Ranibizumab dosing regimen in order to further evaluate the mechanisms behind the lack of response.
Methods: The study comprised 802 eyes in 802 patients with DMO who started treatment with Ranibizumab from 2011 to 2015 in a community based hospital. Patient data was retrieved from a regional database and supplemented with chart review. Non-responders are defined as DMO patients with a decrease in central retinal thickness (CRT) of less than 10% (compared to baseline) after at least 6 intravitreal Ranibizumab injections given within prior 9 months. Preliminary data are shown of 98 eyes in 98 patients. We anticipate having the results ready from all 802 patients prior to the congress.
Results: The mean BCVA in the 98 eyes improved from start to 9 months (baseline, 0.29; 9-months follow-up, 0.37; P = 0.0013) and the mean CRT decreased from start to 9 months (baseline, 450 µm; 9-months follow up, 319 µm; P<0.0001). The mean number of injections in the follow up period was 5.1. The mean duration of diabetes was 21 years. The frequency of type I diabetes is 13% and of type II diabetes 87%. Seventy-one percent had prior treatment with macula laser. Forty-four eyes (45%) received at least 6 injections prior to 9 months. Eight eyes (18%) who received at least 6 injections prior to 9 months met the criteria for nonresponse. The mean BCVA in the 8 eyes who met the criteria for nonresponse did not improve from start to 9 months (P = 0.6).
Conclusions: One fifth of eyes with diabetic macular oedema who received at least 6 Ranibizumab injections within prior 9 months had a decrease in central retinal thickness of less than 10% compared to baseline and no improvement in visual acuity. The mechanisms behind lack of response will be further studied.

SUBGROUP ANALYSIS OF THE FAME TRIAL ASSESSING THE IMPACT OF PRIOR THERAPIES ON VISION OUTCOMES WITH ILUVIENÒ (FLUOCINOLONE ACETONIDE [FAC]) IMPLANT

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Design: Randomised clinical trial.
Purpose: ILUVIEN (0.2 µg/day FAc implant) is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema (DMO) considered insufficiently responsive to available therapies and is supported by two pivotal studies – FAME A and B. Patients in these studies were insufficiently responsive to ≥1 laser treatments. However, in clinical practice, patients are treated with anti-VEGF (with or without IVTA) and this response would be used to assess whether a patient is insufficiently responding.
Evaluate visual and anatomic responses to the 0.2 µg/day FAc implant after 36 months following either prior laser treatment or prior laser treatment and IVTA.
Methods: Patients from FAME A and B were pooled. Changes in best-corrected visual acuity were assessed from baseline levels. A post-hoc analysis was carried comparing patients treated with sham and patients treated with 0.2 ug/day FAc, We analysed both the full study population and the chronic DMO sub-group.
Results: In the full DMO group, the change in VA was: prior laser, 6.9 vs 2.5 letters (0.2 µg/day FAc implant vs sham, respectively); and, prior laser and IVTA, 6.2 vs 2.9 letters. In the chronic DMO group, the change in VA was: prior laser, 9.4 vs 7.2 letters and, prior laser and IVTA, 7.8 vs 0.9 letters.
Conclusions: The greatest visual benefit was seen in chronic DMO patients treated with 0.2 ug/day FAc who had previously been treated with laser and IVTA. Patients previously treated with laser alone showed little benefit.

12 MONTHS OUTCOMES OF PATIENTS WITH DIABETIC MACULA OEDEMA TREATED WITH RANIBIZUMAB IN A REAL WORLD DGH SETTING PRESENTED USING A NOVEL VISUAL METHOD OF CLINICAL OUTCOMES PRESENTATION

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Design: Retrospective longitudinal cohort study over 12 months.
Purpose: To report the clinical outcomes of chronic DMO patients of all retinal thickness treated in a real world NHS setting.
Methods: Clinical audit of 90 eyes with DMO undergoing intravitreal Ranibizumab using 3 loading followed by PRN dosing. All had centre involving chronic DMO despite prior macular grid laser. We designed a novel 2 × 2 quality box to visually present change in retinal structure and function.
Results: 12 month outcomes are available for 20 eyes, mean age 65 years. Baseline VA; 56 letters (range 17-76). Baseline CRT; 442 µ (range 278-770). At 12 months mean VA was 65 letters (range 22-88) and mean CRT was 336 µ (range 245-511 µ). 9 eyes with baseline CRT of <400 µ had mean reduction of CRT of 48 µ. 11 eyes with CRT ≥400 µ had mean reduction of 154 µ. An average of 8 injections per eye (range 5-12) in the first 12 months was required.
Conclusions: DMO can now usually be successfully treated. The outcome (mean 9 letter gain) achieved at year 1 in our patients was compatible with key clinical trials despite the presence of longstanding DMO and prior laser. DMO patients with retinal thickness excluded by NICE guidance also benefited. The quality box method of presentation of outcomes is of merit for retinal services evaluation.

OCT RETINAL THICKNESS RESPONSE AFTER FIRST INTRAVITREAL INJECTION IS A PREDICTOR OF VISUAL ACUITY RESPONSE TO ANTI-VEGF TREATMENT OF DMO

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Design: Prospective, observational study.
Purpose: Identify early predictors of anti-VEGF treatment response in patients with diabetic macular oedema (DMO).

Methods: In a prospective observational study (NCT01947881, CHARTRES Study) seventy-one diabetes type II patients with DMO and indication for intravitreal injection (IVT) of Lucentis® were treated for at least 3 months with monthly IVT of Lucentis® and followed-up for an additional 3 months. All patients underwent best corrected visual acuity (BCVA) measurements according to ETDRS protocol and SD-OCT, and all images were graded by an independent Reading Centre obtaining a complete morphological characterization of DMO before, during, and after treatment. An exploratory predictor analysis for the BCVA change after 3 IVTs (3 months) was carried out with multivariate linear regression for selection of predictors and ROC curve analysis for determination of predictive performance and threshold selection.
Results: Sixty-seven patients completed the study and were included in this analysis. Central retinal thickness (CRT) decrease after first IVT (1 month) was found to be an independent predictor of BCVA treatment response at 6 months on a multivariate regression with baseline BCVA and baseline CRT as covariates ($p = 0.014$). On a ROC analysis, the 8.7% CRT decrease was identified as the threshold that distinguished more accurately patients that recovered more than 5 BCVA letters at 3 months (sensitivity 71.7%, specificity 47.6%, ROC AUC 0.581). Patients with a decrease of 8.7% or more in CRT after first ITV injection (65.7%) experienced a significantly greater improvement in BCVA letters after 3 months (8.5 ± 7.2 letters) when comparing with patients with a CRT decrease <8.7% (4.0 ± 9.7 letters), $p = 0.038$. BCVA improvement at 1 month was not significantly different between groups ($p = 0.102$), but there was already a significant overall increase in BCVA at 1 month (4.0 ± 6.4 letters, $p<0.001$).
Conclusions: CRT decrease ≥8.7% at one month, after the first ITV anti-VEGF injection for DMO predicts a better BCVA recovery at 6 months independently of baseline BCVA or CRT. A more practical threshold of 10% can be used with only a slight reduction in sensitivity.

REAL WORLD OUTCOMES OF VEGF INHIBITOR INJECTION CLINICS FOR CENTRE INVOLVING DIABETIC MACULAR OEDEMA

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Design: A retrospective analysis of the injections and the visual outcomes in eyes given the Ranibizumab treatment for centre involving diabetic macular oedema in a district general hospital.
Purpose: To determine how successful the introduction of vascular endothelial growth factor (VEGF) inhibitor injection clinics for diabetic macular oedema had been in improving visual outcomes for patients with centre involving diabetic macular oedema greater than 400 microns.
Methods: Our district hospital catchment covers 606,000 people; 32,000 over the age of 12 are known to have diabetes. VEGF inhibitor injection clinics for patients with Centre Involving Diabetic Macular Oedema were introduced in 2013 according to NICE guidelines. A protocol was developed, to be followed by ophthalmologists assisted by trained Allied Health Professionals.
Results: During 2013 158 eyes of 125 people were treated with 686 injections. By 2015 the workload increased to 2326 injections in 356 eyes of 283 people. They were aged mean 66 years at first injection, oldest was 97 and 66% were men. Of these, 32% had previously had macular laser, 32% panretinal photocoagulation and 36% neither. At the first injection the letter score in the first treated eye was mean 55, s.d. 15. Of 222 first treated eyes followed for 12 months, the number of injections in the first year was mean 7.4, s.d. 2.1. Of 122 first treated eyes followed for 2 years, the number of injections in the second year mean 4.5, s.d. 2.7. At month 12 the proportion of first treated eyes achieving >5 letter gain was 54%, >10 letter gain was 37% and >15 letter gain was 15%. At month 24 the proportion of first treated eyes achieving >5 letter gain was 44%, >10 letter gain was 28% and >15 letter gain was 17%.
Conclusions: This audit demonstrates that 54% and 37% of first treated eyes with initial centre thickening greater than 400 microns improved by at least 5 and 10 letters respectively. This is maintained with mean 7 injections in the first year and 4 in the second.

INDOCYANINE GREEN-GUIDED TARGETED PHOTOCOAGULATION OF MACROANEURYSMS IN MACULAR OEDEMA: A PILOT STUDY

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Design: Retrospective, interventional, two-centre study.
Purpose: In longstanding diabetic macular oedema (DMO) or retinal vein occlusion (RVO), large vascular abnormalities may cause macular oedema. Indocyanine green angiography (ICGA) has been shown to optimize their detection (Bouhris et al 2010). Here we report the anatomical and functional outcome of the elective photocoagulation of large microvascular abnormalities, termed here macroaneurysms.
Methods: In patients with chronic macular oedema with severe hard exudates due to diabetic retinopathy or to RVO, the presence of macroaneurysms (defined by a diameter larger than 150 µm) was assessed by ICGA and optical coherence tomography (OCT). Macroaneurysms were selectively photocoagulated. Immediate photothrombosis was assessed by post-operative OCT.
Results: Four eyes from 3 patients with DMO and 5 eyes from 5 patients with RVO were included. The median duration of visual loss was 4 years. Median initial visual acuity (VA) was 20/200. The median number of macroaneurysms per eye was 2 (range, 1-8) and their mean size was 484 µm (range, 154-1800). Six months after photocoagulation, there was a significant reduction of macular thickness (mean ± SD, 528 µm ± 200 versus 271 µm ± 152, $p<0.05$) and improvement of VA (mean LogMAR, 0.82 versus 0.58, $p<0.05$).
Conclusions: During macular oedema with severe hard exudates due to DMO or RVO, systematic detection of macroaneurysms by ICGA followed by their OCT-controlled photocoagulation may be of interest. These results may contribute to re-evaluate the role of photocoagulation in the management of longstanding macular oedema.

CLINICAL MANAGEMENT OF DIABETIC MACULAR OEDEMA BY RETINA SPECIALISTS IN CLINICAL PRACTICE IN SPAIN: OBSERVAR STUDY

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Design: Observational retrospective multicentre study.
Purpose: To describe the clinical management of diabetic macular oedema (DMO) by Spanish retinologists in clinical practice.
Methods: Forty-two retinologists participated in the study and collected clinical and demographic characteristics from clinical histories of adult DMO patients and completed the questionnaires about diagnosis, treatments and follow-up patterns.
Results: A total of 256 DMO patients, 351 eyes [161 (46%) unilateral; 190 (54%) bilateral] with a mean (SD) age of 65.2 (10.4) years and mostly men (60.9%) participated in the study. Retinologists considered the progressive loss of visual acuity (VA) as the main symptom suggesting DMO (40.9%). The most frequent diagnostic tests were ETDRS, biomicroscopy, OCT (95.5% each) and fluorescein angiography (68.2%). DMO first-line treatment was mainly based on anti-VEGF drugs (59.1%, and 100% Ranibizumab), and 95.5% of retinologists opted for laser photocoagulation as concomitant treatment. More than half of retinologists (52.3%) used 3 initial anti-VEGF injections, and 47.7% scheduled bi-monthly follow-up visits during the first year post-diagnosis, extended to quarterly visits afterwards (38.6%). The ETDRS showed stabilization or even improvement of VA after treatment, from 60.4 (17.7) to 65.7 (19.6) letters for unilateral and from 59.7 (18.8] to 64.8 (15.2) letters for bilateral DMO patients. A reduction in mean foveal thickness was also observed: 409.9 (119.8) µm to 318.7 (76.8) µm for unilateral and 416.2 (126.5) µm to 346.5 (105.0) µm for bilateral DMO patients.

Conclusions: The results of this study showed homogeneous criteria regarding diagnosis, treatment and follow-up of DMO by the Spanish retinologists in clinical practice. The treatments used achieved clinically relevant improvements in visual acuity and reduction in foveal thickness. The most frequent treatments for VA impairment due to DMO used by the majority of retinologists were anti-VEGF injections.

INTRAVITREAL RANIBIZUMAB FOR THE TREATMENT OF DIABETIC MACULAR OEDEMA: REAL-LIFE 12 MONTH RESULTS

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Design: Retrospective review of patients' data.
Purpose: The aim of the study was to evaluate the visual and anatomic results of 12 months use of intravitreal Ranibizumab for the treatment of centre – involving Diabetic Macular Oedema.
Methods: This was a retrospective review of patients' data. The main criterion for initiation of Ranibizumab treatment, as set by NICE guidelines was centre-involving Diabetic Macular Oedema with Central Subfield Thickness >400 µm. All patients were given a loading dose of 4 monthly injections, followed by monthly follow-up and as needed retreatment.
Results: Eighty-four eyes of 62 patients were included. Mean age of the study cohort at baseline was 71 years (SD = 11). 43 of the patients were male and 19 female. Only 3 eyes were treatment-naive, the vast majority having previous Bevacizumab, laser, triamcinolone acetate or combined therapies. Mean visual acuity at baseline was 62.3 ETDRS letters. Mean Central Subfield thickness was 495 µm. At month 4 mean VA was 65.3 ETDRS letters, mean subfield thickness 374. At 12 months mean VA was 67.5 ETDRS letters (5.2 letters gain) and mean CSFT 351.1 µm. Twenty-two eyes were dry (minimal or no fluid) at month 4 (26.1%), 6 more eyes at month 12 (an additional 9.6%). Seven patients had skipped loading injections due to missed visits. In one patient treatment was discontinued due to decrease in visual acuity and deterioration of macular oedema. Two patients presented with reactivation of pre-existing proliferative diabetic retinopathy, of which one developed an intravitreal haemorrhage.
Conclusions: Our outcomes are not comparable with the multicentre trials, however in a real-life clinical setting the patients' demographics and comorbidities may vary significantly. Also, this cohort included a large proportion of long-standing and refractory-to-previous-treatment cases. Even with these limitations, our data still shows very promising visual and anatomic results of the use of intravitreal Ranibizumab in patients with centre–involving Diabetic Macular Oedema.

RESULTS OF INTRAVITREAL DEXAMETHASONE IMPLANT (OZURDEX®) IN CASES WITH RESISTANT DIABETIC MACULAR OEDEMA AND HARD EXUDATES IN THE MACULAR CENTER

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Design: Retrospective.
Purpose: To evaluate the results of intravitreal dexamethasone implant (Ozurdex®) in the treatment of resistant diabetic macular oedema with predominant hard exudates in the macular centre.
Methods: In this study 12 eyes of 10 patients that were resistant to intravitreal anti-vascular endothelial factor (anti-VEGF) treatment and followed-up at İnönü University Turgut Özal Medical Centre's Retina Department were enrolled. All eyes with resistant diabetic macular oedema and predominant hard exudates in the macula received a single dose of intravitreal dexamethasone implant. The pre- and post-treatment best-corrected visual acuity (BCVA), central macular thickness (CMT), and the presence of hard exudates were evaluated.
Results: We included 6 females and 4 males. The mean age was 59,7 ± 6,5 (50-72) years. The mean number of anti-VEGF injections was 3,75 ± 0,8 (3-5). The mean follow-up duration following the intravitreal dexamethasone implant was 3,08 ± 1,7 (1-6) months. The mean BCVA with the LogMAR chart was 1,12 ± 0,23 (0,7-1,3) before the treatment and 0,9 ± 0,39 (0,5-1,4) after the treatment. The pre-treatment and post-treatment CMT values were 447,9 ± 94,6 (361-671) µm and 330,6 ± 110,3 (188-532) µm respectively. A decrease in the amount of hard exudates was observed on optical coherence tomography sections in all cases.
Conclusions: Intravitreal dexamethasone implant increased the visual acuity while decreasing macular oedema. A standardized method to quantify hard exudates is currently not available. Larger and longer studies are required for more accurate evaluation of the effect of intravitreal dexamethasone implant on macular hard exudates.

ASSESSMENT OF THE REAL-LIFE USAGE OF INTRAVITREAL DEXAMETHASONE IMPLANT IN THE TREATMENT OF CHRONIC DIABETIC MACULAR OEDEMA IN FRANCE

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Design: Observational cohort study.
Purpose: Intravitreal steroids are effective in the treatment of chronic diabetic macular oedema (DMO). There are newly launched short acting intravitreal drug delivery systems, such as the dexamethasone implant (Ozurdex®). Due to the limited data on the dosing regimen for dexamethasone, this study was developed to evaluate in real-life clinical usage, the average number of dexamethasone treatments per year and the time interval between injections.
Methods: Results are presented from 3 studies based on a questionnaire that was sent out by e-mail to physicians; the monitoring of drugs dispensing over time through pharmacies; and French Social Security database for 2011 and 2012.
Results: Study 1 involved 111 ophthalmologists and assessed DMO prescriptions. The number of injections per year and the time interval between 2 successive injections was measured as 2.3 and 4.8 months respectively. In study 2, the survey conducted was performed in retail pharmacies with 570 prescriptions; the mean follow-up period was 13.7 months, and 2.3 injections were administered per year with a time interval of 5.2 months. In study 3 (Reimbursements by social security), 114 patients were initially identified and among them 15 Patients were dispensed with Ozurdex. During 25 months of follow-up, 2.5 Ozurdex on average were injected per year with a 4.7 months' time interval.
Conclusions: These 3 studies were all consistent with an average number of dexamethasone implants injections of 2.4 per year and a time interval between treatments of 4.9 months, thus supporting the need for a study to evaluate the optimal treatment frequency.

EFFICACY RESULTS OF 0.2 MG/DAY FLUOCINOLONE ACETONIDE IMPLANT (FAC) IN DMO VITRECTOMISED PATIENTS

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Design: Multicentric retrospective data collection.
Purpose: In the FAME trials, patients who had a prior history of vitrectomy were excluded from enrollment in the trials. However, during the trial, 24 of the FAc-treated subjects underwent vitrectomy. Based on an assessment of the retinal thickness prior to vitrectomy versus post-vitrectomy in these subjects, there was no evidence of a loss of efficacy. When the retinal thickness of those subjects is compared to the non-vitrectomised subjects randomized to FAc, no difference in the trend related to reduction in retinal thickness was seen that would suggest a loss of effect. Very few data is available on the efficacy of FAc in prior vitrectomised patients. Here, we present a collection of 20 vitrectomised eyes treated by FAc.
Methods: Four centres of three European countries have collected their data on patients treated by FAc with prior vitrectomy from real life evaluation or phase IV study. Efficacy and safety data are assessed and the indication of vitrectomy is indicated when available.
Results: Twenty vitrectomised eyes from 18 patients were treated by one injection of FAc. All patients were pseudophakic. Prior therapies were anti-VEGF alone for 5 patients, steroids alone for 3 patients, anti-VEGF followed by steroids

for 11 patients and no prior intravitreal treatment for 1 patient. The majority of patients had vitrectomy for previous proliferative retinopathy with non-clearing haemorrhage or tractional membranes. The mean duration of follow-up was 201 days (range, 45 to 367 days). Mean change in BCVA was +9 ETDRS letters (range, -6 to +27 letters). Central foveal thickness (CFT) decreased by 224 µm (range, -595 to 126 µm). In 10 eyes from 8 patients, mean IOP increased from 16.2 to 19.6 mmHg (+3.4 mmHg) after 189 days (range, 49 to 367 days).
Conclusions: Our collection of data suggest a possible use of the fluocinolone acetonide implant in vitrectomised patients with clinically relevant efficacy and acceptable safety profile. Other studies have to be conducted to confirm these data with longer follow-up.

EFFECT OF DEXAMETHASONE INTRAVITREAL IMPLANT, OZURDEX®, ON DIABETIC MACULAR OEDEMA DURING PREGNANCY

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Design: Case report.
Purpose: To study the time course effect of Ozurdex® on macular thickness and visual acuity in a pregnant diabetic with sight-threatening macular oedema.
Methods: A 36-year-old pregnant woman with diabetes mellitus type 1 (DM-1) experienced sight-threatening progression of diabetic retinopathy due to the development of clinically significant macular oedema (CSMO) during the 12th week of pregnancy in her right eye. No history of hypertension, preeclampsia or diabetic nephropathy was recorded. However a higher frequency of hypoglycaemia during the first weeks of pregnancy was measured.
The patient was treated with a single dose (700 microgram) of dexamethasone intravitreal implant. Visual acuity and central subfield thickness (Topcon Corporation, Tokyo, Japan) were evaluated before and after the treatment – almost on a daily basis for two weeks following the steroid implant insertion.
Results: Before the steroid implant insertion, central subfield thickness was 393 µm, and the visual acuity on Snellen's chart was 0.4. Three days after the treatment, central subfield thickness regressed to 273 µm and the macular oedema continued to diminish during the following days. One week after the dexamethasone treatment, visual acuity improved to the pre-pregnancy level (1.0 on Snellen's chart), and a full regression of macular oedema was achieved.
Conclusions: The effect of intravitreal dexamethasone (Ozurdex®) on diabetic macular oedema and visual acuity occurs rapidly within few days after implantation, reaching maximum effect during the first week.