EJO European Journal of Ophthalmology

30th Meeting of the European Association for the Study of Diabetes Eye Complications Study Group (EASDec) Barcelona, Spain, Virtual Meeting, 5th-6th November 2020

European Journal of Ophthalmology
2020, Vol. 30(1S) 1–33

DOI: 10.1177/1120672120961310
journals.sagepub.com/home/ejo
SAGE

Retinal Fingerprints of Neurodegenerative Diseases

F. Verbraak

Department of Ophthalmology, Amsterdam University Medical Center, Amsterdam, The Netherlands

DESIGN. Review
PURPOSE. Review of present knowledge on the involvement of the retina in (systemic) neurodegnerative diseases. The use of the retina as a possible biomarker for neurodegenerative diseases.
METHODS. Recent literature with studies of examination of the retina, aimed to proof involvement of the retina in neurodegenerative diseases have been reviewed.
RESULTS. Retinal changes can be measured in several frequently occurring diseases like Alzheimer's Disease (AD), Parkinson's Disease (PD) and Multiple Sclerosis (MS). In some more exceptional diseases like Adrenoleukodystrophy (ALD), Amyotrophic Lateral Sclerosis (ALS), Huntington Disease, and Optic Neuropathies. Also changes have been found in HIV infection and diabetes mellitus (DM). Most studies claim structural changes measured with OCT or OCT-angiography. In AD additional methods have been applied like Fluorescence Lifetime Imaging Ophthalmoscopy and Hyperspectral Imaging aimed at detection of changes on a molecular level.
CONCLUSIONS. Retinal structural changes can be measured in most neurodegenerative diseases, but changes are small and are only significant on a group level. Changes over time differ between patients and controls, but also only on a group level. Detection of molecular changes in AD could provide a promising biomarker but needs confirmation on a larger scale.

Intravitreal Bevacizumab as First Choice Treatment for Vitreous Haemorrhage in Proliferative Diabetic Retinopathy

N. Palarie[1], T. Pasenco[1,2]

[1]*Department of Ophthalmology, International Clinic, Orhei, Moldova*
[2]*Department of Ophthalmology, State University of Medicine and Pharmacy "Nicolae 3 Testemitanu", Chisinau, Moldova*

DESIGN. Retrospective study
PURPOSE. Proliferative diabetic retinopathy (PDR) is a significant cause of blindness in working-age individuals. Until recently, waiting for the haemorrhage to spontaneously resolve or performing pars plana vitrectomy were the only lines of treatment for vitreous haemorrhage due to this condition. Purpose: To evaluate the efficacy of intravitreal Bevacizumab (IVB) in dense Vitreous Haemorrhages (VH) due to PDR.
METHODS. 105 eyes of 92 people aged 54-78 with dense VH (+++, ++++) were included in this study. All patients had type 2 diabetes. At baseline none of the patients had signs of tractional retinal detachment on ultrasonography. Complete ophthalmic examination and ocular ultrasonography were performed at baseline and 1, 6 and 12 weeks and 3, 6, 9 and 12 months after the first injection. Patients were divided into 3 groups according to the duration of VH. Group I included patients with VH less than 6 months (36 eyes), group II included patients with VH occurring 6-12 months ago (39 eyes), group III were assigned patients were VH occurred more than 1 year ago (30 eyes). All patients once a month received 3 consecutive IVB 1,25 mg injections.
RESULTS. All patients in group I had complete resolution of VH. In group II, 9 eyes (23%) did not respond to IVB. In group III, 10 eyes did not respond to IVB (34%). Repeated VH within 1 year after the last injection was

noticed in 5 (14%) cases in group I, 11 cases (28%) in group II and 11 cases (33%) in group III.
CONCLUSIONS. Intravitreal Bevacizumab is very effective in resolving even long lasting dense vitreous haemorrhages in patients with PDR, although its efficacy diminishes when duration of haemorrhage is greater than 1 year. It can be used as a first choice therapy in VH due to PDR with no signs of tractional retinal detachment on ultrasonography.

Regional Changes of Retinal Physiology in Humans: Diabetes vs Retinopathy

P. Fort[1,2], Y. Shan[1], J. Roger[3], T. Gardner[1,2], S. Abcouwer[1]

[1]*Kellogg Eye Center, University of Michigan, United States of America*
[2]*Department of Molecular and Integrative Physiology, University of Michigan, United States of America*
[3]*CERTO: Centre d'Etude et de Recherche Thérapeutique en Ophtalmologie, Paris-Saclay Institute of Neurosciences, France*

DESIGN. Multi-omics analysis of human retina samples from donors with and without DR to assess the pathological signature of DR onset and progression.
PURPOSE. Diabetic etinopathy, the major ocular complication associated with diabetes, remains the primary cause of vision loss in the working age population. Use of non-targeted omic analyses have led to the identification of specific regulatory pathways affected in diabetic rodents. While those animal models have allowed us to gain critical insights on the overall impact of the disease on retinal physiology, translation of these findings has been challenging, in part due to the anatomical differences and the inherent limitations of these models. These limitations are critical as diabetic retinopathy is a regional disease that affects the retina heterogeneously, as demonstrated by macular edema, peripheral non-perfusion and regional loss of receptor fields in diabetic patients.
METHODS. Using non-fixed, freshly isolated retinal tissues from human donors, with and without diabetes and with or without retinopathy, we used RNA deep sequencing, lipidomic and quantitative discovery proteomic to assess the multi-omic changes affecting the retina. In this study, we independently analyzed these changes in a regional manner by dissociating the macular, perimacular and peripheral regions of the retina (n=10-20 per tissue and per group) in order to identify the regional impact of diabetes. Results were validated by orthogonal targeted methods including quantitative pcr and immunoblot analysis.
RESULTS. Principal component analysis confirmed the clustering of the samples while pathway analysis using the GeneGo/MetaCore integrated software identified specific inflammatory, metabolic and neuroglial regulatory pathways. Using qRT-PCR, consistent significant alterations of the expression of genes associated with inflammation (including the alternative pathway of the complement) and neuroglial regulatory pathways (growth factor signalling) were dissected and demonstrated a regional alteration with a primary diabetes component in the central retina and a primary retinopathy component in the peripheral retina.
CONCLUSIONS. This study offers the first regional analysis of the pathophysiological mechanisms of diabetic retinopathy with a high potential of identification of specific therapeutic targets including specific regulators of the inflammatory response and regulation of the neuroglial tissue homeostasis.

The Role of eNOS in VEGF-Induced Vascular Permeability

E. Bosma[1], S. Darwesh[1], I.M.C. Vogels[1], C.J.F. van Noorden, [1,3], I. Klaassen [1,2], R.O. Schlingemann[1,2]

[1]*Ocular Angiogenesis Group, Amsterdam UMC, The Netherlands*
[2]*Department of Ophthalmology, Amsterdam UMC, The Netherlands*
[3]*Department of Medical Biology, Amsterdam UMC, The Netherlands*

DESIGN. Fundamental study with primary endothelial cells
PURPOSE. Vascular endothelial growth factor (VEGF) is a key signalling molecule disrupting the barrier function of the endothelium. When its expression is elevated in the retina, VEGF induces permeability, which may ultimately lead to vision-threating conditions such as diabetic macular edema. The mechanism by which VEGF induces permeability remains still incompletely understood. It is evident that nitric oxide (NO) produced by endothelial NO synthase (eNOS) plays an important role in VEGF-induced permeability. So far, the role of eNOS, and its product NO, in modulating paracellular permeability has been appreciated. However, little attention has been given to the role of eNOS in VEGF-induced transcytosis.
METHODS. Experiments were performed with primary endothelial cells from diverse origin. We used human dermal microvascular endothelial cells (hMVECs; non-barrier like endothelium), human umbilical vein endothelial cells (HUVECs; non-barrier like endothelium) or bovine retinal endothelial cells (BRECs; barrier-like endothelium) for experiments. Cells were treated with the eNOS inhibitor L-NAME to inhibit eNOS activity or treated with siRNA against eNOS to reduce eNOS expression. The barrier function was studied with a transwell permeability assay. In addition, protein and gene expression was analysed by western blotting and qPCR.
RESULTS. We show that lack of eNOS expression partially reduces VEGF-induced permeability for BSA-FITC (66 kda) and FITC-dextran (70 kda) in hMVECs. To explore the underlying mechanisms, we looked at the expression of PLVAP, a protein regulating caveolae-dependent transcytosis in endothelial cells. Inhibition of eNOS activity significantly prevented or reduced VEGF-induced upregulation of PLVAP expression in HUVECs

and hMVECs, respectively, but not in BRECs. In addition, silencing of eNOS expression attenuated basal PLVAP mRNA levels, and prevented VEGF-induced upregulation of PLVAP mRNA levels in HUVECs and hMVECs. It is known that PLVAP expression is regulated in a VEGF receptor 2 (VEGFR2)-dependent manner. We show that VEGFR2 mRNA and protein levels are reduced in HUVECs lacking eNOS.

CONCLUSIONS. This study shows that eNOS is an important player in VEGF-dependent transcytosis in non-barrier endothelium, regulating VEGFR2 and PLVAP expression levels. Preliminary findings suggest that this might be differently regulated in barrier endothelium.

ERM Complex, A Therapeutic Target for Vascular Leakage Induced by Diabetes

O. Simó-Servat, M.G. García-Ramírez, P.B. Bogdanov, H.R. Ramos, C.H. Hernández, R.S. Simó

Diabetes and Metabolism Unit, Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Spain

DESIGN. Experimental

PURPOSE. Ezrin, Radixin and Moesin (ERM complex) are membrane-associated proteins that regulate cytoskeleton organization, being essential for endothelial barrier function. In a previous proteomic-based study we found an increase of ERM complex in retinas from diabetic donors with neurovascular impairment compared with retinas from diabetic donors without neurovascular dysfunction. The aims of the present study are: 1) To assess whether db/db mice reproduce the results on ERM complex observed in human retinas; 2) To investigate the main factor of diabetic milieu involved in ERM regulation in retinal endothelial cells (HRECs) cultures.

METHODS. In vivo: 5 male db/db mice and 5 male db/+ (Charles River Laboratories, Calco, Italy) aged 14 weeks were analyzed. ERM proteins were assessed by Western Blot and by immunohistochemistry. Vascular leakage was determined by Evans blue method. In vitro: HRECs were cultured in a medium containing 5.5 mM D-glucose (mimicking physiological conditions) and 25 mM D-glucose (mimicking hyperglycaemia). Treatment with TNF-α (10 ng/mL), IL-1β (20 ng/mL), or VEGF (50 ng/mL) was added to hyperglycemic condition. The expression of ERM proteins was quantified by RT-PCR. Cell permeability was evaluated by measuring apical-basolateral movements of FITC-dextran.

RESULTS. A significant increase of Ezrin and Moesin in diabetic mice with neurovascular impairment in comparison with non-diabetic mice was observed by both Western blot and immunohistochemistry analyses. We also found an increase of Radixin in the immunofluorescence analysis. The in vitro experiment revealed that high glucose condition did not have any effect in ERM proteins expression. However pro-inflammatory cytokines (TNF-α and IL-1β) induced a significant increase of ERM proteins. Finally, the increase of ERM expression was associated with vascular leakage in db/db mice, as well as with an increase in permeability in HRECs cultures.

CONCLUSIONS. 1) The increase of ERM proteins induced by diabetes could be one of the mechanisms involved in vascular leakage. 2) The upregulation of ERM complex is induced by inflammatory mediators rather than by hyperglycaemia itself. 3) The db/db mice seem a good model to test new treatments for vascular leakage based in ERM modulation.

DPP-IV Inhibitors for Treating Early Stages of Diabetic Retinopathy in an Experimental Model: A Dose-Efficacy Study

H. Ramos[1,2], P. Bogdanov[1,2], J. Sampedro[1,2], M. Valeri[3], R. Simó[1,2], C. Hernández[1,2]

[1]*Diabetes and Metabolism Research Unit. Vall d'Hebron Research Institute. Universitat Autònoma de Barcelona, Spain*
[2]*Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain*
[3]*Unit of High Technology. Vall d'Hebron Research Institute. Universitat Autònoma de Barcelona, Spain*

DESIGN. Experimental dose-response study

PURPOSE. Neurovascular unit (NVU) plays an essential role in the development of diabetic retinopathy (DR). In recent years several studies have demonstrated the efficacy of GLP-1 in preventing and arresting the progression of neurodegeneration and vascular leakage (two essential features of NVU impairment) in experimental diabetes. Since GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase IV (DPP-IV), which is also present at low concentrations in the retina, the inhibition of DPP-IV was postulated as a new therapeutic strategy for treating early stages of DR pathway. In fact, in a previous study we demonstrated that DPP-IV inhibitors (DPP-IVi) prevents retinal neurodegeneration and vascular leakage in db/db mice. The aim of the study is to examine the dose-response effect of topical administration of DPP-IVi.

METHODS. Two different DPPIVi (sitagliptin and saxagliptin) at different concentrations (5 and 10 mg/mL for sitagliptin, and 1 and 10 mg/mL for saxagliptin) one or twice per day were tested. They were administered for 2 weeks and compared to vehicle. Non-diabetic db/+ mice were used as control group. We evaluated reactive gliosis (GFAP immunostaining and WB), neural apoptosis (cell counting), vascular leakage (Evans blue), retinal inflammation (IL-1 beta, IL-6, TNF alpha and NFKB expression), and GLP-1R activation by assessing AKT phosphorylation.

RESULTS. Our results suggest that both DPP-IVi were effective in preventing the dysfunction of the NVU. This prevention was observed without any changes in blood glucose levels. Both, sitagliptin and saxagliptin showed a dose-dependent effectiveness in preventing glial activation, neural death, overexpression of pro-inflammatory cytokines and vascular leakage. In addition, a dose-dependent AKT activation was observed.

CONCLUSIONS. Our findings confirm the beneficial effects of DPP-IVi in preventing neurovascular dysfunction in early stages of experimental DR, and reveal that this effect is dose-dependent. These results could help in the design of clinical trials aimed at treating early stages of DR.

Targeting Plasma Kallikrein with a Novel Bicyclic Peptide Inhibitor (THR-149) Reduces Retinal Thickening in a Diabetic Rat Model

T. Van Bergen, I. Etienne, T.T. Hu, J.H.M. Feyen

Oxurion NV, Leuven, Belgium

DESIGN. To investigate the therapeutic effect of plasma kallikrein (PKal) inhibition on retinal thickening in a diabetic rat model.
PURPOSE. The aim of this study was to test the efficacy of intravitreal (IVT) administration of THR-149 on leakage-associated retinal thickening in the diabetic streptozotocin (STZ)-induced rat model. THR-149 is a novel potent and highly specific peptide inhibitor for PKal.
METHODS. One non-diabetic control group of rats was included (group 1), together with 4 groups of diabetic rats (n=8-10 rats/group), in which treatment was started immediately after diabetes onset. Group 2 and 3 received 3 consecutive IVT injections (with 1-week interval) of THR-149 (12.5 µg/eye) or vehicle, respectively. Anti-VEGF (2 mg/kg) and its vehicle were administered 3x/week via intraperitoneal injection for 3 weeks in group 4 and 5, respectively. Retinal thickness was quantified in all groups at 4 weeks after diabetes onset, by measuring the thickness of the total retina or of the individual retinal layers on FITC-BSA perfused histological tissue sections.
RESULTS. Total retinal thickness was significantly increased at 4 weeks after diabetes onset in vehicle-treated diabetic rats compared to non-diabetic control rats (by approximately 20 µm; $p<0.001$). Administration of 12.5 µg/eye of THR-149 significantly reduced retinal thickness with 12 µm ($p<0.001$) versus vehicle-treated eyes. Administration of anti-VEGF treatment significantly reduced total retinal thickness with 15 µm, as compared to its vehicle ($p<0.001$). Analysis of the individual retinal layers showed that the thickness of the inner plexiform layer (IPL), inner nuclear layer (INL), outer nuclear layer (ONL) and photoreceptor layer (PR) was significantly increased in vehicle-treated diabetic rats, which was significantly reduced in the THR-149 and anti-VEGF treated rats ($p<0.05$). Moreover, THR-149 additionally reduced the ONL thickness with 16%, as compared to anti-VEGF administration ($p<0.001$).
CONCLUSIONS. In this study, it was shown that repeated administration of THR-149, a novel bicyclic peptide, significantly reduced retinal thickening in the diabetic rat STZ model, compared to vehicle-treated eyes. These positive results further strengthen the perspective to use THR-149 as a treatment option for diabetic macular edema (DME).

Diurnal Rhythms of Myeloid Cell Infiltration into the Retina in Type 1 Diabetes (T1D)

E. Beli[1,3], C. Evans-Molina[2], J. Busik[3], M. Grant[4]

[1]*Queen's University Belfast, Belfast, Northern Ireland, United Kingdom*
[2]*Indiana University School of Medicine, Indianapolis, Indiana, United States of America*
[3]*Michigan State University, East Lansing, Michigan, United States of America*
[4]*University of Alabama Birmingham, Birmingham, Alabama, United States of America*

DESIGN. We designed a multicolor immunofluorescence phenotyping of the time of the day at which leukocytes infiltrate the retina.
PURPOSE. Our goal was to investigate whether T1D affects the diurnal rhythmicity of immune cell infiltration into the retina.
METHODS. We used the Ins2Akita mouse model of T1D. Four months old, male, control and diabetic mice were euthanized at (ZT1, ZT5, ZT9, ZT13, ZT17, ZT21, where ZT= Zeitgeber Time, ZT=0, lights on, n=4-8). Mice were perfused with PBS and tissues were isolated and prepared for single cell suspensions or snap frozen. Multicolor flow cytometry (antibodies for CD45, CD11b, Ly6G, Ly6C, CD115, F4/80, CD11c, CD19, CD3, NKp46 and CD43) was employed to dissect the composition of immune cells in the retina at each time point. Control gating was drawn based on FMOs and comparison to splenic composition. Cosine function was used to identify if there is a circadian rhythmicity.
RESULTS. Overall, a complex immune cell landscape of the retinal parenchyma (perfused retinas) was identified with various subtypes of macrophages and dendritic cells that cannot be accurately identified with the markers used in this study. Differences in the subset composition of infiltrating cells into the retina were identified between control and diabetes. Specifically at ZT1 there were statistically significant more ($p<0.05$) dendritic cells and monocytes in the retinas of diabetic mice but this was normalized at later times. Rhythmic behaviour was identified not only in the infiltrating CD45hi cells but also in microglia with peak time around the early morning hours. The only exception

was the CD11blo F480hi myeloid cells, whose numbers peaked during the late hours of the day (ZT13).
CONCLUSIONS. These data indicate that the infiltration of immune cells into the retina is not static but changes throughout the day. It also demonstrates that at early hours of the day there is higher immune cell infiltration in the diabetic mice compared to control. Altogether, these data inform us for the optimal timing of therapeutic targeting immune cell activation in the retina.

Incidence of Referable Diabetic Retinopathy at Patient's First Screening

K. Hazelgrove[1], H. Wharton[1], L. Quant[1], S. Jacob[1,2]

[1]*Department of diabetes and endocrinology, University Hospitals Birmingham, Birmingham, United Kingdom*
[2]*Department of Ophthalmology, University Hospitals Birmingham, Birmingham, United Kingdom*

DESIGN. Retrospective audit of screening data available on patients attending their 1st screening within the Birmingham, Solihull and Black Country diabetic screening programme in a 12 month period.
PURPOSE. To assess the level of referable diabetic retinopathy (DR) present at patient's 1st screening.
METHODS. Patients who attended screening for the 1st time between 01/01/2018-31/12/2018 were analysed. All patients who presented with referable DR were included and retinopathy grades and outcomes were looked at. Demographics collected include age, sex and ethnicity although date of diabetes diagnosis was not available. For patients referred to the hospital eye service (HES) data on outcomes and treatment received was also collected.
RESULTS. 13404 were screened for the 1st time during 2018, of these 475 (3.5%) had referable DR. The average age of those with referable DR was 55 (22-91) years with a male preponderance (66%). Ethnicity was not available for 206 (43%) but where it was the majority were British 95 (20%), Indian 46 (10%) or Pakistani 36 (8%).
Looking at level of DR in worse eye, 304 (64%) had maculopathy alone, 21 (4%) had pre-proliferative changes, 69 (15%) had both pre-proliferative and maculopathy, 16 (3%) had proliferative changes and 65 (14%) had both pre-proliferative and maculopathy. Screening outcomes for these patients were, 240 (51%) referred to digital surveillance, 147 (31%) routinely to HES for DR and 6 (1%) for non DR, 81 (17%) urgently to HES and 1 to GP for non DR. Outcomes from HES for the urgent referrals show that 35 (43%) required PRP laser for proliferative retinopathy.
Based on comments left by the screener it is known that 89 of these referable patients were previously screened elsewhere but screened for the first time when they moved within the area covered by this screening programme.
CONCLUSIONS. This audit suggests that a significant proportion of patients present with referable DR at first screening with 81 patients having proliferative changes. However, the duration of diabetes at the time of first screen is unclear as this is not recorded at screening so this needs to be considered.

Identification and Characterization of Patients with Rapid Progression of Diabetic Retinopathy in the Danish National Screening Programme

J. Grauslund[1,2,3], A.S. Thykjær[1,2,3], R. Kawasaki[3,4], K. Højlund[2,3], K.H. Rubin[3,5], L. Stokholm[3,5]

[1]*Dept. of Ophthalmology, Odense University Hospital, Odense, Denmark*
[2]*Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark*
[3]*Dept. of Clinical Research, University of Southern Denmark, Odense, Denmark*
[4]*University of Osaka, Osaka, Japan*
[5]*Open Patient data Explorative Network (OPEN), Odense University Hospital, Odense, Denmark*

DESIGN. Registry-based, national cohort study.
PURPOSE. While diabetic retinopathy (DR) is a slowly developing disease in most patients, rapid progression has been reported for a minority. In order to achieve a better understanding of this, we aimed to identify and characterize patients with rapid progression of DR in a national screening programme.
METHODS. In Denmark, screening of DR is nationally implemented and results have mandatorily been registered in the Danish Registry of Diabetic Retinopathy (DiaBase) database since 2013. Level of DR is registered according to the 5-step ICRDS scale with levels 0-4 given as no DR (level 0), mild, moderate and severe non proliferative DR (levels 1-3) and proliferative DR (level 4). We defined rapid progression of DR as a 3-level or more increment of DR in both or either eye within two years with no subsequent DR regression. As controls, we included patients with level 0 in both eyes at all screening episodes and at least two years of observation time. Co-morbidity was given by the Charlson co-morbidity index using International Classification of Disease 10 codes from the Danish National Patient Registry.
RESULTS. Among 206,220 patients in DiaBase, we identified 506 patients (0.25%) with rapid progression of DR in both (n=135) or either (n=371) eye as well as 74,157 patients free of DR. Patients with bilateral and unilateral rapid progression did not differ from controls in terms of gender but were younger (63 vs. 63 vs. 66 years, p=0.001). They were also less likely to be married (56.6% vs. 56.9% vs. 61.7%, p=0.002), to have a Charlson comorbidity score of 0 (45.2% vs. 38.3% vs. 78.9%, $p<0.001$), and to have been given a screening interval of at least 12 month at the

last visit prior to progression (42.2% vs. 32.9% vs. 94.5%, $p<0.001$).

CONCLUSIONS. In a real-life, national diabetic eye screening program, one in 400 had rapid progression of DR. Patients with rapid progression differed demographically and by co-morbidity from DR-controls. Shorter screening intervals given prior to progression could indicate that this was somehow expected.

Non-Attendance at Diabetic Eye Screening in the Danish Nationwide Screening Program

A.S. Thykjær[1,2,3], L. Stokholm[3], K. Højlund[2], K.H. Rubin[3], R. Kawasaki[4], J. Grauslund[1,2]

[1]*Department of Ophthalmology, Odense University Hospital, Odense, Denmark*
[2]*Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark*
[3]*Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark*
[4]*Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan*

DESIGN. Registry based national cohort study

PURPOSE. In Denmark, a nationwide screening program for diabetic retinopathy (DR) has been established since 2013. Patients with diabetes are, free of charge, offered regular diabetic eye screenings by practicing ophthalmologists or at selected hospital departments.

The aim of this study was to perform a real-life national evaluation of the DR screening program in Denmark, examining the screening pattern and the ability to remain within the screening program.

METHODS. The study population consisted of a longitudinal, nationwide cohort of diabetes patients (n=206,220) in Denmark, who participated in the nationwide screening program for DR from 2013 through 2018 and were registered in the Danish Registry of Diabetic Retinopathy (DiaBase) database. Data from DiaBase was enriched with demographic data from the Danish Civil Registration register and comorbidity information from The Danish National Patient Register.

We investigated a sub cohort of 28,990 patients in DiaBase with unexplained non-attendance after first diabetic eye screening. Patients, who died, migrated, disappeared or were not due for next screening episode within the observation period, were excluded.

RESULTS. The baseline prevalence of DR in non-attendees was 9.3% as compared to 16.0% in repeating attendees ($p<0.001$).

There was a geographical skewing in the fraction of non-attendees in the five Danish regions; ranging from 9.4% in the Region of Southern Denmark to 18.4% in the Capital Region of Denmark ($p<0.001$).

Non-attendees did not differ from the repeating attendees in regards to age, gender, marital status or screening facility (private practicing ophthalmologist or hospital), likewise they had an equivalent Charlson comorbidity score, as compared to repeating attendees.

CONCLUSIONS. In a real-life, national diabetic eye screening program from Denmark, 14.1% of patients, without evident reason, only attended eye screening once. Data suggests that non-attendance might be related to geographical factors and lower DR severity, as opposed to general comorbidity.

Technical differences between the Danish regions might cause variations in registrations from examining doctors.

Safety, Efficacy and Cost Effectiveness of Individualised Screening for Diabetic Retinopathy: The Individualised Screening for Diabetic Retinopathy (ISDR) Single Centre, Open Label, Equivalence Randomised Controlled Trial

D.M. Broadbent[1,2], S.P. Harding[1,2], M. Garcia-Finana[3,4], M. James[5], I.M. Stratton[6], J.P. Vora[8], M. Gabbay[9]

[1]*Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, University of Liverpool, member of Liverpool Health Partners, United Kingdom*
[2]*St Paul's Eye Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom*
[3]*Department of Biostatistics, University of Liverpool, member of Liverpool Health Partners, United Kingdom*
[4]*Liverpool Clinical Trials Centre, Liverpool, United Kingdom*
[5]*Division of Rehabilitation, Ageing and Wellbeing. School of Medicine, University of Nottingham, Nottingham, United Kingdom*
[6]*Gloucestershire Retinal Research Group, Cheltenham General Hospital, Cheltenham, United Kingdom*
[7]*Mersey Diabetes Support Group. Liverpool, United Kingdom*
[8]*Department of Diabetes and Endocrinology, Royal Liverpool University Hospital, United Kingdom*
[9]*Department of Health Services Research, University of Liverpool, and Brownlow Health Centre, United Kingdom, members of Liverpool Health Partners, United Kingdom*

DESIGN. Two-arm, parallel assignment, equivalence, 2 year randomised controlled trial (RCT)

PURPOSE. Evaluate safety, feasibility, efficacy and cost effectiveness of individualised risk-based variable-interval screening compared to annual screening for diabetic retinopathy (DR).

METHODS. People with diabetes aged ⩾12 years registered with a single programme in the English National Diabetic Eye Screening Programme were randomised 1:1 to annual or individualised screening (6, 12 or 24 months for high, medium and low risk) determined by a risk calculation engine. Dynamic real-time connections between local demographic, screening and clinical data. Primary outcome: attendance at first follow-up. A secondary safety outcome was the development of sight threatening DR (STDR). Cost effectiveness evaluated (2 year time horizon) from UK NHS and societal perspectives. A sample of the first participants

enrolled into the RCT completed EQ-5D-5L and Health Utilities Index Mark 3 (HUI3) questionnaires at baseline and follow-up. Sight threatening DR (STDR, referable retinopathy) was defined as moderate pre-proliferative DR or worse.
RESULTS. 4534 participants were randomised; 2097/2265 (individualised) and 2224/2269 (control) remained after withdrawals. Attendance rates at first follow-up were equivalent (individualised 83.6%, control 84.7%) (difference -1.0, 95% CI -3.2 to 1.2). STDR detection rates were non-inferior: individualised 1.4%, control 1.7% (-0.3, -1.1 to 0.5). No patients required treatment at diagnosis of STDR. The NHS perspective cost effectiveness plane for the EQ-5D-5L and HUI3 showed the dominance of the intervention arm in cost savings and expected maintenance of quality of life; 92.6% EQ-5D-5L iterations and 60.6% HUI3 iterations fell within the south-east quadrant. Incremental cost savings/person were: NHS perspective £19·73 (18·28 to 21·16) / €22·39 (20·75 to 24·01); societal perspective £26·19 (CI 24·41 to 27·87) / €29·72 (CI 27·70 to 31·63). 43.2% fewer appointments were required in the individualised arm.
CONCLUSIONS. Stakeholders involved in diabetes care can be reassured by this largest ophthalmic RCT in DR screening to date that extended and individualised risk-based intervals can be introduced into established screening programmes safely and cost effectively.

Irish National Diabetic Retinascreen Programme: 5 Rounds of Screening and Referrals

R. Pandey[1,2,3], C. Murphy[1], H. Kavanagh[1], D. Keegan[1,2,3]

[1]*Diabetic RetinaScreen*
[2]*Retinal Research Group @ Mater *** Should this be Retinal Research Group, Mater Misericordiae University Hospital, Dublin, Ireland?*
[3]*University College Dublin, Dublin, Ireland*

DESIGN. Screening and grading data was analysed to study the diabetic retinopathy screening outcome and retinopathy grades of patients referred via routine and urgent referral pathways to treatment centres.
PURPOSE. Diabetic retinopathy (DR) has been recognized as the most common cause of blindness in the working age population in Europe. Screening and referral of maculopathy and proliferative retinopathy are effective tools in reducing the risk of patients developing visual symptoms due complications of diabetic retinopathy.
METHODS. Diabetic retinopathy screening has been implemented in Republic of Ireland since 2013. Screening retinopathy grades and referral outcomes of patients screened were analysed. Retinopathy grading used by Diabetic RetinaScreen programme is based on the English retinopathy National Diabetic Retinopathy Screening Programme.
RESULTS. Diabetic RetinaScreen has completed 5 rounds of annual screening from February 2013 to 31st December 2018 (counting roll out years of 2013 and 2014 as round 1 of screening). In the first round of screening 62,951 patients attended screening appointments and in the fifth round 105,475 patients attended screening appointments. Over 5 rounds of screening completed, 88.2% (86.7 – 91.6%), mean (range) of the patients were screen-negative. Background retinopathy (R1M0) was detected in 25.7% (22.8 - 28.9%) of the patients over five rounds of screening. Cumulative sight-threatening pre-proliferative and proliferative retinopathy referrals decreased from 4.5% in round one to 1.5% round five. The majority of patients 64.3% (60.5 – 70%) with proliferative retinopathy are between the ages of 50 and 79 years old. In the first screening round 235 patients (0.4%) were referred via the routine NDED referral pathway. As attendance figures increased, routine NDED referrals increased to 3,032 patients (2.8%) in the fifth round.
CONCLUSIONS. Attendance for retinopathy screening has improved every year since the programme has begun. 88.2% of all patients screened are screen-negative and returned to annual screening appointments. Routine diabetic retinopathy referrals mostly consist of maculopathy assessment referrals. Proliferative diabetic retinopathy cumulative detection has reduced over the first five rounds of screening.

Use of Dilating Drops in the Scottish Diabetic Retinopathy Screening Programme

C. Styles, N. Lee, M. Black, K. Ah-See

Diabetic retinopathy screening, Scotland, United Kingdom

DESIGN. Retrospective audit
PURPOSE. Scotland has had a staged approach to mydriasis in the diabetic retinopathy screening programme since the national programme started in 2006. A single macula centred image is taken initially using a non mydriatic fundus camera. If the image is inadequate for grading, only then are dilating drops used and a repeat image taken. This retrospective audit looks at the requirement for dilating drops in the retinopathy screening service by age in 2018-19 and compares this with uptake rates.
METHODS. Data was obtained from Vector. The use of dilating drops for obtaining an image and age was recorded. Percentages of dilating drop use were then calculated for each age group. Uptake rates over the age ranges were also calculated.
RESULTS. In 2018-19, 211,518 people had fundus photography in the diabetic retinopathy screening programme. The overall use of dilating drops was 30% but varied greatly with age group. The highest rate of dilating drop use (62%) was in the 85 years old and over. The need for dilating drops only went above 50% in the 75-84 year olds. Before then there is an increasing requirement for dilating drop use for adequate imaging with age ranging from 1.3%

in the 12-14 year old group to 32.8% in 2019. The overall photographic technical failure rate (where adequate imaging was not possible even with dilating drops) in Scotland for 2018-19 was 2.7%
The highest uptake rate was 83.4% in the 65-74 year olds (dilation drop use of 33%) and the lowest was 60.2% in the 35-44 age group (dilation drop use 8.9%). The overall uptake rate was 73%. The uptake rate did not correlate with use of dilating drops.
CONCLUSIONS. The use of staged mydriasis is an efficient, effective method of screening for diabetic retinopathy. It does not directly correlate with uptake rate so factors other than being able to drive to an appointment appear to have greater influence on attendance behaviours.

Establishing a Diabetic Retinopathy Screening Service in Eswatini

J.Pons[1], P. Hutinten[2], R. Roberts[1], B. Zetteberg[1], S. Sibusisu[1], T. Peto[3]

[1]*Good Shepherd Hospital, Siteki, Eswatini*
[2]*Optomed, Finland*
[3]*Queens University Belfast, Belfast, Northern Ireland, United Kingdom*

DESIGN. Pilot study of diabetic eye and foot screening
PURPOSE. It has been shown that 84% of those attending the Diabetic Eye Clinic at the Good Shepherd Hospital, Siteki, Eswatini did so with sight threatening diabetic eye disease in the second eye. To enable change, diabetic eye screening was set up using a non-mydriatic camera and an OCT using trained staff and this service was offered to all with diabetes attending the clinic for any reason. It has been noted that the most common co-morbidity was diabetic foot problems and so a pilot study is being set up for dealing with both issues.
METHODS. A database containing demographic details of people with diabetes has been set up. Colour images are taken and grading is conducted by trained and accredited staff overseen by the local ophthalmologist. Three technicians are now being trained to deliver both eye and foot screening while other healthcare providers and patient groups being trained in diabetic complications.
RESULTS. The diabetes population in the Lumbombo/Siteki region is estimated to be 4,500, in the first 12 months, only 7% of the population screened, totalling 326 people with diabetes. Of these, 14% had proliferative diabetic retinopathy and an additional 26% of the images were not of gradable quality, resulting in an overall 40% therefore showing sight threatening significant abnormality. There is laser treatment available in Siteki, and these treatments have been completed as required.
CONCLUSIONS. It has been challenging to include eye-screening into diabetes care, and further challenges are expected for foot screening, especially appropriate after-care for those identified in need of treatment. Many patients travel long distances to the clinic and welcome both screenings to be completed at the same time, however they might struggle to finance treatment options and take time out of work or simply be away from the family for the necessary treatments.

Diabetic Retinopathy as an Independent Predictor of Subclinical Cardiovascular Disease: Baseline Results of the Precised Study

R. Simó, O. Simó-Servat, A. Planas, J. Bañeras, I. Ferreira, C. Hernández

Vall d'Hebron Research Institute, Universitat Autònoma de Barcelona, Spain

DESIGN. Prospective case-control study
PURPOSE. Detection of subclinical cardiovascular disease (CVD) has significant impact on the management of type 2 diabetes. We examined whether the assessment of diabetic retinopathy (DR) is useful for identifying patients at a higher risk of having silent CVD.
METHODS. A total of 200 type 2 diabetic subjects without history of clinical CVD and 60 age-matched non-diabetic subjects were included in the study. The presence of subclinical CVD was examined using two parameters: (1) calcium coronary score (CACs); (2) composite of CACs >400 UA, carotid plaque $\geqslant 3$ mm, carotid intima–media thickness ratio >1, or the presence of ECG changes suggestive of previous asymptomatic myocardial infarction. In addition, coronary angio-CT was performed. DR was assessed by slit-lamp biomicroscopy and retinography.
RESULTS. Type 2 diabetic subjects presented higher CACs than non-diabetic control subjects ($p<0.01$). Age, male gender, and the presence of DR were independently related to CACs >400 (area under the receiver operating characteristic curve (AUROC) 0.76). In addition, an inverse relationship was observed between the degree of DR and CACs <10 AU. The variables independently associated with the composite measurement of subclinical CVD were age, diabetes duration, the glomerular filtration rate, microalbuminuria, and the presence of DR (AUROC 0.71). In addition, a relationship ($p<0.01$) was observed between the presence and degree of DR and coronary stenosis.
CONCLUSIONS. The presence and degree of DR is independently associated with subclinical CVD in type 2 diabetic patients. Our results lead us to propose a rationalized screening for coronary artery disease in type 2 diabetes based on prioritizing patients with DR, particularly those with moderate-severe degree.

Diabetic Retinopathy Grade as Predictor of Outcomes in Patients with Type 2 Diabetes and Lower Extremity Amputations - Multicentric Longitudinal Seven Years Study

K. Shah[1], N. Sundaram [3], V. Shivane[3], V. Parsewar[4]

[1]Diabetes & Thyroid Care Centre, Grant Medical College & Sir JJ group of hospitals, Mumbai Central, Noor Baug, Mazgaon, Mumbai, India
[2]Aditya Jyot Eye Hospital, PVT Ltd, Mumbai, India
[3]Sadhana Diabesity Clinic, Mumbai, India
[4]Parsewar Diabetes Care Centre, Nandad, India

DESIGN. Prospective, multicentric, longitudinal seven years study
PURPOSE. Lower Extremity Amputations (LEA) and Diabetic Retinopathy (DR) are debilitating complications in patients with Type 2 diabetes.
METHODS. We prospectively explored the association of grades of DR with the outcomes and the risk factors in patients (n=2500) with Lower Extremity Amputations (January 2012 to December 2019).Goodness of fit was examined using Pearson Chi Square test.
RESULTS. Severe neuropathy (n=1341, 53.6%), osteomyelitis (n=1274, 50.9%), and gangrene (n=1242, 49.6%), were the predominant comorbidities. DR was observed in 56% (n=1400) of patients (NPDR n=962, 38%; PDR n=438, 16%). DR and LEA were strongly related with the highest association observed for amputations of both lower limbs (n=640), followed by above knee (n=365), below knee (n=249) and toes (n=146) ($p<0.00001$). 73.8% of patients with DR (n=1034) had HbA1c >11%. The seven year follow up was characterised by a high incidence of new diabetic ulcers and amputations (62.8% n=1571, $p<0.00001$). The incidence of new ulcers was highest in the NPDR group (n=483, 50.2%) whereas the incidence of new amputations was highest in the PDR group (n=238, 54.3%). The all-cause mortality was 41.9% (n=1048, $p<0.00001$). Patients with NPDR reported highest mortality (n=508, 48.4%). Myocardial Infarction (n=316, 30.01%) was leading cause of mortality in patients with NPDR (n=237, 42.3%) whereas Congestive Heart Failure (n=604, 57.6%), was predominant cause of mortality in patients with PDR (n=350, 70.5%) ($p<0.00001$). The incidence of mortality 29.4% (n=308) was highest in the 7th year of follow up.
CONCLUSIONS. We observed that grades of DR had independent higher predictive values for new ulcers, new amputations and all-cause mortality. Patients with NPDR had worst outcomes. This long-term prospective study highlights the importance of grades of DR to predict outcomes beyond ocular morbidity and implement an integrated multidisciplinary approach for this composite complication as a consequence of diabetes.

Ocular and Systemic Risk Markers of Diabetic Retinopathy Progression. A Five-Year Longitudinal Study

J. Cunha-Vaz[1], A. Martinho[1], I.P. Marques[1], A.L. Messias[2], T. Santos[1], M.H. Madeira[1], C. Lobo[1]

[1] AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal
[2] Dentistry Department, Faculty of Medicine University of Coimbra, Coimbra, Portugal

DESIGN. A 5-year prospective, longitudinal study was designed to follow 221 patients with type 2 diabetes and mild NPDR (ETDRS grades 20 and 35).
PURPOSE. To compare the relative predictive value of ocular and systemic risk markers of diabetic retinopathy progression and development of diabetic macular edema (DME) or proliferative retinopathy (PDR) in a 5-year prospective study of mild non-proliferative retinopathy (NPDR) in patients with diabetes types 2.
METHODS. Two hundred and twenty one patients with diabetes type 2 and mild NPDR were followed prospectively for a 5-year period. Examinations were performed at baseline, first 6 month visit and annually (BCVA, fundus photography and OCT). Progression was identified by the development of endpoints, namely DME or PDR. The following systemic markers were evaluated: age, sex, diabetes duration, blood pressure and HbA1c. Ocular risk markers considered were: microaneurysm turnover (MAT) and retinal edema (full retina thickness). The five-year risk was also calculated with the RetinaRisk application (www.retinarisk.com), and correlated with endpoint development and severity progression (ETDRS step change).
RESULTS. Of the 221 eye/patients included in the study, followed over a 5-year period, 25 developed DME and/or PDR, which, at a systemic level, revealed risk association with HbA1c levels and age. A multivariate analysis including ocular and systemic markers revealed that MAT has an Odds ratio (OR) of 1.04 (95%CI: 1.01-1.08, P=0.013) and retinal thickness has an OR of 1.27 (95%CI: 1.01-1.05, P=0.006), both identifying the risk for development of DME and/or PDR. HbAc1 (systemic marker) presents the higher risk (OR:1.47 95%CI: 1.06-2.04, P=0.02). When assessing the five-year risk of progression with the RetinaRisk Application, it showed no association with endpoint development, being only associated with severity increase (11.25 OR; 95%CI 2.78-45.25; $P<0.001$).
CONCLUSIONS. In the 5-year risk evaluation, ocular markers as microaneurysm turnover and retinal thickness showed an association with the risk of developing vision-threatening complications (DME and/or PDR), as well as the systemic marker HbA1c.

Different Retinopathy Phenotypes in Diabetes Type 2 Show Different Five-Years Risks for Development of DME and PDR

I. Pereira Marques[1], M.H. Madeira[1], A.L. Messias[2], R. Coimbra[1], T. Santos[1], J. Figueira[1,3], J. Cunha-Vaz[1]

[1]*AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal*
[2]*Dentistry Department, Faculty of Medicine University of Coimbra, Coimbra, Portugal*
[3]*Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC), Portugal*

DESIGN. Five-year longitudinal study.
PURPOSE. To characterize the 5-year progression of mild non-proliferative retinopathy (NPDR), in patients with diabetes type 2, to vision-threatening complications, diabetic macular edema (DME) or proliferative retinopathy (PDR).
METHODS. 213 patients with diabetes type 2 and mild NPDR (ETDRS grades 10-20 (27%) or 35 (73%) were followed in a 5-year longitudinal study. Ophthalmological examinations were performed at baseline, 6-months visit and annually. ETDRS severity grade was identified and MA turnover (MAT) assessed using the RetMarkerDR®. A phenotype classification was performed based on MAT and central retinal thickness on SD-OCT.
RESULTS. Of the 213 eyes/patients included in the study, 173 completed the 5 year follow up or achieved one of the endpoints. 28 eyes developed vision-threatening complications (DME in 24 (85,6%), PDR in 3 (10,7%) and DME with PDR in 1 (3,6%)). DME developed in 11 eyes/patients with phenotype B (11 in 58: 19%) and in 17 eyes/patient with phenotype C (17 in 56: 30.4%). Phenotype A showed no association with development of sight-threatening vision complications. Phenotype C showed higher risk for development of DME, with a 1.86 odds ratio (OR; 95% confidence interval (CI): 0.70-3.92) than phenotype B. All patients that developed PDR were classified in Phenotype C (4 in 56: 7.1%). Concerning the ETDRS severity score, progression was higher for phenotype C patients (OR 1.8, 95%CI 0.85-3.89). HbA1c was higher in patients that developed complications (8.5% vs 7.5%), however not statistically significant.
CONCLUSIONS. Different retinopathy phenotypes in diabetes type 2 show different 5-year risk for development of DME and PDR. Phenotype C identifies eyes at higher risk for development of complications and severity progression. It is the only one associated with PDR. Phenotype B show higher risk for development of DME but not PDR nor retinopathy severity. In contrast, phenotype A identifies eyes that are at very low risk of development of sight-threatening complications.

Mirna Levels as a Biomarker for Anti-VEGF Response in Patients with Diabetic Macular Edema

R. Schlingemann, M. Vader, I. Klaassen

Ocular Angiogenesis Group, Department of Ophthalmology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

DESIGN. Laboratory study, RCT cohort
PURPOSE. The aim of this study was to investigate whether circulating miRNA levels could serve as a predictive biomarker for the responsiveness to anti-vascular endothelial growth factor (VEGF) therapy in patients with diabetic macular edema.
METHODS. Whole blood samples were collected from 135 patients who were included in the BRDME study, a randomized controlled trial comparing bevacizumab to ranibizumab in the treatment of patients with diabetic macular edema (Trialregister.nl, NTR3247). Participants received monthly injections of 1.25 mg bevacizumab or 0.5 mg ranibizumab for 6 months. Visual acuity and central area thickness were measured monthly during follow-up. Blood samples for RNA extraction were collected during screening visit, before administration of the first injection. Circulating levels of selected miRNAs were quantified, which included miRNA-7, miRNA-21, miRNA-133b, miRNA-181a, miRNA-222, miRNA-181c and miRNA-1197.
RESULTS. After linear regression analysis, levels of miRNA-133b correlated with visual acuity at baseline ($P < 0.001$), and were positively associated with the change in visual acuity between baseline and 3 months ($P < 0.001$) and between baseline and 6 months of treatment ($P < 0.001$). In contrast, levels of miRNA-7 were negatively associated with visual acuity outcomes after 6 months ($P = 0.018$). No association was found between circulating miRNA levels and change in central area thickness.
CONCLUSIONS. This study shows that miRNA-133b is positively associated with both baseline visual acuity and with the change in visual acuity from baseline to 3 and 6 months in patients with DME treated with anti-VEGF agents. For miRNA-7, higher concentrations are associated with worse visual outcomes. Our findings suggest that circulating miRNA-133b and miRNA-7 may be positive and negative predictive biomarkers for better visual acuity outcome after anti-VEGF therapy, respectively.

Retinal Vasculature Damage in the Deeper Plexus is More Severe Than in the Superficial Plexus During Very Early Diabetic Retinopathy

Q. Yang[1], M.V. Yasvoina[1], M. Zhu[2], M. Fruttiger[1]

[1]*UCL Institute of Ophthalmology, London, United Kingdom*
[2]*Lions New South Wales Eye Bank, Sydney Eye Hospital, Sydney, Australia*

DESIGN. Histopathology study on human postmortem eyes from diabetic and control donors.
PURPOSE. To measure retinal capillary dropout during early diabetic retinopathy (DR) in the superficial (SVP) and deeper vascular plexus (DVP).
METHODS. Post-mortem eyes were obtained from Moorfields Eye Bank (London, UK) and Lions NSW Eye Bank (Sydney, Australia) from three controls, eight diabetic, and one DR donor. Ulex Europaeus Agglutinin (UEA) staining was used to visualise blood vessels in

retinal wholemounts and to screen for vasculature abnormalities. Subsequently, tissue was sectioned (wax) consecutively and co-stained with UEA and anti-collagen IV to reveal the endothelium and vascular basement membrane. Collagen IV positive vascular profiles without any internal endothelial cells were considered as "ghost vessels" and as non-perfused. We sampled across the entire retina by examining three sections from every hundredth section. Capillary plexuses were separated according to criteria proposed in Campbell et al (2017). Student's t-test was used to test significance and $p < 0.05$ was considered statistically significant.

RESULTS. Results revealed a low capillary dropout (ghost vessels) incidence in non-diabetic retinae (~1%). We identified two subgroups of diabetic retinae: the non-phenotypic group presented a comparable level of capillary dropout as non-diabetic group, where no differences between different retinal vasculature plexus could be found; whereas the phenotypic diabetic group showed an notable increase in dropout incidence in the DVP compared to non-diabetic group (8.38% vs 1.35%, $p < 0.001$), with only a slight increase in the SVP (2.61% vs 0.718, $p < 0.01$). This phenomenon is much more obvious in advanced DR, which presented a considerable level of nonperfusion at both plexuses, with the DVC being more severely affected than the SVP (44.38% vs 15.28%, $p < 0.001$).

CONCLUSIONS. This study shows that even during the earliest stages of DR, the DVP shows more severe damage compared to SVP.

Validation of a Deep Learning Algorithm for Diabetic Retinopathy

N. Relaño-Barambio[1], P. Romero-Aroca[1], M. Baget-Bernaldiz[1], R. Navarro-Gil[1], D. Puig[2], A. Valls[2]

[1]*Department of Ophthalmology, Sant Joan de Reus University Hospital, Spain*
[2]*Department of Informatics Engineering and Mathematics, Rovira & Virgily University, Spain*

DESIGN. Observational

PURPOSE. To validate our Deep learning algorithm (DLA) to read diabetic retinopathy (DR) retinographies

METHODS. The DLA first model was build using 88.702 images from EyePACS, 1.748 from Messidor-2 and 19.230 from our own diabetic population. For validation a total of 38.339 retinographies from 17.669 patients were read by our DLA and also validated by four masked retinologists. The retinographies were made by a single 45º retinography centered between macula and temporal side of the papilla according to EURODIAB recommendation Retinopathy was graded according to MESSIDOR in four levels: 0= Normal [no microaneurisms and no haemorrhages], 1 = level 20 of ETDRS [only microaneurisms ($\leqslant$5)], 2 = moderate diabetic retinopathy [microaneurisms >5 and <15 or haemorrhages <5], and 3 = severe diabetic retinopathy [microaneurisms $\geqslant$15 or haemorrhages $\geqslant$ 5 or new-vessels = 1]. We determined agreement with Cohen's Weighted Kappa index (CWK), sensitivity (S) and specificity (E) between the two methods.

RESULTS. We divide the results of the algorithm analysis comparing DLA vs Ophthalmologists to detect any-DR (levels 1,2,3) or to detect referable-DR (levels 2,3). On our first model, the CWK was 0.886, with S=0.967% and E=0.976% for Any-DR; CWK=0.809, S=0.998% and E=0.968% for Referable DR. Later modifications of the model resulted in CWK=0.919, S=0.982% and E=0.890% for Any-DR; CWK=0.919, S=0.991% and E=0.830% for Referable-DR.

CONCLUSIONS. Our algorithm was able to read retinographies of diabetic patients with a great agreement and can help in diabetic retinopathy screening.

EFFECTS OF MELANOCORTIN RECEPTOR AGONISM IN CELL MODELS OF THE INNER BLOOD-RETINAL BARRIER CULTURED IN DIABETIC-LIKE CONDITIONS

A. Mazzeo[1], E. Beltramo[1], R. Maisto[2], M. Trento[1], M. D'Amico[2], M. Porta[1]

[1]*Dept Medical Sciences, University of Turin, Italy*
[2]*Dept Experimental Medicine, University of Campania "L.Vanvitelli", Naples, Italy*

DESIGN. The pathogenesis of diabetic retinopathy (DR) involves several complex mechanisms, among which oxidative stress and inflammation. Melanocortins are endogenous peptides with several biological activities mediated by the activation of melanocortin receptors (MCR), such as inhibition of leukocyte activation and inflammation. MCR1 and MCR5 receptors are mainly expressed in retinal tissues. An increase in their expression was shown in the retina of diabetic mice, with their agonists exerting a protective role against inflammation. In rat retinal cells cultured in high glucose conditions, the addition of a MCR5 agonist reduced anti-inflammatory cytokines and chemokines, while increasing the levels of the anti-oxidant manganese superoxide dismutase (MnSOD) and glutathione peroxidase (GPx).

PURPOSE. Our objective was to test the role of MCR5 agonism/antagonism on human cell models of the inner blood-retinal barrier, to understand if the beneficial effects of these molecules were exerted on the microvascular district of the retina.

METHODS. Human Microvascular Endothelial cells (HMEC), Human Retinal Pericytes (HRP), and Human Müller cells (MIO-M1) were exposed for 8 days to diabetic-like conditions (intermittent high glucose, intHG, and/or hypoxia). A MCR5-agonist and a MCR5-antagonist were added for the last 48 hrs. The expression of MCR1 and MCR5 were investigated by both RT-PCR and Western blotting, the modulation of the anti-oxidant molecules MnSOD and GPx by WB.

RESULTS. HMEC, HRP and Müller cells express both MCR1 and MCR5 receptors. However, their expression was not modulated by diabetic-like conditions, nor by the addition of MCR5 agonist or antagonist. Similarly, we could not find any significant difference in the expression of MnSOD and GPx among our experimental conditions.
CONCLUSIONS. Prevention of DR is difficult to achieve and there is a need for new pharmacological approaches. Melanocortin receptor agonism seems to have a promising potential. However, our results seem to rule out a direct protective effect on the retinal microvasculature, thus suggesting a major involvement of the neuroretina. Further studies are needed to discern which retinal cell type is directly involved in these beneficial effects.

Fluctuating Hyperglycaemia has the Same Effect as Sustained Hyperglycaemia in an in Vitro Model of Diabetic Retinopathy

N. Varsney, H.L. Levis, J.J.E. Eyre

Department of Eye and Vision, Institute of Ageing and Chronic disease, University of Liverpool, Liverpool, United Kingdom

DESIGN. Laboratory based optimisation study using human retinal endothelial cells (hREC).
PURPOSE. To investigate advances in treatment of DR, in vitro studies should be completed to evaluate efficacy of proposed interventions. To achieve this, a cell culture model mirroring the cellular changes seen in DR would be useful. We have previously developed a model using sustained hyperglycaemia and 2% oxygen conditions to mimic DR using hREC, that has been found to effectively induce the oxidative stress and cell barrier changes found in DR. To further optimise the existing model of DR, this study investigated whether fluctuating hyperglycaemia was more effective at inducing the pathological changes found in DR than sustained hyperglycaemia.
METHODS. hREC were cultured under 2% and 20% oxygen and either sustained healthy glucose (5.5mM), a sustained hyperglycaemia (33mM), or fluctuations between these two values with 33mM administered during the day and 5.5mM administered to cells overnight. Cells were kept in experimental conditions for 72H after which analysis of metabolic activity, immunofluorescence antibody staining of angiogenic and oxidative stress response and tight junction-associated protein expression, cell counts and senescence associated ß-galactosidase (SAß-G) staining were undertaken. Transendothelial electrical resistance (TEER) measurements were assessed as an indicator of cell membrane integrity.
RESULTS. It was observed that hREC cultured under 2% oxygen and treated with fluctuating hyperglycaemia demonstrated increased presence of oxidative stress markers (Ang2, SOD1, SOD2, HIF-1α and VEGF-R2) in comparison to their sustained hyperglycaemia counterparts. However, no significant differences in metabolic activity and cell count within the 72H timeframe suggest this did not lead to hREC loss. Cell-cell membrane integrity was maintained across all experimental conditions, with no significant differences in TEER measurements or immunofluorescence VE-cad, CD31, Cx43 or ZO-1 expression.
CONCLUSIONS. Based on this study, the current conditions of sustained hyperglycaemia and 2% oxygen can continue to be used to model DR in hREC. However, as DR is the sequelae of a chronic disease, 72H may not be a long enough time frame to induce changes. This study should be repeated with a longer culture period.

Anti-Inflammatory (M2) Response is Induced by a Synthetic Glycolipid-Type Molecule ((1R)-1-Dodecylsulfinyl-5N,6O-Oxomethylidenenojirimycin): A New Possible Treatment in Diabetic Retinopathy

A.I. Arroba[1,2], E.M.S.F. Sánchez-Fernández[3], F.C.C. Cano Cano[1,2], J.M.G.F. García Fenandez[4], C.O.M. Ortiz-Mellet[3], A.M.V. Martinez-Valverde[5,6], M.A.D. Aguilar-Diosdado[1,2]

[1]*Research Unit, Instituto de Investigación e Innovación en Ciencias Biomédicas de la Provincia de Cádiz (INiBICA), University Hospital "Puerta del Mar", Cádiz, Spain*
[2]*Department of Endocrinology and Metabolism, Instituto de Investigación e Innovación en Ciencias Biomédicas de la Provincia de Cádiz (INiBICA), University Hospital "Puerta del Mar", Cádiz, Spain*
[3]*Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Sevilla, Spain*
[4]*Instituto de Investigaciones Químicas (IIQ), CSIC - Universidad de Sevilla, Avda. Américo Vespucio 49, 41092 Sevilla, Spain*
[5]*Instituto de Investigaciones Biomédicas Alberto Sols (IIBm) (CSIC/UAM), C/ Arturo Duperier 4, 28029 Madrid, Spain*
[6]*Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERdem), ISCIII, 28029 Madrid, Spain*

DESIGN. Retinal inflammation occurs during an early stage in Diabetic Retinopathy (DR), which is believed to play a crucial role in the development and progression of DR. Retinal inflammation is mediated by microglia activation and there after leads to neuronal apoptosis. Various bioactive extracts from medicinal plant and algae, such as the iminosugar glycosyl hydrolase inhibitors 1-deoxynojirimycin and castanospermine or the immunoregulatory α-linked glycolipids, have shown properties against chronic diseases with an inflammatory component. We have recently reported the beneficial effects of molecules that combine the structural features of iminosugars and glycolipids, namely sp2-iminosugar glycolipids (sp2-IGLs), in reducing inflammatory parameters during DR by modulation of different signalling pathways in the immune system of the retina. Effect of the (1R)-1-dodecylsulfinyl-5N,6O-oxomethylidenenojirimycin (C4) bioactive compound on Microglia cells (BV2) and Retinas from BB rat. Proinflammatory and anti-inflammatory response were evaluated

PURPOSE. The aim of this work was to investigate the effects of the sp2-IGL (1R)-1-dodecylsulfinyl-5N,6O-oxomethylidenenojirimycin on inflammation associated to Diabetic Retinopathy
METHODS. We stimulated microglia cells (BV2) with lypopolysaccharide (LPS), as an inflammatory stimulus and/or C4. Retinas from BB rat at different ages were obtained and retinal explants from BB rat at 6 weeks was cultured in the presence or absence of C4. Cytotoxicity, nitrites production, iNOS, Arginase-1, Iba-1, proinflammatory-(M1 response) / anti-inflammatory-(M2 response) cytokines, stress kinases signalling pathway were analyzed by either RT-PCR or Western blotting. Reactive gliosis was determined by immufluorescence for Glial Fibrillary Acidic protein (GFAP).
RESULTS. Bv.2 microglial cells cultured under diabetic environment and treated with C4 reduces the pro-inflammatory markers, such as iNOS levels and IL1b, IL6 and TNF expression. The activation of the inflammasome complex is blocked and C4 is able to induce a potent M2 response by inducing IL-10 expression and increasing the Arginase-1 levels. The C4 effect was studied in retinas from a diabetic model of Diabetes mellitus type 1, BB rat, where we detected a clear reduction of reactive gliosis, a classical feature of DR.
CONCLUSIONS. The C4 product exerts a beneficial effect on the inflammatory process that precedes the RD and could be an effective alternative for its treatment and / or prevention.

Involvement of PDGF in Neurite Outgrowth Leading to Fibrovascular Membranes in PDR

I. Klaassen[1,2,3], E. Lefevere[2], I. van Hove[2], D.H.W. Steel[2], L. Moons[2], R. Schlingemann[1]

[1]Ocular Angiogenesis Group, Departments of Ophthalmology and Medical Biology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[2]Research Group Neural Circuit Development and Regeneration, Department of Biology, Katholieke Universiteit Leuven, Belgium
[3]Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[4]Sunderland Eye Infirmary, Sunderland, United Kingdom
**** Missing any reference to Institution No. 4 - R. Schlingemann to advise*

DESIGN. Experimental
PURPOSE. The formation of fibrovascular membranes (FVMs) is a serious sight threatening complication of proliferative diabetic retinopathy (PDR) which may result in retinal traction and retinal detachment. An initial step in the formation of these membranes may be neurite outgrowth from neurons and Müller cells, which serve as a template. From vitreous samples of PDR patients, we identified a number of candidates that may be involved in the formation of FVMs. The aim of this study was to test whether these candidates have an effect on neurite outgrowth.
METHODS. Retinal explants of C57BL6/N mouse pups at postnatal day 3 (P3) were cultured in poly-L-lysin and laminin coated four-well dishes. Outgrowth stimulation experiments were performed by addition of potential inducers or inhibitors of neurite outgrowth or BDNF and CNTF as a control. Quantification was performed by morphometric confocal microscopy analysis after staining for β–tubulin III.
RESULTS. Whereas neuregulin 1 (NRG1), placental growth factor (PlGF), connective tissue growth factor (CTGF) or thrombospondin-1 (THBS1) did not result in neurite outgrowth, platelet derived growth factor (PDGF) ligands were found to induce neurite outgrowth initiation in a concentration dependent manner. Of 3 different PDGF-ligands, PDGF-AA gave the highest induction, followed by PDGF-AB and -BB. In addition, incubation of retinal explants with vitreous of PDR patients resulted in a significant induction of neurite outgrowth as compared to control vitreous. This induction could be prevented by addition of CP673451, a potent PDGFR inhibitor.
CONCLUSIONS. PDGF was found to be highly induced in vitreous of PDR patients with FVMs as compared to non-diabetic controls. Incubation with PDGF initiated neurite outgrowth in retinal explants and an inhibitor of PDGFR signalling could prevent neurite outgrowth induced by vitreous of PDR patients. This suggests that PDGF may be involved in neurite outgrowth that leads to the formation of FVMs.

Usability of a Telemedicine Tool Optomed Link Together with a Hand-Held Fundus Camera Optomed Aurora

N. Suvi

Medical and Wellness Technology, Faculty of Medicine, University of Oulu, Oulu, Finland

DESIGN. Approximately 1.3 billion people worldwide live with some form of visual impairment but as much as 80% of all visual impairments could be avoided if they are caught early. A hand-held fundus camera and a teleophthalmology tool could be an effective screening system for retinal diseases.
PURPOSE. The objective of this study was to collect qualitative and partly quantitative data about the usability of the telemedicine tool Optomed LINK together with the fundus camera Optomed Aurora for refining of the products.
METHODS. One Optomed Aurora fundus camera and the Optomed LINK telemedicine tool were delivered to the optical practice of two opticians. The products were introduced to the opticians during a user test. More information regarding the usability of the products were gathered with a questionnaire that was filled after every customer (N = 50), a System Usability Scale survey and a final questionnaire. The consulting ophthalmologist also filled a questionnaire.

RESULTS. Optomed Aurora had a comprehensive user interface and the imaging was successful in 9 out of 10 cases. The camera suited well to be an optician's tool, it supplemented their work and could be considered to be commissioned and recommended to other opticians. Most parts of the user interface of Optomed LINK were considered easy to use and problems occurred in only 2% of the cases. Optomed LINK was thought useful, supported and supplemented optician's work, and could be commissioned and recommended to other opticians. The most significant feedback was about the lack of possibility to add more detailed patient information and this was also mentioned by the consulting ophthalmologist who highlighted that incomplete patient information may increase the risk of misinterpreting findings.
CONCLUSIONS. The set comprising of fundus camera Optomed Aurora and the telemedicine tool Optomed LINK could initially make an effective screening system for retinal diseases. Further investigation is needed with a greater number of participants.

International Students Undertaking UK University-Validated Distance-Learning Courses in Diabetic Retinopathy Screening (DRS)

S. Aldington, M.C. Waite, B.E. Ellsmore, P. Dimmock, P.H. Scanlon

Gloucestershire Retinal Education Group, Dept. of Ophthalmology, Gloucestershire Hospitals NHS Foundation Trust, Gloucestershire Royal Hospital, Gloucester, United Kingdom

DESIGN. Web-based University-awarded distance learning courses
PURPOSE. Providing international staff with access to formalised education and validated qualifications in DR screening concepts, methods and practice to enhance patient care and ultimately reduce visual loss from complications of diabetes
METHODS. One main plus two subsidiary on-line web-based distance-learning courses provided to staff located outside the United Kingdom. The full 'Certificate of Higher Education in DR Screening' (Cert-HE) award comprises 5 modules, each of 8-weeks' duration: 1. Introduction to the study of diabetic retinopathy; 2. Diabetic eye screening: programmes, processes and protocols; 3. Preparing the patient for Diabetic Eye Screening; 4. Performing Retinal Screening; 5. Assessing retinal images. Learners undertaking the subsidiary 'University Certificate in Imaging for DR Screening' take modules 1 to 4. Learners on the 'University Certificate in Grading for DR Screening' complete modules 1, 2 and 5
RESULTS. Since the first course in 2015, 270 learners from 26 non-UK countries have registered on a qualification: 140 taking the full Cert-HE; 109 to take the Univ. Cert. in Grading and 21 on the Univ. Cert. in Imaging. There are 18 current learners (17 on Cert-HE and 1 on Imaging) who only commenced during 2019. Of the 252 learners who could have qualified by end of December 2019, 118 were awarded the full Cert-HE, 107 completed the Grading qualification and 20 completing the Imaging qualification plus 7 learners unfortunately leaving before qualification. Four of the 7 left due to leaving workplace or profession, only one person cited competing work pressures, one had funding difficulties and one who returned to Medical School. Three of the 7 were from Jamaica with one each from Malawi, Nigeria, Philippines and Saudi Arabia. Seventy-six successful learners were from China, 50 from the Republic of Ireland, 23 from Jamaica, 17 from St. Lucia and 10 each from Italy and Tanzania. The remaining 20 countries each provided 1 to 9 successful learners
CONCLUSIONS. Staff working in diabetic retinopathy screening services in 26 non-UK countries had little problem accessing and taking on-line distance-learning courses with fewer than 3% failing to qualify.

Assessing Virtual Clinic Quality and Safety for Patients with Diabetic Eye Disease at Manchester Royal Eye Hospital

R. Creer, R. Wales, Y.B. D'Souza

Manchester Royal Eye Hospital, Manchester, United Kingdom

DESIGN. This project compares grading and management of patients seen within a face to face clinical setting in diabetic ophthalmology eye clinics with a simulated virtual review.
PURPOSE. To assess quality and safety of the virtual clinic service to ensure high quality of care is maintained and to examine specific cases where disagreements occur.
METHODS. Diabetic grading and outcomes were taken for patients seen in the clinic who had undergone both wide-field photography and OCT imaging from that visit from clinic or from correspondence retrospectively. Two specialist trained optometrists who routinely undertake diabetic virtual assessments were asked to review the images taken as if the patient was seen in the virtual clinic. Where disagreements occurred, the simulated virtual visit was repeated by the lead diabetic consultant ophthalmologist.
RESULTS. For all patients assessed (n=139), full agreement was achieved for 83% of patients. This increased to 89% when considering only those patients who fitted the criteria to be seen in the virtual clinic (n=95).
Considering only those fitting criteria for the virtual clinic, of the 10 (11%) cases where there was a disagreement, 7 (7.4%) differed in grading and 3 (3.2%) differed in management or review interval, but overall management only differed in 2 cases (ie listing for treatment or investigations). For one case, the consultant agreed with the

simulated virtual outcome. For the second case, a face to face discussion with the patient or discussion with consultant would have allowed a better basis for the decision.
For cases not suitable for the virtual clinic, 10 cases (7.2% of total cases) differed in grade or review interval but not overall management. Four cases differed in management (2.9% of total decisions) however, in 2 of those 4 the consultant agreed with the simulated virtual clinic outcome.
CONCLUSIONS. High agreement between clinic and simulated virtual clinics reinforces the high quality and safety aspects of the virtual clinic and supports its use in regular clinical activity.

The Use of Virtual Clinics to Manage Diabetic Retinopathy Patients with Delayed Follow Up Appointments in an English Hospital Eye Service

A. Dale, K. Price, L.G. Gardner-Collins, P.H. Scanlon

Gloucestershire Hospitals NHS Foundation Trust (GHNHSFT), Gloucestershire Royal Hospital, Gloucester, United Kingdom

DESIGN. Retrospective study
PURPOSE. The British Ophthalmological Surveillance Unit published a report in 2017 that highlighted up to 22 patients per month may be losing vision by such delays experienced in hospital eye services (HES) in the UK. This study reports on the development of a virtual clinic, run by ophthalmic technicians, to manage a cohort of patients with diabetic retinopathy (DR) who were being monitored under the HES whose follow up appointments had been delayed.
METHODS. Patients under the care of the hospital eye service whose appointment had been delayed to over 12 months were given an appointment in a virtual clinic, in which:
1. Their Visual Acuity was recorded using back surface illuminated LogMAR charts
2. Tropicamide 1% eye drops were routinely inserted with the addition of Phenylephrine 2.5% for those eyes that dilated poorly
3. 2 x 45 degree fields were taken routinely, with 7-fields in eyes with pre-proliferative or proliferative features
4. A macular OCT using the Topcon 2000
Double grading was performed by technicians with an ophthalmologist only giving an opinion when requested.
RESULTS. Over a period of 18 months, 317 patients with delayed follow up appointments were seen in the virtual clinic. Of these 78 (24.6%) were identified as needing follow up review in the Hospital Eye Service because they had proliferative DR, severe non-proliferative DR (NPDR) or significant maculopathy that might need treatment in the near future. 183 (57.7%) had moderate NPDR or milder signs of maculopathy that could be followed up in the virtual clinic environment and 55 (17%) were discharged back to annual diabetic eye screening.
CONCLUSIONS. Monitoring patients who can be routinely followed up in a virtual clinic creates available appointments in the hospital eye service for those who need to be seen by an ophthalmologist and highlights those who need to be seen urgently for treatment.

Insights into Progression of Diabetic Retinopathy (DR) Severity Among Primary Care Patients with Diabetes in the United States

J. Sahni[1, 2], C.Y. Lin[1], V. Steffen[1], Z. Haskova[1]

[1]*Genentech, Inc., South San Francisco, California, United States of America*
[2]*F. Hoffman-La Roche Ltd., Basel, Switzerland*

DESIGN. Retrospective analysis of clinical trial data.
PURPOSE. To assess the risk of DR worsening and risk of progression to vision-threatening forms of DR (clinically significant macular edema [CSME] or proliferative DR [PDR]) among patients with diabetes in the US primary care setting.
METHODS. Eyes of 22,116 patients with diabetes were analyzed using data and images collected from 1999–2016 (Source: Inoveon Corporation, Oklahoma City, OK). DR severity and CSME were assessed from 7-field color fundus photographs by professional graders at a centralized reading center. DR severity was graded using the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS); analyses included eyes with valid baseline and postbaseline DRSS values (42,011 eyes). Occurrence of ⩾ 2-step DR worsening was assessed in the overall population and by baseline DRSS. Development of CSME (using ETDRS criteria) or PDR was analyzed among eyes with no CSME and no PDR, respectively, at baseline.
RESULTS. For all eyes evaluated, the Kaplan-Meier rate for time to first ⩾ 2-step worsening was 2.7% at year 2 and 7.1% at year 4. Rate of DRSS worsening by ⩾ 2 steps was greatest (8%-13%) among eyes with baseline DRSS 43–53 (moderate to severe nonproliferative DR [NPDR]). For eyes with baseline DRSS 43–53, the Kaplan-Meier rate for time to first ⩾ 2-step worsening was 11.6% at year 2 and 26.4% at year 4. The time to first development of CSME, PDR, or either CSME or PDR among eyes with baseline DRSS 43–53 was 9.4%, 6.0%, and 14.3% respectively, at year 2 and 20.4%, 12.3%, and 30.3%, respectively, at year 4.
CONCLUSIONS. The results from this study show that eyes with moderate to severe NPDR were at greatest risk of progression to vision-threatening forms of DR. These data also suggest the existence of 3 clinical subtypes among eyes with DR: one at increased risk of CSME, one at increased risk of PDR, and one at increased risk of developing both.

Incidental Vascular Findings in Diabetic Eye Screening: Do Patients Benefit from Referral?

I. Minty[1], P.B. Burgess[1, 2], T.C. Criddle[2, 3], M.A.R. Al-Roubaie[1], C.H. Hextall[1], A.N. Nunayon[1]

[1]*Department of Eye and Vision Science, University of Liverpool, Liverpool, United Kingdom*
[2]*St Paul's Eye Unit, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, United Kingdom*
[3]*Liverpool Diabetic Eye Screening Programme, Liverpool, United Kingdom*

DESIGN. Retrospective cross-sectional study
PURPOSE. To report the prevalence of incidental retinal vein occlusion (RVO) and retinal emboli in patients attending diabetic eye screening in one English region. To describe the investigations and subsequent management of referred screenees.
METHODS. We undertook a retrospective cross-sectional study of people attending the Liverpool Diabetic Eye Screening Programme in the calendar year 2017. Subjects with RVO or emboli were identified from a database of screening results produced by trained graders. The hospital electronic patient records of identified individuals were studied for investigations and changes in management. In the case of RVO, documentation of 4 systemic variables was recorded: blood pressure, HbA1c, full blood count and ESR.
RESULTS. Of 18190 people who attended screening in 2017, 17 were referred due to retinal emboli (0.09%). 16 patients attended hospital eye service follow-up of which 8 had emboli confirmed by clinical examination. 9 people were referred to the TIA clinic and 8 attended. Twelve patients (75%) had relevant medication changes. Five (31%) patients were found to have carotid stenosis. Two (12%) patients had >70% stenosis and 2 patients underwent carotid endarterectomy. 34 people (0.19%) were referred due to RVO of which 28 attended the hospital eye service. 6 patients had a medication change as a result of the appointment. 32% of patients had 4 documented systemic investigations, 35% had 2 or 3 and 33% had 1 or 0.
CONCLUSIONS. The prevalence of vascular incidental findings was small. A high proportion of people referred with incidental retinal emboli received either medical or surgical intervention.
There is scope for greater standardisation of investigation and management of patients referred with incidental RVO.

Profile, Visual and Maculopathy Outcomes of Patients Referred for the First Time with Pre-Proliferative Diabetic Retinopathy from Screening into a Hospital Eye Service

R. Rehak[1,2], I.M. Stratton[2], S.J. Aldington[2], K. Price[1], C. Kerby[2], P.H. Scanlon[1,2]

[1]*Gloucestershire Diabetic Eye Screening Programme, Gloucestershire Hospitals NHS Foundation Trust, Gloucestershire Royal Hospital, Gloucester, United Kingdom*
[2]*Gloucestershire Retinal Research Group, Department of Ophthalmology, Gloucestershire Hospitals NHS Foundation Trust, Gloucestershire Royal Hospital, Gloucester, United Kingdom*

DESIGN. Retrospective study
PURPOSE. To investigate demographics of patients with pre-proliferative diabetic retinopathy (PPDR) referred to Hospital Eye Service (HES) for the first time from a Diabetic Eye Screening Programme (DESP)
METHODS. Patients screened and graded with PPDR with no maculopathy (R2M0) or PPDR with maculopathy (R2M1) were extracted from electronic medical records (DESP+HES) to identify age, sex, type of diabetes, attendance records and visual acuity
RESULTS. Between 1st April 2016 and 31st March 2017 61 patients were referred into HES for PPDR. 24 (39%) were R2M0 and 37 (61%) were R2M1 when referred. 62% were male with mean age 59 years and 38% female with mean age 53 years. 72% of patients had type 2 diabetes (T2DM) and 28% with type 1 diabetes (T1DM).
Overall 19 (31%) patients had only attended screening once before being referred into HES with PPDR.
In total 12 referred patients (7 men, 5 women) went on to develop macular oedema. 2 patients had T1DM (17%) and 10 (83%) had T2DM.
From 61 patients, 5% progressed to develop proliferative DR requiring laser treatment.
Recorded data revealed that after a 2.5 year follow-up period, vision remained stable in 52% of cases. Vision had deteriorated in 15% of cases by 1,2,3 or 4 logMar lines. In 33% of cases, level of change in vision could not be determined due to DNA, lack of data or death.
CONCLUSIONS. Males with T2DM in this group seemed to be at a higher risk of developing pre-proliferative DR and maculopathy related complications. Chi-squared test p-values of 0.334 and 0.752 for diabetes type and gender respectively did not give enough evidence to say gender and/or diabetes type is associated with developing DMO. Relatively few cohort patients and missing data due to non-attendance or other reasons potentially makes finding inconclusive and hence larger datasets are required.

Association Between Homocysteine and the Risk of Retinopathy in Type 2 Diabetes

M. Tomić[1,3], R. Vrabec[1], S. Vidas Pauk[2], S. Ljubić[3], T. Bulum[3], D. Rahelić[3]

[1]*Department of Ophthalmology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia*
[2]*Department of Ophthalmology, Zagreb University Health Centre, Zagreb, Croatia*
[3]*Department of Diabetes et Endocrinology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia*

DESIGN. Cross-sectional
PURPOSE. To assess the role of homocysteine in development of diabetic retinopathy in patients with type 2 diabetes and determine the parameters important in the prediction of homocysteine.
METHODS. This cross-sectional study included 94 type 2 diabetic patients (39M/55F) with median age 60 years and median diabetes duration 10 years. Glycated hemoglobin (HbA1c), fasting blood glucose (fBG), fasting C-peptide, HDL and LDL cholesterol, triglycerides (TG) and uric acid (UA) were determined using routine laboratory methods. Glomerular filtration rate (GFR) was estimated using CKD-EPI formula. Homocysteine (HCY) in EDTA plasma, serum 25-hydroxy-vitamin D, vitamin B12 and folate were determined by CMIA method. Anthropometric parameters assessed waist circumference (WC) and waist-to-hip ratio (WHR). Ophthalmologic examination included fundus photography according to the EURODIAB methodology and optical coherence tomography of the macula. Patients with PDR and DME were not included in the study.
RESULTS. Patients were divided into two groups: group 1 (no retinopathy; n=69) and group 2 (NPDR; n=25). The groups did not differ in age, gender, WC, WHR, fBG, C-peptide, HDL, LDL, TG, UA, folate and vitamin D. Group 2 had longer diabetes duration ($p<0.001$), marginally higher HbA1c (p=0,059), higher HCY ($p<0.001$), lower B12 (p=0.028) and lower GFR (p=0.004) than group 1. DR was positively associated with diabetes duration ($p<0.001$), HbA1c (p=0.049) and HCY ($p<0.001$), and negatively with B12 (p=0.027) and GFR (p=0.005). Logistic regression analyses showed that diabetes duration (OR=1.13, $p<0.001$), HCY (OR=1.06, p=0.047) and GFR (OR=0.96, p=0.004) were the main predictors of DR in type 2 diabetic patients. However, after adjustment for diabetes duration, HbA1c (OR=1.41, p=0.043) also showed increased risk for DR in these patients. The best model for predicting HCY (R2=0.104) obtained from stepwise regression included vitamins B12 and D.
CONCLUSIONS. Higher serum homocysteine is associated with diabetic retinopathy and may play a role as a risk factor for its development in type 2 diabetes. Vitamins B12 and D seem to modify this association. Further studies are needed to validate these observations and investigate possible role of vitamins B12 and D supplementation in the prevention of retinopathy.

Audit of Referral of Patients Graded as R3 (Proliferative Retinopathy) by Diabetic Eye Screening Programme Northern Ireland (DESPNI)

D. McCullagh, A. Heaney, N. Parker, T. Peto

Royal Victoria Hospital, Belfast, Northern Ireland, United Kingdom

DESIGN. Retrospective audit of patient records
PURPOSE. The DESPNI has gone through modernisation in the past 5 years, and joined the National Standards in January 2017. A nationally accredited software was installed in October 2015 allowing for measuring grading and referral times for patients attending screening. This audit was carried out to assess the baseline characteristics of the grading and referral pathway of R3 patients in DESPNI and suggest improvements where required.
METHODS. Review of patient records of all patients graded as R3 (in either eye) over a 1 year period (October 2015 to September 2016) at DESPNI immediately after the introduction of nationally accredited, auditable software, Optomize.
RESULTS. Altogether, 946 patients were graded as R3 in at least 1 eye, median age of 62 years (range 18-91), and 70% male. Of these 798 (84%) were referred to hospital eye services within 14 days, 116 (12%) within 70 days, and 32 (4%) from 71 to 155 days. There were 181 (19%) new referrals, 173 (18%) were patients previously lost to follow up, and 52 (6%) referred in again having previously been discharged due to repeated non-attendance at clinics. The remaining 540 (57%) had been referred to the hospital eye service in the past, and were either under regular review or had been seen and discharged.
CONCLUSIONS. An acceptable proportion of R3 patients were referred in a timely manner to hospital eye services with a large number of people either lost to follow-up or never attended following prior referral. The remaining patients who were already in the hospital eye service were captured by the new referral system, and if necessary were offered new non-urgent appointments – this largely (but not entirely) represented the group of patients who were referred more than 14 days after grading. If we are to reduce diabetes related blindness in NI in line with England and Wales, this pathway needs to be tightened up and re-audited, preferably by looking at 5 year follow up of this patient cohort.

Diabetic Eye Disease in Patients with Diabetes Mellitus Secondary to Chronic Pancreatitis (DMSCP)

C. Jamison[1], N. Quinn[1], L. Cushley[1], R. D'Aloisio[2], T. Peto[1], P.C. Johnston[3]

[1]Queen's University Belfast, Belfast, Northern Ireland, United Kingdom
[2]Eye Clinic, Surgery and Health Sciences, University of Trieste, Trieste, Italy
[3]Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom

DESIGN. Retrospective observational study
PURPOSE. To investigate diabetic retinopathy (DR) and maculopathy prevalence and severity in patients with DMsCP in Northern Ireland

METHODS. In 2017-19, DMsCP patients living in Northern Ireland attending specialised clinics were audited for severity of DR using both diabetic eye-screening and hospital eye-services databases. The Northern Ireland Diabetic Eye Screening Program (NIDESP) was used for DR and maculopathy grades, and attendance information. Clinical and laboratory data were obtained from "Diamond" diabetes database and electronic medical records. Appropriate statistical analyses were carried out.
RESULTS. A total of 94 DMsCP patients were included in the audit. Mean age was 57±10 years (81% males). Mean pancreatitis duration was 14 years, with mean DM duration at 11 years. In 75% of cases, alcohol abuse caused DMsCP, gallstones represented 9%, with high cholesterol levels, cystic fibrosis gene-carrier, drug-induced, and portal vein thrombosis each accounting for 1%. In 12% no underlying cause was attributed. HBA1C and Body Mass Index (BMI) were 74.3 mmol/mol and 25.3 Kg/m2 respectively. Mean Albumin Creatinine Ratio (ACR) was 13.37. Compared to the 2017 baseline data, did-not-attend rates dropped from 31% to 13%.
Those with no DR reduced to 63% from 85%; while mild non-proliferative DR (NPDR), severe NPDR and proliferative DR were found in 30%, 2% and 5% of cases respectively (previously 12, 3 and 1%); maculopathy was present in 9% (previously 6%).
There was no significant difference between DR or maculopathy grade and HBA1C, sex, BMI, weight, pancreatitis aetiology, clinic/screening attendance, or number of missed appointments (all $p>0.05$). No-DR patients had mean DM duration of 7.5 years while PDRs had 18.5 years ($p=0.001$). Pancreatitis duration was significantly higher in those with PDR (11 years versus 19; $P=0.001$).
CONCLUSIONS. With fuller coverage of the patient population and increased attendance, the profile of DR in DMsCP patients in NI shifted, including more patients with advanced diabetic eye disease. This demonstrates the importance of reaching the full range of patients and providing accessible services to all.

Certification of Visual Impairment in Patients with Diabetes Mellitus in Northern Ireland Over a 5 Year Period

L. Cushley[1,2], R. McCann[2], T. Peto[1,2], T. Moutray[2], A.J. Jackson[2]

[1]*Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom*
[2]*Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom*

DESIGN. Retrospective study
PURPOSE. To determine the number of patients with diabetes mellitus (PwDM) who were certified visually impaired (CVI) over the past 5 years.
METHODS. CVI Data is collected from 11 sites, where services are provided by consultant ophthalmologists, using coded CVI adult and paediatric certification forms. Information regarding patient demographics and visual characteristics, such as visual acuity (VA), visual fields (VF) and diagnosis, are included. Since 2015, a tick box for diagnosed with diabetes was also included. Data are transcribed into excel; entry validation is conducted on 10% of all data and 100% of primary field data including VA, VF and ophthalmic diagnosis. Analysis is undertaken to produce annual CVI reports. Findings are disseminated amongst ophthalmology colleagues. Five years data (2014-2018) has been analysed for diabetic eye disease (DED) diagnosis and also diabetic status.
RESULTS. In 2014, 326 CVIs were submitted; 184 patients were certified severely sight impaired (SSI) and 142 sight impaired (SI). Twenty-four were recognised as having diabetes with 21 certified as a result of diabetic retinopathy (DR); including 2 who were certified with diabetic macular oedema (DMO). Between 2015-2017 the total number of CVI forms submitted were similar with 412, 428 and 453 respectively. Numbers of PwDM were similar at 48, 43 and 41 respectively. Many PwDM were certified due to DED although some were certified due to other conditions such as AMD and Glaucoma (range of 2%-31% and 2-4% respectively).
In 2018, there was a sharp increase in CVI submissions to 575 (SSI: 368, SI: 196, and 11 unspecified). The number of PwDM more than doubled to 107; 51 (48%) certified as a result of DED and 43 (40%) certificated with AMD. The remaining patients had other ophthalmic issues such as keratoconus and optic atrophy.
CONCLUSIONS. Ophthalmic Practitioners in Northern Ireland have recently been attempting to certify all eligible persons in Northern Ireland as it was previously underrepresented. Data from 2018 shows that Northern Ireland is now on par with the rest of the UK for CVI.

Irish Diabetic Retinopathy Screening Programme: An Analysis of Grade R2 Screened Patients in 2015

L. Kennelly, R. Pandey, D. Keegan

Retinal Research Group, Mater Misericordiae University Hospital, Dublin, Ireland

DESIGN. A retrospective screening and treatment record based study, of 250 patients who were referred to an ophthalmology treatment centre with R2 grade retinopathy in the worst eye, in 2015 in the Republic of Ireland.
PURPOSE. To examine patients screened as R2 in the Irish Diabetic Retinopathy Screening Programme in 2015, to establish the number of patients who progressed from R2 (severe non-proliferative) to R3 (proliferative) diabetic retinopathy and the mean time period taken to progress.

METHODS. Patients referred in 2015 with severe non-proliferative (R2 grade) retinopathy in the worst eye were analysed. Patients' screening data and treatment data was extracted and time to proliferation was recorded, based on the first of either treatment with pan-retinal photocoagulation or proliferative retinopathy grading at treatment centres. The study period was between the patient's referral to treatment centre in 2015 to 31st December 2019.
RESULTS. In 2015, 250 patients were referred to treatment centres with R2 grade retinopathy in their worst eye. 42 patient's data were excluded due to incomplete follow-up. The remaining 208 patients provided 416 eyes for this study. The mean age of patients was 64.8 years (23.3 - 85.6 years), 52% males and 48% females. In these 416 eyes, 124 had background retinopathy (R0 or R1) and 292 eyes had R2 graded retinopathy at the time of screening. Of these 292 eyes, 199 (68.2%) did not subsequently proliferate, while 93 (31.8%) progressed to proliferative disease during the study period. The mean time to proliferation was 21.6 months (1.1 - 49.2 months). The mean age of patients who had proliferated was 55 years (24 - 80 years). 35 (12%) patient eyes had proliferated in 12 months, 20 (6.9%) eyes in 24 months, 14 (4.8%) eyes in 36 months, 21 (7.2%) eyes in 48 months, and 3 (1.0%) in 60 months.
CONCLUSIONS. 31.8% of participants progressed to proliferative retinopathy, the mean time to proliferation being 21.6 months. Going forward, we will examine the systemic data of these patients, analysing why they progressed to proliferative retinopathy, compared with the 68.2% who did not.

Grading Data are Only as Good as the Graders - and all Data Depends on Good Quality Questions

A. Sproule, B. Hamill, C. Jamison, T. Peto

Queen's University Belfast, Belfast, Northern Ireland, United Kingdom

DESIGN. Evaluation study on behalf of NetwORC UK graders
PURPOSE. To highlight the impact of using well-structured, detailed and unambiguous grading questions for analysis of ophthalmic images
METHODS. Using expert graders from the NetwORC UK (Liverpool, London and Belfast Grading Centres) grading questions were selected to study the potential impact of their quality on final outcome. These questions, with example images, were distributed to three graders. Graders were asked to review the questions independently, record any wording concerns and propose ways to improve them; and mark them as good or poor quality questions. Graders were subsequently interviewed about the exercise individually and then partook in a group discussion to agree on ways to improve the questions.
RESULTS. NetwORC UK graders identified questions related to availability of all image fields, "worst scan affected by the disease" and if the abnormality was foveal or not as ambiguous. "Presence of haem" in a diabetic retinopathy (DR) study and screening was found to be non-specific enough by the graders. Answering these questions as they were asked resulted in poor concordance as graders interpreted them differently. The main concern was that answering the "presence of haem" question differently would have meant missing DR if only microaneurysms were present. Calculations show that even minor differences between graders when interpreting the grading questions can result in major differences in outcomes, such as if 1:40 are misinterpreted in a population based study or screening programme of 100,000, subsequently 2500 image sets would be misgraded. On the interviews, all graders could defend their viewpoint with good reasoning and therefore differences did not arise from lack of understanding of the underlying pathology.
CONCLUSIONS. This study revealed the importance and impact of good quality, clearly worded questions if good quality grading outcomes are to be achieved. Involvement of image graders in the initial stages of grading form and protocol development will benefit the grading process, improve data accuracy and optimise grading time, and will result in the best possible data-set to be generated for final analysis.

Prevalence of Diabetic Retinopathy in Greenland

H. Lund-Andersen[1,3,4,5], S. Bybjerg[1], M. Valerius[1], T. Jul Larsen[3], M. Lynge Petersen[4], E. Juul[1]

[1]*Steno Diabetes Center Copenhagen, Copenhagen, Denmark*
[2]*State University Hospital, Righospitalet-Glostrup, Glostrup, Denmark*
[3]*University of Copenhagen, Copenhagen, Denmark*
[4]*Region Hospital, Department of Medicine Nuuk, Greenland*
[5]*District Hospitals of Greenland, Greenland*

DESIGN. Photographic examination (Optos wide field) of a representative group of greenlanders with diabetes and prediabetes diagnosed by oral glucose tolerance test.
PURPOSE. To study the prevalence of diabetic retinopathy in the greenlandish population among known diabetics, newly diagnosed diabetics and prediabetics.
METHODS. Participants of population examination B2018 with diabetes and prediabetes diagnosed by oral glucose tolerance test and known diabetics from one of previous health surveys (1999-2001, 2005-2010 and 2014), or HBA1c values >42mmol/l upon participation in B2018, were invited for screening of diabetic complications. After informed consent was obtained autonomic and peripheral nervous function was assessed. Optos wide field camera was used to take at least two pictures of each

eye (undilated). Pictures were graded at Steno Reading Center, Copenhagen.
RESULTS. 493 persons had their retina imaged and graded. Images were ungradable due to cataract (n=2) or poor quality (n=4) and they were excluded from the analysis. 10 persons were identified with DR corresponding to a prevalence of 2%. Only mild or moderate DR was found. Among persons with known diabetes 6/46 had DR (13%). Among persons with newly diagnosed diabetes or prediabetes <1% (4/444) had DR. Persons with HBA1c levels above 48mmol/l at the date of the examination showed DR prevalence of 11% (8/75) below 48mmol/l prevalence was 0.5% (2/409).
CONCLUSIONS. The prevalence of DR is lower in Greenland compared with Denmark and similar countries. DR was almost non-existent among persons with HBA1c below 48mmol/l, and the data show that screening should not be performed in prediabetics.

Young People's View of Diabetic Retinopathy Screening in Northern Ireland

T. Peto[1,2], L. Cushley[1], A. Bell[1], G. Silvestri[2], D. McCance[2], U. Graham[2], S. Miller[3]

[1]*Queen's University Belfast, Belfast, Northern Ireland, United kingdom*
[2]*Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom*
[3]*Southern Health and Social Care Trust, Northern Ireland, United Kingdom*

DESIGN. Mixed-method study
PURPOSE. To determine what young people (aged 12-26) think about the Northern Ireland Diabetic Eye Screening Programme (NIDESP).
METHODS. This study examines views of transitional age patients of the Northern Ireland Diabetic Eye Screening programme using electronic care records and for demographic data, attendance rates and diabetic retinopathy grades. Subsequently, an online questionnaire on SurveyMonkey was distributed among young people through clinics as to what improvements should be made to DESPNI and what they know about their DR.
RESULTS. Altogether 108 000 patients of the 1.8million inhabitants of Northern Ireland have diabetes, of these, 2360 were in the Transition Age in October 2019. Of those responding, 47% were male, main age at diagnosis was 8-11 years (43%). All respondents stated that they were aware that diabetes could affect the eye and that there was a screening programme for it, with 75% receiving this information from their endocrinologist (75%). However, 86% asked for more education to be provided on DR. Overall, 29% said they were not aware the need to attend NIDESP as well as their high street optician. Timing of DR Screening was the biggest barrier (71%) due to school/work commitments; asking for evening/weekend clinic times/appointments. One-stop-shop clinic (screening at the time of diabetes clinic appointment) was favoured by 86%.
CONCLUSIONS. NIDESP could be improved for young people with diabetes by incorporating eye screening into their normal diabetes clinics and by providing better appointment times which fit around school/work hours. Despite this, most respondents were aware of the effect diabetes could have on the eyes.

Retinal Neurodegeneration, Macular Circulation and Morphology of the Foveal Avascular Zone in Diabetic Patients. Quantitative Cross-Sectional Study Using OCT-A

G. Bontzos[1], S.A. Kabanarou[1], I. Gkizis[1], A. Ragkousis[1], T. Xirou[1], T. Peto[2]

[1]*Department of Ophthalmology, Korgialenio-Benakio, Hellenic Red Cross Hospital, Athens, Greece*
[2]*Department of Ophthalmology, Centre for Public Health, Institute of Clinical Sciences, School of Medicine, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom*

DESIGN. Cross-sectional study
PURPOSE. Using OCT-A to investigate the association between neurodegeneration and vascular morphology in diabetic retinopathy (DR).
METHODS. One hundred and sixty two patients were enrolled and following fundoscopy were assigned to two groups according to DR severity: 54 patients, without clinical signs of DR (noDR) and 54 patients with non-proliferative DR (NPDR). Fifty-four age-matched patients without known diabetes were also recruited as the control group. Patients underwent full ophthalmic examination followed by OCT-A. Central retinal thickness (CRT), vessel density (VD) in the superficial and deep retinal layers and foveal avascular zone (FAZ) area were measured. Additionally, ganglion cell complex (GCC) layer thickness along with global loss volume (GLV) and focal loss volume (FLV) indices were measured.
RESULTS. In total, 85 men with mean age of 51.93 ± 9.03 and 77 women with age of 50.14 ± 10.35 were examined. Mean diabetes duration was 4.62 ± 2.16 years in the noDR group and 11.34 ± 2.73 years in the NPDR group ($p<0.001$). Superficial VD and deep VD were significantly different only between noDR and NPDR groups ($p<0.001$ for both comparisons). GLV was significantly higher in the NPDR (4.38 ± 2.22) compared to noDR group (3.24 ± 1.76; $p<0.03$). FLV was significantly higher in both noDR (1.22 ± 1.03) and NPDR (2.09 ± 1.72) groups compared to controls (0.95 ± 0.83) ($p<0.001$ between noDR and NPDR and $p=0.02$ between control and noDR groups). Significant associations were found between GLV and deep VD ($p<0.01$, $r=-0.48$), FLV and superficial VD ($p<0.01$, $r=-0.42$) and FLV with deep VD ($p<0.01$, $r=-0.64$).
CONCLUSIONS. In this study, we evaluated the impact of DR in both the vascular layers and neural components of the retina as expressed by FAZ, SVD, DVD and GCC

thickness, FLV and GLV using OCT-A. We found that FLV was significantly higher in both noDR and NPDR groups indicating that DR progression is reflected in the FLV, which might serve as an early index of neuronal damage in patients with diabetes even in the absence of fundoscopic signs of retinopathy.

Nonmydriatic Widefield Retinal Imaging with an Automatic White Led Confocal Imaging System Compared with Dilated Ophthalmoscopy in Screening for Diabetic Retinopathy

G. Querques, E. Borrelli, L. Querques, R. Lattanzio, M. Cavalleri, R. Sacconi, F. Bandello

Department of Ophthalmology, Ospedale San Raffaele Scientific Institute, University Vita-Salute, Milan, Italy

DESIGN. Prospective, cross-sectional
PURPOSE. To compare nonmydriatic montage widefield images with dilated fundus ophthalmoscopy for determining diabetic retinopathy (DR) severity.
METHODS. In this prospective, observational, cross-sectional study, patients with a previous diagnosis of diabetes and without history of diabetes-associated ocular disease were screened for DR. Montage widefield imaging was obtained with a system that combines confocal technology with white-light emitting diode (LED) illumination (DRSplus, Centervue, Padua, Italy). Dilated fundus examination was performed by a retina specialist.
RESULTS. Thirty-seven eyes (20 patients, 8 females) were finally included in the analysis. Mean age of the patients enrolled was 58.0±11.6 years [range 31-80 years]. The level of DR identified on montage widefield images agreed exactly with indirect ophthalmoscopy in 97.3% (36) of eyes and was within 1 step in 100% (37) of eyes. Cohen's kappa coefficient (κ) was 0.96, this suggesting an almost perfect agreement between the two modalities in DR screening. Nonmydriatic montage widefield imaging acquisition time was significantly shorter than that of dilated clinical examination (P= 0.010).
CONCLUSIONS. Nonmydriatic montage widefield images compare favourably with dilated fundus examination in defining DR severity; however, they are acquired more rapidly.

Baseline Characterization of Retinal Vascular Disease in Eyes with Mild to Moderate Non Proliferative Diabetic Retinopathy (NPDR) in Diabetes Type 2, Using Novel Non-Invasive Imaging Methods, in a Longitudinal, Prospective and Interventional 2-Year Clinical Study (Cordis)

M. Ribeiro[1], I.P. Marques[1], A.R. Santos[1,2], R. Coimbra[1], T. Santos[1], J. Figueira[1,3,4], J.G. Cunha-Vaz[1]

[1]*AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal*
[2]*Department of Orthoptics, Superior School of Health, Porto Polytechnic Institute, Oporto, Portugal*
[3]*Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[4]*Faculty of Medicine, Coimbra University, Coimbra, Portugal*

DESIGN. Longitudinal, prospective and interventional 2-year clinical study
PURPOSE. Characterization of retinal microvascular changes occurring in eyes with mild to moderate non proliferative diabetic retinopathy (NPDR), during a period of 2 years using lower than optical normal reflectivity (LOR) ratios obtained with OCT-Leakage. Capillary closure in the superficial and deep retinal vascular layers using OCT-Angiography (OCTA) will be also analyzed in eyes that are at risk for developing sight threatening diabetic retinopathy (central involved macular edema (CIME) or proliferative diabetic retinopathy (PDR).
METHODS. This prospective interventional study with 4 visits (Months 0, 6, 12 and 24) is ongoing. At screening, type 2 diabetic patients were included with at least in one eye: mild or moderate NPDR with ETDRS NPDR levels 20 to 47, absence of CIME or PDR, presence of at least 1 microaneurysm in the central 6000 microns (field 2), no previous intravitreal injections, BCVA ⩾ 75 letters. All patients also performed low grade serum markers of inflammation assessments (high sensitivity-PCR, IL 6 and IL 8) and laboratory tests (HgA1C levels and lipids). In all visits a complete ophthalmological examination and structural OCT, OCTA and OCT-L and colour fundus photography will be performed. At baseline visit (Month 6) eyes/patients are included as phenotype B (subclinical macular edema) or phenotype C (microaneurysm turnover higher than 6).
RESULTS. At baseline, 125 patients/eyes were included. 74 were identified as phenotype B (ETDRS level 20 – 11 eyes (14,8%), ETDRS level 35 – 51 eyes (69%), ETDRS level 43 – 10 eyes (13,5%) and ETDRS level 47- 2 eyes (2,7%)) and 51 were phenotype C (ETDRS level 20-4 eyes (7,84%), ETDRS level 35 – 22 eyes (43,14%), ETDRS level 43-16 eyes (31,37%) and ETDRS level 47-9 eyes (17,65%)).
CONCLUSIONS. Phenotypes B and C are identified in different ETDRS levels. Identification of different phenotypes and prognostic biomarkers will contribute to personalized management of diabetic retinopathy.

Automated Diabetic Retinopathy Quality Image Assessment: Diagnostic Accuracy in Clinical Practice

M. Lopez[1], R. Romero Oraa[2], M. Garcia Gadañon[2], R. Hornero Sanchez[2], J . Oraa[2]

[1]*Instituto de Oftalmobiologia Aplicada (IOBA), Universidad de Valladolid, Valladolid, Spain*
[2]*Grupo de Ingenieria Biomedica, Universidad de Valladolid, Valladolid, Spain*

DESIGN. Basic research. Big data and neural network development applied to images of patients with and without diabetic retinopathy (DR)
PURPOSE. To develop an automatic algorithm able to detect inadequate quality images in the primary care centers so the screening of DR would be safer and robust
METHODS. Deep learning architectures were used and adapted to images of various characteristics. Both a private and a public database were used. Private database contained fundus photographs of patients of the screening programme of the local Government and consisted of 564 retinal images with a 45-degree Field of View (FOV). They were captured using a Topcon TRC-NW400 retinal camera and stored in 24-bit JPEG format. Images had a resolution of 1956 × 1934 pixels. Two images were captured per eye: a fovea-centered image and an OD-centered image. An expert in retinal pathology determined, whether they had sufficient quality or not. The private database was divided into two sets, the training set and the test set. Both contained good and poor quality images. The public set was only used to evaluate the method. The public database (DRIMDB) consisted of 125 good quality and 69 poor quality images
RESULTS. Results were obtained using the test set of the private and all the images of the public database DRIMDB. The accuracy sensitivity and specificity of the private database were 95,29%, 96,82% and 91% respectively and the values for the public data base DRIMDB were 99.48, 99.20 and 100%. This method was successful in detecting all images with poor quality. All images with good quality have been correctly classified. Accuracy reaches 95.29% on the private and 99.48% on the DRIMDB1 database
CONCLUSIONS. This is a simple and effective method to classify fundus images according to their quality level. It can be adapted to different databases, since none of the processing stages depends on the specific characteristics of the images. Integrating this method as part of fundus cameras software would allow detecting poor quality images at the acquisition time.

Neural Networks and Left/Right Classification of Retinal Images

L. Díaz[1], D. Vistisen[1], M.E. Jørgensen[1,2], M. Valerius[3], J.N. Hajari[3], H. Lund-Andersen[3], S. Byberg[1]

[1]*Department of Clinical Epidemiology, Steno Diabetes Center Copenhagen, Gentofte, Denmark*
[2]*National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark*
[3]*Department of ophthalmology, University Hospital Glostrup, Glostrup, Denmark*

DESIGN. Observational study.
PURPOSE. Retinal fundus images, obtained from routine eye screenings, contain important information, not only concerning microvascular lesions of the retina, but potentially also of the progression and manifestation of various other diabetes complications and their interrelationship. Recent advances in the field of machine learning have made it possible to automatically detect retinal lesions from fundus photos. Our overall aim is to develop a deep learning neural network (DNN) to detect retinal vascular lesions. We describe part of the pre-processing of retinal fundus photos using a DNN.
METHODS. At each eye screening, 5 retinal images of parts of the eye are collected into a joint mosaic image, used for grading of diabetic retinopathy. In the database, there is no labelling of the images to identify left or right eyes. To distinguish left- from right- eye images, we used a set of 1,916 unique, high-definition retina mosaic fundus images from diabetes patients followed at Steno Diabetes Center Copenhagen (SDCC) in the time period 2003-2017. We used a DNN which is a trainable algorithm for relating a large set of input (mosaic fundus images) to output (left or right eye). We trained and validated a DNN, using 964 left-eye (training set: 713, validation: 251) and 952 right-eye images (training set: 706, validation: 246). The DNN used was trained for 100 epochs with 100 gradient descent steps pr. epoch.
RESULTS. The classification obtained a validation sensitivity of 0.93 and a validation specificity of 0.90.
CONCLUSIONS. The DNN successfully distinguished left-eye from right-eye images. We plan to use the DNN to identify right- and left-eye images in the SDCC image database of 75,000 left-eye and right-eye images.

Machine Learning to Predict Diabetic Retinopathy Improvement in Patients with Mild NPDR Using Systemic and Retinal Imaging Features

D. Damopoulos[1], L. Mendes[2], B.G. Armendariz[1], T. Santos[2], Z. Haskova[3], R. Weikert[1], J. Cunha-Vaz[2]

[1]*F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[2]*AIBILI- Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal*
[3]*Genentech, Inc., South San Francisco, CA, United States of America*

DESIGN. Post hoc analysis of baseline systemic and/or retinal imaging features from EUROCONDOR (NCT01726075) and C-Tracer (NCT01607190) studies.
PURPOSE. The performance of machine learning (ML) algorithms to predict diabetic retinopathy (DR) improvement was assessed in nonproliferative DR (NPDR) patients with mild disease (DR Severity Scale [DRSS]) 20-35 based on systemic and/or retinal imaging features.
METHODS. Baseline systemic data and retinal imaging features, including optical coherence tomography (OCT) and colour fundus photographs (CFPs), were pooled from the EUROCONDOR trial for neuroprotective eye drop

assessment and the C-Tracer observational study. Data from both systemic and retinal imaging features were used to train random forest ML models predicting DRSS improvement over 2 years. Multifold cross-validation was performed and model performances of ML algorithms were compared when trained with systemic features only, retinal imaging features only, or combining all available features. The area under the receiver operator characteristics curve (AUROC) was used to quantitatively compare both features.

RESULTS. Baseline data from 309 patients/eyes with mild NPDR were used to train the ML models and test them in a 10-fold cross-validation setting. At baseline, 130 patients/eyes had a DRSS level of 20 and 179 patients/eyes had a DRSS level of 35. After 2 years, DRSS level was improved in 133 (43%) of these patients, remained the same in 159 (51.5%) patients, and worsened in 17 (5.5%) patients. DR severity improvement was predicted with an AUROC = 0.62 (95% CI, 0.56, 0.67) based on systemic features only and an AUROC = 0.71 (95% CI, 0.65, 0.77) based on retinal imaging features only. DR severity improvement based on both systemic and imaging features was predicted with an AUROC = 0.76 (95% CI, 0.70, 0.82).

CONCLUSIONS. We found that structural measurements from retinal images (OCT and CFP) had a higher predictive value than systemic features alone in predicting future DR improvement in patients with mild NPDR. The combination of both feature families provided the best predictive outcome. Predictive ML models in patients with NPDR could be used to inform personalized monitoring and follow-up.

Using Semantic Segmentation for Detection of Microaneurysms in Retinal Images

J. Andersen[1,2], T.R. Savarimuthu[1], J. Grauslund[2,3,4]

[1]*SDU Robotics, The Mærsk Mc-Kinney Møller Institute, University of Southern Denmark, Odense, Denmark*
[2]*Steno Diabetes Center Odense, Odense, Denmark*
[3]*Department of Ophthalmology, Odense University Hospital, Odense, Denmark*
[4]*Research Unit of Ophthalmology, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*

DESIGN. Diagnostic Study

PURPOSE. Retinal microaneurysms (MAs) are the earliest signs of diabetic retinopathy (DR) which is the leading cause of blindness in the western world. MAs independently predict the risk of sight threatening DR and early detection is important to identify patients at risk. Deep neural networks (DNNs) applied to retinal image analysis have been studied extensively in recent years, showing promising results for automatic disease classification and segmentation of retinal features. Detection and segmentation of retinal MAs present a particular challenge due to a large class imbalance between MA pixels and non-MA pixels in retinal images. In this work we investigate the influence of the network objective during optimization by training a residual U-net for segmentation of MAs using four different objective functions; cross-entropy loss, dice loss, focal loss and focal dice loss.

METHODS. Three networks with different seeds are trained for each objective function using optimized hyperparameter settings on 251 images with pixel level annotations for MAs. The instance level MA detection performance is evaluated as the average free response receiver operator characteristic (FROC) score calculated as the mean sensitivity at seven average false positives per image thresholds on 80 test images. The image level MA detection performance is evaluated as the average AUC on the same images as well as a separate test set of 1000 images.

RESULTS. The highest FROC score of 0.5057 ($\pm$0.0127) is achieved using standard crossentropy loss which achieves AUCs of 0.9450 ($\pm$0.0080) and 0.8038 ($\pm$0.0058) on the two test sets. For detection of images of with no MAs (level 0, n=462) and images with between 1 and 5 MAs (level 1, n=134) the network achieves and AUC of 0.7993 ($\pm$0.0106)

CONCLUSIONS. Segmentation using DNNs can be used to detect MAs in retinal images. Using segmentation results, high accuracy is achieved for detection of any MAs in images from the same distribution as the training images and our method can accurately detect images with low level of DR in images from a separate distribution.

Multicolor Imaging to Detect Different Subtypes of Retinal Microaneurysms in Diabetic Retinopathy

R. Lattanzio, A.A. Arrigo, E.A. Aragona, M.B.P. Battaglia Parodi, F.B. Bandello

Department of Ophthalmology, Scientific Institute San Raffaele, Vita-Salute University, Milan, Italy

DESIGN. Cross-sectional, observational study.

PURPOSE. To characterize morphological features of retinal microaneurysms (MAs) by means of non-invasive MultiColor images and to compare these with structural optical coherence tomography (OCT) and fluorescein angiography (FA) findings.

METHODS. Patients affected by diabetic retinopathy (DR) secondary to type 2 diabetes were recruited at the Ophthalmology Unit of San Raffaele Hospital, Milan, Italy. Multimodal imaging included MultiColor, blue autofluorescence (BAF), infrared (IR), structural OCT and FA images, acquired by means of a Spectralis HRA+OCT device (Heidelberg Engineering, Heidelberg, Germany). We performed a qualitative analysis in order to assess the relationship between MultiColor (green- and red-reflectance components), structural OCT (hyperreflective, hyporeflective and mixed reflectivity) and FA findings; the agreement between all techniques was also assessed. We

categorized MAs detected on our MultiColor images in accordance with previously published histological classification. Finally, we compared MAs detection as achieved by MultiColor, BAF and IR images.

RESULTS. Our study included 153 MAs of 30 eyes (30 DR patients; mean age 55 ± 9; 17 males) detected at the posterior pole by FA images. MultiColor detected 80% of these MAs (122 MAs). We identified green (16%), red (19%) and mixed (65%) MAs, corresponding to specific reflectivity patterns detected by structural OCT; differences in terms of filling and leakage phenomena resulted not so marked on FA. The strict relationship between MAs subtypes and structural OCT suggests that the composition of MAs (cells + endothelium + fibrosis) may influence the signal detected in MultiColor images; remarkably, our imaging findings showed good agreement with histological classification. MultiColor outperformed IR and BAF for MAs detection, because of the presence of edemas, haemorrhages or other types of interference mostly affecting the latter imaging modalities. Furthermore, BAF and IR provided less information regarding MAs content and wall features than MultiColor.

CONCLUSIONS. Our study reported three MultiColor MAs types. These showed a strict relationship with structural OCT findings, suggesting that MAs content, wall features and the amount of fibrotic changes may influence MAs MultiColor properties. MultiColor appears to be a useful technique to investigate MAs in DR.

Retinal Sensitivity and Gaze Fixation: Two Independent and Valuable Measurments that Could be Obtained by Using Microperimetry

A. Ciudin[1,2,3], A.M. Ortiz-Zuñiga[1,3], K. Rahnama[4], E. Lainez[4], N. Raguer[4], O. Simó-Servat[1,2,3], R. Simó[1,2,3]

[1]*Institut de Recerca Vall d'Hebron, Universitat Autònoma de Barcelona (VHIR-UAB), Barcelona, Spain*
[2]*CIBER de Diabetes y Enfermedades Metabólicas Asociadas. Instituto de Salud Carlos III, Spain*
[3]*Endocrinology and Nutrition Department, Vall d'Hebron University Hospital, Barcelona, Spain*
[4]*Neuropsyaiology Department, Vall d' Hebron University Hospital, Barcelona, Spain*

DESIGN. Cross-sectional observational study

PURPOSE. We have previously reported that retinal sensitivity evaluated by retinal microperimetry was able to identify type 2 diabetic (T2D) subjects with cognitive impairment. Furthermore, the predictive value in identifying those T2D subjects with mild cognitive impairment was significantly increased by adding fixation parameters to retinal sensibility. This added value could be explained because retinal sensitivity (RS) and gaze fixation (GF) are examining different neural circuits. In this regard it could be hypothesized that RS depends only on the visual pathway while GF depends on white matter complex connectivity networks. The aim of the study is to shed light to this issue.

METHODS. T2D patients older than 65 years and with absence or only mild diabetic retinopathy DR were evaluated from the outpatient clinic of our hospital between June-December 2019. All patients underwent retinal microperimetry (MAIA 3rd generation) and evoked ophthalmic potentials (EOP) (Nicolet Viking EDX). RS (dB), GF (BCEA63%, BCEA95%) from retinal microperimetry and Latency 100ms from EOP were used for the analysis.

RESULTS. A total of 33 T2D patients (45% women, mean age 72.1±4.6 years) were included. The diabetes duration was 15.55± 7.4 years and HbA1c of 7.38± 0,8%. EOP parameters significantly correlated with RS but not with GF (R: 0.728, p= <0.001 and R 0.174, p=0.333 respectively).

CONCLUSIONS. RS but not GF depend on the visual pathway in T2D patients. Our results reinforce the concept that RS and GF are complementary examinations and could be used together to further increase the value of microperimetry as screening test of cognitive impairment, at least in T2D population.

Validation of the Siva-Plus Deep-Learning Algorithm on Retinal Vascular Calibre in Patients with Treatment-Naive Proliferative Diabetic Retinopathy Before and After Panretinal Photocoagulation

T.L. Torp[1,2,3], C.Y.L. Cheung[4], R. Kawasaki[2,5], T. Peto[6], T.Y. Wong[7], J. Grauslund[1,2,3]

[1]*Department of Ophthalmology, Odense University Hospital, Odense, Denmark*
[2]*Department of Clinical Research, University of Southern Denmark, Region of Southern Denmark, Odense, Denmark*
[3]*Steno Diabetes Center Odense, Odense University Hospital, Odense C, Denmark*
[4]*Department of Ophthalmology and Visual Sciences, Faculty of medicine, The Chinese University of Hong Kong*
[5]*Department of Vision Informatics, Osaka University Graduate School of Medicine, Osaka, Japan*
[6]*School of Medicine, Dentistry and Biomedical Science, Queen's University Belfast, Belfast, Ireland, United Kingdom*
[7]*General Cataract and Comprehensive Ophthalmology, Singapore National Eye Center, Singapore, Singapore*

DESIGN. Cross-sectional image grading study.

PURPOSE. The worldwide prevalence of diabetes is expected to rise to 700 million by 2045. Despite advances in screening and treatment modalities, patients are still faced with microvascular complications such as diabetic retinopathy (DR), which could lead to blindness. However, screening programs for DR are challenged by financial availability, human resources, and time. The overall purpose of this study was to validate the SIVA plus algorithm on vessel calibre in patients with proliferative diabetic retinopathy (PDR) before and after panretinal photocoagulation (PRP).

METHODS. Optic disc centered 45° fundus images (3D OCT-2000 Spectral domain OCT) were used for retinal vascular calibre analyses in treatment-naive patients with PDR before (n=57) and after (n=98) PRP. Two different grading methods were used. Method I: The vessel calibers were manually graded by the same grader (TLT) using the SIVA semi-automated software (Singapore I Vessel Assessment, National University of Singapore, software version 4, Singapore). The software automatically detects and marks the retinal vessels and places a three zone-grid around the optic disc (OD). The grader was allowed to adjust the arterioles (red), venules (blue) and OD/grid (white). Method II: The vessel calibers were graded on the same set of images using the fully automated SIVA plus algorithm. No adjustments were allowed after auto-grading.
The vessel calibers were analyzed in zones B and C. All images were masked between the substudies, and intergrader intraclass correlation (ICC) was calculated (Two-way mixed-effects model) before and after PRP.
RESULTS. For manual and automatic grading, retinal arteriolar calibre were 151.9±13.4μm (mean ± standard deviation) and 148.4±9.8μm (ICC 0.75) before PRP, and 152.2±13.7μm and 146.0±10.4μm (ICC 0.76) after PRP. Corresponding values for retinal venular calibre were 234.2±24.4μm and 223.8±25.3μm (ICC 0.80) before PRP, and 232.5±25.6μm and 220.6±26.0μm (ICC 0.80) after PRP.
CONCLUSIONS. The fully automated SIVA plus algorithm has a substantial agreement with manual grading in retinal vascular caliber grading in patients with PDR independent of laser treatment.

Examining the Impact of Type 2 Diabetes on Longitudinal Changes in Fovea Thickness

K. Gooding[1,2], A.C. Shore[1,2], F. Casanova[1,2], C. Ball[2], L. Wilkes[2], R. Ling[3], E. Agardh[4]

[1]Diabetes and Vascular Medicine, University of Exeter Medical School, United Kingdom
[2]NIHR Exeter Clinical Research Facility, Royal Devon and Exeter NHS Foundation Trust, United Kingdom
[3]West of England Eye Unit, Royal Devon and Exeter NHS Foundation Trust, United Kingdom
[4]Department of Clinical Sciences Malmo, Ophthalmology, Lund University, Sweden

DESIGN. Observational study
PURPOSE. To examine whether change in fovea thickness over 3 years differs between people without diabetes and people with type 2 diabetes and no diabetic retinopathy (DR).
METHODS. The SUMMIT DR study recruited individuals with type 2 diabetes (T2DM) and either no or early signs of DR across 2 centres. A non-T2DM group of a similar age range were also recruited. For this study, data was utilised from individuals withT2DM who remained DR free over study duration and also the control group. Fovea thickness was measured in both eyes by optical coherence tomography (OCT) (512 x 128 scanning protocol). Participant characteristics were recorded. Participants were invited for repeat OCT and clinical assessments after ~3 years. OCT data from a single eye (randomly selected) for each participant entered data analysis. Baseline analysis: regression analysis data was utilised to examine whether diabetes altered fovea thickness when adjusted for potential confounders (age, gender and centre). Regression analysis was also utilised to examine whether change in fovea thickness over time was altered by diabetes, adjusting for age, gender, centre and duration of follow-up.
RESULTS. 432 and 72 individuals with and without T2DM from the SUMMIT DR study were eligible for this analysis (age range: 37-88 years). At baseline, there was no difference in fovea thickness withT2DM (Control group: mean (SD) 272 (18)μm; T2DM group: 267 (23)μm) when adjusted for age, gender and centre (standardised beta: -0.071, p=0.123). Change in fovea thickness (follow-up ⩾30months) was available in 300 and 48 individuals with and without T2DM. Change in fovea thickness was significantly different between the two groups (control median (25th,75th quartiles): 2.0(-1.8,7.0)μm; T2DM: 0.0 (-4.0,4.0)μm), which remained with adjusting for age, gender, centre and duration of follow-up (standardised beta: -0.160, p=0.010).
CONCLUSIONS. This data, adjusted for age and gender, suggest that diabetes per se alters fovea thickness change over time. A small increase in fovea thickness was observed in the non-T2DM group, whilst no net change was observed in the T2DM who remain DR free group.

Pilot Artificial Intelligence based Diabetic Retinopathy Screening Programme in Poland

A. Grzybowski[1,2], P. Brona[3]

[1]Department of Ophthalmology, University of Warmia and Mazury, Poland
[2]Institute for Research in Ophthalmology, Foundation for Ophthalmology Development, Poznan, Poland
[3]Department of Ophthalmology, Poznan City Hospital, Poznan, Poland

DESIGN. We aimed to find out whether AI based diabetic retinopathy screening can be effective in a real-life setting of the local polish population.
PURPOSE. Currently only a few affluent, developed countries were able to establish a nationwide DR screening. With the recent advances in machine learning artificial intelligence based DR screening presents an alternative to traditional screening. We decided to establish a screening programme on a local scale in order to assess its effectiveness, deployment method, locate and mitigate any arising issues before attempting to establish larger-scale AI based screening.

METHODS. Patients, who visited a diabetic clinic in Poznan, Poland were offered DR screening based on non-mydriatic retinal images taken by local staff with an automatic fundus camera. The images were then analysed with IDx-DR autonomous DR screening software and a recommendation was given to the patient based on the outcome. Images were later reviewed by an ophthalmologist.
RESULTS. Although initially the programme was hindered by numerous obstacles related to locale, hardware, staff training and public perception issues, these were quickly alleviated. IDx-DR was able to analyse 78% of 450 screening episodes. Among the patients analysed, according to the single clinician reference standard, IDx-DR had 94% sensitivity and 95% specificity.
CONCLUSIONS. The DR-screening process with IDx-DR for the image-analysis was relatively easy to implement and use. The percentage of poor quality images decreased with staff training and experience with both the fundus camera and the software. The final almost 80% non-mydriatic imaging rate was deemed satisfactory. After the pilot programme a much larger scale AI-based screening initiative is now underway in the region.

Hyperreflective Dots on Optical Coherence Tomography Scans of Diabetic Retinopathy - Can Some of them Represent Non-Perfused Capillaries?

M. Torm[1,2], M. Larsen[1,2]

[1]Department of Ophthalmology, Rigshospitalet-Glostrup, Glostrup, Copenhagen, Denmark
[2]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

DESIGN. Retrospective image analysis.
PURPOSE. The characteristics of hyperreflective dots on optical coherence tomography (OCT) are largely unknown. The purpose of this study was to enable three-dimensional mapping of the dots into those that are of comparable height and width (globules) and those that are elongated, with a further subdivision of the latter into those that are perfused (capillaries) and those that are not (ghost vessels, presumably).
METHODS. The study included 8 patients with type I diabetes and mild retinopathy or quiescent proliferative retinopathy after laser photocoagulation and 8 age-matched healthy subjects. Exclusion criteria were presence of macular edema or hard exudates. Structural OCT (Heidelberg Spectralis OCT2) was made as a fovea-centered 15x5 degree volume scan consisting of 131 horizontal B-scans spaced 11 μm apart. Angiographic OCT was made as a 10x10 degree volume scan consisting of 512 B-scans spaced 5.9 μm apart. Hyperreflective dots in the hyporeflective outer and inner nuclear layers of the retina, within a zone 500-1500 μm temporal of the foveal center, were registered manually for size, location and perfusion signal.
RESULTS. In the inner nuclear layer, three-dimensional dot analysis identified that elongated elements showed a perfusion signal in 61% of dots in healthy subjects and 46% of dots in patients with diabetes (capillaries). Ten percent of such elongated elements had no perfusion signal in patients with diabetes (ghost vessels). No such element was found in healthy subjects. The fraction of dots that could be classified as globules was 14% in healthy subjects and 12.5% in patients with diabetes. The fraction that could not be indisputably classified was 25% and 31.5% in the two groups respectively. In the outer nuclear layer, the hyperreflective dots had a width of 11-33 μm and no perfusion signal (globules).
CONCLUSIONS. A simple manual classification procedure was applied to hyperreflective dots on OCT in patients with diabetes and healthy subjects. The classification into globules, capillaries and ghost vessels can potentially be automated. Capillary non-perfusion, an early feature of diabetic retinopathy, will then be possible to identify non-invasively.

Association between Retinal Nerve Fiber Layer, Ganglion Cell Layer with Inner Plexiform Layer and Diabetic Retinopathy in Type 2 Diabetes

R. Vrabec[1], M. Tomic[1], I. Lovric[2], S. Ljubic[3], T. Bulum[3], D. Rahelic[3]

[1]Department of Ophthalmology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia
[2]Division of Ophthalmology, Zagreb Health Center - East, Zagreb, Croatia
[3]Department of Diabetes et Endocrinology, Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia

DESIGN. Cross-sectional study
PURPOSE. Aim of this study was to evaluate thickness of retinal nerve fibre layer (RNFL), ganglion cell and inner plexiform layer (GCL/IPL) in patients without diabetic retinopathy and mild diabetic retinopathy, which are markers of retinal neurodegeneration, in type 2 diabetic patients using spectral domain optical coherence tomography.
METHODS. This was a cross-sectional study including 50 eyes of 25 type 2 diabetic patients (15M/10F) with median age 64 years and median diabetes duration 13 years. Type 2 diabetes was defined according to the ADA classification, and hypertension according to the ESC/ESH classification. Ophthalmologic examination included binocular indirect slit lamp fundoscopy and color fundus photography of two fields (macular field, disc/nasal field) of both eyes according to the EURODIAB

retinal photography methodology and optical coherence tomography (SDOCT) with evaluation of optic nerve head (ONH) parameters, thickness of retinal nerve fiber layer (RNFL) macular thickness parameters, ganglion cell and inner plexiform layer (GCL/IPL). Patients with proliferative DR and diabetic macular edema were not included in the study.

RESULTS. 50 eyes of 25 patients were divided into two groups: group 1 (no retinopathy; n=16) and group 2 (non-proliferative DR; n=34). There was no difference in age between groups. In group 2, there were more men compared to women than in group 1 (87.5% vs. 47.1%, p=0.016)

Group 2 had longer diabetes duration (p=0.042), marginally more often hypertension (p=0.058) and significantly lower GCL (p=0.027) than group 1. No difference in RNFL was observed between groups. GCL was positively associated with RNFL ($p<0.001$), and negatively with diabetes duration (p=0.042) and DR (p=0.024). The best model for predicting GCL (R2=0.176) obtained from backward regression included age, gender and DR.

CONCLUSIONS. There was a statistically significant reduction of GLC-IPL in patients with mild diabetic retinopathy, but no difference in RNFL was observed between groups. Further study on a larger group of patients is needed for evaluating neurodegeneration of retina as marker of preclinical phase of diabetic retinopathy in type 2 diabetic patients.

Deep Capillary Plexus Impairment as a Biomarker of Diabetic Retinopathy Progression in the Long-Term Follow Up in Type 1 Diabetes

M. Parravano[1], F.S. Scarinci[1], F.P. Picconi[2], G.V. Virgili[3], D.D.G. De Geronimo[1], S.F. Frontoni[2], M.V. Varano[1]

[1]IRCCS –Fondazione Bietti, Rome, Italy
[2]Unit of Endocrinology, Diabetes and Metabolism, S. Giovanni Calibita Fatebenefratelli Hospital, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy
[3]Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Firenze and AOU Careggi, Italy

DESIGN. Longitudinal case–control exploratory clinical

PURPOSE. The aim of this study was to investigate microvascular retinal changes, using automated, quantitative measurements from OCTA data, and the structural changes of selected retinal layers on SD-OCT in DM1 patients diagnosed with mild sign of non-proliferative diabetic retinopathy (NPDR) over a period of two years follow up.

METHODS. DM1 with mild NPDR and healthy control subjects were included. OCTA parafoveal vessel density (PVD) and foveal avascular zone (FAZ) area were analyzed. The thickness of three predefined retinal slabs was measured on SD-OCT including the inner limiting membrane (ILM)-inner plexiform layer (IPL), the IPL-inner nuclear layer (INL) and IPL-outer nuclear layer (ONL) at baseline, 12 and 24 months.

RESULTS. Twenty-two DM1 and 21 controls were included. There was no significant difference in FAZ area between cohorts over time. Baseline SCP-PVD was about 10% lower in diabetics compared to controls (p=0.001), and was 12% lower at 2 years (p=0.002). Baseline DCP-PVD was slightly lower in diabetics compared to controls (-4.4%, p=0.047) and the difference increased at 2 years (-12.6%, $p<0.001$). The annual linear trend was -2.7% in diabetics vs. controls (p=0.009). Despite apparent between-group differences at baseline for structural OCT parameters, these were modest and not statistically significant such as for ILM-IPL (p=0.273) and for IPL-INL (p=0.708), and for IPL-ONL (p=0.054) with time.

CONCLUSIONS. In the early stage of DR parafoveal vessel density decrease of the DCP appears to be the most robust parameter to provide objective imaging biomarkers to monitor NPDR clinical progression using OCTA in our population.

Neovascular Glaucoma Drainage Surgery, Remote Results for Diabetic Patients

V.A. Biletskaya[2], D.V. Lipatov[1,2], M.A. Frolov[1]

[1]RUDN University, Moscow, Russia
[2]Endocrinology Research Centre, Moscow, Russia

DESIGN. Retrospective analysis

PURPOSE. Evaluation of the draining operations effectiveness (Ahmed implant and Molteno drainage) for patients with diabetic post primary non-compensated glaucoma; estimation of the number of complications and the analysis of the after-surgery complications.

METHODS. From 2005 to 2018 and for the first half of 2019 (including) 136 patients with NG (139 eyes) have been operated in Endocrinology Research Centre, average age – 67.9+3.2, diabetes duration- 16.1+4.7 years, level of glycated heemoglobin before surgery - 9.9+1.7%. All the patients had antiglaucoma drainage surgery using Ahmed (125 eyes) and Molteno (14 eyes) implants. Statistics profile of the patients who had Molteno drainage was ignored due to unreliability of the results caused by lack of patients.

RESULTS. In 100% cases patient's pain syndrome was stopped and in 107 cases (77%) intraocular pressure was steadily reduced. Stable eyeball hypotension was obtained in 4 cases (3%) because of choroid detachment which was stopped by medication. In rest 28 cases (20%) intraocular pressure was not compensated and remained high (but not above 35 mmHg) which required additional valve

implantation (2 cases), institution of combined medication (5 cases), contact transscleral diode-laser cyclocoagulation (21 cases). In early postoperative period hyphema (24%), cataract (7%), shallow anterior chamber (4%), drainage blockage (3%) and choroid detachment (1%) were occurred. In late postoperative period infringement of the iris (2%), drainage tube exposure (2%), vascular cataract of the cornea (8%) and epithelial-endothelial dystrophy of the cornea (9%) were diagnosed.

CONCLUSIONS. Despite a number of complications, drainage surgery of diabetic glaucoma for diabetic patients remains to be the main method of surgical treatment of such patients.

Optical Coherence Tomography Biomarkers to Predict Anti-VEGF Response in Diabetic Macular Edema

E. Cagiltay[1,2], Y.Z. Guven[2], F. Koc[2], F. Akay[2]

[1]University of Health Sciences, Sultan Abdülhamit Han Educating and Research Hospital, Department of Endocrinology, İstanbul, Turkey
[2]İzmir Katip Çelebi University Atatürk Educating and Research Hospital, Department of Ophthalmology, İzmir, Turkey

DESIGN. The patients with central involved diabetic macular oedema (CI-DME) were treated with three doses of anti-VEGF, 31 eyes were grouped in group responder (RR) and 27 eyes in group resistant (Rt).

PURPOSE. To evaluate the predictive baseline spectral domain optical coherence tomography (SD-OCT) biomarkers for functional and morphologic outcome after intravitreal anti-VEGF injection to treat CI-DME.

METHODS. Bilateral CI-DME patients with asymmetric response to a loading dose of anti-VEGF (Ranibuzumab or Aflibercept) treatment were included in the study. After three doses of injection, eyes were divided into two groups as responder (RR) and resistant (Rt) eyes according to the defined morphologic and functional response criteria. The morphologic response criteria were defined as the final central subfield thickness (CST) ⩽300μ and a 10% more decrease in CST compared to the other eye, whereas the functional response criterion was an increase in logMAR acuity of ⩾3 lines. The effects of baseline diabetic retinopathy stage and OCT biomarkers (type of DME, CST, epiretinal membrane/ERM, disorganization of the inner retinal layers/DRIL, external limiting membrane/ELM, ellipsoid zone/EZ and subretinal fluid/SRF) on the defined final morphologic and functional responses were evaluated.

RESULTS. There was no difference in the baseline median logMAR visual acuities, median CST's and distribution of DRP stages between the groups. While presence of SRF or simple ERM and baseline DME subtypes determined by OCT did not cause any difference on treatment responses, tractional-ERM, extensive (⩾500μ) DRIL, ELM and EZ disruptions in central 1000μ zone were found to be important OCT biomarkers in predicting resistance ($p < 0.001$). Artificial neuronal network analysis was performed, to rank the predictive power of these biomarkers. The most important predictor of anti-VEGF resistance was extensive ELM disruption (100%), tractional ERM (51.7%), extensive DRIL (25.4%) and EZ disruptions (24.5%) were following it.

CONCLUSIONS. Extensive ELM disruption is the strongest OCT biomarker that have a potential to predict anti-VEGF resistance. T-ERM, extensive EZ disruption and DRIL have the same potential with decreasing power. Evaluation of baseline OCT, paying attention to these biomarkers might guide us in management decisions of CI-DME.

Short Term Effects of Intravitreal Bevacizumab Injection on Retinal Nerve Fiber Layer Thickness

E. Doğan, K. Boncukçu, N. Özkan Aksoy

[1]Sakarya Training and Research Hospital Ophthalmology Department, Sakarya, Turkey

DESIGN. Retrospective

PURPOSE. The aim of this study was to evaluate the effects of intravitreal bevacizumab injection on retinal nerve fiber layer (RNFL) thickness

METHODS. Data of patients treated with intravitreal bevacizumab injection for senile macula degeneration, diabetic macular edema and retinal vascular occlusion between April- August 2019 were retrospectively analyzed. Intraocular pressure (IOP) measurement by Goldmann applanation tonometry, mean RNFL thickness measurement by HD-OCT (Carl Zeiss Meditec Dublin. CA, USA) were evaluated preoperatively and postoperative 1st month. Also additional complications were recorded.

RESULTS. The study included 44 eyes of 33 patients (19 male,14 female) who had no previous history of ocular surgery, intravitreal injection, laser treatment and optic disc pathology (glaucoma, optic neuritis). The mean age of the patients was 61.6 ± 8.5 years. The number of patients with diabetic macular edema, senile macula degeneration and retinal vascular occlusion were 16 (48%), 12 (36.3%) and 5 (15.1%) respectively. Preoperative and postoperative mean IOP was 15.6 and 15.1 mmHg respectively and statistical difference was not found (p:0.391). Transient IOP elevation controlled with antiglaucomatous medication was present in 5 (15.1%) eyes. Preoperative and postoperative mean RNFL thickness were 106.8±22.8 and 103.5 ±24.1μm respectively and not statistically different (p:0.349). Preoperatively mean superior, nasal, inferior and temporal quadrant RNFL thicknesses were 126.8±26.0, 79.5±17.7, 128.8±30.2, 94.9±42.9 μm respectively. Postoperative 1st month mean superior,

nasal, inferior and temporal quadrant RNFL thicknesses were 123.9±27.2, 75.8±16.9, 125.2±36.0, 91.4±43.8 μm respectively and significant statistical difference was not found(p: 0.440, p: 0.074, p: 0.506, p: 0.500). No serious ocular/systemic complication was observed after intravitreal injections.
CONCLUSIONS. Our results showed that intravitreal bevacizumab injection did not have a significant effect on RNFL thickness in the early period.

Prognostic Value of Subretinal Fluid Volume in Patients with Ranibizumab-Resistant Diabetic Macular Edema Treated with Intravitreal Dexamethasone

M.M. Uzel, E. Karahan, M. Köroğlu

Balıkesir University, School of Medicine, Department of Ophthalmology, Turkey

DESIGN. Retrospective, observational cohort study
PURPOSE. To investigate the prognostic effects of baseline Optical coherence tomography (OCT) parameters, especially subretinal fluid volume (SFV), in patients with ranibizumab (RNB) resistant diabetic macular edema (DME) who underwent an early switch to the dexamethasone (DEX) implant.
METHODS. Fifty-four eyes of 34 patients who underwent a loading dose of three-month RNB injection and then underwent a single dose of intravitreal DEX implantation were examined. Prior to RNB treatment, OCT scans were evaluated in terms of presence and volume of submacular fluid, size and localization of cystic changes, continuity of internal segment-external segment (IS-OS), number and localization of hyperreflective foci (HRF). Best corrected visual acuity (BCVA) and central macular thickness (CMT) were recorded at baseline RNB injection, at baseline DEX implant, at 1,2 and 4 months after DEX implant. Prognostic factors were evaluated by univariate and multivariate logistic regression analysis.
RESULTS. The mean age of 34 patients (21 females, 61.7%) was 64 years. Multivariate analysis showed a significant relationship between SRF (ß coefficient -5.615; 95%CI -10.96 to -0.27; p=0.04) increase and poor anatomical outcome (CMT reduction <20% of the baseline). As a result of multivariate analysis, the partially disrupted ISOS (ß coefficient -3.67; 95%CI -6.96 to -0.39; p=0.028), the number of HRF> 20 (ß coefficient -3.38; 95%CI -6.47 to -0.30; p=0.030), presence of a giant outer nuclear layer cyst (ß coefficient -3.56; 95%CI -6.22 to -0.89; p=0.009) and poor baseline BCVA (ß coefficient 4.82; 95%CI 0.20 to 9.45; p=0.041) are poor prognostic markers for visual change of <5 letters. According to the receiver operating characteristic analysis, 8.5 mm3 SRV was obtained as a cut-off value, as the best balance between sensitivity and specificity to predict anatomical failure. (75% sensitivity, 86% specificity, area under the curve 0.863, p<0.01)
CONCLUSIONS. SFV is a predictor in patients with RNB resistant DME who underwent an early switch to the DEX implant. Concomitant DEX implantation with anti-vegf instead of conventional anti-vegf therapy may be beneficial for prognosis in patients with high SFV.

Retinal Vascular Oxygen Saturation in Response to Panretinal Photocoagulation in Proliferative Diabetic Retinopathy: Detection of a Dose-Response Relationship?

A.S. Vergmann[1], A.S. Vergmann[1,2,4], T.L. Torp[1,2], R. Kawasaki[2,5], T. Yin Wong[6,7], T. Peto[2,8], J. Grauslund[1,2,3]

[1]Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[2]Research Unit of Ophthalmology, Department of Clinical Research, Faculty of Health Science, University of Southern Denmark, Denmark
[3]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark
[4]OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark
[5]Department of Vision Informatics, Osaka University School of Medicine, Osaka, Japan
[6]Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[7]Duke-NUS Medical School, National University of Singapore, Singapore
[8]School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom
****There are 2 entries for A.S. Vergmann – with different institutions. Possibly merge the 2? T. Peto to advise*

DESIGN. The study was a prospective, interventional study of patients with treatment-naïve PDR.
PURPOSE. The purpose of this study was to evaluate the association between laser burden and retinal vascular oxygen saturation in patients with treatment-naïve proliferative diabetic retinopathy (PDR) treated with different amounts of retinal laser.
METHODS. Patients were treated with navigated retinal laser (Navilas® (OD-OS GmbH, Teltow, Germany)) in different doses according to protocol. Retinal oximetry was obtained at baseline (BL), prior to laser, and again after six months (M6). Patients were divided into three groups according to total laser spots applied: <1500 spots (Group 1, n=10); 1500-2000 spots (Group 2, n=11); >2000 spots (Group 3, n=12).
RESULTS. We included 33 eyes of 28 patients with treatment-naïve PDR. The three groups did not differ according to age (53.5±13.0 vs. 52.0±12.0 vs. 54.5±18.0, p=0.78), sex (male)(60.0% vs. 55.0% vs. 58.0%, p=0.97), diabetes type 1 (40.0% vs. 55.0% vs. 42.0%, p=0.76), diabetes duration in years (22.0±16.0 vs. 17.0±23.0 vs. 20.5±17.0, p=0.87), HbA1c (mmol/mol) (61.5±14.0 vs. 65.0±15.0 vs. 71.5±20.5, p=0.87) or best corrected visual acuity (ETDRS)(85.0±4.0 vs. 83.0±8.0 vs. 84.5±8.5, p=0.41). It was found that Group 1 developed a lower retinal

arteriolar oxygen saturation (-0.9%, p<0.01) at M6. Groups 1 and 2 had a lower retinal venular oxygen saturation at M6 (1: -4.5%, p=0.05; 2: -1.8%, p=0.05). Focal retinal venular oxygen saturation located to quadrants with neovascularizations was statistically significantly lower in Group 2 at M6 compared to BL (-6.0%, p=0.02).
CONCLUSIONS. In this prospective study of patients with treatment-naïve PDR, we showed that a less extensive laser treatment caused a decrease in both retinal venular and arteriolar oxygen saturation 6 months after treatment. Our results suggest that less extensive laser treatment leads to less damage of the retina, indicated by the lowering of retinal venular oxygen saturation. This could in terms imply re-perfusion.

Changes in Retinal Microvasculature Parameters after Low-Carbohydrate, High-Fat Diet in Type 2 Diabetes: A Randomized-Controlled Trial of Danish Type 2 Diabetic Patients

S.L. Blindbæk[1,2,3], D.M. Møller[1,2], E.M. Gram-Kampmann[3,4,5], M.H. Olsen[6,7], K. Højlund[3,8,9], J. Grauslund[1,2,3]

[1]*Department of Ophthalmology, Odense University Hospital, Odense, Denmark*
[2]*Research Unit of Ophthalmology, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*
[3]*Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark*
[4]*Cardiovascular and Metabolic Preventive Clinic, Department of Endocrinology, Odense University Hospital, Odense, Denmark.*
[5]*Odense Patient data Explorative Network (OPEN), Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Odense, Denmark*
[6]*Cardiology Section, Department of Internal Medicine, Holbaek Hospital, Holbaek, Denmark*
[7]*Centre for individualized Medicine in Arterial Diseases (CIMA), Odense University Hospital, University of Southern Denmark, Odense, Denmark*
[8]*Department of Clinical Research, Section of Molecular Diabetes and Metabolism, University of Southern Denmark, Odense, Denmark*
[9]*Department of Molecular Medicine, Section of Molecular Diabetes and Metabolism, University of Southern Denmark, Odense, Denmark*

DESIGN. Single-center randomized controlled clinical trial.
PURPOSE. To estimate the effects of low-carbohydrate, high-fat (LCHF) dieting as compared to sustained regular diabetic (RD) diet on retinal microvasculature in patients with short duration of type 2 diabetes (DMII).
METHODS. Between June 2016 and May 2019, participants were recruited from the Departments of Endocrinology at OUH and Soenderborg Hospital and the Departments of Gastroenterology and Hepatology at OUH and Svendborg as well as via the Danish Diabetes Association in the Region of Southern Denmark and trial advertisement on various local and national media platforms. Inclusion criteria were DMII with duration of six months-five years, stable diabetic treatment prior to inclusion, age>18 years, serum cholesterol<4.5 mmol/l, and LDL cholesterol<2.5 mmol/l. Exclusion criteria were low carbohydrate diet prior to inclusion, pregnancy, hypoglycaemic unawareness, recent excessive weight loss or treatment with glucocorticoids or steatosis-inducing drugs. Patients were randomized 2:1 to LCHF diet or RD diet in a 26-week prospective trial. Forty-five degree disc-centred fundus photos (3D OCT-2000 Spectral domain OCT, Topcon, Tokyo, Japan) were acquired at baseline and follow-up and analysed for central retinal arteriolar and venular equivalent (CRAE and CRVE), and arteriolar-venular-ratio (AVR) using a semi-automated software (VAMPIRE-Web, Vessel Assessment and Measurement Platform for Images of the Retina, Universities of Dundee and Edinburgh, UK).
RESULTS. Ninety-seven eyes of 57 participants without baseline DR and with gradable retinal photos at both baseline and follow-up were analysed. Following LCHF dieting, CRAE was unchanged (-0.15 pixels, p = 0.16), whereas CRVE decreased by -1.17 pixels (p = 0.037). Following RD dieting, CRAE decreased by -0.82 pixels (p = 0.004), while CRVE was unaffected (+0.19 pixels, p = 0.30). No differences were observed in CRAE and CRVE between groups, and AVR did not change within or between groups during the study.
CONCLUSIONS. In a prospective, randomized trial, LCHF diet associated with retinal venular narrowing and halted the retinal arteriolar constriction observed in the RD group. These effects have previously been associated with lower risk of incident DR.

Subthreshold Micropulse Laser in Diabetic Macular Edema: OCT and OCT-Angiography Biomarkers of Treatment Response

S. Vujosevic[1], C. Toma[1], E. Villani[2,3], E. Torti[4], F. Leporati[4], P. Nucci[2,3], S. De Cillà[1,5]

[1]*University Hospital Maggiore della Carità, Eye Clinic, Novara, Italy*
[2]*Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy*
[3]*Eye Clinic San Giuseppe Hospital, IRCCS Multimedica, Milan, Italy*
[4]*Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy*
[5]*Department of Health Sciences, University East Piedmont "A.Avogadro", Novara, Italy*

DESIGN. 12-month prospective, longitudinal, consecutive case evaluation.
PURPOSE. To quantitatively evaluate changes in inflammatory and microvascular parameters on OCT and OCT-angiography (OCT-A) in patients with diabetic macular edema (DME) treated with subthreshold micropulse laser (SMPL).
METHODS. Thirty-seven eyes/patients with previously treatment-naïve DME and treated with SMPL and 15 fellow eyes with central microaneurysms were included.

Main inclusion criteria were: previously treatment-naïve DME, central macular thickness (CMT)⩽400 μm; no retinal disease other than diabetic retinopathy(DR); proliferative DR; good quality of OCT and OCT-A images. Treatment was performed using a subthreshold 577-nm yellow light micropulse laser with standard settings. The following OCT parameters were evaluated: CMT; number of hyperreflective retinal spots (HRS); presence and extension of disorganization of inner retinal layers (DRIL). As for OCT-A parameters: number of microaneurysms in the superficial and deep capillary plexus (SCP/DCP); cysts area at the SCP and DCP;macular perfusion parameters at the SCP and DCP and in the choriocapillaris (MATLAB).
RESULTS. Mean BCVA at baseline was 69.4±12.0 letters, 72.8±10.8 at 3 months (p=0.009), 74.4±9.4 at 6 months (p=0.0007) and 76.0±9.1 at 12 months (p<0.0001). The number of HRS and of MA at the SCP and DCP significantly decreased during the follow-up in the treated group (p<0.001) whereas it remained stable in the controls. MA significantly decreased in the DCP starting as early as 3 months after treatment (9.2±4.9 at baseline, 7.9±3.7 at 3 months,p=0.015, 6.2±3.7 and 4.8±3.2 at 6 and 12 months,p<0.0001). DRIL was present at baseline in 17 patients and progressively decreased during the follow-up. The area of the cysts significantly decreased both in the SCP (p=0.03 at 12 months) and DCP (p=0.02). No significant changes were found in other parameters.
CONCLUSIONS. A significant decrease in the number of HRS (sign of activated microglia) and MA, especially in the DCP (where capillaries are tightly interconnected with the bodies of Müller cells), and in the area of the cysts was documented. The anti-inflammatory effect of SMPL warrants further studies, and in particular if this effect is direct or indirect through RPE.

The Use of Prolonged Corticosteroids for the Prevention of Macular Edema after Cataract Surgery in Patients with Diabetes Mellitus

I. Bashina[1], M. Frolov[1], D. Lipatov[2,1]

[1]RUDN University, Department of Eye Diseases, Russia
[2]National Endocrinology Research Centre, Russia

DESIGN. Mono-center prospective randomized non-blind trial
PURPOSE. To determine the safety and efficacy of the use of prolonged corticosteroids for the prevention of cystoid macular edema (CME) after cataract surgery in patients with DM.
METHODS. 66 patients with DM and cataract were divided into two groups. The control group included 34 patients who received topical Dexamethasone in combination with Nepafenac 0,1%; the main group included 32 patients who received a subconjunctival injection of a prolonged corticosteroid (CS) Betamethasone 7 mg/ml in addition to topical treatment. The best corrected visual acuity (BCVA), intraocular pressure (IOP), the fovea thickness on optical coherence tomography (OCT) were measured before surgery and 4 weeks after surgery to evaluate the efficacy of anti-inflammatory therapy. The glycemic profile was studied to assess the effect of therapy on the glycaemia.
RESULTS. 6 patients (17.6%) developed subclinical CME in the control group; in the main group no cases (0%) of subclinical CME were identified. There was no significant difference in BCVA between two groups (p > 0.05) 4 weeks after the surgery. In the main group, the average IOP level was significantly higher than the initial values and also differed from the IOP level in the control group (p<0.001). The subconjunctival injection of a prolonged CS was accompanied by more severe hyperglycemia during the first day after surgery (p = 0.001).
CONCLUSIONS. The subconjunctival injection of Betamethasone 7 mg/ml prevents the development of postsurgical CME in patients with DM. However, this procedure leads to an increase in IOP and more severe hyperglycemia.

Investigation of Choroidal Thickness Changes after Intravitreal Bevacizumab Treatment in the Treatment of Diabetic Macular Edema

M.U. Işık[1], Y.Z. Güven[2], A.E. Öztürk[2], E. Çağıltay[3]

[1]Balıklıgöl State Hospital, Department of Ophthalmology, Şanlıurfa, Turkey
[2]Katip Çelebi Üniversitesi Atatürk Training and Research Hospital, Department of Ophthalmology, Izmir, Turkey
[3]Sağlık Bilimleri Üniversitesi İstanbul Sultan 2.Abdülhamid Han Training and Research Hospital, Department of Endocrinology, İstanbul, Turkey

DESIGN. Retrospective, consecutive case series study
PURPOSE. To detect possible changes in choroidal thickness with intravitreal bevacizumab treatment used in the treatment of diabetic macular edema (DME)
METHODS. Thirty-nine eyes of 24 patients who had diabetic macular edema and underwent intravitreal bevacizumab treatment were included in the study. Thirty right eyes of 30 patients were included as the control group. Complete ophthalmic examination and imaging with the Heidelberg Spectralis spectral-domain OCT (870 nm) device (Heidelberg Engineering, Heidelberg, Germany) were performed as part of the standard evaluation for patients with DME. Choroidal thicknesses were measured before the treatment, at the first month after the first injection and at the 1st month after the last injection.
RESULTS. The mean age was 63.2±7.6 in the patient group and 62.5±5.3 in the control group8p:0.785). There was no difference between the patient and control groups in terms of spherical equivalent, intraocular pressure and axial length (p>0.05). The mean number of intravitreal injections

applied was 5.4±1.8. In the patient group, temporal, nasal, subfoveal and mean choroidal thicknesses were significantly lower than the control group in all 3 measurement times($p<0.0001$). When repeated measurement analysis was performed, it was observed that the final measurements in temporal, nasal, and average choroidal thickness were thinner compared to the first measurements (p:0.021, p:0.024, p:0.029, respectively). However, there was no difference between subfoveal choroidal thickness measurements (p:0.178). In the correlation analysis, as the number of intravitreal bevacizumab administered increased, the thinning of the choroidal thicknesses (temporal, nasal, subfoveal, and average) increased(r:-0.445, p:0.007; r:-0.340, p:0.042; r:-0.459, p:0.005; r:-0.473, p:0.004, respectively).
CONCLUSIONS. In addition to the reduction in choroidal thickness in diabetic retinopathy patients, it was observed that choroidal thickness decreased with intravitreal bevacizumab treatment. Current results can be considered as evidence that this treatment may also have an impact on choroidal microvasculature or choroidal perfusion in DME.

Outcomes in Patients with Diabetic Macula Oedema Treated with Aflibercept for up to Three Years

I. Stratton[1], J. Talks[2], A. Lotery[3], R. Mukherjee[4], S. Kashani[5], U. Chakravarthy[6], P.H. Scanlon[1]

[1]*Gloucestershire Retinal Research Group, Gloucester, United Kingdom*
[2]*Newcastle University, Newcastle, United Kingdom*
[3]*Southampton University, Southampton, United Kingdom*
[4]*Leeds Teaching Hospitals, Leeds, United Kingdom*
[5]*East Sussex NHS Trust, Sussex, United Kingdom*
[6]*Queens University Belfast, Belfast, Northern Ireland, United Kingdom*

DESIGN. Audit of routinely collected electronic patient record data from 21 UK hospital eye departments from July 2015 to December 2019.
PURPOSE. To describe patients starting first treatment for diabetic macula oedema with aflibercept, retention, vision outcomes and number of injections.
METHODS. Data were extracted from Medisoft electronic records in December 2019 from 21 hospitals in UK. Subjects were included if treated with aflibercept only, reason for treatment given as diabetic macular oedema and with coherent data. LogMAR scores were converted to letter counts. First eye treated was included, better eye included if both treated at first treatment date.
Life tables were used to estimate proportion followed at 12, 24 and 36 months. General linear models and life table analysis were used (SAS 9.4)
RESULTS. 4255 people had at least one injection of aflibercept, aged 64 (56 to 73) years (median (25th to 75th centile)), 40% women, 13% T1DM, 87% T2DM, time since diagnosis 15 (10 to 21) years.
Proportion still being followed at 12, 24 and 36 months was 89%, 81% and 70% respectively.
Visual acuity (VA) at first injection was 65 (55 to 74) letters. The 12 month cohort of 1637 patients had VA 71 (61 to 79) letters after 6 (5 to 8) injections, 2 years cohort of 1027 had VA 71 (60 to 79) letters after 2 (0 to 4) further injections and 3 year cohort of 361 had VA 70 (58 to 77) letters after 2 (0 to 4) further injections. At 12 months those under 65 gained 5(0.8) (estimate (s.e.)) more letters than those 75 or older and those with worse vision (under 50 letters) gained 19.0 (1.4) more letters than those with 80 or more letters. Each injection in first 12 months gained 0.57 (0.15) letters.
CONCLUSIONS. In this cohort of patients in routine clinical care mean vision gain of 6 letters after 12 months was maintained in those attending at 24 and 36 months after mean 2 further injections per year.

Evaluation of Real-Life Clinical Outcomes of Intravitreal Anti-VEGF Injections for Diabetic Maculopathy in Diabetic Retina Treatment Unit, Mater Misericordiae University Hospital, Dublin, Ireland

D. Minasyan, D.K. Keegan

Diabetic Retina Treatment Unit, Mater Misericordiae University Hospital, Dublin, Ireland

DESIGN. Retrospective chart analysis of patients undergoing intravitreal therapy for DME between July 2018 and July 2019.
PURPOSE. To evaluate the clinical effectiveness and treatment outcomes of the Intravitreal anti-VEGF injections for DME over 12 month period
METHODS. A retrospective analysis of best corrected visual acuity (BCVA), Optical Coherence Tomography (OCT) findings before and after treatment, treatment agent, number of injections was undertaken on patients undergoing intravitreal therapy for DME between July 2018 and July 2019 in the Diabetic Retina Treatment Service at MMUH.
RESULTS. A total number of 209 eyes (179 patients) were included in this study. 67% of eyes received Bevacizumab therapy, with 19% receiving Aflibercept. The total number of injections was 1919, with mean number of Bevacizumab injections was 7.8, and Aflibercept injections 1.8.
Visual Acuity: Mean BCVA pre-treatment was LogMar 0.5(range 0.1-1.5). Mean BCVA post-treatment was LogMar 0.3(range 0.0-0.3), with mean difference BCVA pre and post treatment of patients receiving Bevacizumab only was LogMar 0.02,and patients who was switched

from Bevacizumab to Aflibercept was 0.14 LogMar. OCT findings: Central retinal thickness showed improvement with treatment from a mean of 442μm pre-treatment to 358 μm post-treatment. Patients who received Bevacizumab therapy only had a mean difference in CRT pre and post treatment 92.6 μm, with switching to Aflibercept 136 μm.
CONCLUSIONS. This review of real-life clinical analysis of Intravitreal Anti-VEGF injections for DME demonstrated a favourable outcome for patients. Bevacizumab being the main first line agent in treatment of DME, however timely switching to Aflibercept for non-responders shown to be clinically effective. Worse outcomes were associated with delayed treatment, macular ischaemia and previous pan-retinal photocoagulation therapy.

Outcomes of Hybrid Mixed-Gauge by Bimanual Vitrectomy for Diabetic Tractional Retinal Detachment

L. Konstantinidis, T. Stapler, E.M. Wardani, J. Potij, T.J. Wolfensberger

Jules Gonin University Eye Hospital, Lausanne, Switzerland

DESIGN. Retrospective, interventional, case series
PURPOSE. To evaluate the outcome of bimanual pars plana vitrectomy for repair of diabetic tractional retinal detachment (TRD) using combined 23-gauge and 27-gauge instrumentation
METHODS. Nineteen consecutive cases of patients operated with this technique for complex diabetic tractional retinal detachment in Jules Gonin University Eye Hospital were included in this study
RESULTS. Primary reattachment was achieved in all 19 eyes. Mean follow-up was 11 months (SD:2) Vitreous haemorrhage developed in 2 eyes (10%) requiring repeated vitrectomy in one eye (5%). Vision was stabilized or improved in 18 eyes (95%). Visual acuity of 20/200 or better was achieved in 15/19 eyes (79.0%) and 20/50 or better in 8/19 eyes (42%). No surgical complications were encountered.
CONCLUSIONS. Concurrent use of the 27-gauge vitreous cutter with 23-gauge instrumentation was effective during diabetic tractional retinal detachment repair. This combination allows the advantages of the 27-gauge cutter when dissecting fibrovascular membranes associated with improved aptitude of movements within the larger-diameter cannula and furthermore have access to the variety of ancillary instrumentation available in 23-gauge.

Short-Term Effectiveness of Subthreshold Laser Therapy for Predominantly Non-Centre Involving Diabetic Macular Oedema

E. Lim, M. Stahl, C. Andrews, S. Fatum, N.V. Chong, C.A. Kiire

Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

DESIGN. Retrospective analysis of real-world clinical outcomes.
PURPOSE. 1. To determine the short-term effect of subthreshold macular laser therapy on visual acuity (VA), macular volume (MV) and central subfield thickness (CST) in patients with predominantly non-centre involving diabetic macular oedema (NCI-DMO).
2. To evaluate the proportion of patients who have had one application of SMLT for NCI-DMO and go on to require further treatment.
METHODS. Assessed the change in VA, MV and CST from baseline to the first review occurring 5-10 months following SMLT for NCI-DMO.
Eligible participants were treated for the first time between 2013-2018, had no co-pathology to account for their macular oedema, and had no other ophthalmological treatment at that time. MV (central 3mm) and CST were obtained from Heidelberg Spectralis OCT scans. A change in VA of <0.1 LogMAR was considered stable. A generalised estimating equations approach was used in the statistical analyses, adjusting for HbA1c and baseline values where appropriate.
RESULTS. 202/364 eyes (156/292 patients) were eligible for inclusion in the analysis. Median follow up interval was 7 months. Mean HbA1c was 7.9% (SD 2.4%). Baseline VA, MV and CST were 0.15 (SD 0.20) LogMAR, 2.50mm3 (SD 0.28mm3), and 317 (SD 49) um, respectively.
76% of eyes had a stable VA, 11% had an improvement in VA, and 12% had a deterioration in VA by the 5-10 month follow up visit. There was no significant change in VA (p=0.84, 95% CI -0.02 to 0.03). There was a significant change in MV (rose 0.05mm3; p=0.03, 95% CI 0.01 to 0.1) and CST (rose 14 um; p=0.01, 95% CI 2.95 to 25.53), but these were of questionable clinical significance. Adjusting for HbA1c and baseline values did not significantly alter the results. 44% of eyes had SMLT repeated and 31% of patients progressed to having treatment with intravitreal injections over the follow up period.
CONCLUSIONS. There appears to be little change in the mean VA, MV and CST at 5-10 months after SMLT. $>50\%$ of eligible eyes treated with SMLT for NCI-DMO for the first time have (to date) had further treatment.