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ABSTRACTS

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PATIENT PERSPECTIVES OF ACCEPTABILITY OF RISK-BASED INDIVIDUALIZED DIABETIC RETINOPATHY

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Design: In-depth ethnographic qualitative study.
Purpose: There is increasing worldwide interest in developing variable interval protocols in screening for sight threatening diabetic retinopathy (DR). However the acceptability and therefore safety of a change from annual intervals has not been well evaluated, particularly from a patient perspective. We used in-depth qualitative methods to develop a detailed, contextualized understanding of patient perspectives of introducing individualized risk-based screening intervals.
Methods: People with diabetes (PWD) who attend for DR screening were recruited through primary care providers, using purposive sampling. Qualitative in-depth semi-structured interviews following a grounded theory method explored patient experiences of screening, diabetes care, and views on individualized variable screening intervals.
Results: In 34 interviews, PWD expressed a range of views. Many agreed in principle to intervals being individualized and risk-based. However, some considered a 24 month interval to be too long. Some felt that extended durations would introduce an unacceptable level of risk of developing DR. Some felt annual eye screening offers an important role in reassuring patients of good eye health. Some found the screening appointments unpleasant and inconvenient but would rather attend more frequently so that DR could be detected.
In contrast, many recognized the need for NHS resources to be concentrated where they are most needed but suggested that if extended intervals are introduced, safeguards must be put in place to enable patients to re-enter the screening system should risk factors worsen.
Some highlighted that being assigned to particular risk groups may impact upon their likelihood to attend screening appointments and perceptions of the importance of general diabetes management.
Poor levels of understanding of DR, eye screening and risk appeared to influence patient perspectives.
Conclusions: Findings suggest that for individualized screening programs to be successful there is a need for improved patient education surrounding diabetes related eye health and specifically around the risks and benefits associated with extended intervals.
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DIABETIC RETINOPATHY IN EUROPE INITIAL RESULTS OF THE E3 CONSORTIUM DIABETES GROUP

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Design: Pan-European cross-sectional study as part of the European Eye Epidemiology (E3) Consortium Diabetes Study Group program.
Purpose: The purpose of this study is to estimate the prevalence and review risk factors for diabetic retinopathy (DR) in Europe, and to investigate the presence or absence of regional variations between European countries.
Methods: E3 consists of 24 study groups from all regions of Europe. E3 members were invited to participate in the DR study by sharing data and images from patients involved in their studies. Cohort studies as well as case-control and case-only studies are all included. For cohorts, where patients are not graded for DR the images are being graded either by the study group or by the Reading Centre at Moorfields Eye Hospital. Grading is a combination of human and semi-automated grading utilizing the University of Surrey software.
Results: Only 2 studies have no relevant data at present, the rest of the E3 are willing to participate. Of those with relevant data, results have been received from 10 studies involving 102,997 patients. The rest of the studies are in image analysis or data analysis phase within the cohort. Analysis of the 6 case-only studies shows a total population of 68,483 patients of which 50.75% was men. In the 6 case-only studies 4.95% had Type 1 diabetes, 22.61% had Type 2 and 72.43% was either unknown or not collected in the studies population. Duration of diabetes between 1-20 years accounts for 75% of the sample size. The first analysis shows that 73% of subjects have no DR, 22.9% have non-proliferative DR and 1.5% have proliferative DR, 2.6% was either not gradable or image could not be taken.
Conclusions: This is the first pan-European DR study of such scale. The first results show agreement with prior knowledge of most patients having Type 2 diabetes mellitus and having no DR. The results will be useful for establishing and planning further development of diabetic eye services in the relevant regions.

INCIDENCE AND PROGRESSION OF RETINOPATHY AND VISUAL IMPAIRMENT IN PEOPLE WITH DIABETES IN SUB-SAHARAN AFRICA; RELATIONSHIP WITH POPULATION SPECIFIC VARIABLES

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Design: Prospective cohort study.
Purpose: Sub-Saharan Africa faces an epidemic of diabetes. We performed the first prospective cohort study of diabetic retinopathy (DR) in this region. We report progression of DR and associations with demographic, clinical and biochemical variables in people with diabetes in Southern Malawi.
Methods: Subjects were systematically sampled from two hospital-based diabetes clinics providing primary diabetes care to a population affected by high levels of infectious disease. Clinical examination and biochemical testing was performed to assess visual acuity, glycemic control, systolic BP, HIV status, urine albumin-creatinine ratio, hemoglobin and serum lipid levels. DR was graded using modified Wisconsin grading at an accredited reading center. Sight-threatening diabetic retinopathy (STDR) was defined as moderate pre-proliferative DR or worse, circinate maculopathy or exudates within one disc diameter of the foveal center.
Results: Of 357 subjects recruited 295 were assessed at 24 months, 28 were confirmed dead (90.5% follow-up). At baseline 13.4% subjects were HIV-positive and 15.1% anemic. At follow-up (median 2.0 yrs) rates of progression were: 2 step (or greater) 58/293 (19.8%); STDR 23/225 (10.2%). Cumulative incidence at 24 months of STDR for subjects with Level 10 (no retinopathy),

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Level 20 (background) and Level 30 DR at baseline were 2.7% (95% CI 0.1-5.3), 27.3% (16.4-38.2) and 25.0% (0-67.4), respectively. In multivariate logistic analysis 2 step progression of DR was associated with HbA1c (OR 1.27, 95% CI 1.12-1.45), baseline grade of DR (1.39, 1.02-1.91) and HIV infection (OR 0.16, 0.03-0.78). 85 persons required laser photocoagulation. Rates of progression to visual loss were: ≥15 letters lost 17 subjects (5.8%), moderate visual impairment (<60 letters) 3 (1.0%), severe visual impairment (<50 letters) 5 (1.7%).
Conclusions: Progression to STDR from no DR and background DR occurred approximately 3 and 2.5 times more frequently than reported in recent European studies, respectively. The negative association of HIV infection with DR progression is a new finding. Our results highlight the urgent need for provision of services for DR detection and management to avoid a large burden of vision loss.

REGISTRY STUDY OF DIABETIC MACULAR EDEMA IN TURKEY: TURK-DEM STUDY

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Design: National, multicenter, observational study.
Purpose: To determine characteristics of newly diagnosed patients with diabetic macular edema (DME) and thereby to identify the disease characteristics and local treatment approaches.
Methods: This study was conducted at 38 centres representing all geographic areas in Turkey. Patients aged ≥18 years and newly diagnosed with DME but had not received any treatment specific for DME were enrolled. Patients' data regarding demographic characteristics, vital signs, body mass index, general and ocular medical history, comorbid diseases, history for and clinical findings related to diabetes, routine biochemical test results, DME type and central macular thickness (CMT), as well as diagnostic methods and treatment plans of the centres were recorded on electronic case report forms.
Results: This study included 1890 eyes of 945 patients (mean age, 61.3 ± 9.9 and male, 55.2%), of whom 96.4% had type II diabetes. Time after diagnosis was >5 years in 88% of the patients. With regard to diabetes treatment, 48.3% were on insulin and 43.9% on oral antidiabetics; 20.7% received no treatment. At least one comorbid disease was present in 80%. The reason for admission to ophthalmology departments was visual problems in 52.2%. DME diagnosis was confirmed by fundus fluorescein angiography in 73.0% and optical coherence tomography in 98.8% of the patients. Diffuse, focal, and mixed DME was present in 39.2%, 36.9%, and 9.7% of the eyes, respectively. The rate of CMT >300 µm was 66.6%. Primary treatment plans were laser photocoagulation and/or anti-vascular endothelial growth factor therapy. The rate of receiving antidiabetic treatment was significantly lower in the right eyes with diffuse DME compared to other types; however, it did not differ regarding DME types in left eyes. The rate of receiving antidiabetics was also significantly lower in patients with CMT >300 µm. CMT was greatest in patients without any diabetes treatment.
Conclusions: TURK-DEM is the most widespread and detailed local study in Turkey in which characteristics and treatment plans of newly diagnosed DME patients are registered. Further clinical trials are needed to detect predictive values of various characteristics of patients with DME on treatment success.

INHIBITION OF PROTEIN TYROSINE PHOSPHATASE 1B IMPROVES IGF-I RECEPTOR SIGNALING AND PROTECTS AGAINST INFLAMMATION-INDUCED GLIOSIS IN THE RETINA

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Design: Insulin like growth factor-I receptor (IGF-IR)-mediated signaling mediates growth and survival in the retina, its failure may contribute to aggravated diabetic retinopathy (DR). Protein tyrosine phosphatase 1B (PTP1B) has emerged as a negative modulator of IGF-IR-mediated signaling. However, the involvement of PTP1B the modulation of IGF-IR signaling cascade in the context of the pro-inflammatory milieu and gliosis during DR remains unknown.
Purpose: We aimed to investigate the role of PTP1B in the cross-talk between stress pathways activated by pro-inflammatory cytokines and IGF-IR-mediated survival signaling in the retina, as well as in inflammation-mediated retinal gliosis.
Methods: Retinal cells (RCG-5 and 661W) and retinal explants were treated with a mixture of pro-inflammatory cytokines containing TNFα, IL6, and IL1β (CK). The early activation of JNK and p38 MAPK was analyzed. IGF-IR-mediated Akt signaling was evaluated in both retinal cells and retinal explants in the absence or presence of CK. PTP1B mRNA was analyzed by real-time PCR. PTP1B expression was reduced by siRNA in retinal cells and retinal explants. GPAP was analyzed by western blot and immunofluorescence in the presence of CK in combination with a PTP1B inhibitor.
Results: In retinal cells, IGF-I induced a rapid phosphorylation of the IGF-IR and Akt. Stimulation of retinal cells with CK triggered an early activation of stress kinases (JNK and p38 MAPK), resulting in insulin receptor substrate 1 (IRS1) phosphorylation at serine 307 that precedes its degradation. Similar responses were found in *ex vivo* mouse retinal explants. Pre-treatment of both retinal cells and retinal explants with CK for 24 h induced IRS1 degradation and reduced IGF-IR and Akt phosphorylation. However, reduction of PTP1B by siRNA ameliorated the negative effects of CK on IGF-IR signaling in both retinal cells and explants. The pro-inflammatory milieu induced by CK increased GFAP expression in retinal explants and this response was ameliorated by treatment with a specific PTP1B inhibitor.
Conclusions: Our results suggest that targeting PTP1B might be useful for modulating the beneficial effects of IGF-I in the inflammatory states during DR.

DOWN-REGULATION OF MIR-126 IN HUMAN RETINAL PERICYTES AFTER EXPOSURE TO EXTRACELLULAR VESICLES IN DIABETIC-LIKE CONDITIONS

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Design: Loss of pericytes in the early phases of diabetic retinopathy (DR) may disrupt their stable association with endothelial cells (EC), leading to EC proliferation and, eventually angiogenesis. We have recently shown that extracellular vesicles (EV) derived from mesenchymal stem cells (MSC) in diabetic-like conditions may play a role in vessel destabilization by interfering with the strict EC/pericyte/extracellular matrix interactions. Thus they might contribute to angiogenesis through paracrine signaling; in particular, a role for MMP-2 has been described. MicroRNAs (miR) are short RNA sequences acting as gene modulators and playing important roles in angiogenesis and inflammation. In particular, down-regulation of miR-126 was observed in experimental models of DR, in diabetic retina extracts and in chorioretinal EC in hypoxic conditions, correlating with an increase in VEGF and MMP.
Purpose: Our aim in this study was to investigate miR-126 expression in pericytes in diabetic-like conditions and the possible influence of EV.
Methods: Pericytes (HRP) were cultured in physiological (NG), stable high (HG) and intermittent high (intHG) glucose conditions for 8 days. EV were extracted from the supernatant of MSC cultured in hypoxic (hypo) and/or HG conditions and added to HRP cultured in NG for 6, 24 and 48 hrs. Real-Time PCR for miR-126 was performed on RNA extracts.
Results: HRP express miR-126 and this expression is down-regulated by 20% in intHG. miR-126 expression is not significantly modified by 6- and-24 hr EV exposure. After 48 hrs, miR-126 is upregulated by exposure to NG-EV (+100% vs ctrl, $p<0.05$). HG-EV do not influence significantly miR-126 expression, while EV obtained in hypoxic conditions (NG-hypo and HG-hypo) down-regulate miR-126 by 50 and 70%, respectively ($p<0.005$, both).
Conclusions: We show for the first time in our knowledge that HRP express miR-126 and that its expression is down-regulated in diabetic-like conditions. Moreover, exposure of HRP to EV in hypoxic conditions is able to decrease miR-126 expression, consistently with previous observations of its involvement in DR and providing further insights for our findings of EV contribution to vessel destabilization.

THE REGULATION OF RETINAL ARTERIOLAR DIAMETERS IN DIABETIC PATIENTS INVOLVES NO AND COX PRODUCTS

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Design: Open interventional cross-over study.
Purpose: Diabetic retinopathy is characterized by vascular changes in the retina leading to hypoxia in the retinal periphery and accompanying dilatation

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of the larger vessels in the central retina. Previous studies have shown that cyclooxygenase (COX) and nitric oxide (NO) modify the regulation of retinal vessel diameters during hypoxia both *in vitro* and *in vivo* under normal conditions. The aim of the present study was to examine whether this could be reproduced in diabetic patients and thereby potentially point to new treatment strategies for vascular changes in diabetic retinopathy.
Methods: Twenty patients (20-30 years) with type 1 diabetes mellitus and without visible diabetic retinopathy were examined using the Dynamic Vessel Analyzer (DVA). The resting diameter and the diameter response secondary to isometric exercise and flicker stimulation of retinal arterioles were studied before and during breathing of a hypoxic gas mixture (12.5% oxygen/87.5% nitrogen). The examinations were performed before and during intravenous infusion with the NOS inhibitor L-NMMA and all examinations were repeated on a second study day 45 minutes after administration of the COX-inhibitor diclofenac as eye drops.
Results: The resting diameters of retinal vessels decreased significantly during L-NMMA infusion and increased significantly during hypoxia with and without L-NMMA infusion ($p<0.0001$ for all comparisons), but was not affected by diclofenac ($p = 0.27$). Contraction of arterioles during isometric exercise decreased significantly during hypoxia and L-NMMA infusion separately and together ($p = 0.02$), and was non-significantly increased by diclofenac ($p = 0.08$). The dilatation of arterioles during flicker stimulation was significantly reduced during hypoxia ($p<0.0001$), but was not affected by neither L-NMMA infusion nor diclofenac ($p>0.05$).
Conclusions: NO and COX products are involved in the regulation of retinal arteriolar diameters in diabetic patients without visible diabetic retinopathy. These mechanisms of action may be used as targets for normalizing pathologic diameter changes of retinal vessels in patients with diabetic retinopathy.

HYPOXIA AND HYPERGLYCAEMIA-INDUCED PERICYTE APOPTOSIS: IDENTIFICATION OF PRO-APOPTOTIC MARKERS

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Design: Loss of pericytes is the key-event in the pathogenesis of microvascular diabetic retinopathy. We have previously demonstrated that human retinal pericytes (HRP) are more vulnerable to intermittent than stable high glucose concentrations, with an increase in their apoptosis.
Purpose: The aim of the present study was to investigate the effects of hypoxia combined with high glucose on HRP and explore the expression of molecules involved in the pro-apoptotic and survival pathways, in order to clarify the mechanisms of action of these diabetic-like stress stimuli.
Methods: HRP were exposed intermittently at 48 hr-intervals to high (28 mM)/physiological (5.6 mM) glucose for 8 days (intHG) and/or hypoxia for the last 48 hrs, with or without the addition of somatostatin. Cell proliferation was assessed by cell counting and BrdU incorporation and apoptosis as DNA fragmentation (ELISA). The expression of pro-apoptotic (FasL, pro-caspase-8, active-caspase-8, Bid, t-Bid, Bax, calpain-2) and anti-apoptotic (PCNA, p-Akt) molecules were evaluated by Western blot.
Results: Hypoxia, alone and combined with intHG, is able to increase HRP apoptosis (+27 and +34%, respectively, $p<0.05$ vs ctrl) and decrease their proliferation (-28 and -31% vs ctrl, $p<0.005$). Pro-apoptotic molecules (FasL, active caspase-8, t-Bid, Bax) were significantly increased in HRP cultured in hypoxic conditions, both in physiological and intHG conditions, while no significant differences, but a trend towards decrease, were observed in the expression of survival markers (PCNA, p-Akt). Addition of somatostatin did not determine any variation.
Conclusions: Diabetic-like conditions (intHG and hypoxia) are able to stimulate pericyte apoptosis through activation of pro-apoptotic molecules, thus leading to an imbalance between pro-apoptotic and survival signaling pathways. Our identification of such intermediates could help finding new therapeutic approaches for the prevention of DR.

MODULATION OF CAMP SIGNALLING PREVENTS TNFα-INDUCED ENDOTHELIAL BARRIER DISRUPTION IN AN *IN VITRO* MODEL OF THE BLOOD-RETINAL BARRIER

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Design: An *in vitro* model of the inner blood-retina barrier (BRB) was employed to study the role of cAMP signaling and the effects of TNFα stimulation in blood-retinal barrier (BRB) stabilization and disruption.
Purpose: Breakdown of the BRB is an important feature in the pathology of diabetic macular edema (DME), but cellular mechanisms underlying BRB dysfunction are poorly understood. In recent years, the involvement of inflammatory cytokines in BRB breakdown has gained attention. In the present study, we investigated the effects of TNFα on the BRB *in vitro*, and studied the involvement of the cAMP pathway in TNFα-induced barrier breakdown.
Methods: For this study we employed an *in vitro* BRB model, consisting of primary bovine retinal endothelial cells (BRECs) grown on Transwell filters. Barrier integrity was assessed by measurements of trans-endothelial electrical resistance (TEER) and permeability to a 70-kDa molecular tracer. mRNA levels and protein expression of BRB-specific components in BRECs were investigated by qPCR and immunostaining. cAMP levels in BRECs were measured with a cAMP ELISA kit. Student's *t*-test was used to determine statistically significant differences between groups.
Results: TNFα disrupted the BRB *in vitro* at the molecular level. Stimulation of BRECs with TNFα (10 ng/ml) for 2 h and 24 h caused a significant decrease in mRNA and protein expression of the tight junction components claudin-5 and ZO-1, and caused increased stress fiber formation. However, pre-incubation with 8-(4-Chlorophenylthio)-cAMP, a membrane permeable cAMP analogue, prevented these effects. Interestingly, claudin-5 and ZO-1 expression was also significantly higher in non-stimulated cells treated with cAMP. In addition, basal TEER levels were increased and permeability was decreased in BRECs treated with cAMP. Importantly, stimulation of BRECs with TNFα significantly decreased intracellular cAMP levels at different time points, whereas pre-incubation with cAMP countered this effect.
Conclusions: Together these results demonstrate that cAMP has a stabilizing effect on the basal barrier properties of retinal endothelial cells, and importantly, that pre-incubation with cAMP can prevent TNFα-induced barrier breakdown in our *in vitro* BRB model. In conclusion, this study shows that cAMP is essential in the maintenance of the BRB.

ADIPOSE-DERIVED STROMAL CELLS CONTRIBUTE TO MICROVASCULAR STABILIZATION IN DIABETIC PROLIFERATIVE RETINOPATHY: TO BE OR NOTCH TO BE?

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Design: Type 2 diabetes is a chronic disease with microvascular complications. Pericytes and endothelial cells constitute the outer layer of capillaries which degenerate under the influence of glucose. Pericytes loss occurs before endothelial cells impairment, being them essential for the regulation of endothelial cell proliferation, migration and stabilization. ADSC (adipose-derived stromal cells) have been shown to resemble pericyte activity and phenotype, making them promising for cell-mediated therapies. However, little is known about cellular pathways controlling ADSC-endothelial cells communication.
Purpose: In this study, we hypothesized that Notch signaling in ADSC contributes to the homeostasis and stabilization of retinal microvascular endothelial cells in diabetic retinopathy.
Methods: Molecules of the Notch pathway were identified on primary cultured ADSC and HUVEC (human umbilical cord endothelial cells) by rt-qPCR. The same analysis was performed on monoculture of ADSC to address the role of hyperglycemia on Notch activity. The effects of ligand-dependent Notch signaling were analyzed in a mono- and coculture system of a preformed network of sprouted HUVEC and ADSC by Notch pathway inhibitors.
Results: Primary cultured ADSC enclosed key molecules of Notch pathway showing a solid expression of ligand jagged 1 and receptor Notch 2 associated with a refraction to hyperglycemia. Besides, HUVEC displayed expression of delta-like ligand Dll4 and receptor Notch1, indispensable coordinators of cell behaviour during angiogenesis. Moreover, the perivascular positioning of ADSC co-cultured with angiogenically sprouting HUVEC was inhibited by DAPT a strong γ-secretase inhibitor and hence blocker of Notch signaling. Inhibition of ligand Jagged 1 increased ADSC connection and wrapping on HUVEC sprouting network. In addition, molecular analysis on monocultured ADSC in the presence of jagged 1 inhibitor identified downregulation of

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downstream target genes of Notch signaling such as HEY1. The latter linked to downregulation of pro-angiogenic genes such as VEGF-A and Ang-2, well known as growth factors upregulated during DR.
Conclusions: Our findings have identified key Notch components on ADSC and suggest their therapeutic function upon cell-to-cell communication in turn regulating microvascular endothelial cells homeostasis and survival.

SCREENING FOR DIABETIC RETINOPATHY IN THE CENTRAL REGION OF PORTUGAL: ADDED VALUE OF AUTOMATED "DISEASE/NO DISEASE" GRADING

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Design: The diabetic retinopathy (DR) screening program described here covers the central region of Portugal. It is a non-mydriatic screening program for sight-threatening DR conducted under the authority of Regional Health Administration in the Central Region of Portugal (ARSC). The program has been running continuously since 2001. However, in July 2011, the central reading center, Coimbra Ophthalmology Reading Centre (CORC), introduced the Retmarker Screening technology (herein referred as Retmarker SR; Retmarker SA, Coimbra, Portugal). Between the introduction of new screening methodology in July 2011 and the end of the current study period, June 2014, there were another 45,148 screenings.
Screening covers the selection of patients and their invitation for screening, the implementation of the screening program itself, and the return of the results back to the health units, physicians and patients.
Purpose: To describe the procedures of a non-mydriatic diabetic retinopathy (DR) screening program in the central region of Portugal and the added value of the introduction of an automated disease/no disease analysis.
Methods: The images from the DR screening program are analyzed in a central reading center using first an automated "disease"/"no disease" analysis, followed by human grading of the "disease" cases. The grading scale used is R0 – no retinopathy, RL – non-proliferative DR, M – maculopathy, RP – proliferative DR and NC – not classifiable.
Results: Since the introduction of automated analysis in July 2011, 89,626 eyes (45,148 patients) were screened with the following distribution: R0 - 71.5%, RL - 22.7%, M - 2.2%, RP - 0.1% and NC - 3.5%. The implemented automated system showed the potential for human grading burden reduction of 48.42%.
Conclusions: Screening for DR using automated analysis aligned with a simplified grading scale identifies vision-threatening complications of diabetic eye disease while at the same time it decreases the burden of human grading.

AUTOMATED HIGH-THROUGHPUT SCREENING OF DIABETIC RETINOPATHY IS SAFE AND EFFECTIVE

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Design: For a total of 874 patients with diabetes at risk for diabetic retinopathy (DR), we study sensitivity, specificity, and area under the receiver operating characteristic curve (AUROC) of EyeArt's ability to provide a "refer" recommendation for patients with at least one retinal image showing signs of moderate NPDR or higher on the International Clinical Diabetic Retinopathy (ICDR) severity scale.
Purpose: To study safety and effectiveness of EyeArt—an automated, computerized DR screening tool—for detecting referable DR defined to be moderate non-proliferative DR (NPDR) or higher on the ICDR severity scale and assess its ability to reduce the workload of retina experts.
Methods: The publicly available Messidor-2 dataset consists of retinal images from 874 patients that were captured in clinics in France using video 3CCD camera on a Topcon TRCNW6 non-mydriatic fundus camera with a 45-degree field-of-view. Two fovea-centered retinal images were captured for each patient, one per eye, giving a total of 1748 images in the dataset. These images were graded for DR severity as per the ICDR scale and for macular edema by a trained retinal grader. EyeArt analyzed the same images and produced for each patient a "refer" and a "no refer" recommendation.
Results: EyeArt screening sensitivity was 93.8% (95% CI 91.0%-96.6%) and specificity was 72.2% (95% CI 68.6%-75.8%). This corresponds to 424 "refer" recommendations, 214 of which were "confident refer" recommendations (with high confidence). There were only 9 false negatives out of the total 874 patients, none of which met the general treatment criteria. No macular edema cases were missed. The AUROC was 0.941 (95% CI 0.920-0.959).
Workload reduction: If the "confident refer", and "no-refer" recommendations are not seen by the graders, using EyeArt the workload is reduced to only 24% (cases needing to be read by human graders).
Conclusions: EyeArt has high sensitivity and specificity for identifying patients with referable DR, making it safe and effective for integration into DR screening workflow. It can help save costs by greatly reducing the workload of image graders.

COMPARISON OF SCREENING FOR DIABETIC RETINOPATHY BETWEEN CLINICAL EXAMINATION BY OPHTHALMOLOGISTS AND AUTOMATED DETECTION FROM RETINAL COLOR IMAGES

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Design: Cross-sectional prospective.
Purpose: To compare the sensitivity and specificity of the automated IDx-DR device to clinical examination by ophthalmologists to identify referable diabetic retinopathy (rDR).
Methods: 528 subjects with diabetes mellitus were examined by one of 12 retinal specialists/ophthalmologists, and corresponding retinal color images were analyzed at the University of Pennsylvania Reading Centre (RC), both by their readers and by the IDx-DR device located there. IDx did not have access to the device or the images during the study. rDR was defined as more than moderate or more DR, or macular edema (ME) within one disc diameter from the fovea - as determined either at the RC or by ME noted by the clinician during exam. Sensitivity and specificity for detecting rDR were compared between clinical exam and IDx-DR, with the RC as reference standard.
Results: Sensitivity was significantly better for the IDx-DR device, 86.1% (173/201), than for the clinicians 53.7% (108/201). All 23 patients with severe non-proliferative or proliferative DR and a similarly high proportion (≥95%) of the 59 patients with ME were classified as having rDR by both the device and clinical examination. Specificity was significantly worse, 68.5% (224/327) for IDx-DR, compared to 99.1% (324/327) for clinical examination. Area under the ROC curve was 0.85 (95% CI 0.82-0.89).
Conclusions: Automated detection of referable DR by a device such as IDx-DR is significantly safer than the clinical exam. However at the setting in this study, the lower specificity leads to a substantially higher overcall rate. Potentially, changing the setpoint for IDx-DR can lead to a lower overall rate.

THE APPLICATION OF MACHINE LEARNING TO THE AUTOMATED DETECTION OF MICROANEURYSMS IN DIFFERENT ETHNIC GROUPS WITH DIABETIC RETINOPATHY

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Design: This was an observational study.
Purpose: The automated detection of microaneurysms (MAs) in diabetic retinopathy (DR) using Hidden Markov Modelling (HMM) has been shown to perform comparably to human graders. However, digital fundus images (DFI) show significant variations in their appearance due to factors including degree of pigmentation, pupil size, illumination variance, camera type and imaging settings, amongst others. This study aimed to apply HMM to DFIs from four different ethnic groups to evaluate if variation in retinal background affects automated MA detection.

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Methods: DFIs were acquired from four different racial groups (located in Kenya, Norway, China and United Kingdom) and used for this study. Two 45° fundus images (one fovea centered, one disc centered) were taken. The anonymized images were analyzed by the machine algorithm in order to identify individual MAs over varying retinal background. The statistical analysis was conducted by R-studio (v0.98.1028) and the Cohen's kappa coefficient (κ) applied to measure the agreement between the human graders and the automated system.
Results: A total of 1819 DFI images were enrolled: 500 from Kenya, 311 from Norway, 508 from UK and 500 from China. The respective sensitivities and specificities using human grading as the benchmark, and the comparison between automated system and human grading through Kappa (K) values, standard errors of K (SE) and confidence intervals (CI) were: Kenya 83.54%, 92.50% (K: 0.702, SE: 0.041, CI 0.621-0.783); Norway 81.48%, 92.07% (K: 0.712; SE: 0.046; CI 0.621-0.802); UK 93.50%, 89.53% (K: 0.711, SE: 0.037; CI 0.638-0.784); and China 86.36%, 91.11%, (K: 0.649, SE: 0.047, CI 0.557-0.741).
Conclusions: The HMM automated system maintained high performance levels across different racial groups and camera systems and so showed promise for scalability across different populations and regions.

NEURO - DEGENERATION OF CORNEA AND RETINA IN PATIENTS WITH TYPE 1 DIABETES WITHOUT CLINICAL EVIDENCE OF DIABETIC RETINOPATHY AND NEUROPATHY

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Design: This was an observational, cross sectional study.
Purpose: Diabetic retinopathy (DR) is considered to be the earliest microvascular complication of diabetes mellitus (DM). However, recent studies have shown that retinal nerve fiber layer abnormalities may be present in patients with DM but without DR. Additionally, recent studies have also shown an abnormality in corneal nerves in patients without DR. The exact temporal relationship between the development of neural and vascular damage in the form of DR remains to be established.
The aim of study was to establish if structural and functional changes in the nerve fiber layer of the retina and cornea occur in patients with Type 1 diabetes (T1DM).
Methods: 30 patients with T1DM, without current DR and past history of photocoagulation (Age: 47 ± 2.5 years; Duration diabetes: 27 ± 3 years) and 12 aged matched healthy control subjects underwent detailed structural and functional assessment of the nerves in the retina and cornea. In addition patients and control subjects underwent full examinations for assessment neuropathy, nephropathy to assess the presence of other microvascular complications of diabetes.
Results: Retinal ganglion layer function assessed using Flickering Defined Perimetry (FDF) was not significantly reduced in patients with DM. However, retinal nerve fiber layer thickness (RNFL) was significantly reduced in the superior nasal (P = 0.001) and inferior temporal (P = 0.004) areas in DM patients. Corneal sensitivity (p = 0.001), a measure of corneal function and corneal nerve fiber density (CNFD) (p = 0.01), branch density (CNBD) (P = 0.006) and length (CNFL) (p = 0.01), measures of corneal sub-basal nerve structure were significantly reduced in patients with DM. The percentage of abnormality in patients with T1DM for RNFL was 32%. The FDF was abnormal in 61% patients. Corneal abnormality was observed at 47% for NCCA, 27.8% for CNFD, and 16.7% for CNFL. No correlations were observed between neuro-retinal and neuro-corneal changes. However both were correlated with HbA1c.
Conclusions: Neuronal alterations at retinal and corneal structure and function were observed in T1DM patients without clinical evidence of retinopathy. These findings may suggest that neural damage may occur independent of vascular changes in diabetes.

TO EVALUATE THE CHOROIDAL THICKNESS İN TYPE-2 DIABETIC PATIENTS WITH OR WITHOUT DIABETIC POLYNEUROPATHY

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Design: Prospective randomized controlled trial.
Purpose: To compare the choroidal thickness (CT) in patients with Type 2 diabetes mellitus (T2DM) in the presence of diabetic polyneuropathy (dPNP).
Methods: We examined 91 patients recently diagnosed with T2DM and referred to the neurology department to evaluate the presence of dPNP using electromyelogram (EMG). A total of 41 patients (82 eyes) were found to have both DM and PNP (DM+PNP+); while 50 patients (98 eyes) were negative for PNP (DM+PNP-). All 91 patients underwent enhanced depth imaging choroidal OCT (EDI-OCT) and a complete dilated fundus examination. Altogether 41 age and sex-matched healthy subjects (82 eyes) had EDI-OCT as well. All patients had either no or mild-moderate non-proliferative diabetic retinopathy (DR).
Results: Altogether, 262 eyes were available for analysis (180 eyes DM patients and 82 control eyes). The mean sub-foveal choroidal thickness was 270.5 ± 51.7 micron in DM+PNP- group; 302.5 ± 51.7 in DM+PNP+ group and 242.3 ± 54.6 in the control group. The mean sub-foveal choroidal thickness in neuropathy group was significantly increased compared with the control and non-neuropathy group. In all groups the thickest choroid was in the sub-foveal area. The CT decreased from the sub-foveal area to the nasal and temporal choroid; in particular, the nasal CT was thinner.
Conclusions: Diabetic neuropathy is a factor affecting the CT in patients even where there is no or minimal diabetic retinopathy.

TOPICAL ADMINISTRATION OF GLP-1 RECEPTOR AGONISTS PREVENTS RETINAL NEURODEGENERATION IN EXPERIMENTAL DIABETES

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Design: Experimental randomized intervention study.
Purpose: Retinal neurodegeneration is an early event in the pathogenesis of diabetic retinopathy (DR). Since glucagon-like peptide-1 (GLP-1) exerts neuroprotective effects in the central nervous system and the retina is ontogenically a brain-derived tissue, the aims of the present study were: 1) To examine the expression and content of GLP-1R in human and db/db mice retinas. 2) To determine the retinal neuroprotective effects of systemic and topical administration (eye drops) of GLP-1R agonists in db/db mice. 3) To examine the underlying neuroprotective mechanisms.
Methods: After 15 days of treatment by using subcutaneous or topical GLP-1R agonists the neurodegenerative features were examined. Functional abnormalities were assessed by electroretinography and neurodegeneration was assessed by measuring glial activation and the apoptotic rate. In addition, proapoptotic and survival signaling pathways were examined. Glutamate and its main transporter GLAST (glutamate/aspartate transporter) were also determined.
Results: We have found abundant expression of GLP-1R in the human retina and retinas from db/db mice. Moreover, we have demonstrated that systemic administration of a GLP-1R agonist (liraglutide) prevents retinal neurodegeneration (glial activation, neural apoptosis and electroretinographic abnormalities). This effect can be attributed to a significant reduction of extracellular glutamate and an increase of pro-survival signaling pathways. We have found a similar neuroprotective effect using topical administration of native GLP-1 and several GLP-1R agonists (liraglutide, lixisenatide and exenatide). Notably, this neuroprotective action was observed without any reduction in blood glucose levels.
Conclusions: These results suggest that GLP-1R activation itself prevents retinal neurodegeneration. Our results should open up a new approach in the treatment of the early stages of DR.

THE CORRELATION BETWEEN RETINAL VASCULAR FRACTALS AND NEURODEGENERATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Design: An observational cross-sectional study.
Purpose: To investigate the correlation between changes in the retinal vascular system and the neuroretina in the early stages of diabetic retinopathy (DR).

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Methods: We examined 105 patients with type 2 diabetes mellitus (T2DM) and no or mild DR. The patients were recruited from the local DR screening and 49 patients were part of the baseline population of the EUROCONDOR study. Retinal vascular changes were evaluated using a disc-centered cropped Optos 200Tx image (Optos plc, Dunfermline, Scotland, UK) and a specialized semi-automatic software: SIVA-Fractal (Singapore University, Singapore). The output from the vascular analysis was the fractal dimension (Fd) describing the density and complexity of the vascular system in the retina. The structural composition of the neuroretina was evaluated by the thickness of the ganglion cell layer (GCL) in the macula and thickness of the retinal nerve fiber layer at the optic disc as measured by Topcon 3D OCT-2000 Spectral Domain OCT (Topcon, Tokyo, Japan). RETI-scan multifocal ERG system (Roland Consult, Brandenburg a.d. Havel, Germany) in ring 1-6 of the macula was used to evaluate the functional variations of the neuroretina. Seven-field fundus photos were performed to determine the level of DR by a single trained grader using the Early Treatment Diabetic Retinopathy Scale (ETDRS). Diabetic neuropathy was defined by the presence of neuropathic symptoms or as diagnosed according to the patient.
Results: Fd correlated with GCL-thickness (r = 0.20, p = 0.04) and with multifocal ERG implicit time of ring 1 (r = -0.25, p = 0.01) in univariate models.
In a multivariable linear regression model Fd was significantly correlated with multifocal ERG implicit time of ring 1 (coefficient -0.0021 pr. ms, p = 0.03), GCL (coefficient 0.0013 per µm, p = 0.03) and neuropathy (coefficient -0.0200 for neuropathy present versus absent, p = 0.04).
Conclusions: We found independent correlations between retinal vascular fractals and structural and functional neurodegeneration in patients with T2DM and none or early DR.
Early events in DR include a decreased retinal vascular Fd, GCL-loss and a prolonged central implicit time. Retinal vascular fractal analysis might help to identify patients with early neurodegenerative changes.

CORRESPONDENCE BETWEEN CENTRAL MFERG CHANGES AND THINNING OF GANGLION CELLS AND RETINAL NERVE FIBER LAYERS IN THE INITIAL STAGES OF DIABETIC RETINOPATHY

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Design: Prospective, randomized study.
Purpose: To evaluate the presence of multifocal ERG (mfERG) changes and retinal cells layers changes in eyes of patients with Type-2 diabetes mellitus (T2DM), using Spectral-Domain Optical Coherence Tomography (SD-OCT), in order to identify the correspondence between functional mfERG changes and retinal structural changes.
Methods: 211 out of 450 T2DM patients enrolled in the EUROCONDOR study (NCT01726075) had available SD-OCT Cirrus (Zeiss Meditec) for analysis: 109 patients with diabetic retinopathy (DR) of ETDRS level 10 and 102 patients with DR ETDRS level 35. All patients performed mfERG (103 hexagons) and SD-OCT Cirrus at baseline. P1 amplitude and implicit time (IT) of mfERG central rings (rings 1, 2 and 3) were analyzed by the number of hexagons with altered z-scores (z-score ≥2 for IT and ≤-2 for amplitude). The number of altered hexagons was compared with retinal thickness and retinal cells layers changes detected by SD-OCT.
Results: Mean age and duration of T2DM were 63.9 and 11.3 years, respectively; 71% were males. In the 109 eyes classified as ETDRS level 10 (without microaneurysms) there were central mfERG changes in 57% of eyes. A decrease of thickness in the ganglion cells (GC) or retinal nerve fiber (RNF) layers was observed in 13% of the eyes. 64% of eyes with thinning of GC or RNF layers showed correspondence with mfERG changes. In the 102 eyes with ETDRS level 35 (mild non-proliferative DR), central mfERG response was altered in 68% of eyes and GC and RNF layers thinning was present in 12% of the eyes. Correspondence between mfERG changes and GC or RNF thinning was present in all cases (100%; p = 0.011). This data shows a good correspondence between mfERG changes and thinning of the GC and RNF layers.
Conclusions: There is good correspondence between central mfERG changes (ring 1, 2 and 3) and thinning of GC and RNF layers in the initial stages of DR in patients with diabetes type-2. Therefore, functional and structural measurements used for assessing neurodegeneration run in parallel in the early stages of DR.

RETINAL LAYER LOCATION OF INCREASED RETINAL THICKNESS IN EYES WITH SUBCLINICAL AND CLINICAL MACULAR EDEMA IN DIABETES TYPE 2

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Design: Prospective observational study.
Purpose: To identify the layer location of increased retinal thickness (RT) in eyes with subclinical and clinical macular edema (ME) in patients with Type-2 diabetes mellitus (T2DM) using SD-OCT Cirrus (Carl Zeiss Meditec) and semi-automated segmentation of retinal layers.
Methods: 194 T2DM patients/eyes with mild non-proliferative diabetic retinopathy (NPDR) (ETDRS levels 20/35) enrolled in the ECR-RET-2010-02 study (NCT01145599) were examined with Cirrus SD-OCT at the baseline visit. Eyes were classified as presenting subclinical ME (62 eyes) or clinical ME (12 eyes) based on SD-OCT central subfield (central 1000 µm) and DRCR.net standards (i.e. retinal thickness (RT) >260 µm and ≤290 µm in women and >275 µm and ≤305 µm in men, or RT ≥290 µm in women and ≥305 µm in men, respectively). Automated segmentation of the retinal layers on OCT was performed in these two groups using an in-house developed segmentation tool based on the IOWA reference algorithm followed by human grader verification and correction as needed. RT of 7 retinal layers was calculated (RNFL, GCL+IPL, INL, OPL, ONL, IS+OS and RPE) and compared between groups and with a control group of 86 healthy eyes.
Results: From the 194 T2DM with mild NPDR, 62 were classified as presenting subclinical ME and 12 as having clinical ME. When comparing the different retinal layers thickness with normal controls, the largest increase in RT was found in the INL (41.0% increase in subclinical ME and 90.5% in the clinical ME). Increases were also found in the neighboring layers (GCL+IPL: 8.9% and 36.6%, OPL: 26.2% and 55.5%, for the subclinical and clinical ME groups, respectively). Less increase was found in the ONL (8% for both groups) and no changes were found in the IS+OS and RPE complex.
Conclusions: The increase in RT eyes with subclinical and clinical ME is predominantly located in the INL but extends to a lesser degree to the GCL+IPL and OPL indicating that it is probably due to extracellular fluid accumulation originating from the deep retinal vascular capillary net and not from any specific neuronal or glial cell swelling.

INDIVIDUALISED RISK-BASED SCREENING FOR DIABETIC RETINOPATHY: THE LIVERPOOL RISK CALCULATION ENGINE

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Design: Risk model development and validation.
Purpose: To develop a risk calculation engine (RCE) to estimate risk of progression to screen positive diabetic retinopathy (DR). To assign personalized screening intervals and estimate improvements in applicability of screening interval.
Methods: Data from established digital photographic screening and primary care systems were combined in a purpose built repository. Consent was through an opt-out. A development dataset of candidate covariates likely to predict progression was created using a qualitative/quantitative approach.
A series of Markov mathematical models were fitted. Disease state (background retinopathy in neither, one, both eyes) informed baseline risk. Multiple imputation dealt with missing data. Covariates were selected using 2 steps: ranking (Wald statistic), selection (corrected Akaike Information Criterion). A patient group reviewed alternative risk thresholds.
Results: Data were from 11,806 people with diabetes (46525 episodes) who were screen negative at the first of at least 2 episodes in 5 years to February 2014. 388 screen positive events occurred. Covariates selected as of having sufficient predictive value were: duration of known disease, HbA1c, age, systolic BP, total cholesterol.

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Corrected C-index for the model was 0.687 and corrected AUCs (95% CI) were: 6 months 0.88 (0.83-0.93); 12 months 0.90 (0.87-0.93); 24 months 0.91 (0.87-0.94). 4-way random data split gave sensitivities and specificities (ranges) for a risk threshold of 2.5% at 6, 12 and 24 months: 0.64-0.72, 0.93-0.94; 0.63-0.72, 0.90; 0.79-0.84, 0.81-0.82.
We estimate that implementing personalized RCE based intervals could reduce the % of people in the dataset who become screen positive before their allocated screening date by >50% and the number of screening episodes by 30%.
Conclusions: The Liverpool RCE has sufficient performance to allow its introduction into clinical practice within a robustly monitored environment. This generalizable approach offers the potential for an important enhancement in screening with significant improvements in performance and cost-effectiveness.
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VALIDATION OF A RISK STRATIFICATION ALGORITHM FOR PROGRESSION TO REFERABLE DIABETIC RETINOPATHY

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Design: A model to estimate risk of progression to sight threatening diabetic retinopathy (STDR) in those with no referable diabetic retinopathy (DR) was developed in one English screening program. This uses results from one screening episode, HbA1c and duration of diabetes to provide a risk stratification score. Grading protocols differ between programs and rates of DR are affected by duration of diabetes, ethnicity, deprivation and glycemic control. We examine the performance of the model in three more programs.
Purpose: To validate this stratification in datasets from other English programs.
Methods: Screening data from 3 English screening programs and clinical information for a subset of those patients were obtained. Patients free of STDR were categorized into those with No DR, those with mild non proliferative DR (NPDR) in one eye and those with mild NPDR in both eyes. Using the stratification algorithm, risk scores for progression to STDR were obtained.
Results: The programs had 17,634, 1083 and 1223 people respectively. There were few non-White Caucasian patients in the first program, but 30% of those in the third program were of African or African-Caribbean ethnicity. Duration of diabetes was 6 (2 to 11) (median [25th to 75th centile]), 2.9 (0.6 to 6.2) and 3.6 (1.4 to 6.8) years, HbA1c 56 (48 to 66), 53 (46 to 53) and 52 (45 to 64) mmol/mol, follow-up from date of index screening 2.9 (2.1 to 3.0), 4.2 (2.2 to 5.3) and 4.1 (2.1 to 6.9) years. In the first program the rate of progression to STDR in the lowest risk quintile was 4.1 per 100 patient years and in highest quintile 74.0 per 1000 patient years, in the second 2.4 and 79.2 respectively and in the third 1.7 and 49.0 respectively. Area under the ROC curve at 3 years was 0.78, 0.82, and 0.84.
Conclusions: Within each of the 3 programs the risk model discriminates well between those with very low and with high risk of progression to STDR. The algorithm would be suitable for calculation of personalized screening intervals. Validation in more screening programs is required.

COST-EFFECTIVENESS OF A RISK-BASED SCREENING PROGRAMME FOR DIABETIC RETINOPATHY: A MODELLING APPROACH

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Design: Economic evaluation using decision-analytic Markov model.
Purpose: Use of local data and modelling to estimate whether a risk-based screening program is likely to be more or less cost-effective than two alternative standardized programs.
Methods: A Markov state transition model, based on NHS Diabetic Eye Screening Programme 'R0M0' gradings, to estimate the expected cost-effectiveness of 3 policies for routine screening of diabetic retinopathy: i) annual screening, ii) biennial screening and iii) a risk-based variable-interval screening program. The risk-based screening program used a risk calculation engine, maximum acceptable risk of screen positive at next screen episode of 2.5% and 3 possible recall periods; 6, 12 and 24 months. We combined administrative datasets, including screening episodes and hospital procedures for more than 16,000 people with diabetes between 2005 and 2014. Published disease progression rates were used to estimate transition probabilities; local data to estimate treatment frequencies and costs; health state utility values elicited by systematic review and meta-analysis to estimate quality-adjusted life year gains/losses. We used probabilistic sensitivity analysis to characterize uncertainty in our estimates.
Results: The modelling approach using local data proved feasible, and applicable to the evaluation of screening in the UK. Simulations showed the majority of people in the risk-based screening program would be invited to attend screening 2 years after a negative outcome. We found that the risk-based screening program is more likely to be cost-effective than either alternative and/or cost-saving compared with annual screening, which has the lowest probability of being cost-effective. The point-estimate incremental cost-effectiveness ratio indicated that risk-based screening would be cost-effective at a threshold of £20,000/QALY.
Conclusions: Our results suggest a risk-based screening program is likely to be the most cost-effective policy in our setting. This modelling study is based on historical data; observational studies must be carried out to elicit the effects on attendance and the performance of screening tests within risk-based programs.
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COGNITIVE FUNCTION MAY BE A PREDICTOR OF RETINOPATHY PROGRESSION IN PATIENTS WITH TYPE 2 DIABETES

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Design: 8-years of observational prospective study of patients with type 2 diabetes (T2DM).
Purpose: In a study designed to monitor a number of clinical, psychological and cognitive variables over time, we aimed at identifying the possible predictors of progression of diabetic retinopathy (DR).
Methods: Patients (n = 498) with T2DM, of which 249 not treated by insulin (NIT) and 249 on insulin treatment (IT), were enrolled. The following variables were recorded: age, gender, diabetes duration, schooling, occupation, social status, smoking, self-monitoring of blood glucose, hypertension, menopausal status, fasting blood glucose, HbA1c, BMI, total and HDL cholesterol, triglyceride, retinopathy grading, presence of foot ulcers, depression and anxiety scores (Zung questionnaire) and cognitive function (Minimal Mental State Examination, MMSE). The same variables were collected again after 4 (JEI 37, 79-85, 2014) and 8 years. DR was graded on digital 45° photographs of the macular and nasal areas. DR of the worst eye was considered.
Results: Out of 477 patients for whom grading was available at baseline, 240 (160-IT and 80-NIT) had no DR, 110 (48-NIT and 62-IT) had mild non proliferative DR and 127 (24-NIT and 103-IT) had moderate or more severe DR ($p<0.01$). After 8 years, 357 patients were available for analysis, of whom 191 had remained with no or mild DR and 166 had developed moderate or more severe DR. Patients who had moderate or more severe DR at baseline were not included in the follow-up analysis. On multivariate analysis, being on insulin treatment (OR 1.97, 95% CI 1.1-3.5, p = 0.017) and having higher HbA1c (OR 1.33 per percentage point, 95% CI 1.1-1.7, p = 0.009) at baseline were associated with progression to moderate/more severe DR, whereas male gender (OR 0.53, 95% CI 0.3-0.9, p = 0.031) and a higher MMSE score (indicative of better cognitive ability) (OR 0.90 per scoring point; 95% CI 0.8-0.98, p = 0.018) were protective. None of the other baseline variables was associated with progression of DR in this cohort.
Conclusions: Lower MMSE score may represent a novel risk factor for progression of DR. Microangiopathy might develop at both brain and retinal level and manifest itself with changes in cognitive function and retinopathy.

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EVALUATION OF DEPRESSION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND DIABETIC RETINOPATHY

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Design: Qualitative clinical research.
Purpose: To evaluate depressive symptoms in patients with Type 2 diabetes mellitus (T2DM) with no or manifest diabetic retinopathy (DR).
Methods: Consecutive T2DM patients attending an eye policlinic between 2011 and 2014 were included. DR status was determined by the same physician according to standard protocols as: none, background, pre-proliferative, proliferative, macular edema (ME). The Beck Depression Inventory (BDI, 1999) was applied to assess depression; this contains 21 questions to measure the severity of depression. The standard cut-offs are as follow: a score between 0-9 indicates minimal, 10-18 mild, 19-29 moderate, and 30-63 severe depression. χ-square test used to compare depression rate across the groups and Pearson-test to evaluate the correlation between the severity of depression and the severity of DR.
Results: 1184 patients were recruited; 778 (65.7%) were female. Numbers of patients (%) with no DR, background DR, pre-proliferative DR, proliferative DR and ME were 454 (38.3%), 292 (24.7%), 193 (16.3%), 122 (10.3%), and 123 (10.4%), respectively. There was no statistical difference between mean age of patients in terms of gender. 195 (16.5%) had severe depression. Proportions of patients within DR groups with severe depression were: no DR - 0, background - 0, pre-proliferative 76/193 (39.4%), proliferative 89/122 (73.0%), macular edema 30/123 (24.4%). We found a statistically significant difference between patients with no or background DR compared to more severe DR groups (p = 0.0001). Additionally, there were a correlation between the severity of DR and the severity of the depression (p = 0.001).
Conclusions: Depression may accompany DR and the severity of the depression and DR are closely related; these problems may effect quality of life. Patients with DR should be evaluated for depressive symptoms in all stages of the disease to improve their quality of life.

POSTER SESSION

THE CORRELATION BETWEEN AQUEOUS AND SERUM LEVEL OF APOLIPOPROTEIN A1 AND B AND DIABETIC RETINOPATHY

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Design: Prospective study.
Purpose: The purpose of this study was to determine the correlation between age, diabetes duration, hypertension, fasting blood glucose level, glycated hemoglobin level, serum lipid markers and diabetic retinopathy (DR).
Methods: Sixty patients with Type-2 diabetes mellitus (T2DM) and 61 healthy controls underwent cataract surgery and were included in this study. Serum and aqueous levels of Apo A1, Apo B and Apo B/A1 were measured. Serum samples for Apo A1 and B were determined with immunoturbidimetric method and aqueous samples for Apo A1 and B were measured using ELISA method.
Results: The mean duration of diabetes was 14.1 ± 7.3 years. There were no significant differences between patients with T2DM and healthy controls for serum Apo A1 and Apo B, serum apo B/A1 and the level of aqueous Apo A1 (all p>0.05). Aqueous Apo B level was 34.3 ± 9.5 ng/ml in controls and 234.9 ± 222.3 ng/ml in T2DM patients. Aqueous Apo B level was detected as abnormal in 4.9% of health controls and in 61.7% of T2DM patients and these T2DM patients had more severe DR (P<0.05). Aqueous Apo B levels were detected in all T2DM patients with severe non-proliferative DR and proliferative DR. As the severity of DR increased, the aqueous and serum Apo B/A1 levels were also increased (p<0.05).
Conclusions: The serum and aqueous Apo B/A1 ratio may contribute to the severity of DR.

AQUEOUS HUMOR AND SERUM LEVELS OF NITRIC OXIDE, MALONDIALDEHYDE AND TOTAL ANTIOXIDANT STATUS IN DIABETIC AND NONDIABETIC SENILE CATARACT PATIENTS

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Design: Prospective study.
Purpose: To investigate the aqueous humor and serum levels of nitric oxide (NO), malondialdehyde (MDA) and total antioxidant status (TAS) in patients with diabetes mellitus (DM) and healthy controls with senile cataract.
Methods: This prospective study included 35 eyes of 35 patients with DM and 35 eyes of age- and sex-matched healthy subjects in whom cataract surgery was indicated. Aqueous humor and serum MDA, NO and TAS levels were measured with enzyme-linked immunosorbent assay and chemiluminescence methods, respectively.
Results: The analysis of MDA levels in the serum and aqueous humor revealed no significant differences between any of the groups (p>0.05). At the level of aqueous humor, patients with DM had significantly increased NO levels, compared to the controls (p = 0.003). However, there was no statistically significant difference in serum NO levels between the groups (p>0.05). The control group also presented significantly higher TAS levels than those with DM in serum (p = 0.001), but there was no significant difference in the TAS levels of aqueous humor between the groups (p>0.05).
Conclusions: Our results seem to suggest that high levels of aqueous humor NO and reduced serum antioxidant defenses might play a role in diabetic eye disease. Therefore, inhibition of reactive oxygen species production and substitution of serum antioxidant status may be a therapeutic target for oxidative stress-involved eye diseases.

IMMUNOLOCALISATION OF TUBULIN POLYMERISATION PROMOTER PROTEIN/P25 IN THE DIABETIC RETINA

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Design: Diabetes can be associated with rod-cone dystrophy and visual loss, such as in Bardet-Biedl syndrome. Deterioration of photoreceptor cilium due to intraflagellar transport malfunction and microtubule (MT) instability due to altered tubulin methylation is thought to underpin these pathological changes. Tubulin Polymerization Promoter Protein/p25 (TPPP/p25) is a regulator of tubulin methylation, but has not been previously described in the retina.
Purpose: Here we examined whether TPPP/p25 is present in the retina and whether it is associated with diabetes.
Methods: Paraffin embedded sections of human eyes with and without diagnosis of diabetes were obtained from the pathology archive from University College London with Institutional Ethics Committee approval. Immunohistochemistry was performed using specific polyclonal TPPP/p25 and methylated tubulin antibodies. Fluorescent secondary antibody labeling was visualized by confocal microscopy.
Results: We examined sections from 10 human eyes without diabetes and 3 with diabetes as indicated on the pathology report. TPPP/p25 was not detected in ciliated structures in the retina but it was identified in the inner plexiform layer (IPL) as distinct puncta in striations S1, S3 and S5. Immunoreactivity in flat-mount retina showed that less than 10% of cell bodies of the innermost cells in the inner nuclear layer were labelled with TPPP/p25 antibodies. These observations were true for both control and diabetic eyes, however qualitative assessment of immunoreactivity for TPPP/p25 indicated that in retina with diabetes the number of TPPP/p25 immunoreactivity have decreased.
Conclusions: These results indicate that tubulin acetylation is mediated by proteins other than TPPP/p25 in the retina supporting a 'moonlighting' role of the protein in retinal function. However, the results highlight a potentially highly specialized role for this protein in amacrine cell function. These results suggest that TPPP/p25 might be associated with the amacrine cell degeneration reported in diabetes.

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BENFOTIAMINE PREVENTS EXPERIMENTAL DIABETIC RETINOPATHY THROUGH REGULATION OF ENDOTHELIAL ANGIOPOIETIN-2 AND PROTEIN GLCNAC MODIFICATION

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Design: An *in vivo* and *vitro* study to identify the mechanisms of protective effect of benfotiamine in diabetic retinopathy.
Purpose: Our previous data showed that benfotiamine reduces flux through the hexosamine pathway in diabetes, and prevents experimental diabetic retinopathy by decreasing formation of acellular capillaries without affecting pericyte loss. Furthermore, we demonstrated that diabetic angiopoietin-2 (Ang2) deficient retinas are protected from diabetic retinopathy. Moreover, Yao et al found that the upregulation of endothelial Ang2 in diabetes correlates with increased modification of transcription factors by O-GlcNac. Thus, in this study we sought to identify the mechanisms by which the protective effect of benfotiamine in the diabetic endothelium occurs.
Methods: Streptozotocin-induced diabetic wild type (WT) and heterozygous Ang2+/- mice were treated with benfotiamine, and terminated at 6 week after diabetes induction. Blood glucose, body weight and HbA1c were measured. Retinal protein GlcNac modification was detected by western blot. The Ang2 promoter region responding to high glucose and benfotiamine in endothelial cells was assessed using a luciferase reporter assay. The effect of Ang2 depletion by specific siRNAs on protein GlcNac modification was assessed by western blot in cultured endothelial cells.
Results: Benfotiamine treatment did not alter metabolic parameters in the diabetic wild WT and Ang2+/- mice. However, benfotiamine significantly lowered protein GlcNac modification in diabetic retinas of WT mice. The loss of Ang2 expression in the retina from Ang2+/- mice reduced protein GlcNacylation in the diabetic retina to a similar extent than benfotiamine treatment in WT mice. Befontiamine did not further reduce protein GlcNac modification in diabetic retinas of Ang2+/- mice. Using a luciferase expression constructs a region spanning positions -109/+476 in theAng2 promoter was identified to respond to high glucose in endothelial cells. The glucose enhanced Ang2 promoter activity was completely suppressed by benfotiamine. Moreover, Ang2 knockdown in endothelial cells significantly suppressed high glucose-induced protein GlcNac modification
Conclusions: Our data indicate that benfotiamine exerts its protective effect in the development of diabetic retinopathy by regulating endothelial Ang2 expression and Ang2-dependent protein GlcNac modification.

THE ROLE OF LIPOPROTEIN PHOSPHOLIPASE A2 IN PATHOGENESIS OF DIABETIC RETINOPATHY

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Design: Diabetes was induced in lipoprotein-phospholipase A2 (Lp-PLA2) knockout, heterozygous and wild-type mice and maintained for six months. Retinal structure and function was assessed by immunohistochemistry, optical coherence tomography (OCT), and electroretinography (ERG) respectively.
Purpose: Lp-PLA2 is a biomarker of vascular inflammation in macrovascular disease states. Lp-PLA2 is produced by inflammatory cells, and hydrolyses oxidized low-density lipoproteins (oxLDL) into pro-inflammatory lysophosphatidylcholine (LysoPC) and oxidized non-esterified fatty acids (OxNEFA). Since the pathogenesis of diabetic retinopathy is known to have both oxidative damage and pro-inflammatory components, we hypothesized that genetic deletion of Lp-PLA2 in mice may ameliorate vascular and neural associated changes in the diabetic retina.
Methods: Lp-PLA2 expression was localized in normal and diabetic human retinal specimens by immunohistochemistry. Lp-PLA2 deletion (Lp-PLA2 -/-), partial Lp-PLA2 deletion (heterozygous) (Lp-PLA2 +/-), and wild-type (WT +/+) mice were rendered diabetic by streptozotocin injection. Control animals received citrate buffer. Mice were maintained for 6 months, after which retinal function and thickness were assessed by ERG and OCT measurement. After sacrifice, retinal flat-mounts were stained with collagen IV/isolectin B4 to assess acellular capillary formation.
Results: The degree of hyperglycemia in diabetic WT, Lp-PLA2 +/- and Lp-PLA2 -/- mice was comparable. ERG analysis indicated that ON-bipolar cell function (b-wave amplitude) was significantly attenuated in diabetic WT mice when compared to non-diabetic controls. Diabetic Lp-PLA2 +/- mice were protected from these ERG defects. OCT measurement of retinal thickness showed a significant thinning of the retina in diabetic WT mice and diabetic Lp-PLA2 (+/-) mice compared to non-diabetic controls ($p = 0.0252$, $p = 0.0385$, $p<0.05$). Retinal thickness in diabetic Lp-PLA2 (-/-) mice was comparable to non-diabetic controls. Increased numbers of acellular capillaries were observed in diabetic mice compared to non-diabetic control mice across all genotypes.
Conclusions: Our studies suggest that Lp-PLA2 may play a role in modulating retinal function and vascular damage under diabetic conditions.

RETINAL GENE EXPRESSION SHOWS COMPARTMENT SPECIFIC DIFFERENCES IN HEALTH AND DISEASE

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Design: This project is an experimental animal study, analyzing one transgenic rat group and the control group at one explicit timepoint.
Purpose: Diabetic retinopathy shows a time course of specific morphological changes, e.g., pericyte loss, acellular capillaries and degeneration of neuronal cells. These changes do occur in the PKD2mut rat in a reverse order starting with neurodegeneration followed by vasoregression with the same morphological features. As these two different pathologies are located in different parts of the retina, this project aimed towards an answer to the question, if there are intraretinal differences in gene expression in between the different sites of these pathologies.
Methods: Retinas from two months old PKD2mut and Sprague Dawley rats, the genetic background of the PKD2mut rat serving as controls, were isolated ($n = 6$/group). Using the laser microdissection technique these retinas were divided in an inner retinal part, containing the ganglion cell, inner plexiform, inner nuclear and outer plexiform layers, and an outer retinal part, consisting of the outer nuclear layer and the rods and cones. From these compartment preparations the RNA was isolated and amplified followed by an Affymetrix GeneChip profiling and deeper analysis with the Array Studio software and the Ingenuity pathway analysis.
Results: Overall the array analysis showed 4908 transcripts to be expressed significantly different in-between the compartments and 351 transcripts in between the two groups ($p<0.01$). Out of these 351 transcripts, 287 were differently regulated in the outer and 82 in the inner retinal part. Several compartmentalized genes were identified as candidates related to the disease e.g. Lipocalin-2 specifically expressed in the inner part of PKD2mut retinas (17.5-fold vs SD, $p<0.001$). Possible upstream regulators involved in the different expression patterns were revealed by the mechanistic transcriptomics data interpretation consisting of cytokines (e.g. IL-4/IL-1β) and transcription factors (e.g. STAT1/STAT3).
Conclusions: In this study we demonstrate that in fact there are significant intraretinal differences in gene expression in health and retinal disease. Using this method we were able to identify several new candidates possibly involved in the development of retinal disease which might be overlooked in full retinal analysis.

HYPERGLYCAEMIC MEMORY - MECHANISMS RELEVANT TO THE DIABETIC RETINA

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Design: Translational research - streptozotocin induced hyperglycemic C57Bl6 mice with benfotiamine treatment and normalization of blood glucose through beta-cell transplantation.
Purpose: The evaluation of irreversible damage to the diabetic retina caused by hyperglycemia.
Methods: C57Bl6 streptozotocin induced diabetic mice treated with benfotiamine for the blockage of the hexosamine pathway and normalization of blood glucose by beta-cell transplantation. Following groups were established:
NC3M - Normoglycemic 12 weeks
DC3M - Hyperglycemic 12 weeks
Tx - Hyperglycemic 6 weeks + normoglycemia 6 weeks
B6 - Hyperglycemic 6 weeks + benfotiamine 6 weeks
B12 - Hyperglycemic + benfotiamine 12 weeks.
We analyzed pericyte coverage of the vascular network in retinal digests and tested retinal lysates with Affymetrix whole genome expression chips.
Results: Beta-cell transplanted mice showed a reduction of HbA1c from 11,8% in the diabetic group to 6,3%, the control group had a HbA1c of 5,5. Our results show a reduction of pericytes between the control and the other groups (NC3M: 1981 PC/mm^2; DC3M: 1571 PC/mm^2; Tx: 1606 PC/mm^2; B12: 1681 PC/mm^2; B6: 1559; $p<0.0001$). Consequently, normalization of blood glucose after a period of hyperglycemia and treatment with benfotiamine did not prevent pericyte loss as marker of vascular damage. The short time of diabetes did not affect endothelial cell numbers even though we had significantly more endothelial cells in the diabetic and benfotiamine treated animal groups compared to the normal control, but no relevant changes. Data from the Affymetrix Chips were analyzed with Ingenuity Pathway Software (Quiagene) and from those genes influenced by hyperglycemic memory revealed as top 3 effected networks:
-1 RNA Post-Transcriptional Modification, Cancer, Cellular Movement (Score 53)
-2 Cancer, Organismal Injury and Abnormalities, Cardiac Dysplasia (Score 50)
-3 Developmental Disorder, Hereditary Disorder, Inflammatory Disease (Score 42)
Conclusions: As previously shown in dog retinas (Kern TS et al. 1987), we found equal damage in mouse retina of hyperglycemic and hyperglycemia treated animals (beta-cell transplantation/benfotiamine). This phenomenon was referred to as hyperglycemic memory (Giacco & Brownlee, 2010). From the data collected, in addition to the retinal damage, we found, via the Affymetrix chips, genes detrimentally influenced by hyperglycemic memory.

MICRORNA SIGNATURE IN DIABETIC RETINOPATHY

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Design: Experimental study.
Purpose: MicroRNAs are change during disease, but not much is known about microRNAs in diabetic retinopathy (DR). This study shall answer if the microRNA signature changed in DR and what its impacts are.
Methods: Retinae of InsAkita mice (3M, NC vs. DC, n = 8) were isolated and RNA was extracted using Trizol. Using Affymetrix Array analyses, over 3.000 microRNAs were screened for. Top 5 increased and decreased, human analogous microRNAs were analyzed by KEGG and gene enrichment analyses. Retina digestion was used to describe the retinal phenotype of the mice. PCR and Western Blot are going to confirm Array results and in silico data.
Results: Over 83 microRNAs are changed in the retina of diabetic mice compared to the control group. Especially miR-409-5p (+1.3), miR-744-5p (+1.3), miR-7b-3p (+1.3), miR-1a-1-5p (+1.3) and miR-16a-2-3p (+1.2) are increased, whereas miR-708-3p (-2.4), miR-199a-5p (-1.9), miR-1298-5p (-1.8), miR-670-5p (-1.7) and miR-501-5p (-1.7) are decreased ($p<0,05$). Only miR-199a-5p has been confirmed by PCR yet, showing a down regulation of eight fold ($p<0.05$). According to in silico analysis, the microRNAs mainly affect the MAPK, Erbb, Wnt, TGF-beta and Axon guidance pathway. These changes in the microRNA signature are associated with an almost three fold increase of acellular capillaries ($p<0.001$), but not with pericyte drop-out.
Conclusions: The signature of microRNAs is changed during DR and is likely to contribute to its progression. Although not all microRNAs have been validated by RT-PCR yet, the example of miR-199a-5p shows that RT-PCR is much more sensitive than Array data, giving a realistic hint to which extent microRNAs are really changed. The in silico analysis of pathways affected by microRNAs reveals key players that have already been associated with DR, such as the Wnt- or MAPK-pathway, again stressing the importance of microRNAs. That the change of microRNAs is associated with an increase of acellular capillaries suggests that miRNAs are involved in their creation as well as in the succeeding pericyte drop-out which is a hallmark of DR. Modifying microRNAs might therefore open up a new road to therapeutic strategies and targets.

OCULAR DISTRIBUTION OF FENOFIBRATE AND ITS ACTIVE METABOLITE FENOFIBRIC ACID AFTER OCULAR AND ORAL ADMINISTRATION IN RABBITS

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Design: To compare ocular tissue distribution of fenofibric acid after repeated eye drop and oral administration of fenofibrate in rabbits.
Purpose: Fenofibrate has been shown to reduce progression of diabetic retinopathy in two long term studies FIELD and ACCORD. The objective of the study was to measure the concentrations of its active metabolite fenofibric acid (FA) in the different parts of the eye after systemic or topical administration.
Methods: Three groups of 3 rabbits received fenofibrate 3 mg or 30 mg as oral gavage or 3 mg (100 µL) as an eye drop suspension in the right eye two times a day for 4.5 days to measure FA concentrations in plasma, posterior and anterior parts of the eye 4 hours after last application.
Results: Low dose oral and ocular administration of the same fenofibrate dose, lead to the same FA concentrations in plasma of approximately 10 µg/mL, corresponding to the therapeutic plasma concentrations in man. FA levels in the retina of 200 ng/g were reached either with low dose oral or with topical administration of the same dose. Non-metabolized fenofibrate was found in the retina only after topical administration. The exposure of the active metabolite FA in the posterior eye correlated directly to the systemic exposure. Conversely, topical treatment with fenofibrate eye drops lead to high FA levels in the cornea and the conjunctiva of approximately 25 µg/g, which is considerably higher than after high dose oral treatment. This indicates that fenofibrate is directly transformed into its active metabolite in the anterior part of the eye.
Conclusions: This pilot study in rabbits showing similar concentrations of fenofibric acid in the posterior part of the eye after oral and topical administration supports the positive effects of fenofibrate oral treatment on progression of diabetic retinopathy in patients. Further work is needed to extend these findings in other eye diseases.

INTRAVITREAL DELIVERY OF IGG AGGREGATES INDUCES IMMUNE CELL ACTIVATION IN THE HEALTHY RETINA

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Design: This study has assessed the impact of intravitreally delivered IgG and IgG aggregates on normal mouse retina.
Purpose: Intravitreal delivery of therapeutic antibodies exposes the neural retina to IgGs which are normally excluded by the blood retinal barrier. Off-label use of the IgG Bevacizumab (Avastin) is often dispensed in hospital pharmacies and evidence suggests that some aliquots of bevacizumab may form IgG aggregates depending on the techniques used.
Methods: IgG at a concentration of 23.8 mg/ml was used in the study (which is comparable to dosage of bevacizumab, Kahook et al., 2010). This IgG solution was divided into three aliquots. One solution was left at 4°C (control), room temperature (RT) and -20°C for 3 days and then returned to 4°C Formulation buffer for bevacizumab was produced in-house. Aggregates were assessed using a 9% SDS-PAGE electrophoresis. 1 µL of formulation buffer was injected by intraocular injection into the right eye of healthy young adult C57BL6J mice. 1 µL of IgG solution was injected into the left eye. The mice

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were sacrificed at 48 hours later. The retinas were excised and immunostained with Isolectin B4, Iba1 and F480. Z stacked images were taken using Nikon confocal microscope and used to assess the number and activation state of microglia.
Results: Using SDS-PAGE, distinct 27 and 56 kDa bands were identified for denatured IgG samples. In the RT and -20°C exposed samples, there were large molecular weight aggregates observed. When the IgG samples were injected into the vitreous of mice, the number of Iba1/Isolectin B4-positive microglia in the retina was markedly higher when compared to the formulation buffer controls. There was also a significant activation marked increase in activated (amoeboid) cells in retinas that had been exposed to RT ($p<0.05$) and -20°C ($p<0.05$) IgG samples. The number of F4/80 positive macrophages in the retina were increased in all IgG groups compared to formulation buffer ($p<0.05$).
Conclusions: Storage temperature of aliquoted IgG influences aggregate formation. Injection of IgG into murine eyes causes microglia and macrophage activation and this increases when aggregates are present. This study illustrates that IgG administered into the vitreous in high concentrations causes immune cell activation.

MODULATION OF MICROGLIA POLARITY IS A NEW TARGET AGAINST DIABETIC RETINOPATHY: AN EXPERIMENTAL APPROACH IN DB/DB MICE

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Design: Retinal diseases linked to inflammation are often accompanied by macrophage/microglia cells activation. Inflammation is an early event during diabetic retinopathy (DR) and the polarity of microglia may be involved in underline its functional properties. However, the changes in the microglia status after GLP-1 treatment have not been investigated.
Purpose: Our goal was to study the modulation of microglia polarity using GLP-1 during DR in db/db mice, a mouse model of DR.
Methods: The visual function of db/db mice at 4, 8 and 20 weeks of age has been analyzed by ERGs. Immunofluorescence was used to identify the presence of microglial cells in the retina. The polarization of microglia was analyzed by measuring the expression of inflammatory markers (M1/M2 response) by western-blot and quantitative PCR. As an *in vitro* system, we analyzed the M1/M2 polarization profile in Bv.2 cells treated with GLP-1 (10-6M) together with two diabetic stimuli: pro-inflammatory cytokines induced by LPS (Lipopolysaccharide) or hypoxia (3% oxygen). The M1 or pro-inflammatory versus M2 anti-inflammatory response was analyzed.
Results: db/db mice presented hyperglycemia at 4-5 weeks of age time at which body weight was slightly increased. At this age, changes in microglia polarity were detected compared to db/+ control mice since arginase-1 levels were increased but pro-inflammatory M1 cytokines remained unchanged. By contrast, in retinas from db/db mice at 8 or 20 weeks of age the opposite pattern of polarization was observed. The responses of microglial cells cultured under diabetic conditions showed M1 polarization and, interestingly, modulation towards M2 polarization in the presence of GLP-1.
Conclusions: Our results suggest that GLP-1 modulates microglia polarization towards an immune M2 response at early stages of DR. This finding open up a new mechanism of action of GLP-1 that should be added to its neuroprotective action recently reported.

MECHANISMS OF ACTION OF CALCIUM DOBESILATE IN THE EARLY STAGES OF DIABETIC RETINOPATHY

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Design: Experimental intervention study.
Purpose: Calcium Dobesilate (CaD) has been prescribed to prevent the progression of DR. However, its clinical efficacy is still a matter of controversy. In addition, the underlying therapeutic mechanisms of CaD remain to be fully elucidated. Recently, it has been reported that administration of the CaD in patients with DR may reduce the serum levels of endothelin-1 (ET-1). It should be noted that ET-1, a potent vasoconstrictor, is involved in the development of DR. In addition, it is worth mentioning that ET-1 also contributes to retinal neurodegeneration.
On this basis, the aims of the present study were to assess the effect of CaD in preventing retinal neurodegeneration and early microvascular abnormalities induced by diabetes in a murine model (db/db mouse). In addition, the effect of CaDo in ET-1 and its receptor was also assessed.
Methods: Diabetic (db/db) mice (aged 8 weeks) were randomly assigned to daily oral treatment with CaD (200 mg/Kg/day) (n = 12) or vehicle (n = 12) for 14 days. In addition, 12 non-diabetic (db/+) mice matched by age were used as control group. Functional abnormalities were assessed by electroretinography. Neurodegeneration and microvascular abnormalities were evaluated by RT-PCR, immunohistochemistry, Western blot and HPLC.
Results: We found that CaD significantly decreases the hallmarks of retinal neurodegeneration (glial activation and apoptosis). In addition, a significant improvement of ERG parameters was observed. CaD also reduces glutamate excitotoxicity induced by diabetes. Furthermore, CaD prevented the up-regulation of ET-1 and its receptors in diabetic retinas. Finally, we have found that CaD treatment reduces the expression of VEGF and preserves the sealing function of the blood retinal barrier (BRB).
Conclusions: Our results suggest that CaD treatment could be effective in preventing neurodegeneration and microvascular abnormalities (disruption of BRB) in early DR. Better understanding of the mode of action of CaD could be important to guide physicians in targeting the treatment appropriately.

ADSC THERAPY FOR TREATMENT OF DIABETIC RETINOPATHY: THE BEST OR LAST RESOURCE?

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Design: Diabetic retinopathy (DR) is the most common complication of diabetes. In DR, the disordered metabolism of glucose causes the early loss of retinal capillary pericytes as well as capillary endothelial cells. Stabilization of retinal capillaries by stem cells offers a novel treatment modality. Promising candidates are adipose derived stromal cells (ADSC), which are easily harvested from subcutaneous fat in which ADSC are abundant.
We and others showed that ADSC have a direct role in providing microvascular support and replace pericytes in oxygen-induced and hyperglycemia-induced rodent models of diabetic retinopathy. *In vitro* ADSC readily differentiate to pericytes.
Purpose: Since glucose is important in the cellular energy metabolism we set out to investigate its influence on the ADSC. Furthermore, ADSC are multifunctional through their secretion of a provisional extracellular matrix for vessels, while modulating the inflammatory response although its exact mechanism of action in DR is unknown.
Methods: Human ADSC were cultured in 5 mM glucose or under 30 mM glucose. The viability and proliferation rate were examined. Reactive oxygen species (ROS) production correlated with mitochondrial membrane potential and glucose uptake potential were measured. The extracellular Flux was analyzed (by Seahorse Extracellular Flux Analyser) to detect the bioenergetics pathways. The anti-inflammatory and pro angiogenic effects of ADSC were examined in ADSC-endothelial cells co-culture.
Results: Hyperglycemia-cultured human ADSC showed increased apoptosis, likely caused by increased production of ROS. ROS production correlated with mitochondrial membrane potential. Similarly, glucose uptake and extracellular flux measurements showed these were altered. The bioenergetics pathways had altered Oxygen Consumption Rate (OCR) and Extra Cellular Acidification Rate (ECAR) in ADSC.
Our data further showed that under hyperglycemia ADSC influence vascular network formation *in vitro* is altered through dysregulated proteoglycans (NG2 and Perlecan) and upregulated VEGF expression. Finally, we charted the influence of hyperglycemia on the expression of anti-inflammatory and pro-angiogenic genes.
Conclusions: Our results show that the retinal diabetic microenvironment influences the fate and function of ADSC, but also that ADSC appear more resilient compared to retinal pericytes.

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FETAL METABOLIC REPROGRAMMING: FETAL PLACENTAL GESTATIONAL DIABETES MELLITUS VASCULAR PROGENITOR CELLS RESEMBLE ADULT TYPE 2 PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Using the International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria, placentas and umbilical cord blood was isolated from 12 women with gestational diabetes mellitus (GDM: fasting blood glucose >82 mg/dl, glucose after 1 hr >158 mg/dl and glucose after 2 hours of >120 mg/dl) and 12 healthy pregnant women (fasting blood glucose 60-75 mg/dl, glucose after 1 hour 100-140 mg/dl and glucose after 2 hours 80-100 mg/dl). We strictly excluded women with pre-gestational diabetes, pre-eclampsia, cardiovascular disease and who had a body mass index (BMI) greater than 35.
Purpose: The objective of the study was to examine the effect of short-term hyperglycemia on angiogenic potential of placental vascular progenitor cells of GDM as compared with healthy controls.
Methods: We optimized protocols for the isolation, characterization and expansion of fetal placental EPCs and pericytes cultured from the placental disc and umbilical cord blood from GDM and healthy controls. Placental samples were also subjected to histological examination, transmission electron microscopy, gene expression and *in vivo* transplantation into CB17/Icr-Prkdcscid/IcrIcoCrl severe combined immune deficient (SCID) mice.
Results: Transmission electron microscopy of blood vessels in five sections of each placenta was examined and a total of 250 blood vessels per placenta were examined. GDM placental vasculature demonstrated pericyte ghosts, increased microvessel density and thickening of capillary basement membranes reminiscent of adult Type 2 Proliferative Diabetic Retinopathy that was not seen in healthy placentas ($p \leq 0.001$). Endothelial cell irregularity was noted in 76% GDM vs. 10.4% healthy placentas ($p \leq 0.001$). Mann Whitney Non-Parametric test was used. Placental fetal GDM -EPCs and pericytes showed functional abnormalities *in vitro* and *in vivo* when implanted in subcutaneous matrigel plugs in SCID mice, as compared with healthy control placental EPCs and pericytes.
Conclusions: We have detected phenotypic and functional changes of placental fetal vascular progenitor cells from GDM that resembles proliferative diabetic retinal cells. The GDM placenta could be used as a research tool that would enhance our understanding of pathophysiology and molecular signatures of adult type 2 proliferative diabetic retinopathy.

VASOREPARATIVE POTENTIAL OF A UNIQUE POPULATION OF STROMAL STEM CELLS (SSCS) IN ISCHAEMIC RETINA

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Design: Current therapies for diabetic retinopathy (DR) fail to address the primary vascular insufficiency that underlies the progression of the disease. As DR progresses, the retina becomes increasingly hypoxic, driving the stimuli for edema and/or aberrant neovascularization. As a novel therapeutic approach, we have assessed the vasoreparative and ischemia-reversing potential of a novel, highly-defined population of human bone marrow-derived SSCs in the retina.
Purpose: This study evaluates the effect of a unique SSC subpopulation on retinal vasculature in an experimental model of oxygen-induced retinopathy.
Methods: Human bone marrow-derived SSCs were sorted on the surface protein CD362+ (CD362 + SSCs), CD362- (CD362-SSCs) and plastic adherent SSCs (PA-SSCs). C57/Bl6 mice pups (postnatal day 7, P7) were exposed to high oxygen (75% O2/5 days). P13 mice received 1 µl intravitreal injection (in one eye) containing Qdot nanocrystal-labelled SSC-subtypes of low [1×10^3], medium [1×10^4] or high [1×10^5] cell numbers, or conditioned media (CM) from CD362+SSCs. Contralateral (control) eye was injected with vehicle (DMEM). After 3 days, retinal flatmounts were stained with isolectin B4/streptavidin-AlexaFluor488, and imaged using confocal microscopy. ImageJ software was used to quantify retinal vasculature (avascular or neovascular area/total area, in %). Two-tailed, paired *t*-test was used for statistical analysis.
Results: Intravitreal delivery of CD362 + SSCs showed significantly reduced avascular area compared to control, at medium ($p = 0.03$, $n = 6$) and high doses ($p = 0.04$, $n = 11$). No difference was found for low dose ($p = 0.51$, $n = 5$). CD362-SSCs promoted revascularization at medium dose only ($p = 0.04$, $n = 9$). PA-SSCs did not have a significant effect on avascular areas for all doses (low: $p = 0.74$, $n = 4$; medium: $p = 0.09$, $n = 8$; high: $p = 0.74$, $n = 12$). The increased revascularization may be a result of some CD362 cells associating with host vasculature in a perivascular manner as observed in confocal microscopy. No difference was found in neovascularization areas ($p > 0.050$) for all groups. When treated with CD362 + SSC-CM, both avascular ($p = 0.01$, $n = 9$) and pre-retinal neovascular areas ($p = 0.02$) were significantly reduced.
Conclusions: CD362 + SSCs promote revascularization of the ischemic retina, likely via secretion of complex paracrine factors. These findings suggest that human CD362+SSCs may be a novel cell therapy approach for ischemic disease, such as diabetic retinopathy.

FUNCTIONAL EVALUATION OF THE RETINA USING MULTIFOCAL ELECTRORETINOGRAPHY IN THE EARLY STAGES OF DIABETIC EYE DISEASE IN THE SETTING OF A MULTICENTER CLINICAL TRIAL

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Design: Prospective, randomized study.
Purpose: Development of a multicenter multifocal electroretinography (mfERG) normative database to evaluate early functional changes of the retina in patients with yype-2 diabetes (T2DM) with no diabetic retinopathy (DR) or mild non-proliferative DR (NPDR).
Methods: mfERG (103-hexagons) was performed in 111 healthy eyes and 450 T2DM patients - 194 had no DR and 256 had mild NPDR (ETDRS levels 20-35) - aged 45-75 and BCVA ≥20/25, using the RETI-port/scan21 (Roland Consult) in 11 European clinical sites of the EUROCONDOR study (NCT01726075). All the equipment was set up with fixed acquisition parameters. Standardized mfERG acquisition protocol was established and the equipment and technicians were trained and certified by the Coimbra Ophthalmology Reading Center. At each failed attempt in the training/certification activities, review notes and advice were given and new cases were requested to achieve certification. A mfERG normative database was established and used to calculate the Z-score value for all diabetic eyes responses. Abnormal P1 implicit time (IT) and amplitude were defined as a Z-score≥2 and Z-score≤-2, respectively.
Results: P1-IT (35.8 ± 1.8 ms) and amplitude values (50.3 ± 8.3 nV/deg2) were obtained from 111 healthy eyes (75% females) after technician's certification. Of the 36 technicians from the 11 clinical sites that achieved certification, 16 (44.4%) were certified at the 1st attempt; 16 (44.4%) at a 2nd and 4 (11.2%) only at a 3rd. When comparing the 450 T2DM patients/eyes (34% females) with normal controls the P1-IT was shown to be delayed (no DR: 36.7 ± 2.1 ms [$p = 0.0006$] and mild NPDR: 36.6 ± 2.5 ms [$p = 0.0025$]); P1 amplitude was found to be decreased (no DR: 46.0 ± 14.4 nV/deg2 [$p = 0.0044$] and mild NPDR: 42.9 ± 12.8 nV/deg2 [$p = 0.0000$]). In T2DM eyes the P1 IT was in the same range ($p = 0.883$) for eyes with no DR and with mild NPDR, whereas eyes with mild NPDR showed more decreased amplitude than eyes with no DR ($p = 0.0164$).
Conclusions: mfERG is a sensitive retinal functional examination that requires certification on acquisition procedures and methods but as shown it can be performed in the environment of a clinical trial. Eyes of patients with T2DM show delayed P1 IT and decreased P1 amplitude when compared with a normal population.

INNER RETINAL LAYER CHANGES IN TYPE 1 DIABETES MELLITUS WITHOUT CLINICAL DIABETIC RETINOPATHY

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Design: Retrospective study.
Purpose: To determine the changes of the inner retinal layers in patients with Type 1 diabetes mellitus (T1DM) without clinically detectable diabetic retinopathy (DR).

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Methods: Ninety patients with T1DM (90 eyes) and 100 healthy controls (100 eyes) were examined in İzmir Military Hospital between January 2012 - December 2014. DR status was evaluated by indirect funduscopy. Patients were included in the study if they were diagnosed with no clinical DR. Age, gender, duration since diagnosis of diabetes, fasting glucose level and serum glycosylated hemoglobin (HbA1c) were gathered from the patient charts. Right eyes of the each study and control subjects were examined with spectral domain optical coherence tomography (SD-OCT). Mean macular thickness, central foveal thickness and ganglion cell layer + inner plexiform layer (GCL + IPL) thicknesses were calculated using the macula map. Peripapillary retinal fiber layer thickness (RNFL) was measured by the instrument. Age, sex, spherical equivalent (SE), intraocular pressure (IOP) and axial length (AL) were compared among groups by means of analysis of variance (ANOVA). Groups were compared with Student *t*-test.
Results: Mean age of patients with T1DM was 23.9 ± 2.7 years and 23.4 ± 2.1 years for control group. The mean HbA1c was 8.3 ± 0.9% for T1DM group. Mean duration of the T1DM was 6.1 ± 2.9 years. There were no statistical differences in age, gender, SE, AL, and IOP between groups (p>0.05). Global RNFL was significantly decreased in T1DM group versus control (p<0.05). There were no differences in average and central macular thickness between groups. Average GCL/INL thickness were decreased in the T1DM group compared to controls (p<0.05).
Conclusions: Results of our study suggest that the decrease of the inner retina in T1DM patients with no DR caused by primarily by a thinning of the GC/INL in the pericentral area of the macula. These results may guide the development of neuroprotective therapeutic strategies for avoiding the complications T1DM in the future.

RETINAL VASCULAR GEOMETRY AND ITS ASSOCIATION TO 16-YEAR DEVELOPMENT OF MICROVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 1 DIABETES

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Design: Prospective, cohort subanalysis.
Purpose: To examine associations between baseline retinal vascular geometry (tortuosity, deviation from optimum branching coefficient [DFOBC] and length-diameter-ratio [LDR]) and 16-year incidences of diabetic proliferative retinopathy (PDR), nephropathy (DN) and peripheral neuropathy (DPN) in patients with type 1 diabetes mellitus (T1DM).
Methods: A cohort of 185 patients with T1DM participated in a clinical examination in 1995 and 2011, where blood and urine analyses were done and retinal images taken. PDR was defined as Early Treatment Diabetic Retinopathy Study level 61 or above, DN as albumin-creatinine-ratio ≥300 mg/g and DPN as vibration perception threshold >25 Volt. Retinal vessel parameters were measured using semi-automated software (Singapore I Vessel Assessment). Images obtained at baseline were, however, not disc-centered as needed by the software. Retinal vascular analyses could therefore not be performed in all cases. Images were re-evaluated and analyses were performed in the most disc-centered images as a small sub-study. These images were chosen masked to clinical data and data on complications.
For correlations between 1995 retinal vascular parameters and 2011 outcomes, Mann-Whitney's test was used.
Results: At baseline 22 patients had a nearly disc-centered image. Retinal vascular analyses and comparisons by outcomes were done in these cases. Mean age and duration of diabetes at baseline were 21.1 years and 13.4 years, respectively, and 50% were male. Patients with PDR, DN, or DPN at baseline were excluded for the respective analyses, and 16-year incidences were: 22.7%, 5.0%, and 11.1%, respectively.
Patients who later developed PDR had significantly higher arteriolar tortuosity (1.122 vs. 1.104, p = 0.031) and patients who developed DPN had significantly higher DFOBC (0.95 vs. 0.47, p = 0.049). No associations were found between retinal vascular parameters and the risk of developing macroalbuminuria.
Conclusions: Retinal vascular parameters as tortuosity and DFOBC may be used in early risk stratification in patients with T1DM. However, larger samples need to be examined and other baseline variables need to be taken into consideration before implementation in the clinic. Development in retinal vascular analysis software could ease the analysis in non-centered retinal images.

ASSESSMENT OF CORNEAL EPITHELIAL THICKNESS IN PATIENTS WITH DIABETES

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Design: Cross-sectional study.
Purpose: To investigate the features of corneal epithelial thickness with Fourier-domain optical coherence tomography (FD-OCT) in diabetes mellitus (DM) patients.
Methods: In this study, 60 DM patients; 23 with no diabetic retinopathy (NDR), 20 non-proliferative diabetic retinopathy (NPDR), 17 proliferative diabetic retinopathy (PDR) and 25 normal subjects (NDM) were enrolled. The inclusion criteria were no dry eye symptoms and signs (ocular surface index scores lower than 20, tear breakup time greater than 10 seconds, Schirmer test 1 value greater than or equal to 10 mm/5 minute), non-ocular surface abnormalities, glaucoma, ocular surgery and trauma. FD- OCT (RTVue; Optovue, Inc, Fremont, CA) with a corneal adaptor module was used. Central cornea (CET), paracentral cornea (PCET) and at the nasal (NLET), and temporal (TLET) limbal cornea epithelial thickness were compared with all groups. Correlations of epithelial thickness with the duration diabetic retinopathy were calculated.
Results: The mean age of NDM group was 53.7 ± 8 years (range 43-76), in NDR 7.2 ± 6 years (range 44-65), in NPDR group 55.6 ± 8.5 years (range 44-70), in PDR group 56.7 ± 8.6 years (range 44-68). Fisher exact test and analysis of variance showed that there were no statistical difference in sex (p = 0.449) and age (p = 0.708) among groups. The mean CET, PCET, NLET, and TLET was 53.9 ± 1 µm, 53.4 ± 0.7 µm, 52.2 ± 0.6 µm, and 52.1 ± 0.6 µm in NDM group, respectively. The mean CET, PCET, NLET, and TLET were 53.9 ± 0.7 µm, 53.3 ± 0.6 µm, 52.2 ± 0.8 µm, and 52.2 ± 0.8 µm in NDR group, respectively. The mean CET, PCET, NLET, and TLET was 53.4 ± 0.9 µm, 52.9 ± 0.8 µm, 51.7 ± 0.5 µm, and 51.6 ± 0.5 µm in NPDR group, respectively. The mean CET, PCET, NLET, and TLET were 52.9 ± 0.5 µm, 52.6 ± 0.7 µm, 51.4 ± 0.5 µm, and 51.3 ± 0.4 µm in PDR group, respectively. All corneal epithelial thickness measurements were statistically significant thinner in PDR group (p = 0.0003). The average CET, PCET, NLET, TLET positively correlated with DM duration (r = 0.433, p = 0.001; r = 0.323, p = 0.120; r = 0.228, p = 0.080; r = 0.262, p = 0.044, respectively).
Conclusions: FD-OCT demonstrated that corneal epithelial thickness was thinner in PDR eyes than no in healthy patients, no DR and NPDR eyes, implying that neuronal changes might play an important part in DM.

DIABETIC RETINOPATHY WITH A PICTURE OF LEBER'S HEREDITARY MICROANEURYSMS

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Design: Case report.
Purpose: To evaluate an unusual appearance of diabetic microaneurysms.
Methods: This 52-year-old male patient presented with subtle asymmetrical diabetic retinopathy with unusual superior temporal group of microaneurysms in one eye and relatively silent appearance in the other eye. The fundus fluorescein angiography, optic coherence tomography was done.
Results: Fundus fluorescein angiography revealed few aneurysms in the other eye. The microaneurysms close to the macula caused focal edema and decreased vision that was hardly controlled after several episodes of laser photocoagulation.
Conclusions: Diabetic retinopathy rarely may present a picture like Leber's heredity aneurysms. The clinical picture requires careful follow up for early detection of leakage from these abnormal vessels that may be controlled with several episodes of intensive laser photocoagulation.

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INTRA- AND INTERGRADER RELIABILITY OF SEMIAUTOMATIC MEASUREMENTS OF FUNDUS FLUORESCEIN ANGIOGRAPHY LEAKAGE IN PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Cross-sectional image grading study.
Purpose: Panretinal photocoagulation (PRP) is the gold-standard treatment for proliferative diabetic retinopathy (PDR). Fundus fluorescein angiography leakage (FFAL) is often used as a marker of disease activity, but evaluation of the difference between pre- and post-treatment FFAL is often difficult and not standardized. We propose a new model to quantify FFAL as a marker of PDR-activity. The purpose of the study was to evaluate the intra- and intergrader reliability of the model.
Methods: Two sub-studies were performed. In Sub-study A the area of FFAL of 50 images of PDR was measured by two independent graders, and intra- and intergrader intraclass correlation coefficients (ICC) were calculated. In Sub-study B the same two graders evaluated the area of FFAL from 14 sets of images taken at two different times. The amount of FFAL was determined and each grader categorized if there had been regression, steady state or progression. Regression/progression was defined as at least 10% change in area of FFAL. In both sub-studies all images were masked for each grader and between the graders. Intra- and intergrader kappa was calculated.
OPTOS widefield FFA (Optomap; Optos PLC., Dunfermline, Scotland, UK) was used and images 5 minutes after injection were chosen. Images were measured for FFAL using Image J (National Institute of Health, Bethesda, Maryland, USA), allowing for auto-marking of areas with FFAL. The grader then verified and/or adjusted the boundaries and measured the FFAL area in number of pixels.
Results: For the 50 images evaluated in Sub-study A, intragrader ICC was >0.99 for both graders, and intergrader ICC was >0.99. For the categorization of the 14 sets of images in sub-study B, intragrader kappa was 82.5% and 67.1% for grader 1 and 2, respectively, and intergrader kappa was 55.1%.
Conclusions: Measuring FFAL on Optomap images reliably has been a challenge historically. With our method, we have been able to achieve high intra- and intergrader reliability for area size, and moderate for progression.

REAL-WORLD WORKFLOW EFFECTS OF AUTOMATED DIABETIC RETINOPATHY SCREENING IN A PRIMARY DIABETES CARE SETTING WITH THE IDX-DR DEVICE

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Design: Cross-sectional study.
Purpose: Automated methods for detecting retinopathy from retinal color images have been previously described and validated. Though automated screening has the potential to increase the effectiveness of screening in primary care, it has not been clear how to integrate these devices into clinical workflow. We document the accuracy of an automated retinopathy screening device (IDx-DR) and changes in workflow resulting from using the IDx-DR in a real world primary diabetes care setting in the Netherlands.
Methods: Over the course of three months, 1,500 type 2 diabetes patients treated by the Diabetes Care System West-Friesland (DCS) in the Netherlands underwent screening for retinopathy where the IDx-DR device was deployed into the workflow. Each patient underwent digital fundus photography with results submitted to the IDx-DR automated screening system. IDx-DR provided automated results for both exam grading and image quality analysis. We analyzed changes to the workflow resulting from deployment of IDx-DR from the retaking of photographs until adequate image quality is determined by the IDx-DR system and from the time to report the IDx-DR results to the patient. Each fundus photograph was also graded by three retina specialists, which is considered the gold standard. The diagnostic accuracy of the IDx-DR device was tested and compared to the results from the three retina specialists using sensitivity, specificity, the positive predictive value and the negative predictive value. An ROC curve was plotted of the Sensitivity versus (1-specificity) of the IDx-DR device.
Results: Workflow changes were minimal; average in the chair time increased slightly due to extra imaging to ensure high quality photographs and turnaround time decreased significantly over manual grading. Additional clinical results for the 1,500 patients of sensitivity, specificity, accuracy, positive predictive value and negative predictive value of IDx-DR for retinopathy screening with respect to the gold standard will also be presented.
Conclusions: Small changes in workflow are acceptable and imply that automated diabetic retinopathy screening can be successfully translated into lab settings.

USING BOTH OPTOS WIDE-FIELD AND STANDARD TOPCON 7-FIELD IMAGES IN A CLINICAL TRIAL SETTING: ADVANTAGES AND CHALLENGES

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Design: Retrospective study.
Purpose: The current study enrolled bilateral, laser naïve patients with proliferative diabetic retinopathy (PDR). Either Optos wide-field scanning laser ophthalmoscope (SLO) or Topcon fundus camera was used for imaging. The aim of the current study was to assess the advantages/disadvantages of both platforms in grading for PDR.
Methods: Topcon standard 30° 7-field color and fluorescein angiographic (FFA) images were taken following pupil dilation while Optos wide-field images were taken un-dilated. PDR was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS). To assess the visibility and relative role of the retinal periphery in ETDRS grade, an outline of the composite boundaries of 7-field imaging was created in Adobe Photoshop and superimposed on Optos images. Lesions inside and outside the 7-fields area contributing to the ETDRS grades were recorded. FA image resolution was assessed based on the visibility of the FAZ boundaries. The presence and type of artefacts in both color and FA images was recorded.
Results: Images of 94 eyes of 47 participants were graded, taken at baseline and at 6-months. Topcon was used in 26 eyes of 13 patients while 68 eyes of 34 patients had Optomap. Lesions visible outside the ETDRS 7-field zone did not have a significant effect on the grading outcome of patients with PDR ($p = 0.91$). Optos images provided a significantly wider view of the fundus, however, variability in quality was higher, affecting measurements of FAZ and ischemic areas. Artefacts on Topcon were halos due to lens misalignment and specks due to lens surface impurities while on Optos mainly included obstruction of retinal view by lids/lashes. Optos had higher patient acceptance due to no pupil dilation and less flashing light.
Conclusions: For advance bilateral PDR Optos produced as good images as Topcon with advantage of a view of peripheral retinal lesions and it had higher patient acceptance. We found that wide-field imaging would more likely have an impact on ETDRS grade in eyes with less advanced disease.

INTRODUCING PERSONALISED RISK BASED INTERVALS IN SCREENING FOR DIABETIC RETINOPATHY: THE ISDR STUDY

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Design: Introduction and validation of a service intervention.
Purpose: Conventional screening involves annual review without evidence or an individualized approach. ISDR is a 5 year NIHR funded research program aiming to introduce a step-change in screening. We report the development, implementation into clinical practice and preliminary validation of risk-based screening in the context of a randomized controlled trial.
Methods: A purpose designed data warehouse (DW) was developed containing pseudonymized routinely collected NHS risk factor data from 1° care and the national retinopathy screening program (OptoMize v4) linked to research trial data. A risk calculation engine (RCE) with imputation for missing data was developed and validated. Patients randomized to individualized risk-based

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screening were allocated to a 6, 12 or 24 month interval. End-to-end testing between DW, RCE, randomization and OptoMize systems was completed. Data flows and suitability of interval assignment underwent statistical and credibility checks.
Results: 78/91 (85.7%) of general practitioners and 18,604/21,583 (86.2%) patients agreed to pseudonymized inclusion of their data in the DW, allowing development of the RCE. Data processing proved complex due to volume of data (2.86×10^{10}), algorithm complexity, missing data and the impact of widely diverse workforces. Between 12.11.14 and 23.01.15, 237 patients were randomized: 9 screen positive, 7 STDR, 1 ungradable, 1 significant other eye disease. 118 were allocated to the variable arm of the RCT: 6 months interval - 15, 12 months - 11, 24 months - 92. Electronic and clinical review showed correct allocations. 253/472 (54%) patients approached consented to enter the RCT. Patients declining consent had concerns about taking part in research and randomization.
Conclusions: Personalized risk-based screening based on routinely collected data appears feasible and is acceptable to professionals, patients and regulatory bodies. Patients engaged with data collection to form a local updating risk dataset. It proved possible to link different types of datasets into a fully automated electronic system.
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BARRIERS AND MOTIVATORS FOR ATTENDANCE AT DIABETIC RETINOPATHY SCREENING

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Design: Qualitative study using Thematic Analysis via semi-structured telephone interviews, questionnaires and focus-groups.
Purpose: The English NHS Diabetic Eye Screening Programme (NDESP) aims to reduce visual loss from diabetes through provision of annual screening by 84 local programs. Our local Diabetic Eye Screening (DES) program currently has in excess of 30,000 patients on its register from the 87 primary care GP practices in the area. Diabetic eye screening in this area is predominantly carried out at GP practices, with some clinics held in other locations. In 2013-14, our local screening program achieved an overall 73% screening uptake against minimum 70% and 'achievable' 80% NDESP targets with notable differences in uptake between GP practices. The program needs to increase uptake by identifying barriers and motivators for screening attendance
Methods: This qualitative study researched patients and staff from two GP practices representing high and low screening uptake when screening had recently taken place. After the annual screening visit to the GP practice, patients were contacted to ascertain if they would participate in this study. Six patients regularly attending screening and 6 who had not attended for over 2 years were recruited from each practice for semi-structured telephone interviews. Practice staff completed questionnaires and attended focus groups
Results: Communication was the main theme. Non-attenders were younger, prioritized work issues above eye health and were unaware of screening opportunities outside the annual practice visit. Few reported attending screening on GP recommendation and most were unaware that uncontrolled diabetes could lead to blindness. Practice nurses appeared reluctant to mention blindness in association with diabetes. Most patients thought screening was a 'once a year' opportunity at their practice. Practice staff were unaware of flexible appointments or other screening venues. The practice with higher uptake reviewed attendance, sending out letters to non-attenders whereas the other practice did not. Neither knew their previous year's screening uptake figures
Conclusions: Communication between DES, patients and primary care created misunderstandings. Information on flexible appointments and venues should be sent to GPs and to non-attenders. A performance report should be routinely provided by DES to GP practices.

FOUR YEARS RESULTS OF DIABETIC RETINOPATHY SCREENING SYSTEM IN INSTITUTE FOR CLINICAL AND EXPERIMENTAL MEDICINE IN PRAGUE

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Design: Our descriptive cohort research presents four years outcomes of diabetic retinopathy screening system in Institute of Clinical and Experimental Medicine in Prague (IKEM).
Purpose: To emphasize advantages of the screening system, ease of data acquisition and possible statistical evaluation of the correlations among them.
Methods: The screening system is based on the complex information system ZLATOKOP, which has a mode for an eye examination. It is connected to non-mydriatic fundus camera and offers pre-set parameters of evaluation and pre-defined editable texts. Patients screened and followed by this system are the in- and out- patients of IKEM suffering from diabetes or suspected of it.
Results: 2922 patients were examined by this screening system. 1500 suffered from diabetes type 1 (DM1), 1130 from diabetes type 2 (DM2), 82 had other type of DM and 210 were diabetes –free patients. In 1148 cases diabetic retinopathy was detected. Incipient non-proliferative diabetic retinopathy was found in 563 patients with DM1, 270 patient with DM2 and 16 patients with other types of DM. Moderate non-proliferative diabetic retinopathy was found in 128 patients with DM1, 56 patients with DM2 and 4 patients with other types of DM. Advanced non- proliferative diabetic retinopathy was detected in 29 DM1 patients and 23 DM2 patients. Proliferative diabetic retinopathy was diagnosed in 37 DM1 patients and 22 DM2 patients. Diabetic macular edema was detected in 76 DM1 patients, 38 DM2 patients and 1 patient with other type of DM. The number of patients referred to further ophthalmic evaluation or treatment was 83. Other risk factors such as hypertension, dyslipidemia or positive family history were recorded. In the group of diabetic patients, hypertension was found in 1562 cases, dyslipidemia in 1427 cases. Glycosylated hemoglobin levels and incidence of nephropathy were also observed in each group.
Conclusions: Data acquired from the ZLATOKOP screening system could be used in statistical analysis of diabetes and its complications, as well as to describe the correlation between the incidence of diabetic retinopathy and other risk factors.

A BASELINE SITUATION ANALYSIS OF DIABETIC RETINOPATHY (DR) SERVICES (DRS) IN 11 COMMONWEALTH COUNTRIES

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Design: A 5-year project funded by The Queen Elizabeth Diamond Jubilee Trust is designed to facilitate development of DRS to reduce unnecessary blindness in 11 countries, 8 in Africa, then Indonesia (self-funded), Pacific Islands and Jamaica.
Purpose: Approximately 80% of those with diabetes mellitus (DM) live in low/middle income countries where ophthalmic services cannot cope with the incoming tide of DR. Here we describe the situational analysis for the current provisions
Methods: A DR Network (DR-NET.Comm) was established amongst 14 eye institutions in the 11 countries, all participating in the VISION 2020 LINKS Programme based at the London School of Hygiene & Tropical Medicine. Two waves of questionnaires with increasing levels of details required on DRS were developed and distributed by the Steering Group. The information was collated as a situation analysis to guide planning, training and development of DRS at each location over this five-year project
Results: All 14 institutions returned all questionnaires (100%). Six DRS have a relevant database, 10 a fundus camera, 13 treatment facilities, 10 dedicated trained staff and 11 a public awareness program. In 2013, between zero to 4368 patients were imaged per DRS. In November 2014, the DR-NET.Comm workshop (held in London, UK) was attended by over 80 delegates. Using the situation analysis data, a country specific plan was developed by each partner to increase the number of patients accurately diagnosed and treated. These plans concentrated on the first two years of deliverables for developing their DRS model further and these were shared with the other groups.

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Data on numbers of patients actually treated and on the progress of the plan will be shared via a virtual network platform
Conclusions: The answers to the questionnaire confirmed that the 14 partners are in differing stages of development of DRS. The teams now provide support to each other and share resources as a consequence of the workshop, with the support of their UK LINKS partner. Progress will be reviewed during the second workshop in 2016 where plans for the following three years will be developed.

PREVALENCE OF DIABETIC RETINOPATHY AND ITS RISK FACTORS IN THE PAMDI POPULATION OF THE MEDITERRANEAN BASIN

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Design: Population-based cross-sectional study.
Purpose: To assess the prevalence of diabetes mellitus (DM) and diabetic retinopathy (DR) and to evaluate the associated risk factors in the PAMDI (Prevalence of Age related Macular Degeneration in Italian population) study of the Mediterranean basin.
Methods: Population based cross sectional study in (urban area) and around (rural area) of Padova, Northern Italy. Prevalence of DM in the studied population was assessed using self-reported and biochemical measures. Color fundus photography images were graded for characteristics of DR at the Moorfields Eye Hospital Reading Centre, London, UK. A multivariate logistic analysis evaluated the correlation of the factors with the presence of DM and DR.
Results: All 885 subjects from the PAMDI study were studied for DM and DR. The mean age was 71.6 years, with 45.5% being male. The overall prevalence of DM was 15.8%. Gradable images were available for 831 (93.9%) patients. Of those gradable, the prevalence of DR was 7.9%. The presence of DR was significantly associated with male gender ($p = 0.011$), high blood sugar level ($p<0.0001$), younger age ($p = 0.039$) and urban area of residence ($p = 0.004$). The 77.4% of all cases were mild DR with only 1 case with proliferative DR. There were 18 cases of DR but no DM, 7 were male and the average age was 71 years. There were 13 urban residents. Hypertension was diagnosed in 12 cases.
Conclusions: There is a high prevalence of DM in this Northern Italian population with significant increase in the urban area, especially in the younger male patients. IDF estimates (2014) show that Italy has a 7.71% global prevalence of DM, with nearly 25,000 diabetes related deaths being recorded per year and an average cost of USD3371.23. These are likely to be underestimates given our findings and this will need to be investigated further in more recent and extensive cohorts.

THE STRUCTURE OF DISABILITY IN PATIENTS WITH OCULAR COMPLICATIONS OF DIABETES AND THE ORGANISATION OF CARE

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Design: Retrospective analysis.
Purpose: To study the nature of disability due to ocular complications of diabetes mellitus (DM) in Tashkent, Uzbekistan and the knowledge amongst patients and health professionals of the same topic
Methods: In Tashkent, during the last 10 years 347 patients with DM had examination carried out in a specialized ophthalmic center by experts who determined their level of disability. The average age of DM patients was 55 years, 59% were males, and 87% had Type 2 DM. A survey on knowledge of diabetic eye disease using a questionnaire of 711 doctors from 72 family health centers in Tashkent city was also carried out. Groups of respondents were general practitioners (82.8%), endocrinologists (9.6%) and ophthalmologists (7.6%). 154 patients with diabetic retinopathy also completed the questionnaire (12.6% with type 1 DM); 89 patients were residents of Tashkent while 65 came from other regions of the country.
Results: The analysis concentrated on disability due to ocular complications of DM and its prevalence for 2003-2012 years. 35 new cases of disability was found, of which 23 (66%) were in the most severe group of disability, 10 (29%) in the second severest group of disability, and only 3 (6%) with minor disability; indicating that most people are at least severely affected by DM. According to the medical practitioners' survey, nearly half of GPs (43.5%) only sent DM patients for ophthalmological examination when there were already visual complaints. In the survey of DM patients, 59% were not aware of the need for regular eye exams and the possible eye complications.
Conclusions: This study found insufficient treatment and prophylaxis coverage of DM patients with ocular complications in our city. To effectively monitor the status of patients with DM and development of its eye complications, coordinated work between primary health care and team of specialists is necessary.

PREVALENCE OF DIABETIC RETINOPATHY IN NEW ONSET DIABETES AFTER KIDNEY AND LIVER TRANSPLANTATION

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Design: Retrospective study.
Purpose: The audit aims to analyze the microvascular complications of a cohort of patients with new onset of diabetes after transplantation (NODAT).
Methods: Records of 552 transplantations (343 kidney and 209 liver) at the Queen Elizabeth Hospital Birmingham over 2007-2014 were examined for evidence of NODAT. Patients with pre-existing diabetes and those living outside the screening area were excluded. The timing and results of retinal screening using digital photography were analyzed in all patients with NODAT. The UK national diabetic retinopathy grades were used.
Results: NODAT was diagnosed in 50 kidney transplant patients and 6 liver transplant patients (mean age is 56 (range 80-21 years) 27 male 29 female). 34 (60.7% were first screened within one year of diagnosis of NODAT). 13 (23.2% after one year), 5 (8.9% after 2 years or later) and 3 (5.4%) have not been screened. Those screened within one year showed 27 R0M0, 5 R1M0 and 3 with R1M1. Those first screened after one year showed 9 R0M0, 3 R1M0 and 1 R1M1. Those first screened after two years or later showed 3 R0M0, 1 R1M1 and 1 was un-assessable. No patient had features of pre-proliferative or proliferative retinopathy
Conclusions: NODAT provides evidence of the minimum rate of retinopathy to be expected at the diagnosis of type-2 diabetes. This was not different from reports in type-2 diabetes in general. Whether the retinopathy is due to diabetes, hypertension or other factors is not certain but further follow up will help to document the natural history of retinopathy in these patients.

THE EFFECTS OF OBESITY, DIABETIC REGULATION, HYPERLIPIDAEMIA AND INSULIN PREPARATION ON DIABETIC RETINOPATHY

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Design: Qualitative descriptive clinical study.
Purpose: To evaluate the effects of body mass index (BMI), diabetic control, lipid parameters, serum C-reactive protein (CRP), insulin usage and blood pressure on diabetic retinopathy (DR).
Methods: Consecutive patients with Type 2 diabetes mellitus (T2DM) attending an eye polyclinic between 2011 and 2014 were evaluated retrospectively. Data collected according to standard protocols included: demography, medical history, DR status (none, background, pre-proliferative, proliferative, macular edema (ME)), BMI (kg/m^2), blood pressure at rest (30 minutes), HbA1c, CRP and fasting glucose and lipids. Funduscopy was performed by the same physician. Medications used for treatment of T2DM and smoking status were also recorded.
Results: Altogether 1184 T2DM were recruited: 778 (65.7%) were female. Numbers of patients (%) with no DR, background DR, pre-proliferative DR, proliferative DR, and ME were 454 (38.3%), 292 (24.7%), 193 (16.3%), 122 (10.3%), and 123 (10.4%), respectively. There was a strong correlations between the severity of DR and CRP, HbA1c and low-density lipoprotein cholesterol (LDL-C) levels (all $p = 0.001$). DR was more severe in patients with a BMI $\geq 30\ kg/m^2$ and those with hypertension ($p = 0.001$). More severe DR was found in patients using insulin compared to those on oral antidiabetic drugs ($p = 0.001$). No statistically significant association was detected for gender or smoking status.

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Conclusions: In this study we found more severe DR in patients who had a higher CRP, HbA1c, LDL-C levels, were obese, used insulin and who had hypertension. We recommend that patients who have any of these risk factors should be monitored more closely for development and progression of DR.

THE RELATION BETWEEN OPEN-ANGLE GLAUCOMA AND THE SEVERITY OF DIABETIC RETINOPATHY: A SINGLE CENTRE EXPERIENCE

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Design: Qualitative clinical research.
Purpose: To investigate the relationship between the severity of diabetic retinopathy (DR) in patients with type-2 diabetes mellitus (T2DM) and primary open-angle glaucoma (POAG) in an adult population in the South Eastern region of Anatolia.
Methods: Consecutive patients with T2DM were included. Data collected according to standard protocols included: demography, medical history, retinopathy status (none, background, pre-proliferative, proliferative, ME), perimetry, pachymetry and Goldman's applanation tonometry. χ-square test was used to compare the POAG rate between groups and Pearson test to evaluate the correlation between the severity of POAG and DR.
Results: Altogether 1184 T2DM patients were recruited; 778 (65.7%) were female. Numbers of patients (%) with no DR, background DR, pre-proliferative DR, proliferative DR, and ME were 454 (38.3%), 292 (24.7%), 193 (16.3%), 122 (10.3%), and 123 (10.4%) respectively. Mean ages of all DR groups were similar apart from patients with no DR who were younger, but not statistically significantly. POAG was detected in 11 patients (2.4%) with no DR, 10 (3.4%) with background DR, 12 (6.2%) with pre-proliferative DR, 14 (11.5%) with proliferative DR, and 8 (6.5%) with ME (6.5%). There was a statistically significant difference between DR groups in terms of POAG prevalence ($p = 0.0001$), and there was a significant correlation between the severity of DR and POAG ($p<0.00001$). POAG prevalence was higher (4.6%) than in the non-diabetic population.
Conclusions: Previous studies have demonstrated the relationship between the duration of diabetes, blood glucose levels and the risk of glaucoma, but there is little data about the possible relationship between the severity of the DR and glaucoma. We found an increased risk of glaucoma in patients with more severe DR. However, larger scale studies are needed to support these findings.

EVALUATION OF SEXUAL DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES AND DIABETIC RETINOPATHY

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Design: Qualitative clinical study.
Purpose: To evaluate the possible correlation between (DR) and sexual dysfunction among diabetic patients in South Eastern Anatolia.
Methods: Consecutive diabetic patients referred to our eye clinic from internal diseases polyclinics between 2011 and 2014 were included. Retinopathy status was determined by the same physician according to standard protocols as: none, background, pre-proliferative, proliferative, macular edema. The Arizona Sexual Experience Scale (ASEX) was used to evaluate sexual dysfunction. ASEX is a user-friendly 5-item rating scale that quantifies sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. Total score higher than 20 is considered as severe sexual dysfunction.
Results: 1184 patients were recruited; 778 (65.7%) were female. Number of patients (%) with no DR, background DR, pre-proliferative DR, proliferative DR and macular edema were 454 (38.3%), 292 (24.7%), 193 (16.3%), 122 (10.3%), and 123 (10.4%), respectively. The proportions of patients with severe sexual dysfunction were 15/454 (3.3%) in those with no DR, 9/292 (3.1%) with background DP, 68/192 (35.2%) with pre-proliferative DR, 66/122 (54.1%) with proliferative DR, and 55/123 (44.7%) with macular edema. We found a statistically significant difference between patients with no and background DR and the other more severe DR groups ($p<0.0001$). Additionally, there was a correlation between the severity of DR and the severity of sexual dysfunction ($p = 0.001$).
Conclusions: The relationship between diabetes and sexual dysfunction has been demonstrated in previous studies. In this study we have shown a correlation between the severity of DR and the severity of the sexual dysfunction in both genders. Screening of sexual dysfunction should become a part of routine care in the management of type 2 DM patients.

DOES DIABETES WORSEN MACTEL?

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Design: International prospective study.
Purpose: In the worldwide Type 2 Macular Telangiectasia (MacTel) Study, increased prevalence of diabetes mellitus (DM), obesity, hypertension, and cardiovascular diseases were observed. Up to 28% of the cohort had diabetes, but relatively little is known if progression of MacTel differs in patients with and without DM.
Methods: Patients with 6-year follow-up from the cohort of the MacTel Natural History Study with a confirmed diagnosis of MacTel, and gradable color and fluorescein angiography (FA) images were included. Patients with MacTel and DM and a relevant number of subjects matched by age/gender but without DM were selected. The stage of MacTel was determined by grading of the fundus images and FAs according to the Gass and Blodi classification.
Results: In this present study, 140 eyes of 70 patients with MacTel and DM (MT/DM) and 216 eyes of 108 patients with MacTel only (MT) were graded at baseline and at 6 years follow-up. The mean age for the MT/DM group was 61 years with 42% being male and for the MT group was 59 years with 30% being male ($p = 0.26$). Of the MT/DM group, altogether 7 eyes had diabetic retinopathy (DR) at baseline and 14 eyes at 6 years follow-up, with no cases developing severe or proliferative DR. There were 3 eyes with diabetic maculopathy (DMac) at baseline, and 8 at 6 years follow-up, with only one with visually threatening features. No patient had treatment for DR/DMac during the follow-up.
There was a significant correlation between DR/DMac with increasing age and VA at baseline and after 6 years ($p = 0.01$ and $p = 0.1$ respectively). Patients in the MT/DM group had worse stages of MacTel initially, but progression of MacTel was not statistically different between the two groups (% average change = 5.49%, $p = 0.77$).
Conclusions: The purpose of our study was to investigate if DR/DMac has an impact on progression of MacTel. Our results confirm that patients with DM have slightly worse initial disease, but the speed of progression does not seem to be influenced by DM.

THE PREVALENCE AND RISK FACTORS OF DIABETIC MACULAR EDEMA: A CROSS-SECTIONAL STUDY IN TURKEY

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Design: A cross-sectional study.
Purpose: To investigate the relationship between diabetic macular edema (DME) and potential risk factors.
Methods: Clinical and metabolic parameters were determined and ophthalmic examinations were performed by stereoscopic fundus examination, fluorescein angiography and optical coherence tomography.
Results: A total of 413 patients were evaluated and in 15.3% DME was identified. Duration of diabetes mellitus, serum creatinine levels and presence of microalbuminuria/albuminuria were significantly higher in the patients with DME ($p<0.05$). There was a positive correlation between DME and duration of DM ($r = 0.386$, $p<0.001$), and hemoglobin A1c (HbA1c) ($r = 0.115$, $p = 0.022$).

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Logistic regression analysis revealed that patients with HbA1c levels ≥6.5% had a 3.57 fold increased risk and male patients had 3.27 fold increased risk. The presence of proteinuria (2.42 fold in microalbuminuria, 2.12 fold in macroalbuminuria) also increased the risk of DME independently.
Conclusions: We determined that the prevalence of DME in our study population was 15.3% and strict regulation of blood glucose levels reduced the risk of DME.

BASELINE CHARACTERISTICS OF DIABETIC MACULAR EDEMA PATIENTS FROM THE SECOND INTERIM ANALYSIS OF THE REAL-WORLD LUMINOUS STUDY

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Design: LUMINOUS (NCT01318941) is an ongoing 5-year, global, multicenter, prospective, observational study.
Purpose: To present the baseline characteristics of patients with visual impairment due to diabetic macular edema (DME) recruited prior to March 2014 (n = 1758).
Methods: LUMINOUS is the largest prospective observational trial in medical retina to date designed to evaluate long-term safety, effectiveness, treatment patterns, and health-related quality of life outcomes in patients treated with ranibizumab 0.5 mg across all approved indications in routine clinical practice as per the local product label. Consenting adult patients, treatment naïve or those previously treated with ranibizumab or other ocular treatments were recruited. Scheduled annual interim analyses are performed in March of each study year
Results: 20,085 patients were enrolled before March 2014, 1758 had DME (481 were treatment-naive, 709 previously treated with ranibizumab, 568 received prior ocular treatments other than ranibizumab (treatment history defined as in the primary treated eye). The mean age was 64.2 years, 54% were male, and baseline HbA1c was 7.8%. The top recruiting countries were the UK (26.8%), Canada (18.1%), and Russia (14.7%). Median time from diagnosis of DME to first treatment was 0.003 years for treatment-naïve patients and time from diagnosis to study entry was 1.59 years for the prior-ranibizumab and 0.25 years for the other ocular treatment group. Overall, the prior-ranibizumab treated group had higher baseline visual acuity (VA) and lower central retinal thickness (CRT) than the treatment-naïve or other ocular treatment groups (57.8 vs 55.5 and 55.8 letters; 378.6 vs 432.6 and 435.1 µm). Baseline comorbidities included 7.4% of patients with prior myocardial infarction, 6.1% with prior stroke, 14.1% with family history of coronary artery disease, 67.2% were hypertensive and 23.5% were obese.
Conclusions: There are limited real world data regarding the use of ranibizumab in patients with DME. Patients recruited to LUMINOUS are reflective of those in clinical practice. LUMINOUS will provide an invaluable source of long term real-world data regarding the use of ranibizumab in such patients with DME across diverse geographies.

THE COMPARISON OF SHORT TERM EFFECTIVENESS OF GRID LASER PHOTOCOAGULATION, INTRAVITREAL TRIAMCINOLONE ACETONIDE AND INTRAVITREAL BEVACIZUMAB IN DIFFUSE DIABETIC MACULAR EDEMA

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Design: Retrospective study.
Purpose: We aimed to compare the short term effectiveness of grid laser photocoagulation (GLP), intravitreal triamcinolone acetonide (IVTA) and intravitreal bevacizumab (IVB) injections in diffuse diabetic macular edema (DDME) and the effect of these treatment modalities on macular function.
Methods: The medical records of 44 patients with DDME who had received GLP, IVTA or IVB treatment between January 2010 and February 2012 with a minimum 3 months post-treatment follow-up were studied. Patients were divided into 3 groups as GLP (15 eyes), IVTA (14 eyes) and IVB (15 eyes). Best corrected visual acuity (BCVA), central macular thickness (CMT), macular sensitivity (MS) using microperimetry and intraocular pressure (IOP) were evaluated before treatment and 1 and 3 months after treatment. The correlation of these parameters with baseline HbA1c level was also investigated.
Results: There was no significant IOP change in any group during follow-up (p = 0.887, p = 0.283, p = 0.822). In the GLP group there was no significant change in BCVA or CMT, but an insignificant decrease in MS was observed at 3 months (p = 0.102, p = 0. 281, p = 0.147, respectively). In the IVTA group there was a statistically significant increase in BCVA and SMK at months 1 and 3 and an insignificant increase in MS at month 3 (p = 0.006, p = 0.005, p = 0.272, respectively). In the IVB group, BCVA and CMT showed insignificant increases at month 1 (p = 0.054, p = 0.112) and significant increases month 3 (p = 0.006, p = 0.02). Also MS showed a significant increase at month 3 (p = 0.002). We detected that the response to treatment was better if HbA1c level was <7% in GLP group and >7% in IVB group. The IVTA group didn't show a correlation with HbA1c level.
Conclusions: GLP, IVTA and IVB was a successful part of DDME treatment in the short term. If the HbA1c level is higher than 7% delaying the GLP treatment and applying IVB or IVTA instead of this until metabolic control is achieved may be suitable as a rational treatment approach.

CHANGES IN VISION RELATED QUALITY OF LIFE IN PATIENTS WITH DIABETIC MACULAR EDEMA: RANIBIZUMAB OR LASER TREATMENT?

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Design: A prospective randomized study.
Purpose: To compare the changes in vision related quality of life (VR-QoL) in patients with diabetic macular edema (DME) undergoing intravitreal ranibizumab (IVR) injection or focal/grid laser.
Methods: In this prospective study, 70 patients with clinically significant macular edema (CSME) were randomized to undergo IVR injection (n = 35) and focal/grid laser (n = 35). If necessary, the laser or ranibizumab injections were repeated. Distance and near visual acuities, central retinal thickness (CRT) and 25-item Visual Function Questionnaire (VFQ-25) were used to measure the effectiveness of treatments and VR-QoL before and at month 6 following IVR or laser treatment.
Results: The demographic and clinical findings before the treatments were similar in both main groups. The improvements in distance and near visual acuities were higher in the IVR group than the laser group (p<0.01). The reduction in CRT in the IVR group was higher than laser treatment group (p<0.01). In both groups, the VFQ-25 composite score tended to improve from baseline to 6 months. At month 6 the changes in composite score were significantly higher in the IVR group than in the laser group (p<0.05). The improvements in overall composite scores were 6.3 points for the IVR group compared with 3.0 points in the laser group. Patients treated with IVR and laser had large improvements in composite scores, general vision, near and distance visual acuities and VFQ-25 at 6 months, in comparison with baseline scores, and also in the mental health subscale in IVR group.
Conclusions: Our study shows that IVR improved not only visual acuity and CRT, but also vision related quality of life more than laser treatment in DME. These patient-reported outcomes may play an important role in the treatment choice in DME for clinicians.

CASE SERIES EVALUATING INTRAVITREAL FLUOCINOLONE IMPLANT (ILUVIEN®; [FAc]) IN THE TREATMENT OF PATIENTS WITH CHRONIC DIABETIC MACULAR EDEMA (DME) INSUFFICIENTLY RESPONSIVE TO CURRENT TREATMENT OPTIONS

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Design: Patients with chronic DME can be difficult to manage with available therapies. Based on results from the Fluocinolone Acetonide in Diabetic Macular Edema (FAME) studies, ILUVIEN® is NICE-approved for pseudophakic DME insufficiently responsive to available therapies. This case series evaluates outcomes post-FAc implant in patients insufficiently responsive to therapy, with chronic DME defined first anatomically (cystoid morphology), then chronologically (≥18 months).
Purpose: Chronic DME was defined as ≥3 years DME in FAME, but has subsequently been more accurately calculated as ≥1.73 years. Earlier use based on anatomically defined DME may be appropriate in patients insufficiently responsive to therapy.

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Methods: Patients (n = 4 females; n = 4 males; 47-81 years), with type-2 diabetes and DME (first noted between 2008 and 2013), were followed for up to 9 months post-FAc implant. Visual acuity (VA), intraocular pressure (IOP), and central retinal thickness (CRT) were assessed.
Results: All patients had received prior laser photocoagulation and anti-VEGF therapy; 6 had received intravitreal steroid injections, with VA improving in 3. All patients had undergone phacoemulsification with/without vitrectomy, or phacovitrectomy, with no sustained DME improvement. Baseline VA pre-FAc implant was ≤6/12 in 5 of 8 patients, 2 of whom achieved VA of 6/12 at the last recorded visit. Overall, VA improved from baseline in all but one patient (taut posterior hyaloid); CRT still reduced 37.4% in this patient. Best observed improvement in VA was 6/12 to 6/6, with a corresponding 79.7% reduction in CRT (555 µm reduction from 696 µm) and resolution of edema. Patients had a mean change in IOP of -1.65 ± 1.65 mm Hg, with one exception where IOP increased to 50 mm Hg; however, this was effectively managed with IOP-lowering eye drops, dropping to 12 mm Hg within 1 day.
Conclusions: Sustained-release FAc implant provides clinical benefit in patients with type-2 diabetes and chronic DME insufficiently responsive to existing therapies. In these patients, DME was defined first by anatomical measures, then by duration. FAc implant shows promising outcomes in patients with insufficiently responsive DME, including those with duration <3 years.

ANATOMICAL AND FUNCTIONAL RESULTS AFTER DIFFERENT TREATMENT MODALITIES IN SEROUS MACULAR DETACHMENT ACCOMPANYING DIABETIC MACULAR EDEMA

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Design: Nonrandomized interventional.
Purpose: To investigate the effect of a variety of treatment modalities on central macular thickness (CMT), serous macular detachment (SMD) height and best corrected visual acuity (BCVA) in diabetic macular edema (DME) with serous macular detachment.
Methods: Eighteen eyes of 15 female and 20 eyes of 13 male patients with Type 2 diabetes mellitus (T2DM) with DME and SMD attending the Retina Clinic were included. Treatment modalities included single intravitreal bevacizumab (2.5 mg) (9 eyes), three doses (one dose per month) bevacizumab (2.5 mg) (15 eyes), three doses (one dose per month) ranibizumab (0.5 mg) (6 eyes), pan retinal photocoagulation (3 eyes), intravitreal triamcinolone acetonide (4 mg) (3 eyes) and grid laser (1 eye). Clinical evaluation included BCVA, OCT imaging with emphasis to CMT, SMD height change, integrity of external limiting membrane and inner segment/outer segment band (IS/OS) at baseline, months 1, 3 and 6 after treatment. Statistical analysis comprised independent and paired *t* tests.
Results: Proliferative diabetic retinopathy (PDR) was present in 34.2% of the patients. CMT and SMD height decreased significantly when compared to baseline at month 1, 3 and 6 in both PDR and non-PDR groups. BCVA increased significantly during months 1 and 3 in the PDR group and only at month 1 in the non-PDR group. With respect to presence of PDR or non-PDR, there was no correlation between change in SMD height and change in BCVA. DME with or without cysts was present in half of the patients and cystoid macular edema pattern in the other half. Presence of either diffuse or cystoid macular edema OCT pattern was not correlated with BCVA change. Eyes with a disturbance of ELM and IS/OS band integrity (20 eyes) had significantly lower baseline and follow-up BCVA and lower response to treatment when compared with eyes with continuous ELM and IS/OS band integrity ($p<0.05$)
Conclusions: Treatment caused a significant decrease in height of SMD and CMT during 6 months follow-up in this series of DME with SMD. Photoreceptor cell layer integrity was found to be an important factor effecting visual acuity gain after treatment.

RANIBIZUMAB TREATMENT FOR DIABETIC MACULAR OEDEMA (DMO): INITIAL RESPONSE AND NICE COMPLIANCE

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Design: Since April 2013, NICE in the UK has approved the treatment of DMO with a central retinal thickness (CRT) of greater than 400 µm with the anti-VEGF agent ranibizumab. This audit assesses the initial response to treatment in a busy teaching hospital environment.
Purpose: The primary purpose was to assess the anatomical and functional efficacy of initial treatment both in terms of CRT and visual acuity (VA) and time to treatment. The secondary purpose was to identify the proportion with CRT >400 µm.
Methods: Data for were ascertained from a departmental electronic database. The OCT scans, electronic patient records and patient notes were reviewed. Data concerning age, gender, CRT, VA, clinic visits and the dates of treatment were collected.
Results: 153 patients (186 eyes) were studied. 73.6% patients received treatment with ranibizumab within 6 weeks of the decision to treat. VA improvement of at least 5 EDTRS letters occurred in 51.9% of eyes after the first 3 injections. CRT data demonstrated a reduction in 92.7% eyes; 61.3% were at least 20% less. Furthermore, our cohort demonstrated an average increase in visual acuity of 2.8 EDTRS letters and an average improvement of CRT by 134 µm after 3 injections. The audit also showed that 95.4% met the eligibility criteria of CRT >400 µm. In those <400 µm, the improvement of CRT was only 27.6 µm, and only 29% improved by at least 5 EDTRS letters.
Conclusions: Our results show that there was a good response to ranibizumab in the short term, supporting clinical trials, as an effective treatment for DMO. The poorer response in the subgroup of those with a CRT <400 µm further supports NICE guidance in the UK and the results of the RESTORE study. We plan to conduct a one-year follow up study to evaluate the long term response and determine whether there are any late responders in the cohort.

COMPARISON OF EFFECTS OF INTRAVITREAL VERSUS POSTERIOR SUBTENON TRIAMCINOLONE ACETONIDE INJECTION ON INTRAOCULAR PRESSURE IN PATIENTS WITH DIABETIC MACULAR EDEMA

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Design: Retrospective cohort.
Purpose: To compare the effects of intravitreal triamcinolone acetonide (IVTA) (4 mg/0.1 ml) and posterior sub-Tenon triamcinolone acetonide (PSTA) (40 mg/ml) injection on intraocular pressure (IOP) in patients with diabetic macular edema (DME).
Methods: Fifty-eight eyes of 45 patients with diabetic retinopathy (DR) who received IVTA, and 60 eyes of 44 patients who received PSTA for DME were compared retrospectively. Visual acuity, IOP, biomicroscopic anterior and fundus examinations were performed before injections (baseline) and at months 1, 2, 3, 6, and 9 of follow-up, and pre- and post-treatment difference in IOP were compared within groups. Anti-glaucoma therapies were recorded. Paired Student's *t* test was used to compare mean IOP of the groups.
Results: The female/male ratio was 28/17 in the IVTA group and 26/18 in the PSTA group. Mean age was 64.5 and 64.7, respectively. There were no statistical difference between gender and mean ages of the groups. IOP increased 25 mm Hg in 20 eyes of 15 patients (34.5%) of the IVTA group; anti-glaucoma therapy was required for a mean of 6 weeks then decreased to pre-treatment levels. Mean IOPs in the IVTA group at baseline and months 1, 2, 3, 6 and 9 were (p value compared to baseline): 13.7, 24.6 (<0.001), 23.9 (<0.001), 13.2 (0.09), 12.2 (NS), and 13.2 (NS) mm Hg, respectively. In the PSTA group they were 13.3, 13.3, 13.2, 13.1, 13.3, and 13.3 mm Hg, respectively (p values all NS).
Conclusions: Intravitreal and sub-Tenon steroid injections are widely used in DME. Owing to the fact that IVTA is associated with a higher incidence of IOP, PSTA should be considered as a safe supplemental method in the treatment of DME.

INTRAVITREAL RANIBIZUMAB FOR MACULAR EDEMA IN PATIENTS WITH DIFFERENT DIABETIC RETINOPATHY SEVERITY

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Design: Retrospective research study.
Purpose: To demonstrate the efficacy of intravitreal ranibizumab for diabetic macular edema (DME) in patients with variable diabetic retinopathy (DR) severity.

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Methods: Fifty five eyes of 55 patients with a loading dose of 3 monthly intravitreal ranibizumab injections for DME were retrospectively reviewed. Patients were divided into three groups: Group 1: patients treated with only intravitreal ranibizumab; Group 2: patients treated with focal or grid laser before intravitreal ranibizumab and Group 3: patients treated with intravitreal ranibizumab and pan-retinal laser photocoagulation. Patients were examined at 1, 3, and 6 months after a loading dose of intravitreal ranibizumab injection. Patients were evaluated for age, gender, type and duration of diabetes, systemic treatment, type of DME, time of laser, best corrected visual acuity (BCVA), central foveal thickness (CFT). BCVA (logMAR) and CFT of the patients were compared with paired *t* test.
Results: Mean duration of diabetes was 14.4 ± 8.8 years. Mean BCVA at initial examination was 0.6 ± 0.4. Mean BCVA after loading dose was significantly increased to 0.5 ± 0.4 and 0.5 ± 0.4 at 1 and 3 months (p = 0.001, p = 0.001). Mean CFT was 478 ± 138 µm at initial examination, 379 ± 117 µm at 1 month, 423 ± 121 µm at 3 months and 438 ± 140 µm at 6 months. There was a significant decrease in CFT between pre- and post-injections. Group 1 had a significant difference between initial and 1 month CFT, but there were no significant differences in BCVA. In Group 2 the BCVA was significantly higher at 1 and 3 months than initially (p = 0.001, p = 0.002). Group 3 had significantly increased BCVA at 1 month and 3 month (p = 0.009, p = 0.035). CFT was significantly decreased at 1 month, 3 months and 6 months after the loading dose.
Conclusions: Intravitreal ranibizumab may be more effective if it is performed in addition to focal and grid laser. It is useful in stabilizing CFT between 1 to 6 months and BCVA between 1 to 3 months. Even if anatomical improvement or stabilization is observed for 6 months, decreased visual acuity 3 months after the loading dose limits ranibizumab's functional efficacy.

COMBINED INTRAVITREAL RANIBIZUMAB AND POSTERIOR SUB-TENON INJECTION OF TRIAMCINOLONE ACETONIDE FOR THE TREATMENT OF DIABETIC MACULAR EDEMA WITH SEROUS RETINAL DETACHMENT

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Design: Retrospective case series.
Purpose: Our aim was to evaluate the efficacy of intravitreal ranibizumab (IVR) combined with posterior sub-Tenon injection of triamcinolone acetonide (STTA) for the treatment of diabetic macular edema (DME) with serous retinal detachment.
Methods: Fifty-eight eyes of 41 consecutive DME patients with serous retinal detachment were treated with IVR and STTA. The primary outcome measures were change in central macular thickness (CMT) and best corrected visual acuity (BCVA). The secondary outcome measure was the rate of patients with intraocular pressure (IOP) increase requiring medical treatment.
Results: Mean initial CMT was 529.6 ± 126.8 µm. Macular thickness of the eyes with IVR and STTA was significantly reduced both after one (321.9 ± 88.8 µm; p<0.05) and after 3 months (358 ± 131.5 µm; p<0.05) of treatment. The eyes treated with IVR and STTA showed significant improvement in visual acuity, both after 1 (0.28 ± 0.18; p<0.005) and 3 months (0.27 ± 0.17; p<0.005). Elevation of IOP occurred in 3 eyes (7.3%).
Conclusions: Intravitreal ranibizumab and STTA seems to be effective in improving BCVA and DME in patients with diabetes who also have serous retinal detachment.

THE EFFICIENCY OF DEXAMETHASONE INTRAVITREAL IMPLANT IN THE TREATMENT OF MACULAR EDEMA SECONDARY TO DIABETES MELLITUS

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Design: Retrospective study.
Purpose: To evaluate the efficacy and safety of dexamethasone (DEX) intravitreal implant treatment in eyes with diabetic macular edema caused by diabetes mellitus.
Methods: Visual acuity tested in logMAR with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, central macular thickness (CMT) measurements, intraocular pressure (IOP) and side effects after treatment were observed monthly.
Results: 22 eyes of 22 patients with diabetes were studied. LogMAR visual acuity improved significantly in the first four months after 1.1 ± 0.3 (range 1-2) intravitreal DEX treatment (p<0.01), but no statistically significant change was observed in the following four months (p>0.05). A statistically significant decrease in CMT was observed in the first three months, but no statistically significant change was observed in the following four months. A statistically significant increase in IOP was observed in the first two months, but no statistically significant change was observed in the following months. The intraocular pressure was successfully controlled with medication in all the participants with elevated IOP. Two eyes developed cataracts requiring surgery.
Conclusions: Both functional and anatomical effects of intravitreal DEX implantation were obvious in the first three months after injection. Repeated injections and frequent examination were required. Side effects such as cataracts and elevation of IOP may require medical or surgical treatment.

EFFECTIVENESS OF A SINGLE SUBTENON TRIAMCINOLONE ACETONIDE INJECTION ON MACULAR THICKNESS EVALUATED BY OPTICAL COHERENCE TOMOGRAPHY IN DIABETIC PATIENTS AFTER CATARACT SURGERY

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Design: Prospective, randomized controlled study.
Purpose: We aimed to assess the effectiveness of a single sub-Tenon injection of triamcinolone acetonide on the macular thickness, volume and development of cystoid macular edema (CME) detected by optical coherence tomography (OCT) in diabetic patients after cataract surgery.
Methods: Patients with type 2 diabetes mellitus (T2DM) who underwent phacoemulsification and intracapsular lens implantation without any complication were studied. The control group comprised eyes not treated with triamcinolone acetonide injection, and the sub-Tenon group comprised eyes treated with a single posterior sub-Tenon injection of triamcinolone acetonide. Best corrected visual acuity, intraocular pressure (IOP), center (foveal), parafoveal, perifoveal thickness and volume, and CME development were compared between the 2 groups pre-operatively and at postoperatively at week 1, month 1, and month 3.
Results: 44 eyes of 35 patients were included. The sub-Tenon group comprised 21 eyes and the control group 23 eyes. There was no statistically significant difference between the 2 groups in the mean corrected distance visual acuity at any follow-up examination (p>0.05). The mean change in center, parafoveal, perifoveal thickness and volume was statistically significantly lower in the sub-Tenon group than in the control group at postoperative months 1 and 3 (p<0.05). At postoperative week 1, four eyes in the control group and no eye in the sub-Tenon group developed CME (p = 0.065). IOP elevation sufficient to require topical medication was not seen in any eye.
Conclusions: A single posterior sub-Tenon injection of triamcinolone acetonide significantly reduced the amount of postoperative increase in foveal thickness and volume after phacoemulsification at months 1 and 3 in eyes of diabetic patients. Although it also reduced the incidence of CME, it had no effect on visual acuity gain or IOP.

INTRAVITREAL RANIBIZUMAB INJECTION FOR DIFFUSE DIABETIC MACULAR EDEMA UNRESPONSIVE TO MODIFIED GRID LASER PHOTOCOAGULATION

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Design: Prospective case series.
Purpose: To determine anatomical and functional results of intravitreal ranibizumab injection for diffuse diabetic macular edema (DME) unresponsive to prior adequate modified grid laser photocoagulation.
Methods: This case series included 14 (8 male, 6 female) patients with diffuse DME that failed to respond to prior modified grid laser photocoagulation. The response was measured with optical coherence tomography and

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eyes with persistent DME were treated with intravitreal ranibizumab injection (0.5 mg/0.05 ml). At each visit, patients underwent complete eye examination, including determination of best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement and retinal thickness measurement by optical coherence tomography.
Results: Fourteen eyes of 14 patients were included; mean age was 65.2 ± 5.4 years. Mean follow-up time was 6.7 months. Mean visual acuity was 0.9 ± 0.3 logMAR of Snellen letters after prior laser therapy while it was 0.8 ± 0.4 at first month and 0.8 ± 0.5 at third month after intravitreal ranibizumab injection. Mean central retinal thickness by optical coherence tomography was 412 µm before intravitreal ranibizumab injection while it was 322 µm at first month and 294 µm at third month postoperatively. Improvement in visual acuity and decrease in mean central retinal thickness were statistically significant in first and third month (p≤0.05). Transient intraocular pressure increase controlled by topical anti-glaucomatous medication was observed in one eye. No other complications, such as cataract, uveitis and endophthalmitis, were noted related to intravitreal injections.
Conclusions: Intravitreal ranibizumab injection seems to have beneficial effect on anatomical and functional results in eyes with diffuse diabetic macular edema unresponsive to prior adequate modified grid laser photocoagulation.

COMPARISON OF MODIFIED GRID LASER PHOTOCOAGULATION AND INTRAVITREAL RANIBIZUMAB INJECTION FOR DIFFUSE DIABETIC MACULAR EDEMA

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Design: Retrospective study.
Purpose: To compare the effectiveness and safety of modified grid laser therapy (MGLT) and intravitreal ranibizumab (IVR) therapy for the treatment of diffuse diabetic macular edema (DME).
Methods: Seventeen eyes of 17 patients treated with MGLT and 18 eyes of 18 patients treated with intravitreal 0.5 mg/0.05 ml ranibizumab for diffuse DME were compared retrospectively. There was no significant difference between age, central macular thickness (CMT) and duration of diabetes mellitus in two groups.
Results: Mean age of MGLT group and IVR group were 63.5 ± 6.2 and 64.8 ± 5.8 years, respectively. Before treatment best corrected LogMAR visual acuities (BCVA) of MGLT group and IVR group were 0.8 ± 0.4 and 0.9 ± 0.4, respectively. Mean CMT was 488 µ in MGLT group and 491 µm in IVR group, preoperatively. BCVA was 0.8 ± 0.3 in MGLT group and 0.7 ± 0.4 in IVR group at postoperative 3rd month. The mean CMT of MGLT group and IVR group was 358 µm and 316 µm, respectively. The difference of improvement in BCVA and decrease in CMT between both groups were statistically significant (p≤0.05) in both groups. Anatomical and functional results were better in IVR group. No complications, such as endophthalmitis or uveitis were noted. Transient increase in intraocular pressure controlled by topical anti-glaucomatous medication was observed in one eye.
Conclusions: We assumed that both MGLT and IVR therapies seemed to be effective in the treatment of diffuse DME. However, IVR injections revealed better anatomical and functional Results:

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR FOR A COMPLICATION OF PANRETINAL PHOTOCOAGULATION IN PROLIFERATIVE DIABETIC RETINOPATHY

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Design: Case report.
Purpose: To assess the effectiveness of anti-vascular endothelial growth factors for diabetic macular edema (DME) secondary to panretinal photocoagulation (PRP) treatment in proliferative diabetic retinopathy (PDR).
Methods: Retrospective study of a patient with PDR has been treated with PRP. He presented with a cystoid macular edema (CME) in the right eye 1 month after the last session of PRP. He received a single dose of intravitreal injection of ranibizumab in his right eye. Complete ophthalmologic examination and optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) were performed at baseline and 1 month after the injection.
Results: The visual acuity at the baseline was 20/63 in the right eye and 20/40 in the left eye. OCT revealed minimal diffuse edema with a macular thickness of 303 µm. PRP was performed in 3 sessions weekly for each eye. He presented with a visual acuity of 20/200 in the right eye after 1 month of last PRP session. OCT revealed cystoid macular edema and a new subretinal fluid with an increased macular thickness to 532 µm. The patient received one more intravitreal injection of ranibizumab in his right eye. In his follow up of 3 months he had a visual acuity of 20/40 in the right eye. The CME reduced significantly with macular thickness of 212 µm and the macular outline returned back to normal with some residual intraretinal cysts, a minimal subretinal fluid and an epiretinal membrane.
Conclusions: Ranibizumab is a highly effective agent for CME after PRP. We think that the reason for the limited visual acuity gain is related to the minimal sub-retinal fluid and an epiretinal membrane. A longer follow up time and repeated injections according to the clinical and OCT findings may lead to a better final visual acuity.

MORPHOLOGIC AND FUNCTIONAL MODIFICATIONS AFTER ANTI-VEGF TREATMENT IN CENTER INVOLVING DIABETIC MACULAR EDEMA

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Design: Cross-sectional, comparative case-control series.
Purpose: To asses early modifications in foveal choroidal thickness (CT) and inner and outer retinal layers structure after anti-VEGF treatment of naive center-involving diabetic macular edema (DME).
Methods: 20 patients with diabetes mellitus (40 eyes), who underwent 3 consecutive intravitreal anti-VEGF injections in the study eye (the fellow eye served as control), had a complete ophthalmologic examination including spectral-domain OCT and microperimetry at baseline (visit-V1), 1 month after each injection (V2, V3, V4) and at 6 months (V5). Fluorescein angiography was performed at V1 and at V5. CT, central subfield retinal thickness (CSF), number of hyperreflective retinal spots (HRS), best corrected visual acuity (BCVA) and retinal sensitivity (RS) were evaluated by ANOVA test with Bonferroni post hoc. Correlation analysis was performed by Spearman correlation.
Results: In treated eyes: CSF significantly decreased at V2, V3, V4 vs V1 (p<0.03 at least for all); CT significantly decreased after 3 anti-VEGF injections vs V1 (231.9 + 69.3 µm vs 249.4 + 66.7 µm), (p<0.019) and subsequently increased, at V5 (237.0 + 76.6 µm, p = 0.59); mean number of HRS significantly decreased vs V1, (p<0.008 for all); mean RS (within 4° and 12°) did not significantly change vs V1 (p = 0.87 and p = 0.61, respectively), but was significantly higher at V3, V4 and V5 in treated vs fellow eyes (p<0.01 for all); BCVA significantly improved at V3, V4 and V5 vs V1 (p = 0.009 for all). In fellow eyes CSF, CT, HRS, RS and BCVA did not change at any follow-up visit. There was significant and inverse correlation between the number of HRS and RS, (Rho at least -0.31, for all); weak and not significant correlation with BCVA and CSF. A significant and direct correlation was found between CT and RS/BCVA.
Conclusions: A significant decrease in foveal CT and HRS in the retina after anti-VEGF treatment is reported. A decrease in CT was transient, as CT returned to normal values as the treatment stopped, with no changes in RS. A decrease in HRS correlates significantly with functional improvement, specifically RS. New morphologic and functional parameters should be used for the evaluation of safety and efficacy of anti-VEGF treatments in center involving DME.

SHORT TERM FOLLOW-UP OF RETINAL NERVE FIBER LAYER ALTERATION AFTER GRID LASER PHOTOCOAGULATION

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Design: Prospective study.
Purpose: To evaluate the effect of grid laser photocoagulation (GLP) on retinal nerve fiber layer thickness (RNFLT) in patients with diabetic diffuse macular edema.

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Methods: 30 eyes of 21 patients with diabetes mellitus (DM) included the study. All patients had at least six months of follow-up. Detailed ophthalmologic examinations including visual acuity, intraocular pressure, RNFLT and central macular thickness (CMT) were performed at baseline as well as the third and sixth post laser months
Results: There were 12 men and 9 women; mean age was 61 ± 7.2. The initial mean RNFLT was 101.8 ± 12.7 µm, inferior quadrant was 121 ± 24.9 µm, superior quadrant was 119.1 ± 23.6 µm, nasal quadrant was 84.7 ± 11.2 µm and temporal quadrant was 84.3 ± 19.1 µm. The mean (111.1 ± 11.0 µm, p<0.05), inferior quadrant (137.4 ± 11.5 µm, p<0.05) and superior quadrant (133 ± 19.6 µm, p<0.05) RNFLT was significantly increased at the third post-laser month. There was no significant increase in the nasal quadrant (96.5 ± 18.1 µm, p>0.05) and no significant decrease in the temporal quadrant (78.3 ± 10.0 µm, p>0.05) at the third post-laser month. The mean RNFLT was 103.2 ± 9.9 µm, inferior quadrant was 130.9 ± 10.8 µm, superior quadrant was 119.5 ± 18.5 µm, nasal quadrant was 87.6 ± 20.5 µm, temporal quadrant was 77.4 ± 16.2 µm. The mean, inferior, superior and nasal quadrant RNFLT significantly decreased at the sixth post-laser month comparing to the third month's scores. There was no significant decrease in the temporal quadrant between the third and sixth month scores. There was no significant increase in mean RNFLT and all quadrants except temporal quadrant and no significantly decreased in the temporal quadrant between the sixth month and baseline visits.
Conclusions: RNFLT increased in the third month of follow-up after GLP at all quadrants except temporal quadrant. RNFLT mean value significantly decreased at the six month of follow-up.

OUTCOME OF VITREORETINAL SURGERY IN CASES WITH DIABETIC AND IDIOPATHIC VITREOMACULAR TRACTION SYNDROME

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Design: Retrospective.
Purpose: To investigate the etiology, age, gender, accompanying eye examination findings, and outcomes of vitreoretinal surgery (VRS) in cases with diabetic and idiopathic vitreomacular traction syndrome (VMTS).
Methods: 27 eyes of 27 patients with diabetic and idiopathic VMTS that were followed-up at the Ulucanlar Eye Education and Research Hospital between December 2013 and January 2015 were evaluated in this study. A complete ophthalmological examination including optic coherence tomography, and fluorescein angiography were evaluated at pre-operatively, at 1st months, and at 3rd months after the surgery.
Results: There were 16 (59.2%) women and 11 (40.7%) men. The mean age of the patients were 66.9 ± 6.9 years (range 43-76 years) in patients with diabetes mellitus (DM) and 67.3 ± 14.9 years (range 41-85 years) in idiopathic group. There was no difference regarding the age and gender of the patients in the groups studied (p>0.05). Statistically significant improvement in BCVA was established at the 3rd month visits compared to the pre-operative BCVA in both groups (p<0.05). Additionally, statistically significant difference was determined in the central foveal thickness (CFT) at 3rd month in both groups (p<0.05). Through the follow-up visit, none of the 27 eyes developed any complications.
Conclusions: According to the results of this study, VRS appears to be an effective and safe technique for the management of diabetic and idiopathic VMTS. The VRS can lead to a significant reduction of CFT and visual improvements in diabetic and idiopathic VMTS.

THE VITREOMACULAR INTERFACE FOLLOWING INTRAVITREAL INJECTIONS OF RANIBIZUMAB IN PATIENTS WITH CENTRAL INVOLVING DIABETIC MACULAR EDEMA

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Design: Retrospective case series.
Purpose: To determine whether Ranibizumab therapy is associated with the development of vitreomacular interface (VMI) abnormalities in patients with diabetic macular edema (DME).
Methods: The medical records and spectral domain optical coherence tomography (SD-OCT) images of all consecutive patients with center involving DMO (CI-DMO) naïve to previous intravitreal injections, initiating therapy with Ranibizumab between 21/12/2013 and 18/3/2014 at the Belfast Health and Social Care Trust and with a minimum follow-up of 6 months were retrospectively reviewed. Patients were identified through an electronic database. SD-OCT images were evaluated by a single reader masked to clinical findings, and specifically to the number of Ranibizumab treatments received. VMI abnormalities were classified following the International Vitreomacular Traction Study Group classification. Univariable and multivariable regression analysis was planned to investigate the relationship between number of Ranibizumab injections and development of VMI abnormalities at 6 months.
Results: Eighty-eight patients (137 eyes), 66% male, with a median age of 64.3 years (range 30-88 years) were included. Six patients treated during the period of the study were excluded; 1 had a macular hole at presentation whereas the other 5 had no OCT images at baseline. At baseline, a normal VMI was found in 107 eyes (78.1%); in 2 eyes (1.5%) vitreo-macular traction was present, in 19 (13.9%) an epiretinal membrane (ERM) was detected whereas in 1 (0.7%) both vitreo-macular traction and ERM were seen. In 7 eyes (5.1%) images were of poor quality and did not allow grading of the VMI. At 6 months, no statistically significant differences in the VMI were observed when compared with baseline.
Conclusions: In patients with CI-DMO, Ranibizumab therapy appears not to cause short term changes in the VMI.

TREATMENT OF DIABETIC MACULAR EDEMA WITH PARS PLANA VITRECTOMY, PEELING OF INTERNAL LIMITING MEMBRANE AND ADITIONAL TRIAMCINOLONE AND LASERCOAGULATION

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Design: Prospective study.
Purpose: To follow up patients after pars plana vitrectomy (PPV) and internal limiting membrane (ILM) peeling and additional triamcinolone 4 mg and laser coagulation for diabetic macular edema (DME).
Methods: To evaluate the effect of PPV with ILM peeling (group PPV) and PPV with ILM peeling, intravitreal triamcinolone 4 mg at the end of surgery and macular laser coagulation three weeks after surgery (group PPV + TRIAM). The primary objective was to follow up functional and anatomical results at month 12.
Results: 68 eyes of 59 patients with DME unresponsive to previous laser coagulation or existing vitreomacular traction at OCT were enrolled. PPV group had 35 eyes and PPV + TRIAM had 33 eyes evaluated. Median follow-up was 30.3 ± 9.0 in PPV and 19.3 ± 4.9 months in PPV + TRIAM.
Statistically significant improvement of VA was observed from month 3 in both groups (p = 0.037 and 0.045), and was confirmed by the difference between the two surgical procedures (p = 0.11 at 12 months). Mean change of VA at months 12 was 0.11 in PPV and 0.08 PPV + TRIAM. CMT and macular volume were substantially reduced since the first month postoperatively and the improvement was maintained until the end of follow-up (p<0.001). A statistically significant difference between two groups was detected only in the first month after surgery (p = 0.002 for CMT; p = 0.027 for macular volume), which was caused by intravitreal TRIAM 4 mg in group PPV + TRIAM. The most significant improvement after surgery was in eyes with low initial VA≤0.1 and CMT>400 µm. The most common postoperative complication was progression of cataract in eyes in group PPV + TRIAM (p = 0.030) and elevation of intraocular pressure.
Conclusions: Both surgical procedures are shown to be effective in the treatment of DME. Combination therapy PPV with triamcinolone acetonide 4 mg and macular laser coagulation is associated with a higher incidence of postoperative complications (increased intraocular pressure and cataract).

EVALUATION OF A JOINT OPHTHALMOLOGY/DIABETES NURSE SPECIALIST CLINIC TO SUPPORT PATIENTS WITH SIGHT THREATENING DIABETIC RETINOPATHY

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Design: Retrospective review.
Purpose: To assess the impact of the joint clinic on diabetes control and to ascertain patient satisfaction with the clinic model.

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Methods: A monthly clinic was established in January 2014 where patients attending for laser had a consultation with the diabetes nurse specialist. All clinical and laboratory data was entered on an electronic patient record. Evaluation was carried out on 54 patients with diabetes mellitus (DM) by auditing pre and post Hba1c, patient satisfaction questionnaires and monitoring number of patients agreeing to referral and attendance back to structured diabetes care.
Results: 54 patients with DM were reviewed at least once in the 1st year of this clinic. Of these, 18 had Type 1 DM while 36 had Type 2 DM. Average duration of DM was 15.3 years. Macular laser was carried out in 34 patients and/or pan-retinal laser in 20. 64% of patients had at least 1 other diabetic complication. Altogether 18 (33.3%) patients had not attended a diabetic clinic for >1 year, with 7 (13%) not attending for >3 years and 1 not attending for >10 years. The majority of these (12 patients) agreed to be referred back to the endocrinologist and subsequently attended clinic. Four patients were referred and attended BERGER education. One patient was referred to pre–conception clinic; 2 were referred to nephrology. There was an overall reduction in Hba1c (pre 73.2 mmol/mol vs post 65.6 mmol/mol). Patient satisfaction questionnaires revealed high level of satisfaction with the opportunity to avail of this clinic.
Conclusions: The development of this clinic has led to increased opportunity for diabetes services to engage with this group of high risk patients and to provide support, education and referral into appropriate diabetes services. It has resulted in improved glycemic control and improved joint working between ophthalmology, diabetes clinics and primary care.

PRESENCE OF DIABETES MELLITUS ON CORNEAL THICKNESS RECOVERY AFTER UNCOMPLICATED PHACOEMULSIFICATION SURGERY

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Design: Comparative study effect of diabetes mellitus (DM) on corneal thickness recovery after cataract surgery.
Purpose: To evaluate corneal pachymetric changes after uncomplicated phacoemulsification surgery in patient with diabetes mellitus (DM) and non-diabetic controls.
Methods: The study enrolled 118 eyes of 54 patients; 22 of them had DM and 32 patients control subjects. All of them underwent uncomplicated phacoemulsification surgery by the same surgeon with the same technique. Corneal thickness evaluations were performed preoperatively and postoperative one month later. Corneal thickness was measured with the LS-900-LENSTAR and by the same person. The mean corneal thickness (CT) changes due to surgery were compared between the DM patients and the non-diabetic group.
Results: The mean preoperative CT was 515 µm in the patients with DM and 524 µm in non-diabetic group. The difference was not statistically significant (p>0.3). The mean postoperative CT was 529 µm in patients with DM and 527 µm in non-diabetic group (p = 0.9). The mean CT change in DM group (14 µm) was higher than non-diabetic group (3 µm), but still statistically not significant.
Conclusions: Even the increase was not statistically significant; the changes noted will need to be examined in the larger cohort in order to rule out that DM has a negative impact on corneal thickness recovery after uncomplicated phacoemulsification surgery.

THE CORNEAL BIOMECHANICAL PARAMETERS IN TYPE 1 DIABETES MELLITUS

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Design: Prospective observational study.
Purpose: To determine whether biomechanical parameters of the cornea measured as corneal hysteresis (CH) and corneal resistance factor (CRF) are altered in patients with type-1 diabetes mellitus (T1DM) according to duration of disease.
Methods: In this prospective study 129 eyes of 129 patients with T1DM were enrolled. The CH, CRF, Goldman-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPcc) were measured with the Ocular Response Analyzer. Patients were divided into two groups; group 1 with duration of diabetes ≤20 years (n = 54) and group 2 with duration of diabetes >20 years (n = 75). The corneal biomechanical parameters were compared between the group 1 and group 2.
Results: A total of 129 patients, including 65 females (50.3%) and 64 males (49.6%) were enrolled in the study. One hundred right eyes and 29 left eyes were examined. While the mean age was 45.5 ± 18.2 in group 1, the mean age was 63.3 ± 12.3 in group 2. There was no statistically significant difference between the 2 groups in CH, CRF, IOPcc, IOPg measurements (p>0.05).
Conclusions: Our results suggest that the duration of T1DM does not play a crucial role on biomechanical parameters of the cornea.

PUPIL SIZE BEFORE AND AFTER PHACOEMULSIFICATION IN HEALTHY, DIABETIC AND SYSTEMIC ARTERIAL HYPERTENSION PATIENTS BY COMBINED SCHEIMPFLUG-PLACIDO DISK TOPOGRAPHER

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Design: Prospective clinical study.
Purpose: To evaluate the changes in pupil size before and after phacoemulsification surgery in healthy controls, patients with diabetes mellitus and on those with systemic arterial hypertension by Combined Scheimpflug-Placido Disk Topographer (Sirius, CSO Inc.).
Methods: In this study, 65 healthy controls, 45 DM and 30 systemic arterial hypertension patients scheduled for phacoemulsification were recruited consecutively. The pupil diameter was measured preoperatively and approximately 1 month postoperatively with Combined Scheimpflug-Placido Disk Topographer pupillometer. Groups were compared between preoperative and postoperative values of pupil diameter.
Results: The mean pupil size in the healthy group, in those with DM group and systemic arterial hypertension group decreased significantly after 1 month postoperatively (p<0.03). Strong associations were found between preoperative pupil and postoperatively 1 month in groups. The pupil size in patients with DM was smaller than in the other groups.
Conclusions: Pupil size decreased immediately after phacoemulsification. There was a strong association between preoperative and postoperative pupil size. The pupil size in patients with DM was smaller than in the other groups preoperatively and postoperatively.

THE FIXED COMBINATION EFFICACY ASSESSMENT IN PATIENTS WITH SECONDARY NEOVASCULAR GLAUCOMA AND DIABETES MELLITUS

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Design: All patients with an uncontrolled IOP despite appropriate treatment have been proposed to switch current IOP-lowering therapy to Ganfort®, administered once a day in the morning. In case target IOP level was not reached filtration surgery was recommended.
Purpose: To assess IOP-lowering efficacy of bimatoprost/timolol fixed combination in patients with diabetes mellitus (DM) and uncontrolled secondary neovascular glaucoma (SNG).
Methods: Fifty patients (51 eyes) with uncontrolled SNG and DM were enrolled in the study.
Results: IOP-lowering has been observed in all patients when switched to bimatoprost/timolol fixed combination. Mean IOP level was almost 3x lower versus baseline in 72.5% of patients (37 eyes). The patients achieved target IOP of 15-17 mm Hg. As a result, no surgical intervention was required. Significant IOP-lowering has been observed in other group of patients without switch (14 eyes, 27.5%) nevertheless due to glaucoma progression these patients were still subject to surgical treatment.
Conclusions: IOP-lowering fixed combination bimatoprost/timolol can be used in patients with SNG and DM as a drug of choice to lower IOP level. Even in cases when target IOP is not achieved, bimatoprost/timolol fixed combination can be administered in pre-operative period and helps to reduce postoperative complications.

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THE ASSOCIATION BETWEEN METABOLIC REGULATION OF PATIENTS WITH DIABETES AND PHACOEMULCIFICATION INTRAOPERATIVE AND POSTOPERATİVE COMPLICATIONS

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Design: Qualitative descriptive clinical study.
Purpose: To evaluate the complication of phacoemulsification cataract surgery (PCS) in diabetes and to determine the possible relation between metabolic parameters.
Methods: A total of 99 patients with diabetes mellitus (DM) were evaluated retrospectively. Of those, 41 had normal funduscopic examination, 24 had non-proliferative and 34 had proliferative diabetic retinopathy (DR). Blood pressure was measured after 30 minutes resting, body mass index (BMI) was calculated as kg/m^2 and classified as ≥30 and <30 kg/m^2, smoking status were noted and glucose, hemoglobin A1c (HbA1c), C-reactive protein (CRP) and lipids measured with standard biochemical Methods: In addition, usage of insulin and oral antidiabetic drugs were recorded. Pre- and postoperative detailed ophthalmologic examinations was carried out by the same physician. All surgeries were performed by one surgeon using the same phacoemulsification technique of clear cornea incision. Intra- and postoperative complications: glaucoma, corneal edema, fibrinous exudation, posterior capsule rupture and macular edema were noted.
Results: In the combined surgery group, the best corrected visual activity (BCVA) increased in 61 (61.6%) eyes, while 26 (26.2%) eyes remained stable and 12 (12.1%) eyes decreased. Postoperative complications included elevation of intraocular pressure in 25 (25.3%), corneal edema in 26 (26.3%), fibrinous exudation in 29 (29.3%), macular edema in 27 (27.3%) and posterior capsule rupture in 7 (7.1%) eyes. All postoperative complications were found in higher incidence in patients with a longer duration of DM, and in patients who had proliferative DR ($p = 0.001$). Similar correlations were detected between postoperative complications and the HbA1c ($p = 0.001$) and CRP ($p = 0.001$) levels, the severity of obesity ($p = 0.001$), hyperlipidemia ($p = 0.001$), usage of insulin preparations ($p = 0.001$) and blood pressure ($p = 0.001$). We did not find any correlation between complications and usage of oral antidiabetic drugs or smoking status of patients.
Conclusions: PCS is one of the most commonly performed surgical procedures, including in patients with DM. Patients with higher levels of CRP, of HbA1c, of lipids, had higher BMI, and higher blood pressure may face a higher risk of intraoperative and postoperative complications. Larger scale studies are needed to define this finding and the possible ways of mitigate these risks.

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