EJO European Journal of Ophthalmology

34th Meeting of the European Association for Diabetic Eye Complications (EAsDEC) University of Milan, Milan, Italy 30th May – 1st June 2024

European Journal of Ophthalmology
2024, Vol. 34(1S) 1–40

DOI: 10.1177/11206721241244945
journals.sagepub.com/home/ejo
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RETINAL CHANGES IN OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FINDINGS IN PATIENTS WITH DIABETES MELLITUS TYPE 2

D. Risimic[1,2], J. Ćuk[2], J. Vasilijević[1,2], M.Jeremić[2], A. Risimić[2], L. Repanić[2], J. Jaksić[2]

[1]Medical Faculty University of Belgrade, Serbia
[2]Clinic for Eye Diseases, University Clinical Centre of Serbia, Belgrade, Serbia

DESIGN. Cross sectional study.
PURPOSE. To investigate quantitative differences in optical coherence tomography angiography (OCTA) data between patients with Type 2 diabetes mellitus (DM2) without retinopathy or with non-proliferative diabetic retinopathy (NPDR) without diabetic macular oedema (DME) and a group of healthy individuals.
METHODS. All patients and healthy individuals were examined on Clinic for Eye Diseases, Clinical Centre of Serbia, where OCTA was performed. OCTA imaging was performed on twenty DM2 patients without diabetic retinopathy, twenty patients with NPDR but without diabetic macular oedema (DME) and twenty healthy (without DM2), age-matched controls. Parafoveal, foveal, macular and perifoveal vessel density in the deep capillary plexus (DCP) and superficial capillary plexus (SCP), as well as foveal avascular zone (FAZ) area, outer retinal and choriocapillary flow were calculated with automated quantification software and compared between cohorts.
RESULTS. A significant decrease in parafoveal vessel density was seen in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in DM2 patients compared to healthy controls ($p < 0.001$). There was significant difference in DCP parafoveal vessel density, between DM2 patients without retinopathy and those with retinopathy ($p < 0.001$).
CONCLUSIONS. Both DM2 patients with retinopathy and without retinopathy have reduced parafoveal vessel density in the DCP and SCP on OCTA when compared to healthy controls. We found that decrease of DCP parafoveal vessel density is an early sign of changes in retinal vascularity seen in DM2 patients without changes found by clinical examination. Our OCTA findings suggest that parafoveal capillary nonperfusion is an early process. Also, we found that retinal changes occur initially at the level of the DCP in DM2 patients. Further investigation is needed to understand the prognostic role of these vascular changes.

METABOLIC AND STRUCTURAL PREDICTORS OF LONG-TERM FUNCTIONAL CHANGES EVALUATED BY MULTIFOCAL ELECTRORETINOGRAM IN TYPE 1 DIABETES.

M. Parravano[1], S. Fragiotta[2], E. Costanzo[1], F. Picconi[3], D. De Geronimo[1], V. Parisi[1], M. Varano[1], L. Ziccardi[1]

[1]IRCCS-Fondazione Bietti, Rome, Italy
[2]Ophthalmology Unit, "Sapienza" University of Rome, NESMOS Department, St. Andrea Hospital, Rome, Italy
[3]Unit of Endocrinology, Diabetes and Metabolism, Fatebenefratelli Isola Tiberina Gemelli Isola, Rome Italy

DESIGN. Prospective observational cohort study enrolled patients with mild non-proliferative diabetic retinopathy (NPDR) with type 1 diabetes mellitus (DM1).
PURPOSE. To analyse a possible pathogenic relationship between metabolic factors, structural derangements of photoreceptors, microvascular perfusion and functional changes through multifocal electroretinography (mfERG) in patients with DM1.
METHODS. Patients underwent comprehensive multimodal imaging, including colour fundus photography, optical coherence tomography (OCT), OCT angiography, adaptive optics (AO), and mfERG. These examinations were obtained at baseline and annually for up to 4 years

of follow-up. OCTA images were processed using ImageJ software for calculating perfusion density (PD) at the superficial (SCP) and deep (DCP) capillary plexuses and flow deficits (FD%) at the choriocapillaris (CC) level. AO images were processed using MATLAB algorithm for calculating cone density (CD), linear dispersion index (LDi), and packing heterogeneity index (Hpi%). All analyses were conducted in the parafoveal region.

RESULTS. A total of 22 patients (22 eyes) with a mean age of 40.5 ± 9.1 years were enrolled. No significant differences were noted in R1, R2, and R1 + R2 RAD and IT averaged values ($p > 0.05$, all) during the FU. A reduced Hpi was directly associated with a decrease in the R1 + R2 RAD at year 2 ($r = 0.72$, $p = 0.006$) and year 4 ($r = 0.77$, $p = 0.02$). Likewise, Ldi was inversely associated with R1 +R2 RAD ($r = -0.64$, $p = 0.01$) at 2-year and 4-year ($r = -0.77$, $p = 0.02$). The best-fitted model considered a combination of duration of diabetes, HbA1c level, CD, Hpi, LDi, SCP, DCP, and CC at the parafovea. Factors influencing R1 +R2 IT included Hpi, and LDi ($p > 0.001$, all), but also microvascular changes in the SCP ($p < 0.001$) and DCP ($p = 0.03$) at the parafovea, while R1 + R2 RAD were influenced by Hb1Ac ($p = 0.02$) and Hpi ($p < 0.001$).

CONCLUSIONS. The involvement of the CC represents an early event and influences the microvascular and cellular reorganisation from the early stages of the disease. As the disease progresses, the microvasculature of the SCP and DCP and glyco-metabolic control represent crucial factors for long-term morpho-functional modifications at the level of photoreceptors.

PROGRESSION OF DIABETIC RETINOPATHY IN WOMEN WITH TYPE 1 DIABETES DURING AND AFTER PREGNANCY - RESULTS FROM A NATIONWIDE COHORT.

J. Ezban Larsson[1], L.M. Stokholm[2,3], J. Grauslund[2,4,5], E.R. Mathiesen[6,7,8], C.S. Laugesen[1], On behalf of the OASIS study group

[1]Department of Ophthalmology, Zealand University Hospital Roskilde, Roskilde, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]OPEN, Open Patient data Explorative Network, Odense University Hospital & University of Southern Denmark, Odense, Denmark
[4]Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[5]Steno Diabetes Centre Odense, Odense University Hospital, Odense, Denmark
[6]Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark
[7]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[8]Novo Nordisk A/S, Søborg, Denmark

DESIGN. Registry-based, national matched cohort study.

PURPOSE. To evaluate the risk of treatment-requiring proliferative diabetic retinopathy (PDR) during or shortly after pregnancy in women with type 1 diabetes (DM1) compared to matched non-pregnant women.

METHODS. Diabetic retinopathy (DR) screening is nationally implemented and registered in the Danish Registry of Diabetic Retinopathy. In this study, we included all women in the register aged 18-50 with DM1, who gave birth in the period 2013-2022. Cases had at least one screening during pregnancy and at least one screening up to three years prior to or up to three years after pregnancy. Each case was age-matched with two women with DM1 (controls) who had at least two screenings recorded and no pregnancy in the study period.

RESULTS. A total of 1041 cases and 2082 controls were included. At inclusion, DR was present in 42.7% of the cases vs 56.7% of the controls ($p < 0.001$), whereof PDR was present in 4.2% vs. 8.3% ($p < 0.001$). 4.2% of the cases and 6.0% of the controls had received prior peripheral laser treatment for PDR, and 0.7% of the cases and 1.2% of the controls had received anti-VEGF. Median HbA1C was 57 mmol/mol vs 63 mmol/mol ($P < 0.001$). In cases, median HbA1C declined to 51 mmol/mol in the first trimester, 44 mmol/mol in the second and third trimester, and then increased to 58 mmol/mol after pregnancy. The HbA1C in the control group remained constant.

During pregnancy, 2.4% of the cases and 0.3% of the controls received peripheral laser ($p < 0.001$). After pregnancy, corresponding numbers were 3.0% and 7.8%, respectively ($p < 0.001$). During and after pregnancy, anti-VEGF was given to eight (0.8%) and less than five women, and 1.8% and 4.0% ($p < 0.001$), respectively.

CONCLUSIONS. In this nine-year nationwide cohort study of pregnant women with DM1, treatment for PDR was slightly more prevalent during pregnancy, but less prevalent the first years after pregnancy when compared to a non-pregnant control group. In the total observation period, the risk for treatment of PDR was lower for women that had given birth.

LONGITUDINAL ASSESSMENT OF STRUCTURAL AND MICROVASCULAR CHANGES IN A PEDIATRIC POPULATION WITH TYPE 1 DIABETES.

M.S. Polito[1,3,4], S. Fragiotta[2], F. Picconi[3], M. Menduni[2], L.Chioma[4], E. Costanzo[1], D. De Geronimo[1], P.I. Patera[4], M. Varano[1], M. Parravano[1]

[1]IRCCS-G.B. Bietti Foundation Rome, Italy

[2]Ophthalmology Unit, "Sapienza" University of Rome, NESMOS Department, St. Andrea Hospital, Rome, Italy
[3]Unit of Endocrinology, Ospedale Isola tiberina-Gemelli Isola, Rome, Italy
[4]Diabetes Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

DESIGN. Prospective cohort study including paediatric/adolescent patients aged between 10 and 21 years with type 1 diabetes mellitus (DM1) under insulin pump treatment.
PURPOSE. The aim of this study was to evaluate the progression over 36 months of structural and microvascular alterations preceding the development of diabetic retinopathy (DR) in DM1 paediatric population.
METHODS. Patients were followed for 36 months, assessing metabolic factors, retinal layers using optical coherence tomography (OCT) (Heidelberg Spectralis and Optovue AVANTI), and microvascular changes using OCT angiography (OCTA, Optovue AVANTI and PlexElite, Zeiss). Structural evaluation was performed using thickness maps of single or combined retinal layers obtained automatically through the built-in software. The OCTA study allowed the assessment of perfusion density in the superficial and deep vascular plexuses and choriocapillaris flow deficits (CC FD%). Metabolic, structural, and microvascular parameters were analysed at baseline, 12, 24 and 36 months.
RESULTS. A total of 26 eyes from 26 paediatric DM1 patients (18 females, 8 males), and no signs of DR, were analysed with a mean age of 14.2 ± 2.7 years. The baseline glycated haemoglobin was $7.7 \pm 1.3\%$.The global thicknesses of the inner plexiform layer (IPL) and outer plexiform layer (OPL) varied significantly over time (all, $p = 0.02$, and all fields, $p = 0.01$). Structural analysis demonstrated a significant variation in peripapillary retinal nerve fibre layer (RNFL) values ($p = 0.01$), perifoveal ganglion cells (GCL) ($p < 0.001$), and perifoveal IPL ($p < 0.001$). Microvascular parameters showed a significant impairment of microvascular density over time, with reduced perfusion in the superficial plexus (whole, $p = 0.05$) overall and at the foveal location ($p = 0.03$), while an increase in microvascular density in the deep plexus at the parafoveal level ($p = 0.002$) was noted. Noteworthy, CC FD% progressively increased over time ($P < 0.001$).
CONCLUSIONS. Our results demonstrated an early involvement of the inner retina and microvasculature in paediatric DM1 patients. The structural alterations of the inner retina are accompanied by significant microvascular changes involving both superficial and deep plexuses preceding clinically significant damage. The increased vascular density at the deep plexus could support a compensatory mechanism in response to cellular distress. CC impairment in paediatric DM1 patients suggests an early diabetic choroidopathy development.

DEVELOPMENT OF AN AUTOMATED ALGORITHM FOR GRADING OF DIABETIC MACULOPATHY ACCORDING ESASO CLASSIFICATION.

M. Vadala'[1,4], G. Lo Bosco[2,4], E. Chisci[1], A. La Felice[1], S. Calderaro[2], D. Amato[2], R. Rizzo[3], F. Vella[3], V.M.E. Bonfiglio[1]

[1]University of Palermo, BIND Department, Section of Ophthalmology, Palermo, Italy
[2]University of Palermo, Department of Mathematics and Computer Science, Palermo, Italy
[3]National Research Council of Italy, Institute for High-Performance Computing and Networking, Palermo, Italy
[4]Euro-Mediterranean Institute of Science and Technology, Palermo, Italy

DESIGN. Deep neural networks optimised for image grading was developed using a data set of 600 OCT images of diabetic maculopathy, which were graded according to ESASO classification. Macular thickness, intraretinal cysts, hyperreflective foci and ellipsoid zone integrity were evaluated. Gradability was compared with two licensed ophthalmologists' judgment.
PURPOSE. Development of an automated grading algorithm for evaluation of ESASO biomarkers for diabetic maculopathy on OCT scans.
METHODS. Features relative to macular thickness, intraretinal cysts, hyperreflective foci, and ellipsoid zone integrity will be extracted by using specific models of deep neural networks, and graded according the ESASO OCT classification. In particular, Convolutional Neural Networks (CNN), U-net Networks (U-net), and Region-Based Convolutional Neural Networks (R-CNN) were used to identify such features, in terms of regions where specific measurements will be computed. Finally, a rule-based system was adopted according to the ESASO classification.
RESULTS. The ESASO grade II - data set consisted of 632 images from 609 (fully gradable images 92%). Classification results the overall methodology, including Deep Neural Network feature extractors and rule-based system, showed high accuracy, precision and recall values (>80%) on the above-mentioned data. Further improvements will be studied, also in terms of new data availability.
CONCLUSIONS. In this work we developed a general model capable of automatically measure OCT biomarkers and consequently grading diabetic maculopathy according the ESASO staging system. It proved to be rapid, reproducible, and reliable for objective quantification of disease severity. Further refinement and validation of our algorithm is addressing its validation and feasibility of applying this algorithm in the clinical setting and exploring its capacity to serve as an essential

tool for optimal, personalized DME care and study, overcoming limitations of manual grading.

EVALUATION OF SITAGLIPTIN EYEDROPS IN TRPV2+/- RATS, A NON-DIABETIC MODEL WITH DIABETIC RETINOPATHY-LIKE LESIONS

H. Ramos[1,2,3,4], J. Augustine[4], B.M. Karan[4], C. Hernández[1,2,3], A.W. Stitt[4], T.M. Curtis[4], R. Simó[1,2,3]

[1]Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Barcelona, Spain
[2]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ICSIII), Madrid, Spain
[3]Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[4]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom

DESIGN. Interventional study in an experimental model mimicking diabetic retinopathy (DR).
PURPOSE. Impairment of retinal neurovascular unit (NVU) is an early event in DR, hence it can be considered an emergent therapeutic target for DR. Topical administration (eyedrops) of sitagliptin, a dipeptidyl peptidase-4 inhibitor, showed beneficial effects against the main hallmarks of NVU impairment in the db/db mouse, a diabetic model of DR. In this study, the approach was tested in a new non-diabetic model of DR, the heterozygous TRPV2 knockout rat (TRPV2 +/-). This model displays impaired pressure autoregulation of blood flow in the retina, leading to lesions similar to those observed in DR.
METHODS. Male and female TRPV2+/- rats, aged 12 weeks, were topically treated twice daily for 2 weeks with sitagliptin (10 mg/mL) or vehicle eyedrops (15 µL/eye). TRPV2 WT (+/+) rats treated with vehicle served as controls. Body weight and glycemia were monitored throughout the study. Once treatment was completed, optical coherence tomography, fundus imaging and euthanasia were performed. RT-qPCR and immunolabelling assays were conducted to evaluate sitagliptin effects in neuronal, glial and vascular components of the retina.
RESULTS. Sitagliptin eyedrops had no effect on body weight or glycemia. Total retinal and photoreceptor layer thickness were significantly reduced in vehicle-treated TRPV2+/- rats, and sitagliptin eyedrops conferred protection against this change ($p < 0.05$). Fundus imaging revealed larger diameters of major retinal blood vessels in vehicle-treated TRPV2+/- rats, an abnormality that was abrogated by sitagliptin eye-drops ($p < 0.05$). Upregulation of inflammatory factors and oxidative markers was found in the retinas of TRPV2+/- rats and prevented by the drug treatment ($p < 0.05$). Sitagliptin eyedrops also protected against downregulation of the Kir4.1 channel, which plays an important role in K + and retinal fluid homeostasis ($p < 0.05$). Additionally, retinas from TRPV2+/- rats exhibited increased acellular capillaries formation, which was prevented by topical administration of sitagliptin ($p < 0.05$).
CONCLUSIONS. Sitagliptin eyedrops exert a protective effect against DR-like lesions in TRPV2+/- rats. Our results suggest that the underlying mechanisms of retinal action of sitagliptin can also be useful for treating NVU impairment induced by retinal diseases unrelated to diabetes.

UNCOVERING POTENTIAL NOVEL BIOMARKERS FOR EARLY DIAGNOSIS OF DIABETIC RETINOPATHY BASED ON TEXTURE ANALYSIS OF OCT-DERIVED RETINAL IMAGES: EVIDENCE FROM AN ANIMAL MODEL OF DIABETES

A.F. Ambrosio[1,2,3], S. Oliveira[1,2,3], P. Guimaraes[4], EJ. Campos[2,3,5,6], R. Fernandes[1,2,3,7], P. Serranho[4,8], P. Matafome[1,2,3,9,10], R. Bernardes[3,4,6]

[1]Univ Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, Coimbra, Portugal
[2]Univ Coimbra, Centre for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal
[3]Clinical Academic Centre of Coimbra (CACC), Coimbra, Portugal
[4]Univ Coimbra, Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT), Institute for Nuclear Sciences Applied to Health (ICNAS), Coimbra, Portugal
[5]Univ Coimbra, Chemical Engineering and Renewable Resources for Sustainability (CERES), Department of Chemical Engineering (DEQ), Faculty of Sciences and Technology (FCTUC), Coimbra, Portugal
[6]Univ Coimbra, Faculty of Medicine (FMUC), Coimbra, Portugal
[7]Univ Coimbra, Institute of Pharmacology and Experimental Therapeutics, Faculty of Medicine, Coimbra, Portugal
[8]Universidade Aberta, Department of Sciences and Technology, Lisbon, Portugal
[9]Univ Coimbra, Institute of Physiology, Faculty of Medicine, Coimbra, Portugal
[10]Polytechnic University of Coimbra, Coimbra Health School (ESTeSC), Coimbra, Portugal

DESIGN. Diabetic retinopathy (DR) is usually diagnosed many years after diabetes onset. Indeed, the early diagnosis of DR remains a remarkable challenge, and the identification of new biomarkers is crucial. Here, a new methodology based on texture analysis applied to optical coherence tomography (OCT) retinal images was used in a type-1 diabetes rat (Wistar) model (streptozotocin-induced).
PURPOSE. We investigated whether diabetes triggers very early changes in retinal texture of OCT images,

analysing different features, and checked whether these changes were concomitant with molecular, cellular and vascular changes in the diabetic retina.

METHODS. Volume retinal OCT scans (N = 40-44 animals; control/diabetic) and electroretinograms (N = 25) were acquired before, and 1, 2 and 4 weeks after diabetes induction. Automated OCT image segmentation was performed to define retinal layers, and retinal thickness was computed. Texture analysis was applied to OCT data. Blood-retinal barrier breakdown, nitrosative stress, glial reactivity and neuroinflammation were also assessed.

RESULTS. Retinal texture was significantly affected by diabetes. The texture metrics, autocorrelation, correlation, homogeneity, information measure of correlation 2 (IMC2), inverse difference moment normalized (IDMN), inverse difference normalized (IDN) and sum average, decreased in all retinal layers, at week 4. Correlation, homogeneity, IMC2, IDMN and IDN decreased at week 2. A significant thinning was detected at all-time points in the inner plexiform and inner nuclear layers, inner/outer photoreceptor segments, and total retina. Regarding retinal function, a delayed response was observed in a-wave and oscillatory potentials 1-4, at all-time points, in diabetic animals. The immunoreactivity of claudin-5 (weeks 2 and 4), occludin (week 4), and ZO-1 (week 4) decreased in diabetic animals, but without vascular leakage. The density of microglia (all time points) and nitrotyrosine immunoreactivity increased in the retina of diabetic animals.

CONCLUSIONS. We show that diabetes induces changes in OCT retinal texture, found when some retinal molecular and cellular changes are already detected, suggesting that retinal texture offers potential to identify novel biomarkers for DR, but clinical studies are needed to confirm these results.

SYNERGY BETWEEN GLYCO-IMMUNO-DRUGS AND METAL-ORGANIC FRAMEWORK-BASED NANOPLATFORMS: A NOVEL THERAPEUTIC TOOL FOR DIABETIC RETINOPATHY (IMMUNOGLYMOFS).

F. Martín-Loro[1], F.C.C. Cano-Cano[1], E.M.S.F. Sánchez-Fernández[2], C.C.C. Carrillo-Carrión[3], C.O.M. Ortiz-Mellet[2], E.B. Beltramo[4], M.A.D. Aguilar-Diosdado[1,5], A.I.A. Arroba[1,5]

[1]Institute for Biomedical Research and Innovation of Cádiz (INiBICA), Cádiz, Spain
[2]Department of Organic Chemistry, Faculty of Chemistry, University of Seville, Seville, Spain
[3]Institute for Chemical Research (IIQ), CSIC - University of Seville, Seville, Spain
[4]Department of Medical Sciences, University of Turin, Italy
[5]Department of Endocrinology and Metabolism, University Hospital "Puerta del Mar", Cádiz, Spain

DESIGN. Diabetic retinopathy (DR) is associated with changes in the expression of inflammatory mediators in the retina. Current approved treatments include frequent intraocular injections of anti-vascular endothelial growth factor or, alternatively, retinal laser photocoagulation, with risk of side injuries. Retinal inflammation in early stages of DR is mediated by microglial cells, which play a crucial role in its development.

The sp2-IGLs constitute a family of glycoconjugates able to promote microglia polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) state. Numerous efforts are focused on designing drug delivery nanosystems to improve ocular administration of therapeutic compounds. Metal-Organic Frameworks (MOFs), a type of crystalline porous solids, have great potential as carrier when synthesized at the nano-scale (nanoMOFs): (1) provide stable conditions for labile compounds, (2) reduce intrinsic drug toxicity, (3) enhance the solubility of lipophilic molecules, (4) allow a high drug accumulation in the retina, (5) allow modulating release kinetics to provide optimal doses while minimizing side effects.

PURPOSE. The prospect of modulating the immune system during DR could represent a new therapeutic option. We hypothesize that the treatment with the encapsulated sp2-IGL@MOF at minimum doses in IM-HMG will favour a M1 to M2 phenotypic switch under diabetic environment, thereby attenuating neuroinflammation and neurodegeneration processes.

METHODS. Immortalized human microglial cells (IM-HMC) were stimulated with a pro-inflammatory cocktail (interleukin-1β + tumour necrosis factor-α + interferon-γ), inducing a significant M1 response. Im-HMC were cultured in presence or absence of sp2-IGLs, MOF, sp2-IGL@MOF at nanomolar concentrations, under pro-inflammatory environment. In these experimental approaches, cytotoxicity and the release of pro-inflammatory-(M1) / anti-inflammatory-(M2) cytokines were evaluated.

RESULTS. sp2-IGL@MOF treatment in IM-HMC reduces different pro-inflammatory markers, such as IL1β and IL6, and induced M2-response by induction of HO-1 and increased of Arginase-1, with a decrease in the effective dose of use to nanomolar concentrations.

CONCLUSIONS. The use of MOFs as nanocarriers to encapsulate molecules with immunomodulatory capacity in microglial cells can improve the methods and treatments for DR developed so far, by controlling the immune-mediated inflammatory response.

THE IMPACT OF MISALIGNMENT WITH THE EXTERNAL LIGHT CYCLE ON DIABETIC RETINOPATHY

E. Beli, H. Winter, K. Dunlop, N. Campbell, T. Friedel, T. Curtis, A. Stitt

Wellcome-Wolfson Institute for Experimental Medicine, QUB, Belfast, UK

DESIGN. We recreated a model of desynchrony that extreme (late or early) chronotypes experience, using a mouse model of type 1 diabetes, Ins2 Akita mice. Late or early chronotypes have internal clocks that are longer or shorter than 24 hours depending on various factors including genetics. Late chronotypes have to shorten while early chronotypes have to expand their clock to match the external 24 hour light/dark cycle. When C57Bl6 mice with an internal period of 23.6hr are housed in a shorter (T22.5hr) or longer (T27hr) light cycle they experience similar to extreme late and early chronotypes social jet lag.

PURPOSE. The aim of this study was to test whether circadian disruption experienced by an early or late chronotype affects the progression of diabetic retinopathy.

METHODS. Control and Ins2 Akita mice ($n = 10$-14) entered misaligned light/dark schedule (T22.5hr or T27hr) at 2 months and were kept for 4 months. At 6 months, eye disease progression was assessed with in vivo retinal imaging (fundus imaging, scotopic ERG, OCT), and ex-vivo for acellular capillaries.

RESULTS. Diabetes, as expected, resulted in significantly increased retina pathology with increased white spots, reduced retina thickness, development of acellular capillaries and impaired scotopic b-wave responses in electroretinography. The light misalignment treatments, either T22.5 (late) or T27 (early), had a significant impact on these endpoints in both control and diabetic mice. Three-way ANOVA showed an effect of chronotype and disease and interactions ($p = 0.0297$) on total retina thickness and photoreceptor layer thickness with late chronotype having significant interactions with disease state ($p = 0.0011$). Similarly, both schedules reduced a- and b-wave amplitudes in the scotopic ERGs in both control and diabetic mice, with effects of chronotype and disease interactions ($p < 0.001$) in both. Finally, T22.5 (late) has significant impact on the vascular phenotype in diabetic and control mice in contrast to T27 (early) chronotype.

CONCLUSIONS. Overall, a light phase misalignment resembling early or late chronotype is detrimental for retina degeneration with particular effects on the outer retina layers. However, only late chronotype increased was more associated with vascular phenotype characteristic of early diabetic retinopathy.

ELUCIDATING THE ROLE OF PENTRAXIN 3 IN DIABETIC RETINOPATHY

R. Medina[1,3], V. Pathak[1], P. Bertelli[1], E. Pedrini[1], K. Harkin[1], E. Peixoto[1], J. Guduric-Fuchs[1], A. Inforzato[2], B. Bottazzi[2], A. Stitt[1]

[1]Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK
[2]Laboratory of Cellular and Humoral Innate Immunity, Humanitas Research Hospital, Italy
[3]Department for Eye and Vision Sciences, Institute for Life Course and Medical Sciences, University of Liverpool, UK

DESIGN. Basic cellular and molecular study using in vitro and in vivo experimental models.

PURPOSE. To understand the biological relevance of Pentraxin 3 (PTX3) in diabetic retinopathy.

METHODS. The streptozotocin-induced diabetes mouse model was followed up for 9 months. Experimental groups included non-diabetic control and PTX3-KO animals. Retinal tissues were sampled, and high-resolution microscopy used to evaluate reactive gliosis, microglia activation, and vaso-neurodegeneration. Visual function was assessed by electroretinograms. Publicly available transcriptomics data for diabetic retinopathy in humans and mouse were harnessed to identify PTX3 expression. Human cell cultures for endothelial cells, microglia, and macroglia were exposed to PTX3 or TNF, and ELISAs performed to measure inflammatory cytokine release. Mouse retinal explants were also exposed to TNF and Muller gliosis evaluated by microscopy for GFAP staining.

RESULTS. PTX3 protein expression was significantly increased in diabetic mouse retinas when compared to non-diabetic controls at 9-months after diabetes induction ($p < 0.01$). PTX3 localised to the nerve fibre and outer plexiform layers. Analysis of publicly available transcriptomics datasets from human samples revealed that PTX3 expression was significantly increased in retina when both diabetic macular oedema and proliferative retinopathy were present, in comparison to non-diabetic or diabetic samples without complications ($p < 0.01$). Microscopy analysis of mouse retinas indicated significantly lesser vasodegeneration, diminished microglia activation, and Muller gliosis in diabetic PTX3-KO mouse retinas when compared to wildtype littermates. Similarly, greater preservation of visual function was seen in diabetic PTX3-KO mouse when compared to diabetic wildtype mice, as shown by the higher b wave amplitudes in electroretinograms ($p < 0.05$). Human retinal macroglia cultures responded to PTX3 treatment by releasing IL6 and PAI1. In addition, retinal explants from PTX3-KO mouse exhibited less reactivity to TNF treatment than wildtypes, as demonstrated by the lack of GFAP upregulation. Taken

together, our findings indicate that PTX3 facilitates the development of diabetic retinopathy.
CONCLUSIONS. PTX3 enhances sterile inflammation in diabetic retinopathy.

NDR2 KINASE REGULATES MICROGLIAL CELLS IN DIABETIC RETINOPATHY

H. Léger[1,2] H.M. Léger[1,2,3], B. Fazendeiro[1,2], A.F. Ambrosio[1,2,3], P.F. Martins dos Santos[1,2,4]

[1]Center for Innovative Biomedicine and Biotechnology (CIBB), Universidade de Coimbra, Coimbra, Portugal
[2]Coimbra Institute for Clinical and Biomedical Research (iCBR), Universidade de Coimbra, Coimbra, Portugal
[3]Associacao para a Investigacao Biomedica e Inovacao em Luz e Imagem, Coimbra, Coimbra, Portugal
[4]Department of Life Sciences, Universidade de Coimbra, Coimbra, Portugal

DESIGN. Ex vivo and in vivo study aimed at evaluating the role of Ndr2 in microglia in diabetic retinopathy.
PURPOSE. Diabetic retinopathy is a chronic inflammatory disease. Recent studies have demonstrated the importance of the Hippo pathway in inflammation. Ndr2 (Stk38L) kinase is known to regulate the IL-17-dependent inflammation in macrophages, immune cells that share similarities with microglial cells. However, the role of Ndr2 kinase on microglial inflammatory response and in the pathophysiology of the diabetic retinopathy awaits to be uncovered. We hypothesize that Ndr2 kinase negatively regulate oxidative stress-induced inflammation mediated by microglial cells in the context of diabetic retinopathy.
METHODS. Ndr2 levels were quantified from the retina of streptozotocin (STZ) induced diabetic mice, and from cultures of BV-2 microglia cells exposed to high glucose (HG) conditions (30.5 mM for 7 h) and to glucose variations (2 times 4 h HG separated by 4 h in normal glucose - 5.5 mM, called 12 h assay). Ndr2 KO BV-2 were generated by introducing frame shift mutations into exon 6, utilizing CRISPR-Cas9 method.
The Ndr2 deleted microglial cells response to HG conditions was assess by measuring the expression of secreted cytokines (flow-cytometry and cytokine array), their phagocytosis efficiency of fluorescent microbeads, their migration rate and their metabolic (resazurin assay) and proliferative (Edu staining) capabilities.
RESULTS. Ndr2 expression in BV-2 is downregulated after exposure to glucose variation and in the OPL, a layer rich in synapses of STZ-induced diabetic mice retina. The deletion of Ndr2 kinase limits the metabolic capability, the phagocytosis efficiency and migration rate of microglial cells exposed to HG. Ndr2 deletion induces an increased secretion of IL-17, IL-6, MCP1 and TNF while inhibits the secretion of sTNFRI, MCP5 and VEGF.
CONCLUSIONS. Ndr2 expression is affected in hyperglycaemia conditions and diabetic retinas. Ndr2 deletion seems to affect the cytoskleton-based functions of the microglial cells (phagocytosis, migration) and is sufficient to limit the adaptability of the microglial cells to hyperglycaemia as well as to promote an inflammatory response. Altogether, these results suggest that NDR2 is a major player in the inflammation regulation in the pathophysiology of diabetic retinopathy.

AQUEOUS HUMOR PROTEOME ASSOCIATED WITH INCOMPLETE ANTI-VEGF RESPONSE IN DIABETIC MACULAR EDEMA

L. Jørgensen. Cehofski[1], J.A. Cao[2], K. Kojima[3], I. Klaassen[4], B. Honoré[5], H. Vorum[1], C.C. Wykoff[2]

[1]Department of Ophthalmology, Aalborg Universitetshospital, Aalborg, North Denmark Region, Denmark
[2]Retina Consultants of Texas, Houston, TX, USA
[3]Department of Ophthalmology, Kyoto Furitsu Ika Daigaku, Kyoto, Kyoto, Japan
[4]Department of Ophthalmology, Amsterdam UMC Locatie AMC, Amsterdam, Noord-Holland, Netherlands
[5]Department of Biomedicine, Aarhus University, Aarhus, Denmark

DESIGN. Translational study of diabetic macular oedema (DME).
PURPOSE. Incomplete response to anti-VEGF therapy is a substantial clinical challenge in the management of eyes with DME, and underlying intraocular proteome changes remain incompletely defined.
METHODS. Aqueous humour from treatment naïve patients with clinically significant DME ($n = 28$) and age-matched controls ($n = 19$) was collected. Aqueous samples were also collected from DME patients undergoing anti-VEGF therapy having reached their plateau phase and classified as either incomplete anti-VEGF response ($n = 11$), minimal fluid ($n = 8$), or no fluid ($n = 11$). Incomplete response was defined as persistent, clinically meaningful central DME despite adequate anti-VEGF dosing. Best corrected visual acuity (BCVA) was recorded in LogMAR and the severity of DME was assessed as central subfield thickness (CST) by OCT. Proteome analysis by label-free liquid chromatography – tandem mass spectrometry was performed. Proteins were considered significantly regulated if $p < 0.05$ at a false discovery rate at 0.05. A human donor eye with treatment naïve DME and a control eye were used for immunofluorescence.
RESULTS. A total of 891 proteins were identified in the combined set of aqueous samples. Treatment naïve DME was associated with VEGF signalling, inflammatory response, vascular occlusion, hypoxia inducible factor-1 (HIF-1) signalling, complement activation, extracellular matrix-receptor interaction, and glucagon signalling.

Proteomic analysis and ELISA demonstrated high levels of VEGF and proteins involved in monocyte recruitment in untreated DME. In treatment naïve DME, proteins involved in complement signalling correlated with BRVA and CST while proteins involved in maintenance of barrier functions, were downregulated in DME and correlated negatively with CST. Immunofluorescence confirmed an upregulation of proteins involved in vascular occlusion at the retinal level. Samples from patients undergoing anti-VEGF therapy (incomplete response, minimal fluid or no fluid) are being processed.

CONCLUSIONS. The proteome analysis identified multiple proteins from distinct signalling pathways that correlated with disease state and severity. Elevated levels of pro-inflammatory proteins were observed in DME while proteins maintaining barrier integrity were reduced. These data provide insights into DME pathophysiology and potential targets for novel therapeutic approaches.

EFFICACY AND SAFETY OF FARICIMAB IN ALTIMETER: A TRIAL EXPLORING BIOMARKERS OF ANG-2 INHIBITION IN PATIENTS WITH DME

S. Vujosevic[1], M. Amador[2], A. Dieckmann[3], K. Gibson[4], C. Glittenberg[3], A. Kotak[4], F. Mar[2], A. Souverain[3], B. Titz[3], A. Fawzi[5]

[1]Department of Biomedical, Surgical and Dental Sciences, University of Milan; Eye Clinic, IRCCS MultiMedica, Milan, Italy
[2]Genentech, Inc., South San Francisco, CA, USA
[3]F. Hoffmann-La Roche Ltd., Basel, Switzerland
[4]Roche Products Ltd., Welwyn Garden City, UK
[5]Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

DESIGN. ALTIMETER (NCT04597918) was a 6-month, open-label, single-arm, exploratory study that enrolled treatment-naïve patients (aged ≥18 years) with Diabetic Macula Oedema (DME).

PURPOSE. Results from the phase 3 YOSEMITE/RHINE trials (NCT03622580/NCT03622593) support the potential for dual angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF)-A pathway inhibition with faricimab to promote vascular stability and extend treatment durability for diabetic macular oedema (DME). The phase 2b ALTIMETER biomarker hypothesis-generating study explored the associations between clinical endpoints, multimodal imaging assessments, and aqueous humour (AH) biomarker patterns in patients with DME treated with faricimab.

METHODS. Patients received 6 doses of faricimab 6 mg every 4 weeks (Q4 W) with a final visit at day 168. Exploratory endpoints included changes from baseline over time in best-corrected visual acuity (BCVA), central subfield thickness (CST), intraretinal fluid, macular leakage on fluorescein angiography, multimodal imaging, and AH biomarker patterns. Exploratory outcomes were analysed in the modified intent-to-treat (mITT) population, defined as patients who received any amount of study drug. Safety monitoring and assessments were performed during the study.

RESULTS. In total, 99 patients were enrolled and included in the mITT and safety populations; 90.9% (n = 90) completed study treatment. Mean (SD) age was 59.5 (9.8) years and most patients were male (n = 61, 61.6%) and white (n = 86, 86.9%). At week 24, adjusted mean (95% CI) change from baseline in BCVA and CST was +9.2 letters (7.5, 10.9) and −200.2 µm (−214.1, −186.2), respectively. Macular leakage area was reduced following treatment with faricimab, from a median (range) of 28.6 mm2 (1.7–40.4) at baseline to 2.8 mm2 (0–38.6) at week 20. High macular leakage was associated with elevated Ang-2-related proteins and immune regulators at baseline, which were reduced following treatment with faricimab. Faricimab was generally well-tolerated, and safety was consistent with the known safety profile of faricimab.

CONCLUSIONS. At 6 months, Q4 W faricimab injections in ALTIMETER demonstrated meaningful improvements in vision and anatomic outcomes consistent with those in the phase 3 YOSEMITE/RHINE trials. Further exploratory analyses are planned to identify biomarkers of vascular instability that may improve with dual Ang-2/VEGF-A inhibition.

CHARACTERIZATION OF RETINAL CAPILLARY NONPERFUSION IN ADVANCED STAGES OF NPDR

I. Marques[1,2,3], D. Ferrreira[1], T Santos[1], C. Yamaguchi[4], A.R. Santos[1,2,5], E. Pearce[6], J. Cunha-Vaz[1,7]

[1]AIBILI, Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal
[2]CORC, Coimbra Ophthalmology Reading Center, Coimbra, Portugal
[3]University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, Coimbra, Portugal
[4]Boehringer Ingelheim, GmBH, Germany
[5]Department of Orthoptics, School of Health, Polytechnic of Porto, Porto, Portugal
[6]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
[7]Faculty of Medicine, University of Coimbra, Coimbra, Portugal

DESIGN. Non-interventional observational cross-sectional and prospective study.

PURPOSE. To evaluate retinal nonperfusion in eyes with moderate-severe non-proliferative diabetic retinopathy focusing on early treatment diabetic retinopathy study (ETDRS) diabetic retinopathy severity scale (DRSS) levels 43, 47 and 53.

METHODS. Sixty eyes from 60 patients with type 2 diabetes were included in the RICHARD study (NCT05112445). Eyes with DRSS levels 43, 47 and 53 were evaluated at baseline on Optos California (Optos plc, Dunfermline, UK) ultra-widefield fundus fluorescein angiography (UWF-FFA) and swept-source optical coherence tomography angiography (SS-OCTA) (PLEX® Elite 9000, ZEISS, Dublin, CA, USA). Skeletonized vessel density (SVD) and perfusion density (PD) metrics were evaluated in the superficial (SCP) and deep capillary plexuses (DCP). Seven-fields colour fundus photographs using Topcon TRC-50DX camera (Topcon Medical Systems, Tokyo, Japan) were obtained for ETDRS DRSS and complemented with Optos California UWF-fundus photography. Optos California UWF-FFA was performed to calculate the total ischemic index.
RESULTS. The total ischemic index showed an increase in association with DR severity (DRSS43: 2.97 ± 2.61; DRSS 47: 3.69 ± 4.86; DRSS53: 3.95 ± 2.80), but the differences between them did not reach statistical significance. Widefield SS-OCTA SVD metrics showed statistically significant differences in the DRSS severity levels mainly in the DCP in the outer ring and midperiphery. Differences between DRSS 43 and 47 levels were found in the outer ring (SVD and PD: $p = 0.009$). Furthermore, differences between DRSS 43 and 53 levels were found in the outer ring (SVD: $p = 0.013$, PD: $p = 0.010$) and midperiphery (SVD and PD: $p = 0.036$). Our results also showed a correlation between total ischemic index and OCTA metrics, i.e. increasing ischemic index with decreasing SVD and PD, for the midperiphery (Ext2: SVD in SCP: β=-0.314, $p = 0.023$; in DCP: β=-0.286, $p = 0.040$).
CONCLUSIONS. Retinal capillary nonperfusion in eyes with DRSS levels 43, 47 and 53 is well identified by differences in the DCP in the outer ring and retinal mid-periphery, using SS-OCTA. SS-OCTA 15 $\times$ 15 mm acquisitions allow the discrimination between moderate-severe DRSS severity levels, which cannot be achieved by ischemic index determination obtained with UWF-FFA.

IDENTIFICATION OF INTRARETINAL MICROVASCULAR ABNORMALITIES IN EYES WITH ADVANCED STAGES OF NPDR: COMPARISON BETWEEN ULTRA-WIDEFIELD FA, CFP AND OCTA

A.C. Almeida[1,2], M. Lopes[1,2], A.R. Santos[1,2,3], T. Santos[1], D. Ferreira[1], I. Marques[1,2,4], C. Yamaguchi[5], M. Telmo[1], E. Pearce[6], J. Cunha-Vaz[1,7]

[1]AIBILI, Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal
[2]CORC, Coimbra Ophthalmology Reading Centre, Coimbra, Portugal
[3]Department of Orthoptics, School of Health, Polytechnic of Porto, Porto, Portugal
[4]University of Coimbra, Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, Coimbra, Portugal
[5]Boehringer Ingelheim, GmBH, Germany
[6]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
[7]Faculty of Medicine, University of Coimbra, Coimbra, Portugal

DESIGN. Observational cross-sectional analysis.
PURPOSE. To identify intraretinal microvascular abnormalities (IRMA) in non-proliferative diabetic retinopathy (DR) in patients with diabetes with Early Treatment Diabetic Retinopathy Study (ETDRS) severity levels of 43, 47 and 53.
METHODS. Sixty eyes from 60 patients with type 2 diabetes were imaged with seven-field Colour Fundus Photography (CFP) using a Topcon TRC-50DX camera (Topcon Medical Systems, Tokyo, Japan), Optos California (Optos plc, Dunfermline, UK) ultra-widefield fundus fluorescein angiography (UWF-FFA), swept-source optical coherence tomography angiography (SS-OCTA) (PLEX® Elite 9000, ZEISS, Dublin, CA, USA), spectral-domain (SD)-OCTA (CIRRUSTM HD-OCT 5000 Angioplex, Zeiss, Dublin, CA, USA) and SD-OCTA AngioVue (Optovue RTVue, Optovue Inc, CA, USA). A free open-source image editing software tool, Gimp (version 2.10), was used to annotate regions suspicious of IRMA using images from different image modalities. IRMA were first identified in the 50° Field 2 CFP and then searched in UWF-FFA early phase image, in SS-OCTA PLEX Elite (Angiography 15×15 mm acquisition protocol), SD-OCTA Cirrus Angioplex (Angiography 6×6 mm) and SD-OCTA AngioVue (HD Angio Retina 6×6 mm). For OCTA analysis, IRMAS were defined as capillary tortuosity covering a minimum circular area of 300 μm calculated to correspond to ETDRS standard photo 8A.
RESULTS. In OCTA images, IRMAs were identified in both superficial and deep capillary plexuses. In sixty eyes, CFP detected 91 IRMAs in the mid-periphery. SS-OCTA PLEX Elite detected IRMAs in similar number to UWF-FFA but only up to the mid-periphery with SS-OCTA detecting 152 and UWF-FFA detecting 169. However, UWF-FFA is capable of detecting also IRMAs in the far periphery ($n = 234$), showing that IRMA are mainly located in the far periphery. Finally, Cirrus AngioPlex and AngioVue, identified in both plexuses 24 and 27 IRMAs, respectively, in the posterior pole.
CONCLUSIONS. Identification of IRMAS in eyes with moderate-severe non-proliferative DR is better achieved by UWF-FFA as it covers both the mid-periphery and the far periphery. However, nearly similar numbers of IRMAs can be detected by non-invasive imaging using

SS-OCTA PLEX Elite, with the limitations that this analysis is restricted to the posterior pole and mid-periphery.

PERSPECTIVE FOR A CONVERSION MODEL OF OCTA METRICS IN DIFFERENT DIABETIC RETINOPATHY STAGES: ANGIOVUE VS ANGIOPLEX

A.R. Santos[1,2,3], R. Coimbra[1,4], I. Pais[1,5], M. Lopes[1,2], T. Santos[1], C. Yamaguchi[6], I. Marques[1,2,7], E. Pearce[8], J. Cunha-Vaz[1,9]

[1]AIBILI, Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal
[2]Coimbra Ophthalmology Reading Centre, AIBILI, Coimbra, Portugal
[3]Department of Orthoptics, School of Health, Polytechnic of Porto, Porto, Portugal
[4]Department of Mathematics, University of Aveiro, Aveiro, Portugal
[5]Neurology Department, Coimbra University Hospital Centre, Coimbra, Portugal
[6]Boehringer Ingelheim, GmBH, Germany
[7]Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[8]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
[9]University of Coimbra, Faculty of Medicine, Coimbra, Portugal

DESIGN. Exploratory cross-sectional analysis.
PURPOSE. To explore measurements variability between 2 different OCTA devices and to develop a conversion model that translates vascular metrics into a standardized and comparable value in patients with different stages of Diabetic Retinopathy (DR).
METHODS. 101 subjects (n = 196 eyes) with type 2 diabetes (68.1 ± 8.1yrs). Each eye underwent 3 × 3 mm OCTA scans centred at fovea in AngioVue (Optovue RTVue, Optovue Inc, CA, USA) followed by Angioplex (Cirrus HD-OCT 5000, Zeiss Meditec Inc). The binarized Vessel Density (bVD) in the Inner Ring (3 mm ø) was collected from the superficial capillary plexus (SCP) images of both devices. Agreement between AngioVue and Angioplex measurements was assessed by Intraclass Correlation Coefficient (ICC) and Bland-Altman plots. A conversion equation was established to transform bVD values from Angiovue into Angioplex-equivalent values. This equation was built using repeated-measures models with generalized estimating equations to account for the correlation in participants with 2 study eyes, with Angioplex measurement as the dependent variable and AngioVue measurement as the independent variable and adjusted for disease severity level.
RESULTS. Twenty-four eyes with no DR (ETDRS level 10-20), 67 with mild DR (ETDRS level 35), 54 with moderate DR (ETDRS level 43) and 51 with moderate-severe DR (EDTRS level 47-53) were included. Binarized VD values measured by AngioVue were significantly higher than by Angioplex (42.9 ± 4.8% vs 35.6 ± 3.3%; $p < 0.001$). ICC between both devices showed a poor agreement of this metric (0.174 [-0.083, 0.444]). Regarding the conversion model, the following equation was derived: Angioplex bVD = (Angiovue bVD x 0.40) + 18.54. With this equation, 81% of the Angioplex-equivalent bVD values fell within 10% of the real Angioplex measurements. The difference between converted and real values of bVD was less than 8.5 bVD units.
CONCLUSIONS. In this study, we propose a conversion model to obtain comparable bVD measurements in eyes of subjects with diabetes and with distinct levels of ETDRS DR severity. This conversion model may allow to pool bVD data from different OCTA instruments, allowing comparison of results within and between groups in clinical trials using both instruments.

STRUCTURE-FUNCTION CORRELATION IN DIFFERENT GRADES OF DISORGANIZATION OF RETINAL LAYERS IN DIABETIC RETINOPATHY

C. Alovisi[2,4], G. Piccoli[2], M. Brambilla[3], P. Nucci[4], S. Vujosevic[2,4]

[1]Eye Clinic, Ospedale Oftalmico, Turin, Italy
[2]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[3]Department of Medical Physics, University Hospital Maggiore della Carità, Novara, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Retrospective case-control study.
PURPOSE. To evaluate the impact of different grades of retinal inner (DRIL) and outer layers (DROL) disorganization on retinal function in patients with Diabetic Retinopathy (DR) without diabetic macular oedema (DME) using best corrected visual acuity (BCVA), retina sensitivity (RS), and fixation impairment as measured by microperimetry (MP) and correlated with OCT images.
METHODS. A total of seventy-six eyes (65 patients) with DR were examined. Patients with centre-involving DME, significant media opacity, nondiabetic macular pathology and active proliferative DR were excluded. Subjects with DRIL or DROL within the central 3 mm were enrolled as cases, while those with DR without retinal disorganization were enrolled as controls. BCVA and RS were correlated with three different grades of severity in disorganization of retinal layers (1-2-3) using Image J software and specific Image Manipulation Program to co-localize the presence of retina disorganization and RS.
RESULTS. BCVA, mean RS at 1 mm and central 3 mm (overall-oRS) were significantly decreased in cases versus controls ($p < 0.001$). Mean RS at 1 mm (21.4dB ± 2.4 vs 13.8dB ± 5.4; $p = 0.002$), oRS (22.0dB ± 2.1 vs 14.4 dB ±4.6 $p < 0.001$) and BCVA (76.1 ± 7.4 vs 61.2 ± 20.4 ETDRS letters; $p = 0.02$) showed a significant reduction

from disorganisation of retinal layers grade 1 to grade 3. Neither BCVA nor RS were correlated with DRIL/DROL extension or area. A stepwise multiple regression analysis found that oRS was the single significant predictor of the grades of retina disorganization with an adjusted coefficient R2 = 0.32. The eyes with retina disorganisation had more dense scotomas (p = 0 .03) versus controls, with a positive correlation between the worsening of fixation and the severity of the disease (K = 0.36, 95% CI 0.09-0.62).

CONCLUSIONS. In patients with DR, different grades of disorganisation of retinal layers corresponded with varying degrees of functional impairment as measured by BCVA and MP. Greater retinal damage occurred when the outer retinal layers and photoreceptors were involved. The present finding suggests that the identification of the cell types implicated in retina disorganization could be employed as a promising biomarker to assess the functional severity of retinal impairment.

REDISCOVERING THE CLINICAL ROLE OF RETINAL MICROANEURYSMS IN DIABETIC RETINOPATHY: A QUANTITATIVE MULTIMODAL RETINAL IMAGING APPROACH.

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

IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

DESIGN. Cross-sectional, observational study.

PURPOSE. The main aim of the present study is to characterise retinal microaneurysms (MAs) perfusion properties and their blood flow network connectivity by means of dense B-scan (DART) optical coherence tomography angiography (OCTA) technology, checking the relationship with multimodal retinal imaging classification and testing the clinical relevance of MAs quantitative assessment in diabetic retinopathy (DR).

METHODS. The study was designed as cross-sectional, observational investigation. Multimodal retinal imaging included confocal multicolour, OCT, OCTA and DART OCTA. We classified retinal MAs following the recently proposed multimodal retinal imaging classification. We tested the role of DART OCTA for detecting retinal MAs properties and their blood flow network connectivity. We also tested the relationship with clinical and multimodal imaging parameters.

RESULTS. We included 206 retinal MAs (36 DR eyes). Retinal MAs were categorized as red (70; 34%), mixed (106; 51%) and green (30; 15%), corresponding to precise characteristics on confocal multicolour, structural OCT and OCTA scans. DART OCTA provided much details regarding MAs filling patterns. Moreover, it over performed enface OCTA for detecting the blood flow network connectivity of retinal MAs. We detected 23% of retinal MAs totally belonging to superficial capillary network, 29% of retinal MAs showed an afferent superficial capillary and an efferent deeper capillary, and 48% of retinal MAs totally belonged to deeper capillary networks. The multimodal retinal imaging classification showed significant correlations with DR duration, DR stage, and macular capillary non-perfusion.

CONCLUSIONS. DART OCTA provided several new insights on retinal MAs perfusion features and their blood flow network connectivity. The study of retinal MAs quantitative characteristics resulted clinically relevant, paving the basis for the development of new multimodal retinal imaging biomarkers.

DIABETIC RETINOPATHY AS AN INDEPENDENT MARKER OF CARDIOVASCULAR DISEASE IN TYPE 1 DIABETES: RESULTS FROM A 5-YEAR NATIONWIDE, LONGITUDINAL, MATCHED CASE-COHORT STUDY.

J. Grauslund[1,2,3], D.S. Mabala[1,2], N. Andersen[4], J. Andresen[4], T. Bek[5], K. Højlund[2,3], S. Möller[2,6], F.N. Pedersen[1,2], A.S. Thykjær[1,2,3], L. Stokholm[2,6]

[1]Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]Steno Diabetes Centre Odense, Odense University Hospital, Odense, Denmark
[4]Organization of Danish Practicing Ophthalmologists, Copenhagen, Denmark
[5]Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark
[6]Research Unit OPEN, University of Southern Denmark, Odense, Denmark

DESIGN. Nationwide, longitudinal, matched, case-cohort study.

PURPOSE. To investigate diabetic retinopathy (DR) as a potential marker of cardiovascular disease (CVD) in adults with type 1 diabetes attending the Danish DR-screening program and non-diabetes adults.

METHODS. In this registry-based matched case-cohort study, we identified 16,547 adults with type 1 diabetes, who were registered in the Danish Registry of Diabetic Retinopathy (DiaBase). Each case was age- and sex-matched by five non-diabetes individuals (n = 82,399), and odds ratios (OR) and hazard ratios (HR) were estimated for incident and upcoming CVD in multivariable models.

RESULTS. Adults with type 1 diabetes (median age 44.5 years, 57.6% male) were more likely to have prevalent

CVD (OR 1.29; 95% CI, 1.20-1.38) and to develop CVD within 5 years (HR 1.19; 95% CI, 1.08-1.30) as compared to non-diabetes controls. However, patients without DR were less likely to develop CVD (HR 0.84; 95% CI, 0.72-0.97) compared to the reference population. For adults with type 1 diabetes, there was an increasing risk for incident CVD for increasing levels of DR (HR 1.33, 1.95, 1.71 and 2.39 for DR-levels 1-4, respectively). Patients with CVD at the time of the first screening had a higher risk to develop DR during follow-up (HR 1.23; 95% CI, 1.02-1.49).

CONCLUSIONS. In a nationwide matched case-cohort study adjusted for potential confounders, DR was identified as an independent marker of prevalent and 5-year incident CVD in type 1 diabetes with increasing risk demonstrated for higher levels of DR. Likewise, CVD also independently predicted the risk of incident DR.

DEEP LEARNING OF RETINAL IMAGING TO PREDICT CARDIOVASCULAR RISK IN PATIENTS WITH DIABETES

O. Simó-Servat[1,2], R.G. Barriada[3], A. Planas[1], C. Hernández[1,2], D. Masip[3], R. Simó[1,2]

[1]Diabetes & Metabolism Research Unit, Vall d'Hebron Institut de Recerca (VHIR), Spain
[2]CIBERDEM,Instituto de Salud Carlos III, Spain
[3]AIWell Research Group, Faculty of Computer Science, Multimedia and Telecommunications, Universitat Oberta de Catalunya, Spain

DESIGN. Cross-sectional pilot study.

PURPOSE. Diabetes is a major cause of cardiovascular disease (CVD), but not all subjects with diabetes present the same risk. The measurement of coronary artery calcium (CACs) by means of a computed tomography (CT) is postulated as the most sensitive risk stratification tool among asymptomatic persons with diabetes. In this regard it has been well established that a CAC score (CACs) > 400 Agatston Units (AU) identify patients at high risk to develop a cardiovascular outcome. Nevertheless, it is not feasible to screen all diabetic subjects with a CT, and consequently, the identification of a more targeted high-risk population seems warranted. Since diabetic retinopathy (DR) is a risk factor for CVD and retinal fundus imaging is regularly performed in those with diabetes, we wanted to explore whether the use of deep learning architectures (AI algorithm) based on retinal imaging could be useful to predict the presence of CACs > 400 in subjects with type 2 diabetes (T2D).

METHODS. Altogether, 152 retinal images from 76 patients with T2D without prior cardiovascular event were used for the study. CACs was assessed in all patients by CT scan. A total of 33 patients presented a CACs >400 AU, and 43 presented a CACs <400 AU. A convolutional neural network was trained on the retinal images to identify the patients with an increased CAC score.

RESULTS. The results showed that the AI algorithm presents positive predictive values, with an accuracy (positive predictive value) of 0.67 for the left eye and 0.72 for the right eye. Moreover, we assessed the accuracy of clinical data for predicting CACs > 400 AU, being the age and the presence of DR the variables selected. We observed that clinical data and the AI algorithm were complementary and by combining both methods we were able to reduce the false negative and increase the true positives, with an accuracy reaching 0.78.

CONCLUSIONS. This pilot study suggests that AI-deep learning based on retinal imaging could be useful for identifying subjects with T2D at high risk of developing a cardiovascular event.

ASSESSING DIABETIC RETINOPATHY STAGING WITH AI: A COMPARATIVE ANALYSIS BETWEEN PSEUDOCOLOUR AND LED IMAGING

M. Vittoria Cicinelli, S.G. Gravina, C.R. Rutigliani, L.C. Checchin, L. La Franca, R.L. Lattanzio, F.B. Bandello

IRCCS San Raffaele Scientific Institute, Milan, Italy

DESIGN. Cross-sectional investigation.

PURPOSE. To compare the diagnostic performance of AI-based diabetic retinopathy (DR) staging system across Pseudocolour, simulated white light (SWL), and light emitting diod (LED) camera imaging modalities.

METHODS. A cross-sectional investigation involved patients with diabetes undergoing imaging with a confocal LED camera (iCare DRSplus, Centervue, Padua, Italy) and an ultra-widefield camera (Optos, California), with and without SWL. Macula-centred and optic nerve-centred 45 × 45-degree photographs were processed using EyeArt v2.1. Human graders established the ground truth (GT) for DR severity on dilated fundus exam. Sensitivity and weighted Cohen's Kappa (wκ) were calculated. An ordinal generalised linear mixed model identified factors influencing accurate DR staging.

RESULTS. The study included 362 eyes from 189 patients. Referable DR detection accuracy remained robust for Pseudocolour and LED cameras, with notable differences in sensitivity and specificity. The LED camera excelled in identifying sight-threatening DR stages (sensitivity = 0.83, specificity = 0.95 for proliferative DR) and had the highest agreement with the GT (wκ=0.71, asymptotic error = 0.02). The addition of SWL to Pseudocolour imaging resulted in decreased performance. Peripheral lesions significantly reduced the

likelihood (odds ratio = 0.20, $p < 0.001$) of being staged in the same or higher DR category by 80%.
CONCLUSIONS. Pseudocolour and LED cameras, while proficient, demonstrated non-interchangeable performance, with the LED camera exhibiting superior accuracy in identifying advanced DR stages. These findings underscore the importance of implementing AI systems trained for ultra-widefield imaging, considering the impact of peripheral lesions on correct DR staging.

REAL-LIFE APPLICATION OF AUTOMATED DIABETIC RETINOPATHY CLASSIFICATION WITH RETMARKER SCREENING FOR R1/R0 DISCRIMINATION

P. Pereira[1], P.M.M. Pereira[1], J.D. Ramos[1], S. Pinto[1], U. Motresku[1], S. Girolami[2], P. Liguori[2]

[1]Retmarker, Portugal
[2]Meteda, Italy

DESIGN. Retmarker's medical device software has been used in Portugal since 2011 to screen for diabetic retinopathy (DR), a leading cause of blindness. Currently, the software acts as a first grader by identifying referable DR (i.e. vision-threatening DR) in many programmes in Portugal, Italy and others. Retmarker screening contributes for human burden reduction since it filters non-referable exams in a safe way. In 2023, for this purpose, Retmarker launched a new software version built of Deep Learning (DL) algorithms that perform automated classification on the typical colour fundus photographs (CFP) used in DR screening. Knowing that screening programs are considering to differentiate the clinical pathway of non-referable patients, Retmarker team has now developed a complementary model to further discriminate non-referable patients into R0 (no DR) and R1 (NPDR).
PURPOSE. The current study aims to provide early insights and awareness to a real-life application of a new Retmarker screening model as a further discriminating filter in DR screening. It does so by applying the new model in a recent cohort of 8192 exams (each with 4 CFP).
METHODS. Retrospective data from one of the biggest screening programmes employing Retmarker technology were used (with permission) to assess the performance of the new model, which was developed with convolutional neural networks (CNN) and trained on a different dataset. The testing subset comprising the cohort of exams was randomly selected from cases with ophthalmological grading, resulting in a prevalence of 72% for the R0 class.
RESULTS. Applying just the new model, results show that it attains 95.94% sensitivity (disease, i.e. R1 or higher) and 99.71% specificity (no disease, i.e. R0 cases). This translates to a direct accuracy of 98.67%.
CONCLUSIONS. Some potential benefits can be attained with the performance achieved by the new model. Without limiting the capacity to differentiate referable DR (as the conceived model can be applied in sequence), the new model acts as a complement that may bring additional cost savings to the screening programmme if, and only if, clinicians agree on a differentiated clinical pathway between R0 and R1 patients.

DIABETIC RETINOPATHY SCREENING WITH ARTIFICIAL INTELLIGENCE: A PIVOTAL EXPERIENCE IN ITALIAN HEALTHCARE SYSTEM

A. Piatti[1,2], C.B.G. Giorda[2], F.R. Romeo[2]

[1]Eye-Unit, Primary Care, ASLTO 5, Regione Piemonte, Italy
[2]Metabolism and Diabetes Unit, ASLTO 5 Regione Piemonte, Italy

DESIGN. Patients with diabetes were enrolled for a prospective observational study attending their annual visit over a period of 4 months.
PURPOSE. Screening for diabetic retinopathy by ophthalmologists is costly and labour-intensive. Artificial Intelligence tools for automated detection of diabetic retinopathy could be a clinically and economically viable alternative.
We present a report of screening performance (sensitivity, specificity and predictive values) conducted with Artificial Intelligence on patients referring to our department of diabetic disease.
METHODS. In this observational cross-sectional study, 45° retinal images obtained with a confocal, non-mydriatic, fully automatic fundus camera (DRSplus ® Centervue Spa, a company of iCare Finland Oy) were collected from 506 consecutive patients during their annual diabetes check-up. Images were graded by a reading centre consisting of 2 ophthalmologists. Then a digital interface (Illume, iCare Finland Oy) through an AI algorithm (RetCAD Thirona B.V, The Netherlands) graded images according to the International Clinical Diabetic Retinopathy severity scale. Less than moderate retinopathy (DR scores 0, 1) was defined as non-referable, while more severe stages (DR scores ≥ 2) were defined as referable retinopathy. The gradings were then compared both at eye-level and patient-level. Key metrics included sensitivity, specificity, positive and negative predictive value, all measured with a 95% Confidence Interval.
RESULTS. The percentage of ungradable eyes according to the AI algorithm was 2.58%. The performances of the AI algorithm for detecting referable DR were 97.18% sensitivity, 93.73% specificity at eye-level and 98.70% sensitivity and 91.06% specificity at patient-level.

Positive predictive value, indicating the percentage of patients with retinopathy among those with a positive AI result was 95.03%. Negative predictive value was 99.8%.
CONCLUSIONS. RetCAD through the digital interface Illume demonstrated an excellent sensitivity in detecting more than mild retinopathy. In addition, specificity was very accurate. This AI system can improve DR screening and monitoring in people with diabetes, also by non-eye care professionals.

EVALUATING THE DIGITAL SURVEILLANCE PROGRAMME FOR NON-CLINICALLY SIGNIFICANT MACULOPATHY WITHIN DIABETIC RETINASCREEN

I. Brennan[1,2,3], J. Harmon[3], I. Brennan[1], M. Philips[4], A. Combes[3], S. McMahon[3], R. Acheson[1], D. Keegan[1,2], L. O'Toole[1,2], H. Kavanagh[2]

[1]Mater Retina Research Group, Mater Misericordiae University Hospital, Dublin, Republic of Ireland [2]Diabetic RetinaScreen, National Screening Service, Dublin, Republic of Ireland
[3]NEC Care Ireland, Cork, Republic of Ireland
[4]NEC Software Solutions, UK

DESIGN. Retrospective cohort study.
PURPOSE. The Irish National Diabetic Retinal Screening Service, Diabetic RetinaScreen, introduced the digital surveillance (DS) pathway in 2019 to alleviate the strain on hospital based Diabetic Retina Treatment (DRT) services. This pathway monitors patients with maculopathy, excluding clinically significant macular oedema (CSMO), using 45-degree retinal imaging and optical coherence tomography (OCT). Patients referred to DS fall into three categories: (A) R1M1 with VA 6/18 or better from initial screening, (B) R1M1 with VA 6/18 or better transitioning from DRT to DS, and (C) R3S initially referred and then discharged to DS. Our study comprehensively examines patient outcomes and grade transitions in this pathway specifically for patients referred with an R1M1 grade.
METHODS. Patient data from 2021 to 2023 were analysed, focusing on referral criteria. This dataset included initial screening results, VA measurements, and subsequent clinical pathways for each of the eligible patients included (n = 7473). Statistical analysis was performed using Excel and R.
RESULTS. Males comprised 62.2% of the cohort and 79.1% of all patients had Type 2 Diabetes. Our analysis of patient outcomes immediately post first referral identified that 1532 patients (20.5%) were returned to annual screening, 5029 (67.3%) continued in DS, 82 (1.1%) were referred routinely and 22 (0.3%) were referred urgently to DRT centres for management of their diabetic retinopathy (DR). Of those who attended two or more DS appointments (n = 3965), 2399 patients (60.5%) remained within DS with a grade of R1M1, 1377 (34.4%) improved to either R1M0 or R0M0 and were returned to annual recall, 18 (0.4%) were urgently referred to DRT for management of their DR.
CONCLUSIONS. We found that the digital surveillance pathway effectively manages eligible patients with R1M1 retinopathy, emphasising personalised care and efficient resource allocation. It plays a vital role in optimising patient outcomes in DR management within Diabetic RetinaScreen.

DIABETIC EYE SCREENING IN PEOPLE OVER THE AGE OF 90 YEARS

T. Peto[1,2], S. Lengyel[1,3], L. Cushley[1,2]

[1]Queen's University Belfast, United Kingdom
[2]Belfast Health and Social Care Trust, United Kingdom
[3]Peninsula Medical School, Plymouth University, United Kingdom

DESIGN. Retrospective analysis.
PURPOSE. To analyse diabetic retinopathy (DR) severity in people over 90 years old registered on the Northern Ireland Diabetic Eye Screening Programme (DESPNI)
METHODS. All patients registered on the Optomize system over the age of 90 (on 31/12/2023) were analysed by SPSS for demographic, DR, other eye diseases and current screening pathway state.
RESULTS. In total, 11,556 people with diabetes aged over 90 were registered on DESPNI since 2015 (8578 were deceased) with 2978 registered as active. Of those, 62.4% were male with an overall age range of 90-104 (mean of 92; median 91 years old). A majority (89%) had a Type 2 diabetes, only 37 (1%) had Type 1, 10% were unspecified. The mean diabetes duration was 9.75 years and median was 6 years (range 0-94 years). Over 60% had been screened in the last year (2022-2023), 6.3% were screened in 2021, 2.8% in 2020 and 9.2% in 2019. Some, (6.6%) had never been screened and 10.8% were screened over 5 years ago. A majority (83.7%) had no DR (57.9%) or had mild non-proliferative DR (NPDR) (25.8%) with 1.4% having some degree of macular oedema as well. Only 1.1% had severe NPDR and 0.1% (5) had active proliferative DR. Over half remained on the screening pathway with 14% on the slit lamp pathway (mostly due to media opacities). A small percentage were in hospital eye services (4.4%) either for diabetic eye disease (1.8% or for other diseases (2.6%). A large proportion of people were deemed medically unfit for screening (20%) and 4% opted out.
CONCLUSIONS. This is a complex patient cohort with multiple co-morbidities. A large proportion cannot attend screening as they are deemed medically unfit, however with handheld cameras and slit lamps, screening could be

completed for these patients. While there are very few people with active proliferative disease within this cohort, many have multiple eye conditions requiring treatment.

ASSOCIATION OF REPERFUSION INCREASE WITH RUNCACIGUAT IN DIABETIC RETINOPATHY MODELS.

Fabio Baschiera[1], Elia J Duh[1], Carsten Terjung[2], Peter Sandner[2], Kai Riecke[2], Neil Bressler[3]

[1]Bayer AG, Basel, Switzerland
[2]Bayer AG, Wuppertal, Germany
[3]John Hopkins School of Medicine, Baltimore, MD, USA

DESIGN OF THE STUDY: The presented study concerns the preclinical stage of runcaciguat development.
PURPOSE: Diabetic retinopathy (DR) is characterized by clinically visible lesions such as microaneurysms, nerve fiber layer infarcts (cotton-wool spots), blot hemorrhages or lipid (hard exudates). Additionally, increasing evidence points towards substantial retinal neural dysfunctions. To address this, the pharmacological effects of soluble guanylate activator (sGC) runcaciguat were assessed in diabetic retinopathy pre-clinical models.
METHODS: Three pre-clinical models were used: 1) in the rat ischemia-reperfusion model; 2) in rats with streptozocin-induced diabetes the association of an sGC activator with ERG potentials; 3) vessel density in oxygen induced retinopathy (OIR) ischemia model in mice assessed with optical coherence tomography- angiography (OCT-A). In addition, sGC expression in the human retina using immunohistochemical staining was assessed.
RESULTS: Runcaciguat was associated with improved OKT spatial frequency (a measure of visual function) and ERG b wave amplitude (a measure of neuroretinal function). Similarly, runcaciguat was associated with improved ERG b wave amplitude in the streptozocin-induced diabetes model compared with the vehicle control. In OIR mice, runcaciguat was associated with reduced retinal vasoobliteration and neovascularization in relation to the total retina compared with control OIR mice.
CONCLUSION: Runcaciguat was associated with features likely representing reduced neuroretinal dysfunction and supported the possibility of protective effects on retinal vasculature in ischemic retinal disease animal models. Taking together the effects on retinal vascular perfusion and its protective effects on retinal vasoobliteration, these findings suggest that runcaciguat could represent a potential novel and effective treatment for ischemic retinopathies including diabetic retinopathy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE (NICE) GUIDELINE FOR DIABETIC RETINOPATHY MANAGEMENT AND MONITORING

Philip. Burgess[1], J. Anderson[2], A. Bedi[3], R. Creer[4], J. Davey[9], C. Dinah[5], N. Lois[6], D. Shah[7], B. Warren[9], M. Burdon[8]

[1] University of Liverpool, Liverpool, UK
[2]Homerton University Hospital, UK
[3]Royal Wolverhampton NHS Trust, UK
[4]Manchester Royal Eye Hospital, UK
[5]Central Middlesex Hospital UK
[6]Queens University Hospital, Belfast, UK
[7]Western Eye Hospital, UK
[8]University of Birmingham Teaching Hospitals, UK
[9]National Institute for Health and Care Excellence (NICE) Diabetic Retinopathy Guidelines Committee

DESIGN. Clinical guideline produced by an expert committee informed by systematic reviews of best evidence and health economic analyses.
PURPOSE. The guideline covers diagnosis, management and monitoring of diabetic retinopathy (DR) in hospital eye services in England and Wales. Recommendations apply to people with non-proliferative DR (National Diabetic Eye Screening Programme Grade R2), proliferative DR (R3) and diabetic macular oedema (DMO)(M1).
METHODS. The scope of the guideline was defined following a public consultation of registered stakeholders. The committee was composed of consultant ophthalmologists specialising in medical retina and vitreoretinal surgery, a consultant diabetologist, a general practitioner, an optometrist, a specialist nurse, an eye clinic liaison officer and 2 lay members (JD and BW). Bespoke evidence reviews and health economic analyses were conducted by specialist teams. 13 committee meetings were conducted between April 2022 and December 2023. Structured discussions were chaired by a consultant ophthalmologist experienced in clinical guideline development.
RESULTS. Evidence-based recommendations focus on: systemic management for people with DR and DMO; cataract surgery for people with DR or DMO; non-proliferative DR monitoring frequencies; proliferative DR and DMO. The guideline also contains recommendations for research and text detailing rationale for recommendations, impact and context. The final draft guideline was subject to public consultation.
CONCLUSIONS. This guideline applies to health professionals and National Health Service care providers in England and Wales. It is a useful resource for experts developing guidance in other countries.

MANAGEMENT OF VITREOUS HEMORRHAGE IN PROLIFERANT DIABETIC RETINOPATHY

M Cristina Savastano[1,2], C. Rizzo[1], C. Fossataro[1,2], S. Rizzo[1,2,3]

[1]Ophthalmology Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy
[2]Ophthalmology Unit, Catholic University of the Sacred Heart, Rome, Italy
[3]Consiglio Nazionale delle Ricerche (CNR), Istituto di Neuroscienze, Pisa, Italy

DESIGN. Review.
PURPOSE. To report the efficacy of intravitreal injections (IVI) of anti-VEGF (vascular endothelial growth factor) and of pars plana vitrectomy (PPV) in vitreous haemorrhage due to proliferative diabetic retinopathy (PDR).
METHODS. A search of the scientific literature was performed on Pubmed and MEDLINE using the following keywords: "vitreous haemorrhage", "anti-VEGF", "pars plana vitrectomy", "proliferative diabetic retinopathy".
RESULTS. Few studies in the current literature have compared anti–VEGF IVI and PPV to treat PDR-related vitreous haemorrhage. Antoszyk et al. reported no statistically significant difference in term of visual acuity, although it improved faster in case of PPV. On the other hand, the recurrence rate of vitreous haemorrhage was remarkably higher in case of IVI. Similar outcomes were reported by Quiroz–Reyes et al., who also observed no statistically significant difference in intra- or postoperative complications among the two procedures.
CONCLUSIONS. In view of the scarce difference in complication rates, IVI could be considered an appropriate treatment choice in terms of visual outcomes. On the other hand, PPV should be preferred in cases requiring faster recovery, especially in patients with one eye.

COMPARISON OF FIVE DIABETIC RETINOPATHY (DR) GRADING SYSTEMS TO SUPPORT REAL WORLD DATA (RWD) STUDIES

N. Shah[1,2], X.C. Chen[2], G.M. Menon[3,4], S.J.T. Talks[5], F.G. Ghanchi[6], G.C.C. Chi[2], Q.Y. Yang[2], D.F. Ferrara[2], T. Peto[7]

[1]Roche Products Ltd, Welwyn Garden City, UK
[2]Genentech, Inc., South San Francisco, California, United States
[3]Frimley Health NHS Foundation Trust, Frimley, UK
[4]NIHR Kent Surrey Sussex Clinical Research Network, UK
[5]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
[6]Bradford Teaching Hospitals NHS Foundation Trust and Bradford Ophthalmology Research Network, Bradford, UK
[7]Centre for Public Health, Queen's University Belfast, Belfast, UK

DESIGN. RWD retrospective analysis (secondary data use/non-interventional/observational study) is currently underway, including patients with the diagnosis of diabetic macular oedema (DME) from four National Health Service (NHS) sites in the United Kingdom (UK).
PURPOSE. Our study objective is to assess the association between anti-VEGF treatment patterns and outcomes, including DR severity, among DME patients by using electronic healthcare record (EHR) data.
DME/DR diagnoses captured in Medisoft (an EHR system) are recorded via different grading systems dependent on clinician preference. To analyse these results, a standardised method of assessing comparability and amalgamating DR grading systems is required.
METHODS. Data were extracted from 2008-2021 from four NHS sites using the Medisoft EHR system. Five DR grading systems (National Screening Committee (NSC), Early Treatment Diabetic Retinopathy Study (ETDRS), American Academy of Ophthalmology/International Clinical Diabetic Retinopathy (AAO/ICDR), Scottish Diabetic Retinopathy (SDRGS) and RCOphth with the addition of one Medisoft adapted grading system, were compared and symmetrised using literature review, current specialist body guidelines (e.g. Royal College of Ophthalmologists [RCOphth]) and expert review. Specifically, comparison of retinopathy, maculopathy and laser (photocoagulation) grading categories was conducted.
RESULTS. Most commonly used grading systems identified were NSC (n = 567,551), ETDRS (n = 263,666), AAO/ICDR (n = 263,639) and modified ETDRS Medisoft grading categories (n = 143,170).
It was possible to standardise all types of retinopathy grading to the NSC (UK preferred) grading system. Maculopathy and laser grading was more heterogeneous between the grading systems with some missing and additional categories identified.
We present a tabular comparison allowing efficient, simple comparison of all of the aforementioned DR grading systems, for example: 53E & 55 (ETDRS/interim ETDRS) = R2 (NSC) = R3 (SDGRS) = R3 (AAO/ICDR) = High Risk (RCOphth).
CONCLUSIONS. Although DR grading systems generally aim to grade disease severity, significant heterogeneity exists between them, which can complicate comparison across studies and datasets. Our method of comparison simplifies transitioning between DR grading systems, allowing more robust analysis of data with different grading systems.

NON-UNIFORM SPATIAL DISTRIBUTION OF MACULAR LESIONS IN TYPE 2 DIABETES

S. Aldington[1], R.R. Holman[2], P.H. Scanlon[1,3], I.M. Stratton[1,4]

[1]Dept. of Ophthalmology, Gloucestershire Hospitals NHS Foundation Trust, UK

[2]Diabetes Trials Unit, OCDEM, Churchill Hospital, UK
[3]Harris Manchester College, University of Oxford, Oxford, UK
[4]University of Southampton, UK

DESIGN. Computer-assisted annotation and analysis of peri-macular lesions from retinal photographs.
PURPOSE. To record and report the location and spatial distribution of retinal lesions in relation to the fovea in patients with type 2 diabetes.
METHODS. Location, type and area of retinal lesions from 1338 digitised macular–centred images in 747 people were quantified using an on-screen recording tool. Location data of microaneurysms (MA), blot haemorrhages (BH), hard exudates (HE) and IRMA from all images (right and left eyes superimposed) were summated to produce distribution data and density maps.
RESULTS. Temporal, superior, nasal and inferior quadrants (centred on the fovea) contained 41%, 22%, 19% and 18% respectively of all MA; 41%, 23%, 15% and 21% of all BH; 49%, 25%, 12% and 14% of all HE and 64%, 15%, 5% and 16% of all IRMA. HE distribution showed an area of high density superior-temporal to the fovea which was not found in the other lesions analysed.
CONCLUSIONS. The distribution of macular field lesions is not uniform. For MA, BH and HE the greatest density is in the region temporal to the fovea, particularly along the horizontal watershed. This unequal spatial distribution may provide new data on diabetic macular physiology and future risk of reduced visual acuity.

POSTER SESSIONS

SUSPENDED SCATTERING PARTICLES IN MOTION (SSPIM) IN DIABETES MELLITUS

A. Coletto, P. Magnano, A. Rossi, F. Ricardi, F. Gelormini, P. Marolo, M. Reibaldi, E. Borrelli

City of Health and Science Hospital, University of Turin, Turin, Italy

DESIGN. Observational, prospective study.
PURPOSE. SSPiM can be described as the presence of simulated blood flow within the fluid in the retina. The aim of this study was to explore whether the presence of SSPiM on OCTA in patients with diabetes with diabetic retinopathy and DME is associated with worse levels of systemic biochemical parameters.
METHODS. Fifteen patients with DR and DME who showed SSPiM and fifteen patients with no evidence of SSPiM were enrolled in this study. OCT, OCTA, HbA1c, glycemia, cholesterolemia, triglycerides, creatininaemia, microalbuminuria, and systolic and diastolic blood pressure were collected for all patients. Inclusion criteria were age of 18 years or older and the presence of diabetic retinopathy and DME; any other retinal diseases, history of laser treatment within the macula, previous refractive surgery were exclusion criteria.
RESULTS. The mean age of patients with SSPiM was 67.5 ± 10.2 years, 69.3 ± 12.2 years in patients without SSPiM. Among patients with SSPiM, 3 out of 15 eyes (20%) had mild nonproliferative DR (NPDR), 5 out of 15 (33.3%) had moderate NPDR, 6 out of 15 (40%) severe NPDR, and 1 out of 15 (6.7%) proliferative DR,; in patients without SSPiM 2 of 15 had mild NPDR (13.3%), 7 of 15 had moderate NPDR (46.7%), 4 of 15 had severe NPDR (26.7%) and 2 of 15 had evidence of proliferative DR (13.3%). We analysed a statistically significant difference in microalbuminuria and in serum creatinine between the two groups. There was no statistically significant difference between the groups for HbA1c, glycaemia, cholesterolaemia, triglycerides and systolic and diastolic blood pressure, despite higher values in patients with SSPiM.
CONCLUSIONS. The presence of SSPiM on OCTA was significantly related with higher levels of microalbuminuria and creatininaemia. Our results may suggest that the presence of SSPiM may also reveal a worse systemic vascular condition. New studies are desirable to better understand OCTA role in systemic diabetes evaluation.

COMPARING AI-BASED EYEART® AND OPHTHALMOLOGIST ASSESSMENT OF DIABETIC RETINOPATHY IN MINORITY WOMEN: A PILOT STUDY OF THE FIRST USE OF AI IN OSLO, NORWAY

M. Karabeg[1,2], B.E. Petrovski[1,2,8], G. Petrovski[1,2,3,4], I-B.K.Haugen[6], M.C. Moe[1,2], S.N.W. Hertzberg[1,2], M.G. Erke[2], D.S. Fosmark[2], G. Russell[5], J. Sokolovska[7]

[1]Center for Eye Research and Innovative Diagnostics, Department of Ophthalmology, Institute for Clinical Medicine, University of Oslo, Oslo, Norway
[2]Department of Ophthalmology, Oslo University Hospital, Oslo, Norway
[3]Department of Ophthalmology, University of Split School of Medicine and University Hospital Centre, Split, Croatia
[4]UKLONetwork, University St. Kliment Ohridski-Bitola, North Macedonia
[5]Eyenuk Inc., Clinical Development, Woodland Hills, CA, USA
[6]Norwegian Association of the Blind and Partially Sighted, Oslo, Norway
[7]University of Latvia, Faculty of Medicine, Riga, Latvia
[8]Institute of Endocrinology, Lithuanian University of Health Sciences, Kaunas, Lithuania

DESIGN. Pilot study.
PURPOSE. To detect diabetic retinopathy (DR) in a cohort of minority women with DM in Oslo, Norway, who have the highest prevalence of diabetes mellitus (DM) in the country, using both manual (ophthalmologist) and autonomous (AI) – grading, and compare the two

settings for their economic costs. This is the first study in Norway, as far as we know, that uses AI in DR-grading of retinal images.

METHODS. On Minority Womeńs Day, 1st November, 2017, in Oslo, Norway, 33 patients (66 eyes) over 18 years of age diagnosed with DM (T1D and T2D) were screened. The Eidon - true color confocal scanner (CenterVue, United States) was used for retinal imaging and the images were graded for DR by an ophthalmologist and also by EyeArt Automated DR Detection System, version 2.1.0 (EyeArt, EyeNuk, CA, USA). The gradings were based on the International Clinical Diabetic Retinopathy (ICDR) severity scale (1) detecting the presence or absence of referable DR. Cost-minimisation analyses were performed for both grading methods.

RESULTS. 33 women (64 eyes) were eligible for the analysis. A very good inter-rater agreement was found: 0.98 ($P < 0.01$), between the human and AI-based EyeArt grading system. The prevalence of DR was 18.6% (95% CI: 11.4-25.8%), and the sensitivity and specificity were 100% (95% CI: 100-100% and 95% CI: 100-100%), respectively. The cost difference for AI screening compared to human screening was $143 lower per patient (cost-saving) in favour of AI.

CONCLUSIONS. Our results indicate that The EyeArt AI system is both a reliable, cost-saving, and useful tool for DR grading in clinical practice.

IDENTIFICATION OF ACTIVE PROLIFERATIVE DIABETIC RETINOPATHY: A PRELIMINARY TEST OF A DEEP-LEARNING MODEL

S. Dinesen[1,2], L.S. Stokholm[3], Y. S. Subhi[2,5], J.K.H.A. Andersen[4], T.R.S. Savarimuthu[4], T. Peto[6], J.G. Grauslund[1,2]

[1]Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]Open Patient Data Explorative Network, Department of Clinical Research, University of Southern Denmark and Odense University Hospital, Odense, Denmark
Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark
[4]The Maersk Mc-Kinney Moller Institute, University of Southern Denmark, Odense, Denmark
[5]Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark
[6]Centre for Public Health, Queen's University Belfast, Belfast, UK

DESIGN. A register-based observational study.

PURPOSE. Distinguishing between active and inactive level 4 diabetic retinopathy (DR) cases on the International Classification of Diabetic Retinopathy (ICDR) scale is diagnostically imperative. We aim to conduct a preliminary test of a deep learning (DL) models diagnostic accuracy for detecting active retinal new vessels among patients with proliferative diabetic retinopathy (PDR).

METHODS. We included 2,816 retinal images from patients with type 1 or 2 diabetes that were citizens of the Funen Region and attended the Danish screening program for DR. The retinal images, classified as ICDR level 4, originated from The Funen Diabetes Database. A certified grader manually dichotomised images into either inactive ($n = 2,196$) or active ($n = 620$) PDR as a gold standard evaluation. Afterwards, we tested our pre-established DL model, which is capable of segmenting eight different DR lesions and classifying DR according to the ICDR scale (0 to 4), on the same set of retinal images. We considered a retinal image graded as active PDR if the DL model marked at least one lesion as a neovascularization or a pre-retinal bleeding, and then calculated the sensitivity and specificity using the certified grader as the reference.

RESULTS. The certified grader identified active PDR in 620 cases (22%) and the DL model identified 1,756 cases (62%) out of a total of 2,816 retinal images with ICDR-level 4. Testing the DL model for detection of active PDR resulted in a sensitivity of 86%, a specificity of 44%, a positive predictive value of 31% and a negative predictive value of 92%.

CONCLUSIONS. The DL model demonstrated a noteworthy sensitivity of 86%, emphasizing its potential to identify a large proportion of the true positive cases. However, the lower specificity of 44% indicates a higher rate of false positive cases, but the DL model did on the other hand demonstrate a negative predictive value of 92%, indicating its proficiency in correctly identifying cases without active PDR.

RELIABILITY OF UWF COLOUR FUNDUS PHOTOGRAPHY IN DIABETIC RETINAL NEOVASCULARIZATION IDENTIFICATION COMPARED TO UWF FLUORESCEIN ANGIOGRAPHY

R. Mahmoud[1], R.A. Mahmoud[1,2], R.G. Estawro[1]

[1]Watany Eye Hospital, Cairo, Egypt
[2]Faculty of Medicine, Aiin Shams University, Cairo, Egypt

DESIGN. Retrospective cross-sectional observational study.

PURPOSE. To assess the efficacy of ultrawide field fundus photography (UWF-FP) in detecting neovascularization associated with diabetic retinopathy, with a comparative analysis against ultrawide field fluorescein angiography (UWF-FA) images.

METHODS. We conducted a retrospective analysis of patients diagnosed with proliferative diabetic retinopathy at Watany Eye Hospital between August 2023 and December 2023. Inclusion criteria comprised individuals who underwent both UWF-FP and UWF-FA on the same day. Exclusion criteria included eyes with prior retinal photocoagulation or intravitreal injections within the preceding 3 months. Neovascularization was independently identified by two graders using UWF-FP and UWF-FA, with classification into three distinct areas: neovascularization on the disc (NVD), mid-periphery (NV-MP) within 10 mm of the fovea centre, and far periphery (NV-FP) located beyond 10 mm from the fovea centre.
RESULTS. Our study included 100 eyes from 62 patients, with an age range of 22 to 83 years (average age: 53.98 ± 11.84). Among these, 53 patients had type II diabetes mellitus, and 9 had type I diabetes mellitus. The identification rates of neovascularization on UWF-FP compared to UWF-FA were as follows: NVD (85.7%), NV-MP (90.3%), and NV-FP (57.7%).
CONCLUSIONS. Ultrawide field fundus photography (UWF-FP) emerges as a valuable tool for the identification of neovascularization associated with diabetic retinopathy within the disc and mid-peripheral retina. However, UWF fluorescein angiography (UWF-FA) remains the preferred modality for a more reliable assessment, particularly in the detection of neovascularization in the far periphery.

OCULAR SURFACE IN PATIENTS WITH TIPE 2 DIABETES MELLITUS

T. Zhmud[1], G. Drozhzhyna[2]

[1]National Pirogov Memorial Medical University, Vinnytsia, Ukraine
[2]SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine, Ukraine

DESIGN. Diabetes mellitus is associated with increased risk of ocular surface diseases in elderly. We consider neutrophil CD15 as a potential marker of ocular surface damage in T2DM patients.
PURPOSE. We aimed to evaluate expression of neutrophil CD15 and correlate it with results of conjunctival impression cytology and routine objective anterior ocular surface tests (TMH, NIBUT, LLT, MGD) in T2DM patients.
METHODS. We prospectively enrolled sixty T2DM patients (120 eyes) into a study group. The control group included forty (80 eyes) age- and sex-matched almost healthy individuals. All patients underwent comprehensive ophthalmological examination, namely, tear meniscus height test (TMH), non-invasive tear break-up time (NIBUT), lipid layer thickness (LLT), Meibomian gland dysfunction (MGD), conjunctival impression cytology (CIC) and expression of CD15.
RESULTS. Abnormal Nelson's grades of squamous metaplasia (grades 2 and 3) were observed in 50% (60 eyes) of the study group, and 13.75% (11 eyes) of the control group. Fifteen patients with T2DM suffered from grade 3 squamous metaplasia. Nelson's grades of squamous metaplasia have shown a positive correlation with the level of CD15 expression either in the study and control groups ($rs = 0.628$, $p=<0.0001$; $rs = 0.746$, $p<0.0001$; respectively). In addition, in 15 (12%) cases, cytological examination revealed signs of an inflammatory process in the conjunctiva. These samples contained elements of inflammatory infiltration, mainly in the form of neutrophils, which characterises an acute process.
CONCLUSIONS. Increased CD15 in the peripheral blood is associated with the development of squamous metaplasia and may be used to evaluate the severity of ocular surface damage in T2DM patients.
Patients with inflammatory infiltration of the conjunctiva, preparations with hyaluronic acid + low-concentration steroids, in particular hydrocortisone 0.001%, were used.

MICROVASCULAR CHANGES IN EYES WITH NON PROLIFERATIVE DIABETIC RETINOPATHY WITH OR WITHOUT MACULAR MICROANEURYSMS: AN OCT-ANGIOGRAPHY STUDY

C. Toma[1,2], E. Cavallari[1], P. Varano[1], V. Gatti[1], D. Ferrante[3], E. Torti[4], A. Muraca[1], S. De Cillà[1,2]

[1]University Eye Clinic, University Hospital Maggiore della Carità, Novara, Italy
[2]Department of Health Sciences, University of Eastern Piedmont "A. Avogadro", Novara, Italy
[3]Department of Translational Medicine, University of Eastern Piedmont "A. Avogadro", Novara, Italy
[4]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Pavia, Italy

DESIGN. A prospective cross-sectional comparative case-control study.
PURPOSE. To evaluate and compare different quantitative non-invasive retinal biomarkers of microvascular impairment and neurodegeneration in patients affected by mild and moderate non proliferative diabetic retinopathy (NPDR) with or without micronaneurysms (MAs) involving the central 3 mm of the macula.
METHODS. Sixty-three consecutive eyes with NPDR, 28 with no central MAs (noMA-group) and 35 with central MAs (MA-group), underwent a complete eye examination, colour fundus photography (EIDON, CenterVue, Padua, Italy), and swept source OCT/OCT-A (DRI OCT Triton plus, Topcon Medical Systems Europe, Milan, Italy). Main exclusion criteria were: any ocular disease other than mild/moderate NPDR, concomitant diabetic macular edema (DME), and poor image quality. Thickness of

central macula, retinal nerve fibre layer (NFL), ganglion cell layer(GCL+) and NFL + GCL + (GCL++) was evaluated on OCT. On 3 × 3 OCT-A slabs of superficial and deep capillary plexuses (SCP/DCP): FAZ area, perimeter and circularity index (ImageJ); perfusion and vessel density (PD/VD) and fractal dimension (FD) (MATLAB). All evaluations were performed on the full image and after subdivision in 4 quadrants (superior, temporal, inferior, and nasal). Statistical analysis was performed using Mann–Whitney U test.

RESULTS. In the MA-group, 53 MAs were detected (13 in the SCP, 23 in the DCP, and 17 involving both SCP and DCP). The MA-group showed increased FAZ area and perimeter in the SCP ($p = 0.049$ and $p = 0.023$); reduced VD in the SCP ($P = 0.006$); and reduced PD, VD, FD in the DCP ($p = 0.016$; $p = 0.006$; $p = 0.007$) compared with the noMA-group. No other significant differences have been detected after subdivision in the 4 quadrants. No differences have been detected in OCT parameters.

CONCLUSIONS. The presence of central MAs seems to be associated with more pronounced macular microvascular impairment in the initial stages of DR. An explanation may be that ischemia, possibly due to the loss of small terminal vascular branches, could drive MA formation in the macula of eyes with DR. Further, larger studies are needed to better understand the relationship between MAs and macular ischemia and their correlation with DME development.

ANALYSIS OF THE CORNEAL SUB-EPITHELIAL NERVE PLEXUS IN PATIENTS WITH DIABETES WITH AND WITHOUT DIABETIC RETINOPATHY

D. Musetti, M.S. Iglesias, R. Rosa, R. Scotto, M. Nicolò

IRCCS Ospedale Policlinico San Martino, Di.N.O.G.Mi Università di Genova, Italy

DESIGN. Single centre, case-control observational study.

PURPOSE. To evaluate the corneal sub-basal nerve plexus in patients with diabetes with and without diabetic retinopathy by in vivo confocal microscopy (IVCM) and to investigate possible alterations associated with the disease.

METHODS. Forty-six patients with diabetes aged between 30-60 years and 23 age-matched controls were recruited from our clinic and underwent IVCM (Heidelberg Retinal Tomography III with Rostock Cornea Module, Heidelberg Engineering, Heidelberg, Germany) by the same expert operator.

Corneal nerve fibre length (CNFL), corneal nerve fibre density (CNFD), corneal nerve branch density (CNBD), corneal nerve fibre area (CNFA), corneal nerve fibre width (CNFW), corneal fibre total branch density (CTBD), and corneal fibre fractal dimension (CNFrD) were measured.

Risk factors for diabetes complications (blood pressure, BMI, HbA1c, triglycerides) were recorded.

RESULTS. The data analysis showed statistically significant differences ($p < 0.05$) between patients with diabetes and healthy subjects for all measured parameters except the average nerve fibre thickness (CNFW).

The global average length (CNFL) and the average number of points branches on the main fibres (CNBD) were lower in subjects with diabetes than controls ($p < 0.05$). The Fractal Dimension (CFracDim) demonstrated a significant increase ($p < 0.05$) of nerve fibre tortuosity in participants with diabetes compared to controls.

The mean nerve fibre density (CNFD) and the mean total nerve fibre area (CNFA) were lower in patients with diabetes than controls ($p < 0.05$) in all corneal sectors except the central one.

CONCLUSIONS. Our data showed significant changes of the corneal sub-basal nerve plexus in patients with diabetes as compared with normal controls.

RETINAL HYPERREFLECTIVE FOCI (HF) AND THEIR AUTOMATIC DETECTION ON OPTICAL COHERENCE TOMOGRAPHY (OCT) THROUGH ARTIFICIAL INTELLIGENCE (AI)

C. Limoli[1], G. Piccoli[2], E. Torti[3], M. Gazzoni[3], P. Nucci[4], S. Vujosevic[2,4]

[1]University of Milan, Milan, Italy
[2]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[3]Laboratory of Custom Computing and Programmable Systems, Department of Electrical, Computer and Biomedical Engineering, Università degli Studi di Pavia, Pavia, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Comprehensive narrative review.

PURPOSE. HF in OCT scans are emerging as potential biomarkers for neuro-retinal inflammation in diabetic retinopathy (DR)/ diabetic macular oedema (DME) and could hold promise for improving the personalized management of DR. An accurate segmentation technique for identifying HRF may hold clinical relevance for predicting visual outcomes and assessing anatomical response to treatment in patients diagnosed with DR/DME. In the last decade, artificial intelligence (AI) has enabled the automatic extraction of measurable biomarkers for personalized disease characterization. Therefore, AI could be employed to automatically analyse HRF through OCT images, enabling together with the evaluation of other DR biomarkers, an

individualised prognosis and management of DR/DME. This study aims to review the AI-based algorithms that can be utilized to automatically analyse HRF through OCT images.

METHODS. The related literature was searched from 2010 to 2023 in PubMed and the Web of Science database.

RESULTS. Eight studies have been conducted on developing AI models for the automated and semi-automated analysis of HF. Approaches based on deep learning, such as neural networks, have yielded superior performance compared to traditional techniques like logistic regression. The studies in this area are predominantly valuable from an informatics standpoint, and only partially scalable to clinical settings. In addition, most models have shown limited efficacy in predicting HF on OCT scans of patients with DME. The inadequacy arises due to the heterogeneous methodology existing in the literature, the absence of standardized and scalable approaches, and the absence of a consensus within the scientific community focusing on this area of research.

CONCLUSIONS. In this review, we highlight the potential utility of AI-driven approaches in enhancing the accuracy of HF prediction in patients with diabetes. To date, there is no consensus on a reliable AI algorithm capable of accurately segmenting HF for practical clinical use in diabetic patients. Further research is needed to assess the optimal methodology and clinical impact of the automated HF quantification in OCT images for an individualized prognosis and management of DR/DME in the real-world setting.

OCT AND OCT-A ASSESSMENT OF PERIPAPILLARY CHANGES AND SYSTEMIC CORRELATIONS IN TYPE 1 DIABETES MELLITUS

G. Li Calzi[1,2], G. Piccoli[1], L.M. Brotto[1,2], S. Ginelli[1,2], S. Caboni[1,2], V. Bucceri[1], E. Cipponeri[2,3], L. Luzi[2,3], P. Nucci[4], S. Vujosevic[1,4]

[1]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[2]University of Milan, Milan, Italy
[3]Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS MultiMedica, Sesto San Giovanni, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Retrospective cross-sectional study.

PURPOSE. To assess radial peripapillary capillary metrics and nerve fibre layer (NFL) thickness in patients with Type 1 Diabetes Mellitus (DM), with and without clinical signs of diabetic retinopathy (DR) and correlate these findings with systemic microvascular damage parameters.

METHODS. Forty-six eyes of forty-six type 1 DM patients were categorized into two groups: no DR (17 eyes) and mild-moderate DR (27 eyes). The study involved comprehensive ophthalmological examinations, Ultra-Widefield colour fundus photos (UWF-CFP) for DR staging, and Optical Coherence Tomography (OCT) with Zeiss Angio Plex Cirrus 6000 to assess peripapillary NFL thickness, macular GCC, and peripapillary perfusion metrics as Perfusion Density (PD) and Flux Index (FI). OCT-A analysis using the radial peripapillary plexus (RPC) slab calculated PD and FI. Systemic microvascular damage parameters (estimated glomerular filtration rate eGFR, fibrosis probability index FIB4, HbA1c, cardiovascular risk percentage CV%, Creatinine Crea) were extracted from electronic clinical records.

RESULTS. The average patient age was 48.8 ± 13 years, with an average diabetes duration of 22 ± 13 years. Of the patients, 91% had no DM complications, 8% had ischemic cardiopathy, and 1% had nephropathy. Statistical analysis revealed no significant correlation between PD, FI, and systemic microvascular damage parameters. However, significant correlations were observed in: macular GCC thinning with eGFR ($p < 0.05$); NFL average thinning with HbA1c and FIB4 ($p < 0.05$); NFL temporal thinning with Crea and eGFR ($p < 0.05$); NFL inferior thinning with FIB4 and HbA1c ($p < 0.05$); NFL nasal thinning with CV% ($p < 0.05$). In the no DR group, temporal NFL thinning correlated with FIB4, HbA1c, and eGFR, while in the DR group, inferior NFL thinning correlated with FIB4 and HbA1c, and nasal NFL thinning correlated with Crea ($p < 0.05$ for all).

CONCLUSIONS. The results suggest early neuroretinal changes in individuals with type 1 DM, in eyes with mild-moderate DR and those without DR, and correlation to systemic microvascular damage parameters. No microvascular peripapillary changes were detected, probably due to a limited sample size. Further exploration is needed to understand the relationship between ocular and systemic markers in diabetic patients.

EFFECTS OF DIABETIC RETINOPATHY ON ANATOMICAL AND FUNCTIONAL CHANGES IN EYES WITH AMD - ASSOCIATED TYPE 1 MACULAR NEOVASCULARIZATION AFTER ONE YEAR OF TREATMENT

L. Landini, P. Viggiano, M.O. Grassi, G. Boscia, R. Buonamassa, G. Alessio, F. Boscia

Università degli Studi di Bari Aldo Moro, Italy

DESIGN. Single centre observational study.

PURPOSE. To evaluate the influence of diabetic retinopathy on functional and anatomical changes in patients with AMD-associated type 1 macular neovascularization.

METHODS. We enrolled forty-six treatment naïve eyes with a diagnosis of exudative AMD and type 1 MNV. Eighteen of the forty-six eyes presented mild diabetic retinopathy, the other thirty-eight were eyes of patients without diabetes.
SD-OCT was performed before the first injection of anti-VEGF therapy (T1) and after one year of treatment with Aflibercept (T2). Central retinal thickness (CRT), height of the pigmented epithelium detachment (PED), presence of subretinal (SRF) or intraretinal fluid (IRF) were considered. Between the same spare of time BCVA was tested.
RESULTS. Non-diabetic eyes showed a reduction in all the considered parameters at T2: CRT ($p < 0.005$) PED height ($p = 0.026$) and BCVA ($p = 0.057$). In diabetic eyes, only CRT showed a significant decrease at T2 ($p = 0.009$) the other parameters were stable. When compared to DR eyes, eyes without DR showed a greater reduction in PED height ($p = 0.039$), CRT ($p = 0.054$) and SRF ($p = 0.036$). We also carried out a predictive analysis on non-diabetic eyes which showed that PED height reduction was correlated to SRF at T1.
CONCLUSIONS. Our analysis revealed that after one year of treatment eyes with type 1 MNV and DR have a poorer response to therapy, both in anatomical and functional terms, than eyes with MNV but without DR.

SPATIAL DISPARITIES IN HEMORRHAGE DISTRIBUTION: EXPLORING VARIATIONS BETWEEN 10MM ON UWF AND 7 ETDRS FIELDS IN DIABETIC RETINOPATHY USING ULTRA WIDEFIELD COLOR FUNDUS PHOTOS.

S. Caboni[1,2], G. Piccoli[2], S. Ginelli[1,2], L.M. Brotto[1,2], C. Limoli[1,2], N. Paolo[3], S. Vujosevic[2,3]

[1]University of Milan, Milan, Italy
[2]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[3]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Retrospective cross-sectional study.
PURPOSE. The aim of the study was to investigate the difference in number of haemorrhages (HEs) allocated in the 10 mm of posterior pole (PP) and in the 7 ETDRS fields, and in the mid and far periphery (> 10 mm and outside of 7 ETDRS fields) on ultra-widefield imaging in patients with diagnosis of moderate and severe non-proliferative diabetic retinopathy (NPDR).
METHODS. 66 eyes of 38 patients with moderate and severe NPDR were included. All patients underwent Ultra-Widefield colour fundus photos (UWF-CFP) with Optos California (Optos, PLC) for the staging of DR severity. With an automatic tool, a mask representing the central 10 mm and a mask representing the 7 ETDRS field were overlapped on the original UWF-CFP. Two graders manually counted the number of HE inside and outside the central 10 mm and inside and outside the 7 ETDRS fields.
RESULTS. There were 16 males and 22 females patients. The mean age was 71 ± 13 years, with 89% having Type 2 Diabetes (DMT2) and 11% having Type 1 Diabetes (DMT1). The mean HbA1c was $9 \pm 2.3\%$. Notably, the median number of HEs within the 10 mm of the posterior pole (PP) was significantly higher compared to the 7 ETDRS fields [8.50 (4.00-16.25) vs. 3.00 (2.00-7.25); $p < 0.0001$]. Conversely, the median number of HEs in areas beyond the 10 mm field was significantly lower compared to those outside the 7 ETDRS fields [8.00 (3.00-15.25) vs. 15.00 (8.00-27.00); $p < 0.0001$].
CONCLUSIONS. This study revealed a significant difference in the number of HEs between the 10 mm and the 7 ETDRS fields. These findings may suggest the importance of UWF-CFP also in the evaluation of the PP and staging of DR. Further research is warranted to explore the clinical /screening implications based on the observed distribution patterns of haemorrhages in diabetic retinopathy.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY ANALYSIS OF CHILDREN WITH DIABETES MELLITUS TYPE 1

J. Vasilijević[1,2], D.R. Risimić[1,2], I.K. Kovačević[1,2], J.J. Jakšić[2], J.Ć. Ćuk[2]

[1]Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2]Clinic for Eye Diseases, University Clinical Centre of Serbia, Belgrade, Serbia

DESIGN. The cross-sectional study.
PURPOSE. The aim of this study is to measure retinal vessel density and flow rate area by optical coherence tomography angiography (OCTA) in children with type 1 diabetes mellitus (T1DM) without diabetic retinopathy.
METHODS. The cross-sectional study included 41 patients divided into two groups. Group I included 30 patients with T1DM, while Group II included 11 age-sex matched healthy subjects. All participants were evaluated using Optovue (Optovue, Inc; Fremont, CA) on a 6.00×6.00 mm macular region, in the central fovea. The foveal avascular zone (FAZ) area, macular vessel density (VD), outer retina (OR) and choriocapillaris (CC) flow rate were analysed. The correlation of these parameters with metabolic factors such as disease duration, mean haemoglobin A1c (HbA1C), body mass index (BMI) and type of treatment was also investigated in the T1DM group.

RESULTS. None of the OCTA parameters was statistically significantly different between the two groups. The patient's age statistically significantly did not influent any of the OCTA parameters. However, the use of insulin analogues tended to reduce the deep perifoveal VD and OR flow rate compared to the use of an insulin pump ($p = 0.011$, $p = 0.024$, respectively). Although patients on insulin analogues had a higher haemoglobin A1c value, this difference was not statistically significant ($p = 0.350$). No correlations were found between the duration of diabetes or HbA1c with changes in OCTA parameters. Yet, an elevated BMI tended to reduce the deep macular ($p = 0.002$), and perifoveal vessel density ($p = 0.003$).
CONCLUSIONS. Vessel density and FAZ area are normal in pubescent children with T1D compared to healthy subjects. Treatment with insulin pump may be a better choice for preventing retinal complications compared with insulin analogue, as insulin pump may be protective against retinal microvascular damage in early diabetic retinopathy stages. The role of OCTA in patients with T1DM remains to be established in future longitudinal studies.

INTERPLAY BETWEEN OCULAR IMAGING AND SYSTEMIC MARKERS: UNRAVELING CORRELATIONS BETWEEN OCT/OCT-A AND BIOCHEMICAL PARAMETERS IN TYPE 1 DIABETES PATIENTS

L.M. Brotto[1,2], G. Piccoli[1], G. Li Calzi[1,2], S. Ginelli[1,2], S. Caboni[1,2], V. Bucceri[1], C. Elisa[2,3], L. Luzi[2,3], P. Nucci[4], S. Vujosevic[1,4]

[1]Eye Clinic IRCCS MultiMedica, Milan, Italy
[2]University of Milan, Milan, Italy
[3]Department of Endocrinology, Nutrition & Metabolism, IRCCS MultiMedica Sesto San Giovanni, Milan, Italy
[4]Department of Biomedical, Surgical and Dental Science, University of Milan, Milan, Italy

DESIGN. Prospective cross-sectional study.
PURPOSE. To evaluate the correlation between Optical Coherence Tomography (OCT) and OCT-Angiography (OCT-A) parameters and biochemical and haematological parameters in patients diagnosed with type 1 diabetes mellitus (DM1), with and without clinical signs of diabetic retinopathy (DR).
METHODS. 46 eyes of 46 patients with type 1 diabetes (19 without DR [noDR group] and 27 with DR [DR group, mild and moderate DR]) underwent a comprehensive ophthalmologic evaluation, including BCVA, slit-lamp biomicroscopy, and macular OCT/OCT-A. Foveal Avascular Zone (FAZ) area, perimeter and circularity index (CI), vessel density (VD), and perfusion density (PD) were automatically calculated with OCT AngioPlex Cirrus 6000 on 3×3 mm fovea scans on the superficial capillary plexus. Considered biochemical and haematological parameters encompassed HbA1c (%), creatinine (mg/dL), eGFR (mL/min), Time in Range (TIR %), Time Above Range (TAR1, TAR2%), Time Below Range (TBR1, TBR2%), and Fibrosis-4 Index (FIB-4).
RESULTS. There was a significant correlation (ρ) between FAZ CI and eGFR (ρ=0.39, $p = 0.0002$) and creatinine (ρ=-0.23, $p = 0.031$) in both groups. FAZ CI also correlated with FIB-4 in the noDR group (ρ=-0.62, $p = 0.004$). PD correlated positively with TBR2 in the DR group (ρ=0.38, $p = 0.038$) and TBR1 in the noDR group (ρ=0.38, $p = 0.047$). VD showed the most significant correlations, including FIB-4 in the DR group (ρ=-0.36, $p = 0.019$), eGFR (ρ=0.23, $p = 0.027$) in both groups, with negative correlations in the noDR group for both TAR 1 (ρ=-0.37, $p = 0.042$) and TAR 2 (ρ=-0.48, $p = 0.026$). Central Retinal Thickness (CRT) correlated significantly with FIB-4 (ρ=0.61, $p = 0.005$) and eGFR (ρ=-0.47, $p = 0.007$) in the noDR group, while in both groups, correlations were observed with HbA1C (ρ=-0.21, $p = 0.052$) and TBR2 (ρ=0.32, $p = 0.021$).
CONCLUSIONS. There is a significant relationship between the parameters obtained from ocular imaging (FAZ CI, PD, VD) and the biochemical factors associated with diabetes. A well-established correlation exists between CRT and HbA1c; however, changes in this parameter may have a multifactorial origin. Other parameters, such as eGFR, FIB-4 and TBR2, could be assessed in clinical practice as early biochemical indicators of retinal damage.

USING ARTIFICIAL INTELLIGENCE IN DIABETIC EYE SCREENING PROGRAMMES: PERSPECTIVES FROM PEOPLE WITH DIABETES AND SCREENING STAFF IN NORTHERN IRELAND.

L.N. Cushley[1], B. Leonard-Hawkhead[1], T. Peto[1], NIDESP Team[2]

[1]Centre for Public Health, Queen's University Belfast, Belfast, UK
[2]Department of Ophthalmology, Belfast Health and Social Care Trust, Belfast, UK

DESIGN. Qualitative questionnaire.
PURPOSE. To assess perspectives on artificial intelligence (AI) in The Northern Ireland Diabetic Eye Screening Programme (NIDESP) among staff and people with diabetes (PwDM).
METHODS. A questionnaire (available online/paper format) was distributed to all NIDESP staff and PwDM (through charities and patient events). The questionnaire

included questions on knowledge of AI, expectations of using AI in DESP and main concerns. Likert Scale questions were scored from 1- 10, 10 being the highest. Questionnaire responses were entered into Excel. Likert Scale and thematic analysis was undertaken.

RESULTS. In total, 13 NIDESP staff and 13 PwDM responded. NIDESP staff felt implementation of AI would be helpful averaging 7 on the Likert scale. Despite this, NIDESP staff were moderately concerned about AI implementation (average 6). Nearly all (92%), expected AI to help with grading including removing R0M0 grades, allowing more focus on other gradings and taking pressure off grading queues and staff. Staff felt AI would be most useful in primary grading, removing R0M0 s and identifying potentially urgent cases in turn reducing staff pressure, prioritising urgent patient care and standardising grading further. Despite this, 46% stated patient safety concerns, 31% process efficiency concerns and several concerned with losses of personnel.

Eighty-five percent of PwDM knew AI could be used in healthcare. They felt AI could speed up results, take pressure off staff, streamline appointments, and identify eye complications. PwDM also felt it could speed up waiting times and prioritise those in need. Nearly all, 92% were happy for AI to be implemented into DESP but 1 patient stated they preferred a 'human touch'. Four patients expressed concerns surrounding safeguarding their private information and over-reliance on AI.

CONCLUSIONS. PwDM were very positive about implementing AI in DESP, many stating it should be embraced. Staff were overall happy with AI for grading prioritisation and efficiency but had several concerns around patient safety and loss of personnel. It is important when implementing AI into the NIDESP that all opinions are considered, and all stakeholders remain informed.

PRELIMINARY RESULTS FROM A NEW EYE-SCREENING SERVICE IN DODOMA, TANZANIA

C. Jamison[1], J.Y. Mmbaga[2], R. Brennan[3], T. Peto[1]

[1]Queen's University Belfast, Belfast, UK
[2]Benjamin Mkapa Hospital, Dodoma, Tanzania
[3]NHS Highland, Scotland, UK

DESIGN. Descriptive, hospital-based study.

PURPOSE. To determine the prevalence and severity of diabetic retinopathy (DR) and other pathologies in patients with diabetes mellitus (DM) screened during the first 6-months of a new diabetic retinopathy screening programme (DRSP) in Dodoma, Tanzania.

METHODS. In April 2022, the first fundus camera (Optomed Auora handheld non-mydriatic camera) was received at Benjamin Mkapa Hospital, Dodoma, Tanzania. During the launch-week staff were trained to use the camera on site and guided screening commenced in diabetes clinics at Benjamin Mkapa and two other local hospitals. All images were assessed to determine DR prevalence and any other pathologies. Patient eyes were not dilated.

RESULTS. During the first 6-months of DRSP, 166 DM patients were imaged at DM clinics. 20 patients (12%) had ungradable images for both eyes, 3% due to cataract. Of the gradable images, 82 (56%) had no DR, 42 (29%) had mild non-proliferative (NPDR), 18 (12%) had severe NPDR and 4 (3%) had proliferative DR (PDR). Overall; 44% of gradable images had some level of diabetic maculopathy including 3% with PDR; in a developed DRSP the expected ratio is approximately 33% for any DR and 1% for PDR. 58% of patients also had drusen, 4% had cataract, 3% had pigmented scars and 1% had suspected glaucoma.

CONCLUSIONS. The higher rate of disease reflects a screening service in its infancy and the fact that the screened population was from a tertiary diabetes clinic; with increased coverage the prevalence will decrease. The lack of free healthcare for those with Type 2 DM in Tanzania leads to late presentation as DR rarely causes visual loss until it is too late to treat. However, the inception of this DRSP is a vital step towards reducing preventable blindness in the region.

BARRIERS AND ADHERENCE TO DIABETIC RETINOPATHY SCREENING SERVICES AMONG CHILDREN AND YOUNG ADULTS IN BANGLADESH

K. Curran[1,5], M. Ahmed[2], M.M. Sultana[2], L. Cushley[1], T. Peto[1], M.A. Hossain[3], L. Husain[2], B. Zabeen[4,5], N. Congdon[1,3]

[1]Centre for Public Health, Queen's University Belfast, Belfast, UK
[2]Orbis International, Dhaka, Bangladesh
[3]Orbis International, New York, USA
[4]Department of Paediatrics, Life for a Child & Changing Diabetes in Children Programme
[5]Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM), Diabetic Association of Bangladesh, Dhaka, Bangladesh

DESIGN. Cross-sectional study.

PURPOSE. Effective diabetic retinopathy screening (DRS) programmes are key in preventing vision impairment and blindness caused by diabetes. This study focuses on identifying the primary barriers that deter children and young adults with diabetes in Bangladesh from attending DRS.

METHODS. This study used structured questionnaires with closed-ended questions, after refining through a pilot study phase. Participants were enrolled as patients at BIRDEM-2 hospital in Dhaka, Bangladesh, and ethics approval was obtained from the Asian Institute of Disability and Development (AIDD) Research Committee.

Data was collected from July 2019 to July 2020. Participants were categorised into two groups: those attending and those not attending their last DRS appointment. Descriptive analyses and logistics regression were performed to describe the population characteristics and evaluate demographic and clinical variables influencing DRS attendance. All analyses were performed in SPSS.

RESULTS. The study examined 400 participant responses, highlighting demographic variations between attendees and non-attendees to DRS. Attendees had a mean age of 17.7 years (SD:3.8), with 177/343 (51.6%) being females. Non-attendees had a mean age of 19.0 years (SD:3.9), and 14/47 (29.8%) were females. Nearly all participants in both groups were Muslim. Attendees demonstrated a median HbA1c of 8.0 mmol (IQR:2.5), whereas non-attendees showed a slightly higher mean HbA1c of 9.1 mmol (IQR:2.8). Diabetes duration was shorter among attendees, with a median duration of 5 years (IQR:7.0), compared to 8 years (IQR:6.0) in non-attendees. Non-attendees, often older males, frequently mentioned financial constraints, distance, and busy schedules as barriers to DRS. The result of the multivariate analysis shows that female patients were more likely to attend their last DRS appointments ($P < 0.05$).

CONCLUSIONS. The results emphasise the challenges related to DRS attendance in Bangladesh, including distance to hospitals and financial limitations. It highlights a significant gap in research regarding the impact of DRS among young individuals in low- and middle-income countries, stressing the need for further investigation in this area. Further research among disengaged individuals is necessary to address specific challenges comprehensively.

ANALYSIS OF FIRST SCREENING VISITS FOR PREGNANT PATIENTS IN THE INAUGURAL YEAR OF THEIR INTEGRATION WITHIN THE IRISH DIABETIC RETINA SCREENING (DRS) PROGRAMME

C. Rizzo[1], I.B. Brennan[2], D.B. Brad[2], SK. Kelly[1], D.K. Keegan[1], L.O. O'Toole[2], H.K. Kavanagh[2]

[1]Mater Misericordiae University Hospital, Dublin, Ireland
[2]Diabetic RetinaScreen, National Screening Service, Health Service Executive, Dublin, Ireland

DESIGN. Retrospective observational study.

PURPOSE. DRS launched a pathway for those with diabetes who are pregnant to be included in their nationwide diabetic retinopathy (DR) screening programme in 2023. This study specifically aimed to determine the prevalence and severity of DR in patients at the time of their first DRS visit during pregnancy. Additionally, we investigated whether this cohort had previously engaged with DRS.

METHODS. A retrospective observational study including patients invited to the pregnancy screening pathway in DRS from January 2023 to January 2024 was performed. Data collected encompassed patient demographics, gestational age, attendance, the occurrence of miscarriage, new registrations with the DRS, retinopathy grade and outcomes.

RESULTS. A total of 451 pregnant patients with diabetes were referred to DRS, 55 patients did not attend despite multiple invitations, and 3 cancelled/postponed with late notice and 3 attended ophthalmology privately. 61 patients are awaiting their first appointment. The mean age of the 318 patients who attended was 34.8 years (SD $\pm$4.89). At the time of referral, 199 patients were in the first trimester of pregnancy, 76 were in the second trimester, and 41 were in the third trimester. The mean time from referral to the first screening was 31.04 days (SD $\pm$ 29.74). Nineteen patients had miscarried by their first screening, of whom 9 attended first screening, and 7 patients who attended were postpartum. 28.3% of patients were not previously registered with DRS. Half of patients 157 (49.37%) were graded as R0M0, 123 (38.68%) as R1M0/M1, 18 (5.66%) as R2M0/M1, 10 (3.14%) as R3SM0/M1, and 11 (3.45%) R3AM0/M1. Notably, the incidence of R3AM0/M1 is markedly higher than through routine DRS (0.71%).Of the 47 patients referred to the hospital services following their initial visit, the majority, 29 (62%) were for management of maculopathy and the remainder were graded as proliferative DR with or without maculopathy.

CONCLUSIONS. Screening for diabetic retinopathy in pregnancy is crucial for its early detection and to allow timely treatment to prevent permanent visual loss. Further analysis to determine causes of prior patient non engagement with the DRS is warranted.

SCREENING FOR DIABETES RELATED RETINOPATHY IN BERMUDA - AN OBSERVATIONAL STUDY WITH THE BERMUDA DIABETES CENTRE

R. Thomas[1], C. Jamison[2], P. Huhtinen[3], L. Rockhead[4], E. Setzu[4], D. Jones[4], T. Peto[2], D.R. Owens[1]

[1]Swansea University Medical School, Swansea, UK
[2]Queen's University Belfast, Belfast, UK
[3]Optomed, Finland
[4]Bermuda Diabetes Association, Bermuda

DESIGN. Observational study.

PURPOSE. Bermuda has a population of 64,000 people with a prevalence of diabetes of 13%. The cost of living in Bermuda is amongst the highest in the world and have an insurance based system of health care. Consequently people with chronic health issues struggle to afford treatment, being uninsured or underinsured. This study aimed to assess the burden of diabetic retinopathy amongst people with diabetes in Bermuda.

METHODS. People with diabetes mellitus (DM) were invited (social media, posters, radio) to attend free for diabetic

eye-screening at the Bermuda Diabetes Association (BDA), or the Patient-Centred Medical Home (PCMH), King Edward VII Memorial Hospital. Lifestyle and diabetes questionnaires were undertaken, and blood pressure, HbA1c, and BMI determined. Following an eye health history and visual acuity testing (optometrists), eyes were dilated (1% tropicamide) and images taken with Optomed Aurora handheld non-mydriatic cameras. A macula-centred and optic disc-centred image were taken per eye where possible and graded by 2 experienced graders and an adjudicator.

RESULTS. 172 people with diabetes were screened (132 at BDA, 40 at PCMH), 61% were female, 88% had type 2 diabetes mellitus. Mean age was 65.5 years (range 15-89), diabetes duration 13.3 years (1-50), HbA1c 7.6% (5.1-13.1) and BMI 31 kg/m^2 (18-56.3). Of 165 with gradable images; 61% had no signs of DR, 28% had a worst-eye grade of mild non-proliferative DR (NPDR), 4% had moderate NPDR and 7% had proliferative DR. Maculopathy was present in 18%, bilaterally in 11%. Letters were sent to GPs for all attendees. Of the 38 persons with no insurance, 11 (29%) required referral, compared to 23 (18%) of the 126 insured individuals with gradable images.

CONCLUSIONS. This inaugural study provides preliminary but concerning relatively high rates of referable DR in this small cohort of people with diabetes in Bermuda. A more extensive study is required to determine the true prevalence of DR in Bermuda to provide the basis for a structured and systematic screening programme to prevent blindness, particularly in the under- and uninsured.

OPHTHALMOLOGISTS' PERCEPTION AND ACCEPTANCE LEVEL FOR ARTIFICIAL INTELLIGENCE USE WITH DEEP LEARNING MODELS, FOR DIABETIC RETINAL SCREENING IN IRELAND: A PATH FORWARD.

F. Ibrahim

Technological University of the Shannon, Midlands Midwest, Ireland

DESIGN. The mixed-methods approach chosen combined quantitative data with a qualitative approach to understand attitudes and perceptions that are precursors to human actions.

PURPOSE. In Ireland, the current screening service standard diagnoses are still performed by human graders, which led to the question of potential use of deep learning (DL) models. The perspective of ophthalmologists concerning integration of AI in this area is an underreported topic. This aims to fill in the gap in the literature and present ophthalmologists' perspectives on the possibility to align with AI integration, specifically for diabetic retinal screening in Ireland.

METHODS. An expert survey questionnaire used at an ophthalmology conference, followed up with one-to-one qualitative interviews. This approach allowed the researcher to compare views of the questionnaire's respondents with the subject matter experts about the acceptance level and possible integration of Deep Learning models for diabetic retinal screening in Ireland.

RESULTS. Overall, there is low level of knowledge about all the limitations and challenges of using AI/machine learning amongst the respondents of this research. The interviewees are vaguely aware of the emerging EU AI regulations, but none can actually name specific regulations relevant to AI use in healthcare/ophthalmology. These Deep Learning models are considered as high-risk systems by the EU AI Act, however, none of the interviewees are aware of this or the EU civil liability regime for artificial intelligence. There were discussion of possible risk to patients and accountability questions. All the respondents accept considerations of Deep Learning models for diabetic retinal screening as an assisting tool currently, not as an autonomous diagnostic tool without any human oversight. A pathway has been developed to highlight the areas needed to support considerations of any Deep Learning model integration.

CONCLUSIONS. This study explored the first important prerequisite needed: the ophthalmologists' perception and acceptance level of AI use, specifically Deep Learning models for diabetic retinal screening (DRS) in Ireland. A pathway to support AI adoption/integration was formulated from actionable insights to address key considerations such as perceived barriers and challenges.

COMMUNITY BASED DIGITAL SURVEILLANCE SCREENING OF PATIENTS WITH STABLE PROLIFERATIVE DIABETIC RETINOPATHY IN THE IRISH DIABETIC RETINOPATHY SCREENING PROGRAMME.

S. Kelly[1,2,3], J. Harmon[3], M. Philips[4], A. Combes[4], S. McMahon[3], R. Acheson[1], D. Keegan[1,2], L. O'Toole[2,3], H. Kavanagh[2]

[1]Mater Retina Research Group, Mater Hospital, Dublin, Ireland
[2]Diabetic RetinaScreen, National Screening Service, Dublin, Ireland
[3]NEC Care Ireland, Cork
[4]NEC Software Solutions, UK

DESIGN. Retrospective cohort study.

PURPOSE. Until recently, Diabetic RetinaScreen (DRS) patients with proliferative diabetic retinopathy (DR) were retained in one of the eight treatment centres (TCs) in Ireland. Patients often lived a significant distance from these centres, and coupled with many frequent diabetes related appointments made DR treatment a burden. The digital surveillance (DS) pathway moves these appointments closer to where patients live, for those that have stable proliferative DR. In addition it reduces the burden on the acute hospitals. This project examines the early results of this programme.

METHODS. Data of patients who were discharged from TCs into DS from its inception in April 2022 were recorded. These data included information on age, diabetes type, duration of diabetes and DR grade. A mixed-effects logistic regression was carried out to determine factors associated with re-referral to treatment centres after discharge.
RESULTS. There was a total of 721 patients who were discharged into treatment centres. The vast majority of patients (560, 77.7%) of patients were discharged to DS with a 1-month follow-up and the remaining (161, 22.3%) with a 6-month follow-up. Under half of these (44.1%) discharges were due to repeat non-attendance with the remaining for completed treatment. The non-attendance rate at DS appointments was 22.7%. There was no follow-up data available for 15% of patients. For those discharged for 1-month follow-up, 86.5% were retained in DS for a 6-month follow-up. Of those re-referred to treatment centres, the median time between discharge and re-referral was 8 months. There was no significant association between age, sex or non-attendance and likelihood to be re-referred.
CONCLUSIONS. Preliminary data shows that a significant majority of patients remain in DS once discharged. The non-attendance of patients with documented proliferative DR presents a challenge for both treatment centres and also for digital surveillance which is within the patient's local setting.

SITAGLIPTIN PREVENTS NEURODEGENERATION IN AN EXPERIMENTAL MODEL OF GLAUCOMA INDUCED BY INTRAVITREAL ADMINISTRATION OF DEXAMETHASONE.

P. Bogdanov[1,3], A. Duarri[2], H. Ramos[1,3], H. Isla-Magrané[2], D. Sabater[1], M.J. Canz[2], A. Deàs[1], J. Huerta[1], C. Hernández[1,3], R. Simó[1,3]

[1]Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Spain
[2]Ophthalmology Research Group, Vall d'Hebron Research Institute, Spain
[3]Diabetes and Associated Metabolic Diseases Networking Biomedical Research Centre (CIBERDEM), Spain

DESIGN. Experimental: interventional study in a mouse model.
PURPOSE. Glaucoma is a neurodegenerative disease that leads to progressive dysfunction and loss of retinal ganglion cells (RGCs) and is more prevalent subjects with diabetes. Although elevated intraocular pressure (IOP) is a major risk factor of glaucoma, a substantial proportion of patients (25-50%) have a normal IOP level. These patients display a similar RGC loss in the absence of high IOP and, therefore, neuroprotection rather than IOP-lowering approach seems the most rational strategy. Since we have found that sitagliptin (a DPP-IV inhibitor) administered in eye drops is useful in experimental diabetic retinopathy (DR) by preventing retinal neurodegeneration, we wanted to examine whether this approach could also be useful in an experimental model of glaucoma.
METHODS. We used a mouse model of primary open-angle glaucoma induced by intravitreal administration of dexamethasone (IV-DEX) (5 IV-DEX during a period of 29 days). Eye drops of sitagliptin (10 mg/mL) vs. vehicle were administered the last 21 days. After euthanasia, retinal sections and wholemount, transverse sections of optical nerve head (ONH) were performed. Measurements in vivo: IOP, and fundus fluorescence angiography. Measurements post-mortem: GFAP, Iba-1, RBPMS, neurofilament, γ-synuclein and galectin-3 by confocal microscopy immunofluorescence.
RESULTS. A significant increase in IOP in mice treated with IV- DEX was observed ($p < 0.01$), which was not reduced by topical administration of sitagliptin. A significant loss of RGCs was found in in mice treated with vehicle in comparison with mice treated with eye-drops of sitagliptin ($p < 0.05$). Topical administration of sitagliptin also prevented the DXM-IV induced loss of neurofilament ($p < 0.01$) and the overexpression of GFAP and Iba1 in both the retina and in OHN ($p < 0.05$). We also observed a significant reduction of galectin-3 and γ-synuclein overexpression in OHN in mice treated with eye drops of sitagliptin in comparison with vehicle.
CONCLUSIONS. Topical administration of sitagliptin exerts a powerful neuroprotective action in glaucoma induced by dexamethasone. Our results pave the way for a new treatment of glaucoma based in neuroprotection, which could be particularly useful in those patients without IOP or in glaucoma induced by intravitreal injections of corticosteroids.

YSTEMIC ADMINISTRATION OF M9 DELAYS THE PROGRESSION OF DIABETIC RETINOPATHY IN THE ANIMAL MODEL OF TYPE 1 DIABETES MELLITUS: SPECIFIC M2-INDUCTION OF MICROGLIAL CELLS.

F. Cano-Cano[1], F.L.M. Martín-Loro[1], L.G.J. Gómez-Jaramillo[1], M.C.G.M. González-Montelongo[1], B.C. Cuevas[1,2], E.Z. Zubía[2], M.J.O. Ortega[2], M.A.D. Aguilar-Diosdado[1,3], A.I.A. Arroba[1,3]

[1]Institute for Biomedical Research and Innovation of Cádiz University Hospital "Puerta del Mar", Cádiz, Spain
[2]Department of Organic Chemistry, University of Cádiz, Cádiz, Spain
[3]Department of Endocrinology and Metabolism, University Hospital "Puerta del Mar", Cádiz, Spain

DESIGN. There are numerous antidiabetic drugs capable of modulate metabolic and glycaemic levels with effects on DR progression. However, it is increasingly interesting to find drugs or therapies for DR that act independently at glycaemic levels, thus understanding the management of DR as a pathology generated by diabetes, but of independent of other factors.
Early retinal inflammation is mediated by microglial cells and its anti-inflammatory modulation will be crucial in the treatment and progression of DR. Currently, new resources with highly potent and non-toxic properties are being used, such as marine compounds. Eye drops treatment of algae bioinspired molecule 3-arilftalidas (M9) has shown properties against DR, with modulation of microglial cell response.
PURPOSE. The aim of this work is to determine if microglia cells could be immunomodulated and generate a protective response during DR by M9 systemic administration, independently of the systemic glycaemic state associated to Diabetes Mellitus.
METHODS. Intraperitoneal administration of M9 or vehicle in BB rats (7 weeks-age) once per day for two weeks. Evaluation of retinal structure preservation (SD-OCT) and molecular approaches: iNOS, Arginase-1, Iba-1, proinflammatory-(M1 response) / anti-inflammatory-(M2 response) cytokines, autophagy signalling pathway were analysed by either RT-PCR or Western blotting. Besides, gliosis reactivity and microglia activation was determined by immufluorescence for glial fibrillary acidic protein (GFAP) and IBA-1). Glucose levels and body weight was monitorised.
RESULTS. Systemic M9 administration in BB rats does not alter the hyperglycaemic status or metabolic parameters analysed. M9 treatment reduces different pro-inflammatory markers, such as iNOS and IL1b, IL6 and TNF expression, and induced M2 response by induction of HO-1 and Arginase-1 levels in the retina, showing a reduction in retinal structure failure associated to DR progression. Microglia activation is modulated and gliosis reactive is reduced by the M9 treatment.
CONCLUSIONS. Marine bioinspired molecule, M9, exerts a beneficial and specific effect on the inflammatory process mediated by microglia cells during DR and could be an effective alternative for its treatment and/or prevention in an independent way of glycaemic diabetes management.

PRELIMINARY RESULTS OF THE RETINAL STUDY: EFFECT OF SARS-COV-2 INFECTION ON RETINAL STRUCTURE IN PATIENTS WITH DIABETES MELLITUS

M. Campanile[1], G. Piccoli[2], D. Toska[1], E. Tagliabue[1], C. Banfi[3], S. Vujosevic[2,4], G. Spinetti[1]

[1]Lab of Cardiovascular Pathophysiology-Regenerative Medicine, IRCCS MultiMedica, Milan, Italy
[2]Eye Clinic IRCCS MultiMedica, Milan, Italy
[3]Centro Cardiologico Monzino IRCCS, Milan, Italy
[4]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Prospective cross-sectional study.
PURPOSE. SARS-CoV-2 infection has long-term consequences on body homeostasis mostly through an imbalance of the inflammatory response and endothelial cell (EC) damage. Here we studied the association between COVID-19 and retinal microvasculature in subjects with diabetes and to collect data on inflammatory microRNAs.
METHODS. We conducted a study on consecutive subjects of >18 years of age with diabetes with or without non-proliferative diabetic retinopathy (NPDR) referring to the eye department for retinopathy evaluation. The study involved complete ophthalmological evaluation, macular OCT/angio-OCT with Zeiss AngioPlex Cirrus 5000. Central macular thickness (CMT), foveal avascular zone (FAZ) area, perimeter and circularity index (CI), vessel density (VD%), and perfusion density (PD%) were automatically calculated on a 3×3 mm fovea scan on the superficial capillary plexus. In addition, we collected information on COVID-19 occurrence and a sample of peripheral blood (PB) to measure circulating mononuclear cells (MCs) and levels of microRNAs known to be associated with COVID-19, inflammation, and angiogenesis (miR-21, miR-210, miR-20b, miR-27b, miR-15a, miR-144, miR-146, miR150, and miR126). In addition, PBMC conditioned medium (CCM) proteomic analysis based on proximity extension assay was conducted. We studied the crosstalk between PBMCs and EC via in vitro Matrigel assay.
RESULTS. We enrolled N = 64 patients with diabetes into 2 groups age and sex-matched: patients that have had COVID-19 (N = 24) or not (N = 40). Although OCT and angio-OCT analysis showed no significant changes associated with post-COVID-19 in relevant parameters, the levels of PBMC miR-21, miR-210, miR15a, miR27b, miR144, miR146a, and miR-20b significantly decreased in post-COVID-19. A subsequent analysis in 4 groups considering NPDR confirmed a significant decrease of hypoxia-miR miR-210 associated with both NPDR and COVID-19. Functional studies showed that PBMC-CCM from patients with NPDR and COVID-19 significantly inhibited EC network formation on Matrigel. Secretome analysis evidenced significant changes COVID-19-associated in several inflammatory cytokines including IL-1β, IL-6, TNF-α, IL-17A, and IL-17F.
CONCLUSIONS. In patients with diabetes, we observed dramatic changes in PBMCs inflammatory miRNA levels and released cytokines that may contribute to EC impairment post-COVID-19. A larger cohort of patients will be required to assess associated microvascular alterations.

DEVELOPMENT OF PREDICTIVE MODELS FOR EXPERIMENTAL DIABETIC RETINOPATHY

Y. Sirman, I.V. Savytskyi

International Academy of Ecology and Medicine, Ukraine

DESIGN. An experimental, longitudinal study on laboratory animals, inducing Type 2 diabetes and diabetic retinopathy with a high-fat diet and streptozotocin. It involves measuring biomarkers (von Willebrand factor, endothelin-1, and 2,3-diphosphoglycerate) at regular intervals to develop a predictive model for diabetic retinopathy progression using logistic regression analysis.
PURPOSE. To analyse the relationship of von Willebrand factor and endothelin-1 (generally accepted markers of endothelial dysfunction) and 2,3 diphosphoglycerate of erythrocytes (an indicator of hypoxia) with the severity of experimental diabetic retinopathy.
METHODS. Type 2 diabetes mellitus and diabetic retinopathy were modelled using intraperitoneal administration of streptozotocin (Sigma, United States) dissolved in 0.1 M citrate buffer with pH 4.5. A streptozotocin dose of 55 mg/kg of animal weight was divided into two administrations. The administration of streptozotocin was preceded by a high-fat diet for 28 days. The calculations of the logistic regression parameters and characteristics that describe the adequacy of the model were carried out in the statistical package PASW Statistics 18. The maximum likelihood method was used as a loss function; the statistical significance of the model was assessed using several Chi-square and Hosmer-Lemeshev tests. According to Hosmer-Lemeshev criterion, the p-level is 1. The measure of certainty (coefficient of determination) according to Cox and Snell in our model is 0.632 (63.2%).
RESULTS. A mathematical model for predicting the pathological condition under study was developed based on the analysis of blood biochemical parameters at the early stages of the experiment. To obtain the percentage of the probability of the transition of nonproliferative diabetic retinopathy to the proliferative stage (in the range from 0-100%), using the obtained logistic regression function, multiply the obtained value of the G (z) function by 100%. The informative value of endothelial dysfunction markers - von Willebrand factor and endothelin-1 - in predicting the transition of nonproliferative diabetic retinopathy to proliferative stage has been proved.
CONCLUSIONS. The established effectiveness of the complex analysis of the level of 2,3 diphosphoglycerate of erythrocytes together with the indicated markers of the functional state of endothelial cells on the thirtieth day to predict the further course of the studied pathological process.

CLINICAL FEATURES RELATED TO OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY ARTIFACTS IN PATIENTS WITH DIABETIC MACULAR EDEMA

S. Tamer Kaderli[1], G. Piccoli[2], C. Limoli[2,3], S. Ginelli[2,3], S. Caboni[2,3], L. Brotto[2,3], L. O'Toole[4], P. Nucci[5], S. Vujosevic[2,5]

[1]Mugla Training and Research Hospital, Mugla, Turkey
[2]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[3]University of Milan, Milan, Italy
[4]Mater Private Network, Dublin, Ireland
[5]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Retrospective study.
PURPOSE. To investigate the frequency of optical coherence tomography angiography (OCT-A) artefacts and their relationship with clinical findings in eyes with diabetic macular oedema.
METHODS. Detailed ophthalmological examinations, OCT and OCT-A images (Spectralis, Heidelberg), and ultra-widefield colour fundus photos (Optos California, UK) of all patients were evaluated. The OCT-A artefacts were classified as segmentation, motion, projection, and low signal. The cases were divided into 2 groups according to the presence or absence of artefacts. The best corrected visual acuity (BCVA), mean central retinal thickness (CRT), foveal avascular zone (FAZ) area, perimeter and circularity index in the superficial capillary plexus (SCP), intermediate capillary plexus (ICP), and deep capillary plexus (DCP), presence of hard exudate (HE) and cataract were compared between the groups. The risk factors for the presence artefacts were assessed.
RESULTS. This study included 192 eyes of 140 patients with DME. The mean age was 71.6 ± 11.4 years and the mean duration of DM was 12.2 ± 7.2 years. The artefacts were observed in 63 (32.8%) of 192 eyes. 29 (15.1%) eyes had segmentation artefacts, 12 (6.3%) motion artefacts, 11 (5.7%) projection artefacts and 18 (9.4%) had low signal. BCVA was significantly lower and CRT, FAZ area and perimeter in ICP and DCP, presence of CME, HE and cataract, higher in eyes with artefacts. ($p < 0.05$ for each) The results of the multivariate linear regression analysis using a backward model showed that the decreased BCVA (OR = 4.42, $p = 0.014$), increased CRT (OR = 1.013, $p < 0.001$), perimeter of FAZ in DCP (OR = 1.775, $p = 0.040$) and increase in FAZ area in DCP (OR = 6.625, $p = 0.026$) were factors considered to increase the risk of segmentation artefact. There is a significant association between the projection artefacts and presence of HE (OR = 2.017, $p = 0.017$); motion artefacts and presence of cataract (OR = 4.102, $p = 0.01$). Low signal was higher in eyes with cataracts, increased FAZ on ICP and DCP, ($p = 0.001$, for all) only in univariate logistic regression analysis.

CONCLUSIONS. Recognizing OCT-A artefacts and comprehending their association with clinical features provides a more accurate and standardized OCT-A interpretation in DR.

COMPARING A 60-DEGREE SCANNING CONFOCAL OPHTHALMOSCOPE (SCO) DEVICE USING STAGED MYDRIASIS WITH THE STANDARD MYDRIATIC DIGITAL CAMERAS USED IN THE NHS DIABETIC EYE SCREENING PROGRAMME (DESP).

U. Javed[1], M. Gruszka-Goh[1,4], J. Hapeshi[1], S. Chave[1], A. Vukic[1], Galsworthy. P[1], Gardner. L[1], S. Vallance[1], S.J. Aldington[1], P.H. Aldington[1,2,3]

[1]Gloucestershire Retinal Research Group (GRRG), Cheltenham General Hospital, Cheltenham, UK
[2]Nuffield Department of Clinical Neuroscience, University of Oxford, UK
[3]University of Gloucestershire, UK
[4]The Royal College of Ophthalmologists' National Ophthalmology Audit, UK

DESIGN. CONCORDIA (Scanning CONfoCal Ophthalmoscopy foR DIAbetic eye screening) study is a clinical trial comparing SCO devices, with the reference standard of two 45-degree field mydriatic digital cameras currently used as standard in English DESP.
PURPOSE. To assess the accuracy and safety of the Eidon camera using staged mydriasis in the English DESP.
METHODS. 1015 patients (2029 eyes) were recruited from people with diabetes and no confounding eye conditions attending DESP clinics or attending virtual eye clinics for those with delayed hospital follow up appointments due to Covid-19. A staged mydriatic approach was used where the Eidon photographs were taken before mydriasis and, if pupils were <3 mm or an image was ungradable, a post-mydriasis Eidon image was taken. Gradable non-mydriatic images were compared unless ungradable, where mydriatic images were compared to the reference standard of two 45-degree field mydriatic digital images. Images were graded using NHS DESP grading criteria by multiple senior graders with arbitration of differences by a third senior grader.
RESULTS. 59.4% of patients were male vs 40.6% female. Median age was 64.0 years. 93.2% of patients were of White Caucasian descent. The Eidon performed accurately in detecting any level of DR using staged mydriasis with a sensitivity of 97.5% (95% CI 96.4%-98.4%) and specificity of 82.3% (95% CI 79.6%-84.7%) compared to the reference standard. For referable DR, the sensitivity was 92.7% (95% CI: 89.9%-94.9%) and specificity was 85.4% (95% CI: 83.6%-87.2%). The ungradable image rate for the Eidon in non-mydriatic and staged mydriatic mode was 4.2% and 1.7% as compared to 1.7% in the mydriatic digital reference standard.
CONCLUSIONS. The Eidon device performed accurately using staged mydriasis as compared to the reference standard. Further work is required to assess the Eidon's performance in ethnically diverse populations and in a cost-effectiveness analysis in DESP. This type of device may reduce the necessity for eye drops in over 2 million patients per year in the English DESP.

OCT ANGIOGRAPHY ANALYSIS OF RETINAL MICROVASCULAR NETWORK IN PATIENTS WITH DIABETES MELLITUS: GENDER-BASED DIFFERENCES

G. Piccoli[1; 2], M. Parravano[2], C. Limoli[1,3], E. Costanzo[2], E. Torti[4], D. Giannini[2], M.S. Polito[2], L. Luzi[5,6], P. Nucci[7], S. Vujosevic[1,7]

[1]Eye Clinic, IRCCS MultiMedica, Milan, Italy
[2]IRCCS-Fondazione Bietti, Rome, Italy
[3]University of Milan, Milan, Italy
[4]Laboratory of Custom Computing and Programmable Systems, Department of Electrical, Computer and Biomedical Engineering, Università degli Studi di Pavia, Pavia, Italy
[5]Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS MultiMedica, Milan, Italy
[6]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[7]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy

DESIGN. Retrospective cross-sectional study.
PURPOSE. A gender-based analysis of microvascular alteration in patients with diabetes mellitus (DM) without diabetic retinopathy (NoDR) and with mild-to-moderate non-proliferative diabetic retinopathy (NPDR) using Optical Coherence Tomography Angiography (OCT-A).
METHODS. 267 DM patients, categorised into those without diabetic retinopathy (NoDR) and those with mild-to-moderate NPDR were included. A single eye was randomly selected for each patient, and foveal-centred 3×3 mm OCT-A images were analysed. For each slab, FAZ area, perimeter, and circularity index (CI) were determined, following manual delineation of the FAZ; perfusion and vessel density (PD, VD), fractal dimension (FD), vessel length density (VLD) and geometric perfusion deficits (GPD) were computed. Flow voids (FV) were determined in the choriocapillaris plexus; and perfused capillary density (PCD) in the full retina slab.
RESULTS. The study population consisted of 87 (32.58%) patients with T1DM and 180 (67.42%) with T2DM, with a mean duration of disease of 16.83 ± 0.85

years and a mean HbA1c level of 7.31%±1.43%. In the whole cohort (49.81% females), the mean age was 60.90 ± 21.34 years. NoDR was more prevalent among female patients (n = 65, 58.55%) while NPDR among males (n = 88, 56.41%) ($p = 0.016$). The analysis of overall population by gender, showed that all density metrics at the level of ICP and DCP were affected in the presence of signs of DR with no gender differences. In the comparison between females and males with NoDR and mild-to- moderate NPDR OCT mean central retinal thickness (CRT) was found to be lower in females than in males ($p < 0.001$). When analysed according to disease severity, males had higher CRT than females in NoDR and NPDR groups. ($p < 0.001$) The following OCTA measurements were significantly higher in females than in males in NPDR: higher FAZ CI in SCP ($p = 0.017$), greater FAZ area ($p = .006$) and perimeter ($p = 0.030$) in DCP. No other OCT-A parameter showed any significant difference between the groups.

CONCLUSIONS. OCT-A analysis suggests that major gender differences are in FAZ metrics. This may suggest that females may show earlier and more advanced retinal microvascular damage than males in DM.

OBJECTIVE ASSESSMENT OF THE DYNAMICS OF RETINAL NONPERFUSION ZONES IN PREGNANT WOMEN WITH PROGRESSION OF DIABETIC RETINOPATHY

N. Pomytkina[1,2], E. Sorokin[1,2], I. Pashentsev[1]

[1]The S. Fyodorov Eye Microsurgery Federal State Institution, the Khabarovsk Branch, Russian Federation
[2]Far-Eastern State Medical University, Khabarovsk, Russian Federation

DESIGN. The progression of diabetic retinopathy is based on obliteration of retinal microvessels, which can be detected by OCT angiography in the form of dynamic expansion of retinal nonperfusion zones.

PURPOSE. To propose a method for objective assessment of the dynamics of retinal nonperfusion zones in pregnant women with progression of diabetic retinopathy (DR).

METHODS. 27 pregnant women (54 eyes) with progression of DR (16 with proliferative, 11 with severe non-proliferative), and 26 pregnant women (52 eyes) with a stable course of retinopathy (13 with proliferative and 13 with severe non-proliferative). In each trimester of pregnancy and after childbirth, OCT angiography (Optovue RTVue XR Avanti) was performed using an HD Angio Retina 6.0 mm scanning protocol. In the GIMP editor, a 600×600 pixels section of the OCT angiograms of the superficial and deep retinal plexuses was cut out from the graphic file and the image was contrasted using the "Threshold" command with a cut-off parameter of 40 units. The percentage of black pixels at the "Histogram" function was interpreted as the part of non-perfusion zones. The obtained data from consecutive studies were compared with each other.

RESULTS. Analysis of changes in the part of nonperfusion zones during pregnancy and after childbirth showed that in the first and second trimesters there were no significant differences in parameters between the groups. There was a progressive increase in the proportion of nonperfusion zones in both plexuses by the third trimester in the subgroup of retinopathy progression, with no changes 3 months after birth. In the stable subgroup there were no significant changes in the studied parameters. The proposed method allows for an objective quantitative assessment of dynamic changes in retinal non-perfusion zones.

CONCLUSIONS. In pregnant women with progression of DR, there was an increase of nonperfusion zones in both retinal plexuses from the first to third trimester. The method for objective assessment of the dynamics of retinal nonperfusion zones allows an accurate quantitative assessment of changes in nonperfused retina areas separately in superficial and deep retinal plexuses.

RETINAL OCT BIOMARKERS ASSOCIATED WITH READING PERFORMANCE IN PATIENTS WITH PERSISTENT VS. RESOLVED DIABETIC MACULAR EDEMA

F. Ricardi[1], I.R. Reccalenda[1], G.B. Boscia[2], F.G. Gelormini[1], F.C. Cimorosi[1], C.N. Novarese[1], P.M. Marolo[1], F.B. Bandello[3,4], E.B. Borrelli[1], M.R. Reibaldi[1]

[1]Department of Ophthalmology, University of Turin, Turin, Italy
[2]Department of Basic Medical Sciences, Neuroscience, and Sense Organs, University of Bari "Aldo Moro", Bari, Italy
[3]Vita-Salute San Raffaele University Milan, Italy
[4]IRCCS San Raffaele Scientific Institute, Milan, Italy

DESIGN. Prospective.

PURPOSE. Recent advancements in imaging technologies, particularly structural optical coherence tomography (OCT), have improved the understanding of diabetic macular oedema (DME) pathophysiology and provided valuable biomarkers for disease progression and visual outcomes. This prospective study aimed to investigate the association between specific retinal biomarkers identified through OCT imaging and reading performance metrics in patients with previously treated persistent versus resolved DME and good visual acuity.

METHODS. Forty-nine eyes from 35 patients with a history of DME were enrolled. Reading performance was assessed using the Radner reading charts, which include

standardised sentences with geometrically progressing print sizes. Structural alterations in the inner and outer retina, as well as the retinal pigment epithelium (RPE), were graded based on OCT images.
RESULTS. Reading performance, measured as maximum reading speed and reading acuity score, was associated with specific retinal biomarkers. The disruption of the ellipsoid zone (EZ) in the parafoveal region and the presence of disorganization of the inner retinal layers (DRIL) in the parafovea were correlated with reduced reading speed. These associations were independent of the presence of intraretinal or subretinal fluid. On the other hand, the reading acuity score was mainly associated with distance visual acuity.
CONCLUSIONS. Understanding the relationship between retinal biomarkers and reading performance could contribute to a comprehensive evaluation of visual function and quality of life in patients with DME, leading to better management strategies and treatment outcomes.

INTER-EYE MICROVASCULAR DIFFERENCES IN PATIENTS WITH SAME-STAGE DIABETIC RETINOPATHY REVEALED BY OCTA

H. Stino[1], K.L. Huber[1], L. Kunze[1], I. Steiner[2], A. Bampoulidis[1,3], U. Schmidt-Erfurth[1], A. Pollreisz[1]

[1]Medical University of Vienna, Department of Ophthalmology, Austria
[2]Medical University of Vienna, Centre for Medical Data Science, Institute of Medical Statistics, Austria
[3]Medical University of Vienna, Vienna Reading Centre, Department of Ophthalmology, Austria

DESIGN. Cross-sectional study.
PURPOSE. To evaluate intraindividual microvascular inter-eye differences in patients with diabetes with same stage diabetic retinopathy (DR) in both eyes as assessed using optical coherence tomography angiography (OCTA).
METHODS. In this cross-sectional study, fovea-centred swept-source 6 × 6 mm OCTA scans were acquired using a 200 kHz OCTA device. Vessel density (VD) and fractal dimension (FD) were calculated on binarized, vessel-segmented images in the superficial capillary plexus (SCP) and deep capillary plexus (DCP). Absolute difference (δabs) and asymmetry index between eyes was assessed and compared across DR stages by Kruskal-Wallis tests. Comparison of VD and FD between left and right side was done by linear mixed models.
RESULTS. 336 eyes of 168 patients with DR stages ranging from mild non-proliferative to proliferative DR were included for analysis. The inter-eye comparison revealed significantly lower VD in the SCP (estimate [95% CI] = -0.009 [-0.01; -0.006], $p < 0.01$) as well as a significantly lower FD in the SCP (-0.007 [-0.009; -0.005], $p < 0.01$) of the left compared to the right eye. Inter-eye δabs and asymmetry index were higher in the IR compared to the OR in the SCP and DCP ($p < 0.01$).
CONCLUSIONS. OCTA metrics provide important information on the retinal microvasculature in systemic diseases such as DR. Our results reveal a significant inter-eye difference with lower VD and FD in the SCP of the left compared to the right eye.

ENDOPHTHALMITIS AFTER INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION FOR DIABETIC MACULAR EDEMA AND DIABETIC RETINOPATHY

B.S. Thinggaard[1,2,3], F.P. Pedersen[1,2], Y.S. Subhi[2,4], J.G. Grauslund[1,2], L.S. Stokholm[2,3]

[1]Department of Ophthalmology, Odense University Hospital, Odense, Denmark
[2]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[3]OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark
[4]Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark

DESIGN. Nationwide register-based cohort study.
PURPOSE. To evaluate the prevalence and relative risk (RR) of post injection endophthalmitis (PIE) following intravitreal vascular endothelial growth factor (VEGF) inhibitor injections for diabetic macular oedema (DME) and diabetic retinopathy (DR).
METHODS. The study included all Danish patients aged 40 years or older diagnosed with DME or DR who received at least one VEGF inhibitor injection between 2007 and 2022. The primary endpoint was PIE, identified by diagnostic codes for endophthalmitis (H440*, DH451, DH598B) or a procedure code for vitreous biopsy (KCKA10, KTCK20) within 120 days following an injection. Patients who underwent cataract surgery between injection and PIE were excluded. To assess the impact of cumulative doses of VEGF inhibitor treatment on the risk of PIE, the RR was calculated using patients who received 1-3 injections as the reference group.
RESULTS. We identified 8,001 patients with DME or DR who received VEGF inhibitor treatment. Median age was 65.2 years (IQR 56.3-72.8 years) at the first injection, and 38.6% were females. In total, we found 29 cases of PIE after 99,188 injections (0.029%). While the annual number of VEGF inhibitor injections among patients with DME or DR increased from

18,502 (2011-2014) to 45,837 injections (2019-2022), the prevalence of PIE remained constant at 0.032% and 0.033%.
The prevalence of PIE among patients receiving 1-3 injections, 4-20 injections, 21-40 injections, and >40 injections was 0.073%, 0.010%, 0.022%, and 0.044%, respectively. As compared to patients receiving 1-3 injections, RR for patients receiving 4-20, 21-40, and >40 injections were 0.14 [95% CI 0.05-0.37], 0.30 [95% CI 0.10-0.90], and 0.60 [95% CI 0.20-1.78], respectively.
CONCLUSIONS. In this nationwide cohort study of all Danish patients with DME or DR who received VEGF inhibitor treatment between 2007 and 2022, we observed a low proportion of PIE, which remained constant over time. Patients receiving few injections and those receiving over 40 injections faced the highest risk of PIE, possibly due to an immunological response in the initial injections and a growing mechanically induced response with an increasing number of injections.

A CORRELATION ANALYSIS BETWEEN RETROBULAR HEMODYNAMICS AND TREATMENT PATTERNS IN DIABETIC MACULAR EDEMA EYES RECEIVING INTRAVITREAL FARICIMAB

F. Chiosi[1,2], G. Manzi[1], F. Natale[2], E. Minutillo[1], F. Calabrò[1]

[1]Department of Ophthalmology, A.O.R.N. dei Colli, Monaldi Hospital, Napoli, Italy
[2]Department of Cardiothoracic Disease, Department of Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, Napoli, Italy

DESIGN. Prospective non-randomized interventional study.
PURPOSE. To evaluate the effect of intravitreal faricimab (IVF) on ocular blood flow velocities and treatment patterns in patients with diabetic macular oedema (DME).
METHODS. This study included injected and fellow eyes of 16 patients with DME treated with IVF. Colour Doppler Ultrasonography (CDU) measures of the central retinal artery (CRA), posterior ciliary artery (PCA), ophthalmic artery (OA) those are peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI) and pulsatility index (PI) were performed in both injected and uninjected eyes at baseline and after a loading dose regimen of 4 injections up front monthly. BCVA, central foveal thickness (CFT) and OCT biomarkers were also measured at the same time point.
RESULTS. Inter-eye comparison of all the measured CDU data showed a decreasing trend by the end of the loading dose in the injected eye. These differences were not statistically significant. RI and PI measures of the CRA, OA, and PCA measures showed statistically decreased values over the follow-up in the injected eyes. Significant visual gain and anatomic recovery were obtained by the end of the loading dose in injected IVF eyes.
CONCLUSIONS. The findings aim to provide insights into the potential advantages of faricimab in managing diabetic macular oedema, considering vascular and structural parameters.

DIABETIC RETINOPATHY AND LOW VISION

A. D'ambrosio[1], R. Volpe[2], G. Giacomelli[3], E. Tedeschi[4], M. Licata[5]

[1]Low Vision and Rehabilitation Service, Ophthalmology UOC, Casa Sollievo Sofferenza Hospital, San Giovanni Rotondo (FG), Italy
[2]Low Vision and Rehabilitation Service, Ophthalmology UOC, San Donato Hospital, Arezzo, Italy
[3]Ophthalmology Unit, NEUROFARBA Department, University of Florence, Florence, Italy
[4]Low Vision Service, ASL Roma 4, Rome, Italy
[5]Regional Low Vision Centre, Ophthalmology SOC, S. Maria degli Angeli Hospital, Pordenone, Italy

DESIGN. Patients referred to the visual rehabilitation centre already have serious clinical condition. We evaluated the incidence of low vision in the population of 5 rehabilitation centres in Italy and its possible optical, electronic or lifestyle solutions.
PURPOSE. To highlight how much diabetic retinopathy leads to low vision and which are possible solutions by sending the patient to the rehabilitation centre.
METHODS. 1) The patient's history about glare and colours perception is being collected to estimate the quality of vision. 2) Assessment of the low vision level through measurement far and near BCVA with ETDRS and contrast sensitivity is being evaluated. 3) Finally the solutions (optical, electronic and lifestyle changes) are proposed to the patient and acceptance assessment evaluated during the time.
RESULTS. Among the proposed solutions, the photoselective lenses were the most accepted by patients in all level of low vision, and those most used over time even after the first prescription. The results, however, vary according to the age of the patient and to his working or daily life attitudes.
CONCLUSIONS. Those with diabetes arriving at the rehabilitation centre already have an advanced clinical condition. The solutions that can be proposed to alleviate the condition of low vision are different and often well accepted by the patient.

ADJUVANT OZURDEX IN CATARACT SURGERY WITH TREATMENT-REQUIRING DIABETIC MACULAR OEDEMA

G. George, O. Erikitola, S. Chakrabarti

Tennant Institute of Ophthalmology, Gartnavel General Hospital, Greater Glasgow and Clyde, UK

DESIGN. Retrospective cohort.
PURPOSE. To assess the outcome of best corrected visual acuity following cataract surgery with adjuvant Ozurdex in patients with treatment-requiring diabetic macula oedema (DMO).
METHODS. Anonymised data was extracted at one centre from an electronic medical record. Eyes undergoing cataract surgery with adjuvant Ozurdex in patients with diabetes with early or centre involving DMO prior to study start. Primary outcome measure: BCVA at 6 weeks, 3-, 6-, and 12-months. Secondary outcome measures: CRT at 6 weeks, 3-, 6-, and 12-months.
RESULTS. Thirty-nine eyes met the inclusion criteria, average age of patients was 67(±11.2, range 25-91). Centre involving DMO was found in 24 eyes. At 6 weeks, 3-, 6- and 12-months, 27, 14, 18 and 18 attended follow-up respectively. At 6 weeks, 6 eyes had no change in visual acuity, whereas 21 had improved vision. Mean improvement in BCVA was 19.51 letters. At 3 months, 2 eyes experienced no change, 1 experienced reduced vision and 11 experienced improved vision. The average letters gained was 24.1 letters. At 6 months, 2 eyes experienced reduced vision whereas 16 improved. The average letters gained was 23.2. At 1 year, 1 eye experienced no change, 1 eye had reduced vision and 16 eyes had improved vision. The average letters gained was 27.3. The average CRT pre-surgery was 283.9µm.
At 6 week review, average CRT was 277.8µm. The average change at 6 weeks was reduction by 11.7µm. At 3 month review, average CRT was 308.5µm. The average change was an increase of 29.4µm. At 6 month review, average CRT was 341.7µm. The average change in CRT was an increase of 48.5µm. At 12 month review, average CRT was 326.25µm. The average change was an increase of 48.7µm.
CONCLUSIONS. This real-world study demonstrates that the visual outcome in the vast majority of patients improves 6 weeks, 3-, 6- and 12-months following cataract surgery with intravitreal Ozurdex implants in patients with early or centre involving DMO. As found in other studies, DMO is associated with poorer outcomes after cataract surgery. Therefore, adjuvant Ozurdex could result in improved visual outcome in patients with DMO undergoing cataract surgery.

REAL-WORLD TREATMENT PATTERNS AND VISUAL OUTCOMES IN THE FIRST 12 MONTHS OF FARICIMAB USE IN DME: UK FARWIDE-DME STUDY

C. Kiire[1,8,9], T. Peto[2], R.R. Reynolds[3], C.B. Bailey[4], L.D. Downey[5], I.P. Pearce[6], S.S. Sivaprasad[7], N.J. James[8], N.S. Shah[8], P.D. Dayal[9]

[1]Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Queen's University Belfast and Belfast Health and Social Care Trust, Belfast, UK
[3]Aneurin Bevan University Health Board and Cardiff University School of Vision Science, Cardiff, UK
[4]University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[5]Hull University Teaching Hospitals NHS Trust, Hull, UK
[6]Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK
[7]Moorfields Eye Hospital NHS Foundation Trust, London, UK
[8]Roche Products Ltd, Welwyn Garden City, UK
[9]Genentech, Inc., South San Francisco, CA, USA

DESIGN. Faricimab Real-World Evidence Diabetic Macular Edema (FARWIDE-DME) is a retrospective, multicentre observational study.
PURPOSE. Faricimab is a bispecific antibody inhibiting angiopoietin-2 and vascular endothelial growth factor-A. This study aims to evaluate the real-world durability of faricimab in DME patients.
METHODS. DME patients who initiated faricimab after June 2022, at one of 21 participating UK National Health Service sites using the Medisoft medical record system were included. Patient characteristics, treatment patterns, and visual outcomes were analysed.
RESULTS. 1,921 DME patients (2,673 eyes) received faricimab up until June 2023. 36% of eyes were anti-VEGF treatment-naive. 71% of naive eyes and 58% of previously-treated (PT) eyes received four initial faricimab doses, administered every ≤6 weeks. 303 eyes (33% naive) had ≥12-months of follow-up on faricimab. The mean patient age was 63.5 (SD 10.2) years and 44% were female. 50% of the patients resided in high deprivation regions (Index of Multiple Deprivation (IMD) deciles 1-4), 46% resided in medium deprivation regions (IMD deciles 5-8) and 15% resided in low deprivation regions (IMD deciles 9-10). Naive eyes received a mean (SD) of 4.5 (0.9) injections in the first 6 months and 1.8 (1.3) injections in months 7-12 of faricimab treatment. PT eyes received 4.6 (1.1) and 2.5 (1.4) injections respectively in the same time periods. The mean (SD) interval between the 5th and 6th faricimab injections was 10.5 (4.0) weeks for naive eyes and 9.0 (4.6) weeks for PT eyes. The mean change (95% CI) in visual acuity after 12 months of faricimab treatment was +5.3 ETDRS letters (2.9, 7.7) among naive eyes and +0.8 letters (-0.5, 2.1) among PT eyes.

CONCLUSIONS. Most study patients resided in low to medium deprivation regions. Early results suggest a rapid extension in faricimab treatment intervals after initial doses. Naive eyes gained a line of vision, whilst vision remained stable in PT eyes. These data support the durability of faricimab in DME.

EARLY REAL LIFE EXPERIENCE WITH BROLUCIZUMAB FOR DIABETIC MACULAR EDEMA IN A TERTIARY REFERRAL CENTER.

A. Gaggino, M.R. Pastore, S. Milan, D. Tognetto

Eye Clinic, Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy

DESIGN. Retrospective observational study.
PURPOSE. To report the early results of brolucizumab in the treatment of diabetic macular oedema (DME).
METHODS. Retrospective observational study on 20 patients affected by DME treated with at least 3 brolucizumab intravitreal injections between June and September 2023. All patients underwent complete ophthalmological exam including fluorescein angiography, OCT, and OCT-Angiography. Outcomes were analysed at baseline and 45 days after each injection.
RESULTS. At last follow-up, a mean change of -153.11 ± 64.6 μm in CST was recorded; 32.5% of patients achieved a CST <280 μm, with a reduction in the proportion of subjects with IRF and SRF, and a final mean gain of 4.5 ± 3.1 letters. FAZ dimension and SCP and DCP density remained stable.
CONCLUSIONS. Brolucizumab is effective in the treatment of DME, providing early reabsorption of fluid, with no impact on macular perfusion.

INITIAL CLINICAL EXPERIENCE WITH FARICIMAB IN DIABETIC MACULAR EDEMA IN AN ITALIAN TERTIARY CENTRE

S. Ginelli[1,2], C. Alovisi[4], G. Piccoli[1], L.M. Brotto[1,2], S. Caboni[1,2], C. Limoli[1,2], P. Nucci[3], S. Vujosevic[1,3]

[1]Eye Clinic IRCCS MultiMedica, Milan, Italy
[2]University of Milan, Milan, Italy
[3]Department of Biomedical, Surgical and Dental Science, University of Milan, Milan, Italy
[4]Ophthalmic Hospital, Turin, Italy

DESIGN. Retrospective longitudinal study.
PURPOSE. To investigate retinal morpho-functional modifications in patients with diabetic macular oedema (DME) treated with Faricimab in the context of a clinical practice with specific focus on decrease in number of Hyper Reflective Foci (HRF) in the retina.
METHODS. 12 eyes of 9 patients treated with 4 monthly injections of Faricimab for DME from March to September 2023 were longitudinally evaluated. Collected data included demographics, metabolic control, best-corrected visual acuity (BCVA), Spectral Domain OCT (SD-OCT) and OCT-Angiography (OCT-A) and Fluorescein Angiography (FA). Besides the usual morpho-functional evaluations, the decrease in number of HRF 1 month after every injection and a correlation with central macular thickness (CMT) and BCVA were determined. The number of HRF was determined in a semi-automated way in the 3 central mm of horizontal B-scan on SD-OCT.
RESULTS. Since the first injection, all 12 eyes have shown improvement in BCVA and CMT, with an increase of 6 letters ($p < 0.0053$) and a decrease of 155.83μm (± 36.96, $p = 0.003$) in CMT. Following the loading phase, results were similar with an increase of 6.5 letters ($p < 0.05$), a decrease of 166.16μm (± 36.96, $p < 0.05$) in CMT and increase in mean retinal sensitivity on microperimetry ($p < 0.05$) for all patients. At baseline the mean number of HRF was 72.91 (± 21.88). There was a mean reduction of 10.91 after the 1st injection, resulting non statistically significant ($p = 0.29$). There was a statistically significant mean reduction of 21.33, 26.00, 33.17 ($p < 0.05$, $p < 0.05$, $p < 0.0001$) after all other injections vs baseline (2^{nd}, 3^{rd}, 4th).
CONCLUSIONS. All eyes had improved morphological appearance in particularly with a decrease of HRF number. In this real-life case series, Faricimab precociously improved morphological and functional retinal outcomes in patients with DME. Further, larger, and longer real-life studies are warranted to confirm this preliminary data.

ANATOMICAL AND FUNCTIONAL EFFECTS OF AN ORAL SUPPLEMENTATION OF BROMELAIN AND CURCUGREEN IN PATIENTS WITH FOCAL DIABETIC MACULAR EDEMA

L. Bifezzi[1], M. Borselli[1], V. Scorcia[1], S. Vaccaro[1], S. Bousyf[1], G. Randazzo[1], G. Giannaccare[1,2], L. Lamonica[1], A. Carnevali[1]

[1]Department of Ophthalmology, University Magna Græcia of Catanzaro, Catanzaro, Italy
[2]Eye Clinic, Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

DESIGN. Prospective, non-randomized, monocentric study, performed at the Magna Graecia University of Catanzaro between July 2022 and August 2023.

PURPOSE. Diabetic retinopathy (DR) is one of the most severe diabetes-related complications, and macular oedema stands as the primary contributor to the loss of central vision in individuals diagnosed with diabetes mellitus. The purpose of this study was to investigate the anatomical and functional effects of the oral administration of bromelain and curcugreen in patients controlled by therapy with non-proliferative DR presenting focal oedema.
METHODS. Patients were enrolled and divided into two groups: group A (n = 18) received two tablets a day of bromelain and curcugreen (Retinil Forte®) orally, and group B (n = 15) underwent observation. The protocol included four visits: the screening visit (T0) and follow-up checks every 3 months up to 12 months (T3–T6–T9–T12). Best-corrected visual acuity (BCVA), central macular thickness (CMT) measured by optical coherence tomography (OCT) and vascular perfusion (VP) in superficial capillary plexus (SCP) and the deep capillary plexus (DCP) measured by optical coherence tomography angiography (OCTA) were analysed. A mixed-design ANOVA was calculated to determine whether the change in BCVA, CMT, VP in SCP and DCP over time differed according to the consumption of Retinil Forte®.
RESULTS. The results indicated that the interaction between time and treatment on the CMT and VP in DCP were significant, with F (4, 124) = 6.866 ($p < 0.0001$) and F (4, 124) = 3.263 ($p = 0.0140$), respectively. Conversely, the interaction between time and treatment was not significant on BCVA and VP in SCP with F (4, 124) = 1.121 ($p = 0.3496$) and F (4, 124) = 1.473 ($p = 0.2146$), respectively.
CONCLUSIONS. In conclusion, our results suggest a protective role of the oral administration of bromelain and curcugreen in patients with DR and focal oedema, in terms of the improvement of baseline CMT and VP in DCP over time.

TO EXPLORE THE EFFECT OF FARICIMAB ON CLINIC CAPACITY IN THE TREATMENT OF DIABETIC MACULAR OEDEMA (DMO)

J. Patel, J. Patel, K. Ananikas, E. Hewson, Y. Wilsher

Colchester Hospital, Colchester, UK

DESIGN. Retrospective review of both follow up and new patients on treatment for centre involving DMO either switched to faricimab from eylea or new patients initiated on faricimab.
PURPOSE. Review of frequency of injections after the initial loading phase of four injection and the ETDRS VA change after initiation of faricimab.
METHODS. Injection frequency and ETDRS visual acuity in Letters were recorded at each visit from initiation of treatment. And the change in the ETDRS Letters from initiation of treatment from august 2022 to December 2023.
RESULTS. There were 37 patients for new and follow up patients. New patients showed a strong ETDRS VA improvement of 11L over a total of 12 faricimab injections with injection frequency increasing to 12-15 weeks. For follow up DMO patients there was minimal VA improvement but injection frequency increased to 12-13 weeks. Whilst on eylea the frequency of treatment was 9-10 weeks with an average of 14 eylea injections before switching to faricimab.
CONCLUSIONS. Faricimab allows for increasing the frequency of treatment with improvement with increased ETDRS VA which helps clinic capacity and patient experience.

THE IMPACT OF DIABETIC RETINOPATHY ON THE CHORIOCAPILLARIS IN NEOVASCULAR AMD

M.G. Pignataro[1], P. Viggiano[1], M.O. Grassi[1], G. Boscia[2], E. Borrelli[3], T. Molfetta[1], F. Evangelista[4], G. Alessio[1], F. Boscia[1]

[1]Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy
[2]Ophthalmology Unit, A.O.U. City of Health and Science of Turin, Department of Surgical Sciences, University of Turin, Turin, Italy
[3]Ophthalmology Department, San Raffaele University Hospital, Milan, Italy
[4]Ophthalmology Clinic, Department of Medicine and Science of Ageing, University G. D'Annunzio Chieti- Pescara, Chieti, Italy

DESIGN. Cross-sectional study.
PURPOSE. To investigate the impact of diabetic retinopathy (DR) on morphological choriocapillaris (CC) modifications in eyes with type 1 macular neovascularization (MNV) secondary to AMD using optical coherence tomography angiography (OCTA).
METHODS. Eyes with AMD-related type 1 MNV with and without DR were prospectively included. We performed 3 × 3 mm OCTA scans at two visits: before the loading phase of intravitreal injections of aflibercept (T1) and 1 month after the last injection (T2). OCTA En-face flow images of the CC were analysed for flow deficit percentage (FD%), FD average area and FD number in a 500-μm-wide ring surrounding the dark halo (DH) around type 1 MNV.
RESULTS. A total of 65 eyes, out of which 30 eyes had mild DR, were included. In the group without diabetes, there was a gradual reduction in FD% in the CC ring around the DH after antiangiogenic therapy, indicating reperfusion of the CC ($p = 0.003$). However, in the DR group, there were no significant changes in CC parameters between the two study visits. Specifically, the FD% in the

CC ring around the DH did not show a significant reduction at T2 compared with T1 values ($p > 0.05$). Furthermore, the comparison of the variation in FD% between the two groups was statistically significant. The nondiabetic group exhibited a gradual CC reperfusion after the loading phase of aflibercept, whereas the diabetic eyes did not show significant changes ($p = 0.029$).

CONCLUSIONS. The CC surrounding the DH associated to type 1 MNV exhibited greater hypoperfusion in diabetic eyes compared with eyes without diabetes, both before starting therapy and after the loading phase. Hence, DR may be a potential risk factor in the development and progression of late-stage AMD and may also influence the response to antiangiogenic therapy.

A METHOD FOR REMOVING THE INTERNAL LIMITING MEMBRANE IN VITREOMACULAR TRACTION SYNDROME IN PATIENTS WITH PROLIFERATIVE DIABETIC RETINOPATHY.

D. Lipatov, O. Ilyukhin

National Research Center for Endocrinology, Moscow, Russia

DESIGN. Currently, pathology of the macular region of the retina steadily occupies a leading position in the structure of vision loss in patients with proliferative diabetic retinopathy (PDR) and diabetes mellitus (DM) in various countries of the world.

PURPOSE. To develop a non-traumatic technique for removing the internal limiting membrane (ILM) for vitreomacular traction syndrome in patients with PDR.

METHODS. An original technique (patent of the Russian Federation №2810243) of the operation was proposed: after a standard 25-27G vitrectomy, the ILM was removed in the shape of a horseshoe facing the optic nerve head. In this case, peeling of the ILM in the area of the papillomacular bundle and in the foveal zone itself was not performed.

Using this technique during 2023, 35 patients with DM and vitreomacular traction syndrome with PDR were operated on (20 women and 15 men with DM type 2). The average age of the patients was 53.7 ± 3.5 years, the level of glycated haemoglobin was 9.8 ± 1.3 mmol/l. The comparison group consisted of 37 patients (21 women and 16 men) with an average age of 55.9 ± 3.8 years, glycated haemoglobin 9.9 ± 1.7 mmol/l, operated on by the «classical» method of ILM removal (a single round conglomerate within the vascular arcades).

RESULTS. In all 72 patients, resorption of traction syndrome was achieved. In the experimental group, by reducing the trauma to the central part of the retina - the fovea, higher rates of visual function were obtained. Thus, the acuity of central vision in the early (up to 3 months) period in the experimental and control groups was 0.45 ± 0.05 and 0.27 ± 0.1, respectively, which was statistically significant. Only 10% of patients in the experimental group reported distortions of central vision, compared with 87% in the control group.

CONCLUSIONS. The proposed surgical technique ensures the preservation of the nerve fibres of the papillomacular bundle, leaves the fovea zone intact, completely removes the traction component, which leads to higher functional results (visual acuity) and preserves central vision for patients.

VISION LOSS DUE TO DIABETES IN LIVERPOOL: CORRELATION WITH DEPRIVATION AND MORTALITY

J. Nash[1,2], P.I.B. Burgess[1], T.C. Criddle[1]

[1]University of Liverpool, UK
[2]St Paul's Eye Unit, Royal Liverpool University Hospital, UK

DESIGN. Retrospective cohort study.

PURPOSE. Despite a long-standing screening programme, diabetic retinopathy (DR) remains a leading cause of vision loss in Liverpool. We aimed to report the number of people registered sight impaired (SI) or severely sight impaired (SSI) due to DR attending the Royal Liverpool University Hospital and to characterise this population.

METHODS. Subjects were identified by certificates of visual impairment. Electronic patient records including Medisight were manually searched for details of demographics, systemic disease and complications of diabetes. Deprivation statistics linked to patient postcode were accessed from the Office for National Statistics.

RESULTS. 113 patients were registered in Liverpool with vision loss from diabetes during April 2016 to April 2021. Of those inhabiting Liverpool ($n = 54$), a larger proportion were from the most deprived decile for index of multiple deprivation (61.1%), income (55.6%), health (72.2%), employment (59.3%), crime (33.3%), living environment (46.3%) and education (31.5%). More patients had type 2 diabetes (54.1%); the majority were hypertensive (55.8%). Mean HbA1c was 71.9 mmol/mol, 95% CI 66.8-76.9. The 5-year mortality after registration was 35.1% for both type 1 and 2 (95% CI 51.2-78.6), 28.2% for type 1 only (95% CI 50.8-92.8%) and 37.8% for type 2 only (95% CI 44.6-79.8).

CONCLUSIONS. Indices of socioeconomic status correlate with vision loss due to diabetes in Liverpool. Patients registered SI or SSI have a high rate of mortality.

HIGHER DEGREE OF DIABETIC MACULAR EDEMA IN REGIONS WITH LOWER SOCIOECONOMIC STATUS

N. Mousavi[1], M.K.N. Nielsen[1,2], J.B.L. Lindboe[1], T.B. Brynskov[1], T.L.S. Sørensen[1,2], C.S.L. Laugesen[1]

[1]Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark
[2]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

DESIGN. Retrospective register-based single-centre study.
PURPOSE. The aim of the present study was to report the prevalence, the initial status and the outcome end-points of treatment-requiring diabetic macular oedema (DME) based on the socioeconomic status of the residential municipality.
METHODS. Retrospective register-based single-centre study including all the patients who commenced intravitreal anti- vascular endothelial growth factor (VEGF) treatment due to DME from 1st May 2011 to 1st May 2020 in the Region of Zealand, Denmark. The follow-up data was registered two years after baseline. Population and income data was based on Statistics Denmark.
RESULTS. A total of 632 treatment-requiring DME patients were included in this study, 273 (43%) were from the high-income municipalities and 359 (57%) from the low-income municipalities. The prevalence of treatment-requiring DME in the population from low-income municipalities was 0.08 ± 0.01 (mean $\pm$ SD) versus 0.06 ± 0.01 (mean $\pm$ SD) for the population from high-income municipalities per 100000 inhabitants, which was significantly different ($p < 0.001$). All the 632 patients were treated for DME with intravitreal anti-VEGF. The number of treatments during the first two years of treatment varied between 1 to 22 intravitreal anti-VEGF injections (5.64 ± 3.4, mean $\pm$ SD). In total 624 (17%) ranibizumab injections and 2,939 (83%) aflibercept injections were administered. The difference between average number of intravitreal anti-VEGF treatments over two-years in patients from low-income municipalities (5.88 ± 3.4, mean $\pm$ SD) and the patients from high-income municipalities (5.32 ± 3.3, mean $\pm$ SD) was statistically significant ($p = 0.038$).The visual acuity and macular oedema improved significantly over two years in both groups of patients. For the total population, best corrected visual acuity (BCVA) increased significantly from 64.5 ± 17.7 to 68.2 ± 15.4 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (mean $\pm$ SD) ($p < 0.001$).
CONCLUSIONS. This study provides insight into the prevalence and treatment outcome for diabetic patients having treatment-requiring DME and signifies the importance of equal healthcare opportunities independent of their socioeconomic status.

THE ROLE OF GENERAL PRACTITIONERS TRAINING IN THE INCREASING AWARENESS ON DIABETES AND ITS COMPLICATIONS IN CHILDREN AND ADOLESCENTS

L. Tsutskiridze[1,2], E. Shelestova[1], R. Kurashvili[3], E. Grishashvili[1], S. Gabritchidze[2], Z. Glonti[1]

[1]Georgian Association for Chronic Diseases Education, Georgia
[2]Non-Communicable Disease Prevention Alliance, Georgia
[3]National centre for Diabetes Research, Georgia

DESIGN. The number of type 1 diabetes (T1DM) is rising. Covid-19 pandemic accelerated the incidence of T1DM further, both globally and in Georgia; while knowledge on T1DM among GPs and school health care providers (SHCPs) in Georgia is low.
PURPOSE. In the framework of the World Diabetes Foundation (WDF) Project the Trainings of General Practitioners (GPs) to increase awareness on the modern aspects of prevention and management of diabetes complications and concomitant conditions was carried out by the Non-Communicable Disease Prevention Alliance, Georgia (NCDA, Georgia). Our aim was to assess and compare the level of their knowledge pre- and post-training.
METHODS. In total, 200 GPs, paediatricians, SHCPs from various regions of Georgia participated in the training. A specialized questionnaire comprised of 25 questions on DM classification, diagnosis, acute/chronic complications, prevention/screening, diet and physical activity. Participants had 45 minutes to complete the questionnaire, both pre- and post-training. A 3-day training programme for GPs and paediatricians, and 1-day one for SHCPs were drown up.
RESULTS. Pre-training tests showed that the level of knowledge among the participants varied significantly, the percent of wrong replies was: 11-15 mistakes – 0.5-4%; 6-10 mistakes -5-6.5%; 3-5 mistakes – 2-6%; none had 1-2 mistakes only. The level of knowledge increased significantly post-training: 11-13 mistakes – 0.5%; 6-10 mistakes – 1-3%; 3-5 mistakes – 0.5-2%; 1-2 mistakes – 1%; no mistakes – 1-2%. Almost all the participants indicated that the training was interesting and necessary, and stressed the importance of having such training on a regular basis.
CONCLUSIONS. The results showed the important role of HCPs training, re-training and education for the proper management of NCDs, and especially DM. The level of acute/chronic diabetes complications is significantly lower when we have well-educated and trained HCPs, who meet people with diabetes on an everyday

basis and manage their patients properly. It is of utmost importance when we deal with children and adolescents with T1DM appropriately in all settings, including schools.

EPIDEMIOLOGY OF DIABETIC RETINOPATHY IN ORHEI REGION OF MOLDOVA

N. Palarie[1,2], O. Tagadiuc[2]

[1]Intarnational Clinic, Department of Ophthalmology, Orhei, Moldova
[2]Department of Biochemistry, Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova

DESIGN. Retrospective analysis.
PURPOSE. Early detection and treatment of diabetic retinopathy (DR) are crucial in reducing blindness. Orhei is the largest region in Moldova with population of 102 000 inhabitants of which 3983 are registered as having diabetes. This study was to evaluate the epidemiology of DR and diabetic macular oedema in patients known to have diabetes in Orhei region of Moldova using digital retinal imaging and optical coherence tomography (OCT).
METHODS. There were 3022 persons with type 1 and 2 diabetes included in this study, 75% of all registered diabetes patients. Digital fundus images and SD-OCT images were obtained using Topcon 3D OCT 2000 FA Plus camera. The severity of DR was assessed using the International Council of Ophthalmology classification. The predominant length of diabetes among the patients was 5-10 years. A total of 2901 (96%) patients had type 2 diabetes and 120 (4%) patients had type 1 diabetes. All patients data were entered in the custom-build database (web application). This study took place in 2021-2023 at the International Clinic, Orhei, Moldova.
RESULTS. Evaluation of the 45° colour fundus photos and OCT images showed that 1450 patients (48%) did not have DR, 1027 (34%) had non-proliferative DR and 665 patients (22%) had proliferative DR. In proliferative DR vitreous haemorrhage was present at least in one eye in 66% of cases, iris rubeosis in 18%, neovascularization at the optic nerve disc in 78%, neovascularization elsewhere in 52%, preretinal haemorrhage in 18%, retinal detachment in 13% of cases. DR was associated with diabetic macular oedema in 67% of cases.
CONCLUSIONS. There is a high prevalence of sight threatening diabetic eye disease such as proliferative DR and diabetic macular oedema in our population. Thus implementation of regular screening programme together with established treatment pathway is highly recommended in Moldova.

GLP-1 RECEPTOR AGONIST THERAPY IN ELDERLY MEN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND RETINOPATHY

P. Senesi[1,2], L. Luzi[1,2], A. Ferrulli[1,2]

[1]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[2]Department of Endocrinology, Nutrition and Metabolic Diseases, IRCCS MultiMedica, Milan, Italy

DESIGN. Retrospective comparison study.
PURPOSE. Diabetic retinopathy (DR) is a growing problem, especially in elderly male patients with diabetes, resulting in increasing hospitalisations and mortality rates. Research evidence suggests that GLP-1 Receptor Agonist (GLP-1RAs) may influence DR, according to the specific GLP-1RA and patients demographic and clinical features. In this real-world study, we compared the effects of GLP-1RAs on body weight loss and HbA1c improvement, in older patients with Type 2 Diabetes Mellitus (T2DM) and overweight/obesity.
METHODS. Male patients with T2DM aged ≥ 65 years and with BMI ≥ 25 Kg/m^2, treated with GLP1-RA were considered for the study. Data were analysed at baseline (T0) and after 6 (T1) and 12 (T2) months, from the start of treatment. Out of 37 total male patients, 22 patients were without DR (no-DR group: 75.87 ± 4 yrs, BMI 31.73 ± 0.8 Kg/m^2) and 15 had DR (DR group 74.6 ± 6 yrs, BMI 30.77 ± 1.2 Kg/m^2) treated with GLP-1RA were included for the retrospective analysis.
RESULTS. In both groups, GLP-1RA therapy induced a significant BMI reduction up to one year from treatment beginning (no-DR group: from 31.73 ± 0.8Kg/m^2 to 30.72 ± 0.93Kg/m^2; DR group: from 30.77 ± 1.2 Kg/m^2 to 28.88 ± 1.35Kg/m^2). A trend toward a higher BMI decrease has been observed in the DR group (-1.882 ± 0.42 Kg/m^2) compared to no-DR group (-1.014 ± 0.3 Kg/m^2) during the one year period. No significant difference was found in HbAc1 reduction between the two groups (no-DR group = -8.091 ± 2.820 mmol/mol; DR group = -3.036 ± 3.396 mmol/mol).
CONCLUSIONS. These results suggest that elderly patients with DR seem to exhibit a better response to treatment with GLP-1RA compared to diabetic subjects without DR. Specific clinical characteristics, i.e. inflammation state, concomitant glucose-lowering medications, retinal GLP-1 receptor expression, might explain such different response.

RETINAL MICROVASCULAR FRACTAL DIMENSION AND EXPRESSION OF MIR-101 AND MIR-146A IN TYPE 2 DIABETES MELLITUS AND ASSOCIATED COMORBIDITIES

N. Popovic[1], M. Ždralević[2], I. R. Dragović[1], I. R. Lukić[1], A. A. Zečević[1,3]

[1]Faculty of Medicine, University of Montenegro, Montenegro
[2]Institute for Advanced Studies, Centre for Biomedicine, University of Montenegro, Montenegro
[3]Clinical Centre of Montenegro, Montenegro

DESIGN. Type 2 diabetes mellitus (T2D) is associated with changes in retinal microvascular complexity measured by fractal dimension (Df). Expression of micro RNAs (miRs), -146a and -101 is also affected by T2D, but studies investigating these miRs in the context of microvascular changes in T2D are scarce. Since hypertension (HTN) and Alzheimer's dementia (AD) frequently coexist in patients with T2D, in the present cross-sectional observational prospective study, participants were divided in two groups - healthy (H, $n = 8$), and with chronic disease (D, $n = 20$, has T2D, HTN and/or AD).

PURPOSE. Study explores association between changes of retinal microvascular Df and expression levels of circulating miR-146a and miR-101 in patients with T2D. The influence of HTN and AD on this association is also investigated.

METHODS. Retinal fundus images were captured by using a non-mydriatic, hand-held MIIS-HORUS scope DES200. The optic disc-centred images were manually segmented, binarized, cropped to 350-pixel radius, and Df was determined by using ImageJ 1.53q. MiRs were isolated from plasma, quantified by qRT-PCR and normalized to expression levels of miR-361-5p. SPSS Statistics 29.0.1.0., t-test and ANCOVA were used to compare the two groups. $P < 0.05$ was considered significant.

RESULTS. Age was not different between the 2 groups (H vs.D mean age $\pm$ SE $= 63.6 \pm 2.9$ vs.68.5 ± 1.8, $p = 0.17$). Df and miR-101 expression were decreased in the group D (H vs.D mean: Df $\pm$ SE $= 1.36 \pm 0.01$ vs.1.32 ± 0.01, $p = 0.016$; miR-101 $\pm$ SE $= 1.68 \pm 0.32$ vs.0.83 ± 0.22, $p = 0.041$). Eight participants in the group D had T2D (1-moderate, and 7-no diabetic retinopathy). All participants with T2D had HTN, and 5 of them also had AD. Next, we used HTN and AD as covariates to account for effects of these comorbidities, and to determine effects of T2D. This analysis showed: in addition to decreased Df and miR-101 expression, T2D was associated with increased expression of miR-146a (H vs.D mean miR-146a $\pm$ SE $= 0.58 \pm 0.29$ vs.1.69 ± 0.17, $p = 0.018$).

CONCLUSIONS. Changes in Df and in expression of miR-101 are non-specific, and can be caused by T2D and concurrent comorbidities. Increased expression of miR-146a might be a part of the unique expression pattern of circulatory miRNAs associated with T2D.