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Release of Pro-inflammatory/Angiogenic Factors by Retinal Microvascular Cells is Mediated by Extracellular Vesicles Derived from M1-activated Microglia

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DESIGN. In vitro study aimed at further evaluating microglia/microvascular cells interactions in diabetic retinopathy.
PURPOSE. Modulation of the immune response to inflammatory stimuli inside the diabetic retina is mainly mediated by microglia. Extracellular vesicles (EVs) derived from M1-activated microglia contain pro-inflammatory cytokines and miRNAs, which induce functional changes in retinal microvascular cells, while addition of thiamine to M1-microglial cultures shows protective anti-inflammatory effects. Here we aimed at verifying the release of inflammatory/angiogenic molecules by human retinal pericytes (HRPs) and endothelial cells (HRECs) exposed to EVs derived from M1-microglia and comparing the damaging effects of EV exposure vs direct stimulation with M1-cocktail on cell function, together with the anti-inflammatory potential of thiamine.
METHODS. M1 pro-inflammatory polarization in human microglial cells was induced through 24h-exposure to a cytokine cocktail (20 ng/ml hIL-1β + 10 ng/ml hTNFα + 50 ng/ml hINFγ). 50 µml/L thiamine, as a potential protective agent, were added. HREC/HRP cultures were exposed for 24 h to EVs isolated from the supernatants, and the release of several pro-inflammatory/angiogenic factors (IL-1β, IL-6, TNF-α, MMP-9, MCP-1, Ang2, VEGF, PDGF-BB), or their concentration in cell lysates (VEGF, PDGF-BB), tested by ELISA. HRECs/HRPs were also directly exposed to the M1 cocktail ± thiamine, to verify their functional response (proliferation, apoptosis, migration, ROS production).
RESULTS. IL-1β, IL-6, MMP-9, MCP-1, and VEGF release increased in HRPs exposed to M1-derived EVs, while HRECs showed augmented IL-6, Ang2, VEGF, and PDFG-BB production. Addition of thiamine to M1-microglial cultures reverted most of these effects. In contrast with previous evidence of induction of functional changes in microvascular cells exposed to M1-derived EVs, direct exposure to M1-cocktail showed no influence on HRP/HREC apoptosis, proliferation, and ROS production, while increasing HRP migration.
CONCLUSIONS. Retinal microvascular cells exposed to M1-derived EVs secrete pro-inflammatory/angiogenic molecules, which may exacerbate inflammatory damage and retinopathy features, in a sort of positive feedback. Anti-inflammatory properties of thiamine are confirmed. The damage induced in microvascular cells by inflammation is mainly due to the paracrine effects of EVs, rather than the direct stimulus of pro-inflammatory molecules.

A Marine Bioinspired Molecule Modulates the Diabetic Retinopathy Progression by M2 Response-induction and Promote the Inflammatory Resolution

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DESIGN. Retinal inflammation occurs during the early stage of Diabetic Retinopathy (DR), and plays a crucial role in the development and progression of DR. Retinal inflammation is mediated by microglia activation and leads to neuronal apoptosis. Currently, new resources with highly potent and non-toxic properties are being used, such as marine compounds, to modulate the disease. Algae bioinspired molecule 3-arilftalidas (M9) has shown properties against chronic diseases with an inflammatory component.

Immunomodulatory effects of the M9 on microglia cells (Bv.2), retinal explants, and eye drops administration in BB rat, a classical animal model for Type 1 diabetes mellitus or autoimmune diabetes, at 7 weeks of age.

PURPOSE. The aim of this work was to investigate the effects of M9 on inflammation associated with early DR by immunomodulation of specific immune retinal system and the delay of DR progression.

METHODS. Bv.2 microglial cells were stimulated with lipopolysaccharide (LPS), as an inflammatory stimulus and/or M9. Retinal explants from BB rat were cultured in the presence or absence of M9. In these experimental approaches, cytotoxicity, nitrites production, 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 was determined by immufluorescence for glial fibrillary acidic protein (GFAP). In topical eye administration of M9 or vehicle in BB rats once per day for two weeks, we evaluated retinal mRNA (RT-PCR) and SD-OCT parameters.

RESULTS. M9 treatment reduces different pro-inflammatory markers, such as iNOS and IL1b, IL6 and TNF expression in Bv.2 microglial cells. The activation of autophagy flux is enhanced by M9 treatment and induced M2 response by induction of HO-1 and increased of Arginase-1 levels. Retinal explants and eye drops M9 treatment reproduced the molecular mechanisms described in in vitro system and the reduction of inflammatory parameters. The eye drops treatment showed a reduction in retinal structure failure.

CONCLUSIONS. The marine bioinspired molecule exerts a beneficial effect on the inflammatory process that precedes DR and could be an effective alternative for its treatment and/or prevention.

The Role of Adrenomedullin in the Regulation of Angiogenesis and Endothelial Barrier Function

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DESIGN. In Diabetic Retinopathy (DR), the blood-retinal barrier undergoes changes that precede or accompany the development of angiogenesis. These pathological events can cause visual impairment and blindness, positioning DR as the leading cause of visual loss among adults in developed countries. Adrenomedullin (ADM) is a peptide hormone found to be increased in patients with DR. ADM exerts functions regulating vascular development, vasodilation and stabilization of the endothelial barrier function (EBF). However, the exact underlying mechanisms of ADM regulation in the retina is still unknown.

PURPOSE. To study the mechanism by which ADM controls angiogenesis and EBF.

METHODS. The effect of ADM knockdown (ADM-KD) by small interfering RNA (siRNA) was studied in our in vitro CD34 + tip cell model using FACS analysis and the spheroid-based sprouting model. The effect of ADM-KD was investigated using the OrganoPlate, a 3D vessel-on-a-chip sprouting assay, in the presence of vascular endothelial growth factor (VEGF). To confirm tip cell-specificity, the ADM mRNA expression in the developing mouse retina was verified by RNAscope in situ hybridization combined with Immunofluorescence (ISH-IF). The effect of ADM on vascular permeability was investigated by measuring the transepithelial electrical resistance (TEER) with the CellZscope system, both in the presence and absence of VEGF.

RESULTS. ADM-KD resulted in a 3-fold reduction in the percentage of CD34 + tip cells and a significant reduction in the number and length of sprouts in the spheroid assay. IF staining of angiogenic sprouts with anti-CD34 antibody in the OrganoPlate was reduced in siADM treated cells, as compared to cells treated with non-targeting siRNA. RNAscope ISH-IF revealed a higher ADM expression in cells residing in the angiogenic front, including tip cells. ADM administration led to endothelial barrier strengthening, reflected by increased TEER values, and partially rescued the disruption of EBF caused by VEGF administration.

CONCLUSIONS. These results indicate that ADM plays an essential role in angiogenic sprouting through the regulation of CD34 + tip cell formation. In addition, ADM was able to reduce VEGF-induced vascular permeability. Therefore, ADM may play a crucial role in pathological angiogenesis and vascular permeability.

Hypoglycemia Induces Autophagy in the Mouse Retina

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DESIGN. We assessed in vivo autophagy using EGFP-LC3 transgenic mice.

PURPOSE. We studied the role of acute hypoglycaemia in the mouse retina and showed in two different studies, that hypoglycaemia induced retinal cell death in mice and that low glucose conditions are associated with autophagy defects in 661 W photoreceptor cells and retinal explants.

METHODS. We used retinal explants of EGFP-LC3 mice and cultured them at different glucose conditions. We injected intraocular Rapamycin into these mice and performed a hyperinsulinaemic/Hypoglycaemic 5-hours clamp, with euglycemic control, to assess autophagy.

RESULTS. On retinal explants, we observed EGFP fluorescence dots (punctuation) due to LC3-II accumulation in low glucose conditions and the presence of fusion inhibitor

(Chloroquine) or autophagy activator (Rapamycin) in both low and high glucose. In comparison, diffuse EGFP was observed when the retina was cultured at 25 mM glucose without any autophagy modulators. but similar dots were observed at 1 mM. Intraocular injection of Rapamycin, as well as 5-hour hypoglycaemia, gave similar results, namely a high level of fluorescence specifically in the ganglion cell layer (GCL). Using EGFP-LC3(+/-) isolated ganglion cells, we showed EGFP fluorescence dots when these isolated cells are cultured at low (1 mM) and high (25 mM) glucose concentrations, suggesting that autophagy is induced at those glucose concentrations, while no autophagy was detected when these cells are cultured at normal glucose condition (5 mM). On the contrary, to a previous study performed on 661 W photoreceptor cells, where autophagosomes formation was also induced by low glucose, but where fusion with lysosomes was drastically impaired due to a decrease of LAMP2a expression; we do not observe any decrease of LAMP2a on isolated ganglion cells cultured at low glucose condition. We assess autophagosome/lysosome fusion on isolated ganglion cells cultured at low glucose using RFP-GPF-LC3 lentivirus enabling us to visualize this fusion. In the case of normal fusion, autophagy could have its protective effect, which was not observed on 661w cells.

CONCLUSIONS. The highlight of hypoglycaemia-induced autophagy in vivo is important and modulation of this pathway, as well as an apoptotic pathway, might be vital to avoid complications in diabetes, especially diabetic retinopathy.

Examining (I) Microvascular Responsiveness to Locally Delivered Glucagon-like Peptide-1 Analogue, Liraglutide; and (II) the Glycocalyx in Individuals with Type 2 Diabetes and Retinopathy

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DESIGN. Cross-sectional study

PURPOSE. This study examines whether (1) the skin microvascular response to the locally delivered glucagon-like peptide-1 analogue, liraglutide, and (2) the endothelial glycocalyx is altered in individuals with type 2 diabetes mellitus (DM) and diabetic retinopathy (DR).

METHODS. Individuals with type 2 DM and moderate/advanced retinopathy (DM + DR group, n = 24); individuals with type 2 DM and no microvascular complications (DM group, n = 46); and individuals without diabetes (Non-DM group, n = 44) were recruited. Liraglutide at 1/10th minimum treatment dose (0.06 mg), acetylcholine (ACh, endothelial-dependent vasodilator), saline (0.9%, microinjection control) were individually microinjected into the dermis of the forearm. Skin perfusion was assessed by laser Doppler imaging at baseline and then every 30 seconds for 10 minutes following microinjection. Skin perfusion response was expressed as stabilised response (SR, mean perfusion between 7.5-10minutes post-injection). Glycocalyx measures included (1) assessing perfusion boundary region (PBR) for all sublingual microvessels in the 5-25 μm range, as well as subdividing into 5-9, 10-19, and 20-25 μm ranges (Glycocheck software), and (2) plasma levels of shed glycocalyx components (e.g. heparan sulphate and hyaluronan).

RESULTS. Skin perfusion response to liraglutide was lower in the DM + DR group compared to Non-DM and DM groups (Non-DM group median SR (25th, 75th quartiles): 1.14 (1.10,1.40)V; DM group: 1.19 (1.12,1.34)V; DM + DR group 1.06 (0.91,1.17)V, p values <0.01). The response to ACh was attenuated in both DM groups compared to the non-DM group, and was significantly lower in the DM + DR group compared to the DM group (Non-DM group mean SR (SD): 2.04(0.39)V; DM group: 1.83(0.29) V; DM + DR group 1.68(0.25)V, p values <0.05). Plasma heparan sulfate was higher in the DM + DR group (mean (standard deviation): 121.5(88.9)ng/ml), compared to Non-DM (96.1(24.8)ng/ml) and DM (100.9(82.6)ng/ml) groups ($p < 0.05$). PBR alterations in larger microvessels were observed with DR.

CONCLUSIONS. Skin microvascular response to liraglutide is attenuated in individuals with type 2 DM and moderate/advanced DR, there is also evidence of glycocalyx perturbations in these individuals.

MDM2 Knockout in Pericytes Prevents Mouse Diabetic Retinopathy

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DESIGN. 6-week old male mice (PDGFßRcre +/-/MDM2flox/flox) were injected with tamoxifen to specifically knockout MDM2 expression in pericytes. Mice at 8 weeks old were induced diabetes by streptozotocin (STZ) injection and retinae were analysed at 32 weeks old (6 month diabetes).

PURPOSE. Diabetic Retinopathy (DR) is the predominant diabetic microvascular complication. DR is characterized by pericyte loss and acellular capillary (AC) formation, and late loss of ganglion cells. Mouse double minute 2

homolog (MDM2) is known as E3 ubiquitin-protein ligase and encoded by the MDM2 gene. MDM2 promotes rapid degradation of p53 and inhibits p53 transcriptional activation and subsequently modulates apoptosis signals (1, 2). The loss of mdm2 induces p53-mediated apoptosis in mouse (2). Our aim of this study is to determine whether MDM2-knockout will affect vasoregression and neuroretinal function in DR.

METHODS. Retinal morphometry was measured at 20- and 32 weeks of age using retinal digestion preparation. MDM2 expression were assessed using qRT-PCR and immunohistochemistry. Glial activation was quantified by GFAP immunofluorescent staining. Neuroretinal function was assessed by electroretinography (ERG).

RESULTS. Pericyte specific MDM2 knockout neither affected basic metabolic data, i.e. bodyweight and blood sugar, nor influenced neuroretinal function of experimental mice. MDM2 is overexpressed in diabetic mice. Pericyte MDM2-KO prevented diabetic vasoregression by reducing AC-formation and pericytes loss in comparison to wildtype diabetic group. Additionally, MDM2-KO reduced Müller glial activation and promotes apoptotic signalling.

CONCLUSIONS. Pericyte specific MDM2-KO prevents vasoregression and inhibits glial activation in diabetic mouse but does not recover the neuroretinal function. Hence pericyte specific MDM2-blockage could serve as a novel therapeutic approach for DR patients.

Histopathological Changes in the Retinal Neurovascular Unit During Progression of Diabetic Retinopathy

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DESIGN. The neurovascular unit (NVU) is a functional entity made up of endothelial cells, pericytes, glial cells and neurons in the blood-retinal barrier. In diabetic retinopathy (DR), dysfunction and damage of the NVU is thought to play a significant role in the development and progression of the disease. However, the cellular and molecular mechanisms involved are not fully characterized.

PURPOSE. Evaluate the changes in histopathology of the NVU during progression of DR.

METHODS. Human post-mortem eyes from patients with T2 Diabetes Mellitus (T2D) (n = 4), DR (n = 4) or non-diabetic control (n = 4) individuals were sectioned. Expression of selective NVU markers for vascular cells, perivascular cells, glial cells, tight junctions and vascular leakage were analysed using immunofluorescence staining followed by confocal microscopy.

RESULTS. We found that early signs of NVU pathology in the retina can be detected in diabetes without DR and progress in DR. Immunofluorescence analysis revealed increased extravascular fibrinogen, indicating vascular leakage in T2D retinae compared to non-diabetic controls, which was further increased in DR retinae. By studying the tight junctions of the NVU, we detected a sharply localized occludin staining in control retina at the cell border of adjacent endothelial cells, whereas in the DR retina a reduced and more intracellular expression was observed. An intermediate phenotype for occludin was found in the T2D retina. Additionally, increased glial fibrillary acidic protein (GFAP) staining was observed in astrocytes and swelling of endfeet in most T2D retinae, indicating glial cell activation. Astrocyte loss was indicated by reduced GFAP expression around capillaries in the DR retina, whereas increased GFAP expression in retinal Müller cell axons suggested gliosis. Since astrocytes are crucial in the water and ion balance of neuronal tissue, we also studied astrocytic water and potassium channels, both of which were affected in pathology in the retina.

CONCLUSIONS. The immunofluorescence staining of markers of the NVU provide further evidence for dysfunction in the vascular facet of the NVU in the retina for both T2D and DR. Our findings will contribute to the identification of impaired cellular and molecular components in the retina that occur in T2D and DR.

Investigation of the Retinal Neurovascular Unit in Diabetic Retinopathy Using 3D Electron Microscopy

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DESIGN. Serial-block face scanning electron microscopy (SBF-SEM) and computational image reconstruction was used to provide the first 3D nanoscale analysis of the neurovascular pathology that occurs during diabetic retinopathy (DR).

PURPOSE. Disruption of the integrity of the retinal NVU has been implicated in the pathogenesis of DR. Despite this, the 3-dimensional ultrastructure of the retinal NVU remains to be fully characterised. In the present study, we have undertaken the first ultrastructural examination of the anatomy of the mouse retinal NVU in three spatial dimensions using SBF-SEM and investigated changes with the onset and progression of DR.

METHODS. STZ- induced diabetic mice retinal samples were extracted and imaged using a Zeiss Sigma SEM chamber combined with Gatan 3View software. For capillaries located in the superficial plexus, the vascular basement membrane, and cells of the retinal NVU were segmented using Microscopy Image Browser (MIB).

Segmented features were visualized and rendered in 3D using Amira or ARIVIS software. Cellular morphologies and cell proximities were quantified using custom-written scripts in MATLAB r2021b.
RESULTS. Initial findings have revealed, with the onset on DR, features of the NVU showed areas of detachment from the Basement Membrane (BM), leaving intermittent gaps between the cell plasma membranes and the BM. Pericyte-endothelial interactions via peg and socket formations in non-diabetic capillaries show both cell membranes in direct contact, however, there appears to be space surrounding the peg in the socket area of diabetic capillaries. Similar electron lucent gaps were present in the endothelium of diabetic capillaries. An increase in the number of leukocytes were present in the luminal space of diabetic capillaries, which were found to make direct communication with endothelial projections.
CONCLUSIONS. This work provides new information on the ultrastructural changes to the murine retinal NVU during the onset and progression DR, which in turn can serve as a platform to inform future studies on how to delay or prevent the progression of the diseased retina.

The Mary Tyler Moore Vision Initiative Diabetic Retinal Diseases Biorepository and Resource Center

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DESIGN. Use of postmortem ocular tissues from donors with and without diabetic retinal diseases to create a deeply characterized tissue and data resource.
PURPOSE. Diabetic retinal disease is the most common eye disease caused by type 1 (T1D) and type 2 (T2D) diabetes. One of the major barriers to research in DRD is the limited availability of human eye tissue from patients with diabetes. Unlike other tissues affected by diabetes, the retina usually cannot be safely biopsied in living patients, hence the key need to obtain post-mortem human tissue. Thus, the Mary Tyler Moore Vision Initiative Diabetic Retinopathy Biorepository and Resource Center was established to provide this critical resource to accelerate development of methods to preserve, restore, and protect vision in people with diabetes.
METHODS. Samples are collected within 6 h postmortem and subsequently rapidly frozen over dry ice (OS) or fixed in a solution of formaldehyde and glutaraldehyde (OD). Fundus photograph and optical coherence tomography (OCT) microscopy (OCM) were performed for phenotyping and confirmation of DRD severity. The fixed eye was then prepared partly for cryosectioning and partly for paraffin embedding while individual tissues from the frozen tissues were dissected and stored at the UM Central Biorepository prior to multi-omics analysis at the UM Advanced Genomics or Mass Spectrometry-Based Proteomics Cores.
RESULTS. Eyes from donors with diabetes and different levels of DRD were collected and closely age, gender and race matched with tissues from donors without diabetes. Histological analysis on retinal cross-sections was combined with OCT and fundus findings to assess DRD levels of severity and specific presentations. Further molecular analysis was performed on retinal and vitreous samples to assess retinal cellular changes as well as retinal/vitreous correlation.
CONCLUSIONS. The continuous development and characterization of this novel resource provides the entire diabetes retinal disease research community with a critical quantity of deeply characterized high-quality samples and associated data necessary to better understand the pathogenesis of DRD to develop novel therapies to improve patients' lives.

Rapid Reduction of HbA1c and Early Worsening of Diabetic Retinopathy: A Real-world Population-based Study in Subjects with Type 2 Diabetes

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DESIGN. Retrospective nested case-control study
PURPOSE. Early worsening of diabetic retinopathy (DR) due to the rapid decrease of blood glucose levels is a concern in diabetes treatment. The aim of the present study was to evaluate whether this is an important issue in subjects with type 2 diabetes with mild or moderate DR, which represent the vast majority of subjects with DR attended in the Primary Care (PC).
METHODS. This was a retrospective nested case-control study of subjects with type 2 diabetes and previous mild or moderate DR. Using SIDIAP Primary Care database, we selected 1,150 individuals with early worsening of DR and 1,150 matched controls (DR without early worsening). Different relevant clinical variables, including the use of antidiabetic agents, were analysed. The main variable analysed was the magnitude of the reduction of HbA1c in previous 12 months. The reduction of HbA1c was categorized in rapid (>1.5% reduction in < 12 months) and very rapid (>2% in <6 months).

RESULTS. Mean age was 68.3 (SD = 11.1) years, 1,330 were (57.8%) men, with an average diabetes duration of 13.6 (SD = 7.20) years, and a mean baseline HbA1c of 7.91% (SD = 1.50%). HbA1c reduction did not show significant association with worsening of DR, neither in the unadjusted analyses nor in subsequent adjustment with 3 statistical models that included the main confounding variables: duration of diabetes, baseline HbA1c, presence of hypertension and antidiabetic drugs.
CONCLUSIONS. Our results suggest that the rapid reduction of HbA1c is not associated with progression of mild or moderate DR.

Development of Diabetic Retinopathy in Relation to Bariatric Surgery: A Nationwide Study

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DESIGN. Nested case-control study
PURPOSE. Bariatric surgery is associated with significant reductions in HbA1c, which can lead to early worsening of diabetic retinopathy (DR). We evaluated the potential impact of bariatric surgery on short- and long-term DR development in individuals with type 2 diabetes (T2D).
METHODS. This nationwide study examined individuals with T2D attending the Danish screening program for DR. Individuals exposed to bariatric surgery were matched 1:5 by age, sex and DR level at index date (date of surgery), with individuals without history of bariatric surgery. DR was classified according to the International Clinical Diabetic Retinopathy Severity Scale, where levels 1-4 indicate increasing severity of DR. Worsening was defined as incident or progressive DR at follow up. We utilized data from national registers, extracting information on DR levels, in- and outpatient treatments, pharmaceutical prescriptions and laboratory values.
RESULTS. Amongst 238,967 individuals with T2D, who attended diabetic eye screening (January 2013-May 2022), we identified 553 individuals that underwent bariatric surgery (0.2%) and 2,677 non-bariatric controls. Median age was 49 years (range 42-55 years) and 62.9% were female. Individuals undergoing bariatric surgery had more comorbidities (8.7% vs. 5.5%, $p < 0.01$), shorter duration of diabetes (5.1 vs. 6.2 years, $p < 0.01$), better glycaemic control (HbA1c) at index date (48.0 vs. 53.0 mmol/l, $p < 0.01$) as well as more frequent use of Metformin (82.1 vs. 70.3%, $p < 0.01$), antihypertensive medication (73.4 vs. 56.6%, $p < 0.01$), GLP-1 analogues (49.6% vs. 21.1%, $p < 0.01$) and SLGT-2 inhibitors (17.7 vs. 14.4%, $p = 0.04$) than controls. There was no difference between cases and controls in regards to marital status, use of insulin or cholesterol lowering medications. In a sex and age adjusted logistic regression analysis the odds of DR worsening, for individuals undergoing bariatric surgery, was lower at month 6 (OR 0.32 [CI 95% 0.12;0.84], $p = 0.02$) but similar at month 36 (OR 0.68 [CI 95% 0.35;1.33], $p = 0.26$).
CONCLUSIONS. In this nationwide study, bariatric surgery did not associate with a transient risk nor long-term benefits in DR development. Frequent assessment of DR, in proximity to surgery, as recommended by current Danish guidelines, might therefore not be warranted.

Patients with Type 2 Diabetes who Have Non-alcoholic Fatty Liver Disease are Less Likely to Have Diabetic Retinopathy

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DESIGN. Prospective, observational study
PURPOSE. The purpose of this study was to see if non-alcoholic fatty liver disease (NAFLD), as detected by ultrasonography, is linked to an increased risk of diabetic retinopathy (DR) in a clinical cohort of Indian patients with T2 diabetes mellitus (T2DM).
METHODS. Abdominal ultrasound was used to check for NAFLD in 500 patients. NAFLD was classified as No fatty liver; Grade 2 (mild): Mild diffuse increase in the echogenicity of the liver parenchyma or increased hepatorenal contrast; Grade 3 (moderate): Moderate diffuse increase in the echogenicity of the liver parenchyma and increased hepatorenal contrast; Mild impairment of the diaphragm and intrahepatic vessel borders; Grade 4 (severe). All patients underwent a dilated seven field fundus photography that was used to diagnose diabetic retinopathy (DR) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) grade.
RESULTS. The prevalence of NAFLD and DR in T2DM patients was 55.4% and 32.5%, respectively. The presence of DR was associated with diabetes duration, systolic blood pressure (SBP), glycated haemoglobin (HbA1c), and proteinuria (all $P < .001$) using univariate and multivariate regression analyses. The prevalence of DR was lower in patients with NAFLD than those without NAFLD (27.2% vs 34.1%, $P = .065$), and significantly lower in patients with moderate and severe NAFLD (19.2% vs 34.1%, $P = .012$; 10.3% vs 34.1%, $P = .024$). The presence of DR in NAFLD patients was associated with diabetes duration ($P = .032$) in Chi-squared analysis.
CONCLUSIONS. Our study found that DR (32.5%) is more prevalent in Indian patients with T2DM, and that

factors that increase the risk of developing DR include longer duration of diabetes, increased levels of proteinuria, higher HbA1c levels, and higher blood pressure. However, the presence of DR was lower in T2DM patients with NAFLD, especially those with moderate or severe NAFLD, compared with T2DM patients without NAFLD. Shorter duration of diabetes may be a major factor in low rates of DR in these patients.

Early Uptake and Treatment Patterns of Faricimab Among Diabetic Macular Edema (DME) Patients in the UK

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DESIGN. Retrospective observational study evaluating the utilisation and outcomes of faricimab from 2022-2024
PURPOSE. Faricimab, a bispecific antibody inhibiting Angiopoietin-2 (Ang2) and Vascular Endothelial Growth Factor (VEGF)-A, was approved in the UK on May 17, 2022 for DME. We report preliminary data from a multicentre real-world data study on faricimab uptake, patient characteristics, treatment frequency and visual acuity (VA) outcomes over time.
METHODS. Patients who received faricimab for DME at participating National Health Service sites using the Medisoft ophthalmic electronic medical record system are included. Site recruitment is currently underway and preliminary data are presented. All analyses are descriptive. As numbers grow, additional analysis of patient demographics, faricimab treatment intervals, anti-VEGF treatment history and the change in VA following faricimab treatment is undertaken.
RESULTS. As of January 9, 2022, three sites were recruited into the study, where 258 DME patients (345 patient-eyes) received at least one faricimab injection. The median duration of patient history available was 56 (Q1-Q3: 25-87) months. 249 (72%) patient-eyes were switched from another anti-VEGF treatment, primarily aflibercept (88%). Previously-treated eyes had a mean (SD) follow-up of 2.2 (1.5) months on faricimab, during which they received a mean (SD) of 2.3 (1.2) injections per eye. Anti-VEGF naive eyes had a similar mean (SD) duration of follow-up of 2.2 (1.5) months, during which they received a mean (SD) of 2.5 (1.2) injections. 71 (21%) patient-eyes had at least 4 months of follow-up on faricimab. Among these, previously-treated eyes (n = 51) received a mean (SD) of 3.5 (1.0) injections and naive eyes (n = 20) received 3.5 (0.9) injections per eye during the first 4 months of treatment.
CONCLUSIONS. Data show that a majority of the faricimab patient-eyes with DME were switched from another anti-VEGF treatment. Previously-treated and naive eyes received a comparable number of injections in the early months of initiating faricimab. Future results will describe the utilisation and outcomes of faricimab over time.

River Study - Registry Data on the Use of Intravitreal Fluocinolone Acetonide Implant for Diabetic Macular Edema in Portugal

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DESIGN. Multicenter, retrospective, non-interventional phase 4 study
PURPOSE. This real-world clinical study aimed to evaluate the long-term effectiveness and safety of the fluocinolone acetonide implant in a Portuguese population with diabetic macular edema (DME) that persisted or recurred despite treatment.
METHODS. The RIVER study assessed the effectiveness and safety of ILUVIEN® (Fluocinolone acetonide implant, FAc 0.19 mg) in 5 Portuguese centers; it was designed to retrospectively audit the patient's electronic medical records (EMR) using the Retina.pt database. Data from follow-up visits and treatments was collected from the 12 months prior to FAc to at least 6 months after its implantation. The analysed outcomes, including best-corrected visual acuity (BCVA) in ETDRS, central foveal thickness (CFT) and intraocular pressure (IOP), were assessed at similar timelines over 36 months. Statistical analysis was performed using IBM SPSS version 28.
RESULTS. The study included 222 eyes (152 patients) with DME who were treated with FAc. Patients had a mean DME duration of 4.6 ± 2.8 years. The mean follow-up time after Fac was 22.5 ± 9.0 months. In the 12 months prior to the implant all eyes had received intravitreal anti-VEGF and/or short-acting corticosteroids (2.2 ± 1.8 injections), presenting a mean loss of 5.6 ± 15.7 letters ($p < 0.001$) and a mean increase in CFT of 51.2 ± 157.5 µm ($p = 0.013$) from baseline. At the time of FAc administration, mean BCVA was 48.0 ± 7.0 letters,

increasing by 8.5 letters ($p < 0.001$) at last observation (LO). Mean CFT decreased 118.56 μm at LO ($p < 0.001$). During the post-FAc follow-up period, 38.4% of eyes required additional intravitreal treatment (0.8 ± 1.1 injections). Mean IOP remained stable during follow-up (+0.48 mmHg from baseline) and only 21% of the eyes required additional topical hypotensive treatment.

CONCLUSIONS. The RIVER study highlighted the Portuguese real-world clinical setting outcomes of DME prior and after the FAc implant. The implant proved to be safe and effective for DME treatment, significantly improving BCVA and reducing CFT, allowing a reduction in treatment burden. No serious IOP-related side effects were reported during follow-up.

High Prevalence of Vision-threatening Diabetic Retinopathy at the First Fundus Examination in Croatia

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DESIGN. Cross-sectional observational study.

PURPOSE. Screening for diabetic retinopathy (DR) in Croatia is usually performed using dilated slit-lamp biomicroscopic fundus examination only by ophthalmologists, mostly medical retina specialists. No new technologies, formal call-recall system, national survey, or system to monitor the screening frequency are introduced into the DR screening in Croatia. This study aimed to evaluate the frequency of fundus examination, and systemic risk factors control in a sample of patients with type 2 diabetes mellitus (T2DM) to determine the quality of DR prevention in Croatia.

METHODS. This cross-sectional study included 160 T2DM with a mean age of 64.28 ± 7.63 years and a mean diabetes duration of 14.01 ± 7.11 years who underwent complete diabetes and ophthalmological examinations in Vuk Vrhovac University Clinic between 15th December 2020 and 15th March 2021. Medical records, demographic, clinical, and laboratory parameters were collected and analysed.

RESULTS. The median of HbA1c was 7.05% (56 mmol/mol), blood pressure was 135/80 mmHg, and the median values of all blood lipids were within the reference range. 82.5% of all patients underwent regular diabetes check-ups two or three times a year, and 17.5% of them underwent it irregularly, once a year, or rarely. The prevalence of DR was 46.3%. 31.25% of all patients underwent a fundus examination regularly, once a year, 30% underwent it irregularly, mainly every 3 to 5 years, and in 38.75% of patients, this was the first fundus examination. Here must be emphasized that in 60% of patients with newly discovered vision-threatening DR, this was the first fundus examination.

CONCLUSIONS. The systemic risk factors control in this sample of T2DM was optimal, but only one-third of patients underwent fundus examinations regularly, once a year. These findings point to the need to introduce a systematic DR screening program into routine diabetes care in Croatia to timely detect and prevent the progression of retinopathy, improve the quality of life of diabetics, and reduce the economic burden due to disability and blindness related to diabetes.

Onset and Progression of Diabetic Retinopathy Within Eight Years in Type 1 Diabetes in the Danish Registry of Diabetic Retinopathy

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DESIGN. Retrospective longitudinal national cohort study.

PURPOSE. To evaluate the 8-year incidences of onset and 2-step-or-more progression of diabetic retinopathy (DR) as well as associated risk factors in patients with type 1 diabetes (T1D).

METHODS. We included all persons above 18 years with T1D from the Danish Registry of Diabetic Retinopathy, who had attended at least two episodes of DR-screening between 2013 and 2022. DR was classified by the International Classification of DR disease severity scale as levels 0-4, according to the worse eye at baseline. Outcomes were incident DR (level 0 to level 1-4) and 2-step-or-more progression of DR. Risk factors and possible confounders were identified in various national registries.

RESULTS. Among 22,530 persons with T1D, median (with interquartile range) age and duration of diabetes were 45.8 (28.3-60.3) and 10.9 (4.1-17.7) years, 58.3% were male, haemoglobin A1C was 64.0 (55.2-75.0) mmol/mol, and 67.6% did not have DR at first visit. During follow-up, the cumulative incidence and 2-step-or-more progression of DR was 20.5% and 7.3%, respectively. In multivariable Cox regression models, independent risk factors for both outcomes were male sex (hazard ratio

[HR] 1.08 [95% confidence interval [CI] 1.00-1.17] and HR 1.22 [95% CI 1.09-1.37]), duration of diabetes (HR 1.79 [95% CI 1.67-1.93] and HR 1.77 [95% CI 1.58-1.97] per 10 years), higher HbA1c (HR 3.22 [95% CI 2.67-3.88) and HR 10.07 [95% CI 7.99-12.70] for levels 100 mmol/mol or above), and being never married (HR 1.18 [95% CI 1.06-1.31] and HR 1.18 [95% CI 1.02-1.37]). Lower HbA1c (HR 0.72 [95% CI 0.61-0.86] and HR 0.72 [95% CI 0.52-0.99] for levels 40-49 mmol/mol) was identified as the only protective factor.

CONCLUSIONS. In a national cohort of patients with T1D, one in five developed DR within eight years. Male sex, longer duration of diabetes, and never being married were all identified as risk factors, but glycaemic regulation was the most important marker with a low risk for patients with well-regulated disease and a raising risk according to the severity of glycaemic dysregulation.

Prognostic Factors for the Development and Progression of Proliferative Diabetic Retinopathy (PDR)

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DESIGN. Systematic review and meta-analysis undertaken under the auspices of the Cochrane Collaboration.

PURPOSE. To determine risk factors for the development of PDR and progression to high-risk characteristics-PDR (HRC-PDR).

METHODS. Systematic review and meta-analysis. CENTRAL, Ovid MEDLINE and Embase were searched with no date or language restrictions. Reference lists of eligible articles were also scrutinized. Prospective or retrospective cohort or case-control studies evaluating prognostic factors for the development and progression of PDR were included. The Quality in Prognosis Studies (QUIPS) tool was used to assess risk of bias. We conducted meta-analyses in clinically relevant groups using a random-effects approach and reported hazard ratios (HR), odds ratios (OR), and risk ratios (RR) separately, stratified by different time points. Where possible, we meta-analysed adjusted prognostic factors. Certainty of the evidence was determined by an adapted version of GRADE for prognosis studies.

RESULTS. Of 6391 records screened 87 articles were found eligible and included. There were 35 prospective cohort studies and 22 retrospective studies, with six of these based on data from electronic registers, two case-control and the remaining cohort studies.

There was evidence that higher HbA1c and more advanced stage of retinopathy are independent risk factors for the development of PDR in people with T1D and T2D (moderate certainty). There was some evidence suggesting several markers for renal disease and, in people with T1D, age at diagnosis of diabetes, increased triglycerides and larger retinal venular diameters may increase the risk of progression to PDR (low/very low certainty). There was no substantial and consistent evidence to support duration of diabetes, systolic or diastolic blood pressure, total cholesterol, low- and high-density lipoproteins, gender, ethnicity, body mass index (BMI), socioeconomic status, or tobacco and alcohol consumption being associated with incidence of PDR. There was insufficient evidence to evaluate progression to HRC-PDR.

CONCLUSIONS. Increased HbA1c seems associated with progression to PDR. Maintaining adequate glucose control throughout life, irrespective of stage of DR severity, may help to prevent progression to PDR and risk of its sight-threatening complications.

Results of the Two-year Screening Interval Initiative within the Irish National Diabetic Retinopathy Screening Programme (Retinascreen)

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DESIGN. Retrospective cohort study

PURPOSE. To evaluate the safety and outcomes of increasing the screening interval to 2-years.

METHODS. Patients who met the criteria for two-year screening (two consecutive R0M0 grades within 11-13 months) after its inception in 2019 were compared against patients who had two consecutive R0M0 grades but outside of the two-year time interval criterion. A logistic regression was carried out to determine which factors (age, sex, diabetes type, diabetes duration, time between visits and two-year/one-year screening interval) were associated with worsening of diabetic retinopathy grade on a subsequent visit. Patients were excluded if the outcome visit was ungradable or was labelled as having non-diabetic eye disease. The worst grade of both eyes was used for each patient in the analysis.

RESULTS. A total of 12,730 of patients were included in the two-year group and 14,042 in the one-year group. The median (IQR) age of the total population was 68.6 (58.9–76.3) years and the mean diabetes duration was 10.6 years. The mean (SD) time between visits was 2.26 (0.29) years and 1.38 (0.51) years in the two-year and one-year groups respectively.

Diabetes duration (OR: 1.04 per decade, $p < 0.001$), diabetes type (OR: 1.07 Type 1, $p < 0.001$), time between visits (OR: 1.04 per year, $p < 0.001$) and two-year screening (OR: 1.01, $p = 0.02$) were statistically significant predictors of progression. The absolute (uncorrected) rates of progression were 19% in the two-year group and 13.5% in the one-year group. The vast majority of these (97% in both groups) progressions were to retinopathy grade R1. There was no difference between the groups noted with respect to progression to retinopathy grades R2 or R3 ($p = 0.2$ for both).

CONCLUSIONS. There was a small, expected increase in non-sight-threatening diabetic retinopathy in the two-year screening interval group. There was no difference in progression to higher grades of retinopathy.

5-year Outcomes for DME Following Anti-VEGF TREatment: Multicentre Analysis in the UK

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DESIGN. Retrospective observational study of diabetic macular edema (DME) patients, mostly referred from diabetic eye screening programs, treated with intravitreal anti–vascular endothelial growth factor (VEGF) injections.

PURPOSE. Studies of long-term, real-world vision outcomes for DME patients treated with anti-VEGF injections are sparse. This study described anti-VEGF treatment patterns/visual acuity (VA) up to 5 years from index treatment for DME patients treated in routine clinical practice in the UK.

METHODS. Data were extracted from Medisoft electronic health records at 4 National Health Service centres in the UK (2008–2021). One treatment-naïve eye per adult DME patient was included (if bilateral, first eye to meet case definition (DME diagnosis)/right eye if both met definition simultaneously). Eyes with <180 days of follow-up after index diagnosis, neovascular age-related macular degeneration, retinal vein occlusion or no anti-VEGF treatment were excluded. Treatment patterns/VA outcomes were summarised descriptively.

RESULTS. The cohort ($n = 2559$) had a median age of 62 years (39% women, 81% White). Median (interquartile range [IQR]) number of anti-VEGF injections received from 0–6 months; 7–12 months; and in years 2, 3, 4 and 5 were 4 (3–5), 1 (0–3), 2 (0–4), 1 (0–4), 1 (0–3) and 0 (0–3), respectively. Percentage of patients with no additional anti-VEGF treatment within a follow-up year ranged from 36% (year 2) to 52% (year 5). Median (IQR) baseline VA was 63 (51–72) letters. Median VA change (IQR) at 6 months and 1, 2, 3, 4 and 5 years were 4 (-1–10), 5 (-1–11), 4 (-3–11), 3 (-5–11), 3 (-5–12) and 4 (-3–13) letters, respectively.

CONCLUSIONS. Anti-VEGFs generally improved vision among DME patients, with medians change of 3–5 letters up to 5 years after index treatment. This is lower than the >10-letter change reported in pivotal randomised clinical trials, potentially due to fewer anti-VEGF injections received in our sample vs pivotal trials. Over time, anti-VEGF frequency declined, and the percentage of untreated patients increased. Novel longer-acting therapies may potentially address this unmet need in vision outcomes.

10-year Outcomes of Patients Referred with Proliferative Diabetic Retinopathy from the United Kingdom Diabetic Retinopathy Screening Service

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DESIGN. This retrospective multicenter study included patients referred to adjacent specialist ophthalmology units with PDR over a 36-month period (2007-9) from two DESPs in the UK. These patients were followed-up for 10-years. The critical outcomes included were severe vision loss (SVL) and the need for vitrectomy in the affected eye. Other important outcomes assessed included moderate vision loss (MVL) in the affected eye, and patient survival time. Univariate and multiple variable Cox proportional hazards regressions were used to analyse survival outcomes.

PURPOSE. This study aimed to determine long-term real-world outcomes of patients referred with proliferative diabetic retinopathy (PDR) from diabetic eye screening programmes (DESP) to tertiary care centres in the United Kingdom (UK).

METHODS. This retrospective multicenter study included patients referred to adjacent specialist ophthalmology units with PDR over a 36-month period (2007-9) from two DESPs in the UK. These patients were followed-up for 10-years. The critical outcomes included were severe vision loss (SVL) and the need for vitrectomy in the affected eye. Other important outcomes assessed included moderate vision loss (MVL) in the affected eye, and patient survival time. Univariate and multiple variable Cox proportional hazards regressions were used to analyse survival outcomes.

RESULTS. The 10-year 'survival' (free from vitrectomy) in all PDR eyes was 74.0% (95% CI: 65.0% to 82.0%). Vitrectomy when required was mostly performed for

vitreous haemorrhage (65.4% eyes) and resulted in significant improvement in best-corrected visual acuity from 42.2 ± 29.2 pre-operatively to 66.2 ± 20.0 ETDRS letter score post-operatively ($p = 0.005$). The 10-year survival in all PDR patients was 76.0% with mean time to death for all deceased patients was 5.37 ± 3.63 years. In multi-variable analysis, none of the ocular or systemic factors were found to have significant association with vision loss and vitrectomy. Only age was found to have significant association with survival of patients with PDR. The risk of death at any time was four times higher in those aged 50 years or over compared to the under 50 years group (95% CI: 1.33 to 13.3, $p = 0.008$).

CONCLUSIONS. The results from this real–world study showed that in eyes with PDR severe vision loss was not a common occurrence, but nearly one-third of eyes fell below UK driving standards for vision with 10-year long follow-up. Vitrectomy is an important intervention for managing these patients, required in approximately 1 in 4 eyes.

Impact on Blindness of Organized Diabetic Retinopathy Screening Including Artificial Intelligence (AI) and Optical Coherence Tomography (OCT) in Urban China - A Lifetime Cost Effectiveness Analysis

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DESIGN. Cost effectiveness analysis

PURPOSE. Many middle-income countries including China have a scarcity of ophthalmologists and have not started organised diabetic retinopathy (DR) screening. Latest developments in DR screening such as AI-assisted grading, low-cost fundus cameras and OCT offer potential solutions in such settings. We investigated the long-term impact of such a next-generation screening programme in urban China on blindness prevention and cost effectiveness.

METHODS. Our cost effectiveness analysis was from a government perspective. An individual Markov model simulated the natural history of 100,000 people with known diabetes. Transitions were estimated from direct observations and published data sense-checked against Chinese data where available. We compared lifetime costs (2020 US dollars) and effectiveness (new blindness from DR, quality-adjusted life years (QALY)) between: i) organised screening (technicians, AI photo grading, OCT, human arbitration) with 80% annual uptake; ii) the current ophthalmologist-led opportunistic screening with 2% annual uptake rate. An incremental cost-effectiveness ratio (ICER) < 1 GDP per capita (11,638 USD for China) was deemed to be highly cost-effective (WHO guidelines). Scenario analysis compared the effect of varying treatment for clinically significant macular oedema (CSMO): laser only, antiVEGF + laser.

RESULTS. Compared to the current screening in China, with laser only for CSMO, organised screening reduced blindness by 52.4% in the model across the lifetime, gained 0.23 QALYs with incremental cost of 682 USD / individual. This generated an ICER of 2,942 USD/QALY gained, 0.25 times GDP per capita. With anti-VEGF + laser for CSME blindness reduced by 61.9%, gaining 0.31 QALYs, with incremental cost of 3,177 USD. The ICER was 10,259 USD/QALY gained, 0.89 times GDP/capita. Results remained robust in sensitivity analyses.

CONCLUSIONS. Introducing systematic screening including AI and OCT based in a middle-income setting with no prior organised screening appears to offer an ICER well within the WHO guidelines for effective interventions. These findings provide strong economic evidence to support the wide introduction of systematic screening in populations not currently undergoing organised screening.

Accuracy of Point of Care Artificial Intelligence Grading Using Handheld Retinal Imaging in a Community-based Diabetic Eye Screening Programme

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DESIGN. Cross-sectional prospective study

PURPOSE. To evaluate the performance of point of care (POC) artificial intelligence (AI) assessment of handheld retinal imaging in a community-based diabetic eye screening programme (DESP) as compared to retinal image graders at a centralised reading centre (RC) in identifying diabetic retinopathy (DR) and diabetic macular oedema (DMO)

METHODS. POC AI assessment of disc and macular handheld retinal images was compared with RC evaluation of validated 5-field handheld retinal images [(5F) disc, macula, temporal, superior and inferior] in identifying referable DR [(refDR) moderate nonproliferative DR (NPDR) or worse, or any level of DMO] and vision

threatening DR [(vtDR) severe NPDR or worse, or any level of center involving DMO (ciDMO)]. RC evaluation of the 5F images followed the international DR/DMO classification. Sensitivity and specificity (SN/SP) for ungradable images, refDR and vtDR were calculated.

RESULTS. 5,585 eyes from 2,820 patients with diabetes (DM) were included in the study. Cohort demographic: age 59.1 ± 10.4, 95.5% type 2, DM duration 7.1 ± 7.3 years. RC distribution of DR severity: no DR 3,758 (67.3%), mild NPDR 540 (9.7%), moderate NPDR 482 (8.6%), severe NPDR 271 (4.8%), PDR 213 (3.8%), ungradable 321 (5.8%). DMO Severity: no DMO 4,490 (80.4%), DMO 430 (7.7%), ciDMO 246 (4.4%), ungradable 419 (7.5%). RefDR was present in 25.3% and vtDR in 17.5% of eyes. Images were ungradable for DR or DMO in 7.5% by RC and 15.4% by AI. SN/SP of AI grading compared to RC evaluation was 0.86/0.86 for refDR and 0.92/0.80 for vtDR.

CONCLUSIONS. This study demonstrates that point of care AI assessment following a defined handheld retinal imaging protocol achieves sensitivity and approaches specificity thresholds of 0.80 and 0.95, respectively, in identifying referable DR. Integrating AI assessment at the time of imaging could substantially reduce centralised reading center burden and expedite information delivery to the patient, allowing more prompt eye care referrals. Additional studies on data diversification and algorithm optimisation may further improve AI performance.

Screening for Telcaps by Oct Thickness Mapping in Patient with Diabetic Macular Oedema

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DESIGN. prospective data from a French national, multicentric, ongoing randomized, controlled trial

PURPOSE. Intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) agents help reducing macular thickness in patients with diabetic macular oedema (DMO). However, they imply long-standing treatment and represent a heavy burden for the patients and the health care system. Anti-VEGF-resistant telangiectatic capillaries (TelCaps) have been reported, which result in persistent focal oedema, on which Indocyanine Green Angiography (ICGA) guided laser therapy is effective. In this study, we investigated the qualitative changes in macular thickness visible on OCT-mapping after intravitreal injection of anti-VEGF agents, in eyes with DMO and TelCaps.

METHODS. prospectively collected data from a French national, multicentric, ongoing randomized, controlled trial evaluating the efficacy of targeted photocoagulation of TelCaps in addition to intravitreal anti VEGF injections in eyes with central involving DME were collected. Ten eyes of 10 patients with Type 2 diabetes (8 males and 2 females, mean age 65 ± 9 years, mean baseline HbA1C 8.3 ± 1.5%) were studied with a 12-months follow-up. After three monthly loading doses of intravitreal injection (IVI) of anti-VEGF agents, a pro re nata regimen was applied. Patients in the laser group received additional targeted photocoagulation of late ICGA staining TelCaps. Imaging protocol for OCT and ICGA was performed with Heidelberg Spectralis HRA + OCT (Heidelberg, Germany). The location of the TelCaps and the corresponding retinal thickening were determined using the OCT- map overlaid on the ICG images, in modulating the contrast and transparency. Evolution of central macular thickness (CMT), as well as a qualitative analysis of topography of macular thickening over time on OCT-map within a 6-mm diameter macular region were studied.

RESULTS. There was a significant reduction of macular thickness between baseline and 3 months after a loading dose of three monthly anti-VEGF agents (± adjunctive laser), decreasing from 426 ± 85 μm to 319 ± 99 μm. Qualitative analysis of the OCT-mapping revealed that macular oedema associated with Telcaps was often asymmetrical and polylobulate. TelCaps were easily identified after IVI, because residual patches of retinal thickening systematically co-localised with TelCaps visible on late ICGA. After relative suspension of anti -VEGF (PRN regimen from 3 to 12 months), new increase in retinal thickness systematically emerged from TelCaps, with a similar pattern to the one before IVI.

CONCLUSIONS. In patients with DMO, persistent patches of retinal thickening despite repeated IVI may indicate the presence of TelCaps, which are often located under the summit of focal edema, and usually correspond to the center of circinate exudation. In the absence of ICGA, OCT mapping may be helpful to screen for TelCaps that may then be identified by high resolution OCT imaging, which may guide photocoagulation.

Abnormal Fluid Accumulation in the Diabetic Retina Quantified by Oct-leakage

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DESIGN. 3-year longitudinal study

PURPOSE. To demonstrate abnormal fluid accumulation in the retina using optical coherence tomography leakage (OCT-Leakage) in the initial stages of diabetic retinopathy during a 3-year follow-up period.
METHODS. Seventy-four eyes from 74 patients with type 2 diabetes were followed in a 3-year longitudinal study with 1-year intervals using OCT-Leakage. The OCT-Leakage algorithm is an image analysis algorithm based on the projection of low optical reflectivity (LOR) voxels to a plane perpendicular to the depth direction. LOR voxels are identified by thresholding the reflectivity intensity of CIRRUS™ HD-OCT 5000 with AngioPlex® OCT Angiography (ZEISS, Dublin, CA, USA) structural data by a reference value calculated from a normative database of healthy control subjects. Extracellular fluid distributions of a given area of the retina can be measured by the LOR area ratio. 3-dimensional distribution of extracellular fluid, amount, extent, and depth location was identified on each retinal layers to assess for abnormal accumulation of extracellular fluid. Central retinal thickness for each participant was collected at each visit to check for the development of center involved macular oedema (CIME).
RESULTS. CIME was identified in the first visit in 9% (n = 2/23) of the eyes in ETDRS 10-20, 10% (n = 3/31) of eyes in the ETDRS 35 and 15% (n = 3/20) of eyes in ETDRS 43-47. The eyes with CIME and subclinical CIME showed progressive increase in retinal extracellular fluid during the 3-year period of follow-up. At the end of the 3-year period all eyes with CIME showed increased LOR ratios independently of the EDTRS level. Increase LOR ratio was also present in 60% of the eyes with subclinical macular oedema. CIME with increased retinal extracellular fluid accumulation was shown to be associated with vision loss.
CONCLUSIONS. The prevalence of subclinical CIME and CIME in non-proliferative diabetic retinopathy occurs independently of the severity of the retinopathy. The accumulation of extracellular fluid can be monitored with the OCT-Leakage algorithm. OCT-Leakage demonstrates a progressive increase in extracellular fluid in long standing CIME. Variations in the increase of extracellular fluid are associated with vision loss.

Sensitivity and Specificity of the Optical Coherence Tomography Angiography for Detection of Neovascularization and Evaluation of Peripheral Ischemia in Diabetic Retinopathy

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DESIGN. Retrospective clinical study
PURPOSE. To identify the sensitivity and specificity of optical coherence tomography angiography (OCTA) parameters for the presence of neovascularization elsewhere (NVE) and to investigate the relationship between ischemic areas.
METHODS. This study included 59 eyes with nonproliferative diabetic retinopathy (NPDR) and 36 eyes with proliferative diabetic retinopathy (PDR). The detailed ophthalmological examination, OCTA (RTVue; Optovue, Fremont, CA) and ultra-widefield fluorescein angiography with the Optos 200Tx (Optos, Dunfermline, UK) were performed in all patients. The foveal avascular zone (FAZ), vessel density (VD) for the superficial and the deep capillary plexus (DCP), choriocapillaris flow area (CCP) and nonperfusion area (unit²) were recorded. The area (AUC) under the receiver operating characteristic curves, sensitivity and specificity were calculated for statistically significant outcomes.
RESULTS. The VD in DCP was significantly lower, FAZ and nonperfusion area were larger in PDR group. ($p = 0.001$, $p < 0.001$, $p < 0.001$) The AUC for presence of NVE, for the VD was 0.710 ($p = 0.012$) with sensitivity and specificity of 64% and 65%, for the FAZ was 0.746 ($p < 0.001$) with sensitivity and specificity of 72% and 72.7%. There was a significant positive correlation between the FAZ and nonperfusion area. (For NPDR, $p = 0.025$, for PDR $p < 0.001$) There was a significant negative correlation between the VD in DCP and ischemic area in PDR group. ($p < 0.001$).
CONCLUSIONS. In cases with decreased VD in DCP and increased FAZ, the probability of PDR increases. Despite the sensitivity and specificity of the OCTA indices for the prediction of NVE being moderate, the OCTA is very useful in evaluating the microvascular structure in DR.

Swept-source Octa Discriminates Severity Staging of NPDR: the Chart Study

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DESIGN. Two year prospective observational longitudinal study

PURPOSE. To test whether the location of a single or composite set of parameters evaluated with widefield swept-source optical coherence tomography angiography (SS-OCTA) and representing retinal capillary closure, can discriminate between advanced stages of non-proliferative diabetic retinopathy (NPDR).
METHODS. Ninety-five eyes from diabetic patients included in the CHART study (NCT04636307) with different severity stages of NPDR were evaluated on SS-OCTA (PLEX® Elite 9000, ZEISS, Dublin, CA, USA) using Angiography 15×15 mm and Angiography 6×6 mm acquisition protocols. These acquisitions were processed on the ARI portal using Macular Density v0.7.3.3 algorithm. 7-field photographs of the fundus were obtained for Early Treatment Diabetic Retinopathy Study (ETDRS) staging. Eyes were separated based on their ETDRS severity grade - ETDRS level 35 and ETDRS levels 43 to 47. SS-OCTA perfusion density (PD) and vessel density (VD) metrics were compared for each macular area.
RESULTS. Widefield SS-OCTA VD metrics show statistically significant differences between ETDRS 35 and ETDRS 43 to 47 severity levels in the mid-periphery, Extended Rings 1, 2 and 3 (3 mm < radius < 7.5 mm) in the deep capillary plexus (DCP, $p < 0.001$) and in the full retina (FR, $p < 0.037$). The VD of superficial capillary plexus (SCP) can discriminate between groups on the Extended Ring 3 (6 mm < Radius < 7.5 mm, $p = 0.037$).
In the perifoveal area, Outer Ring (1.5 mm < radius < 3 mm), the DCP of the Angiography 15×15 mm acquisitions is capable of discriminating between ETDRS groups while Angiography 6×6 mm protocol is not. Although the digital resolution of the 15×15 mm scan is worse than the 6×6 mm scan, the former appears to be more sensitive to blood flow changes, considering its specific binarization threshold, thus providing better separation between ETDRS groups. PD show similar results to VD.
CONCLUSIONS. Information of non-capillary perfusion in the mid-periphery of the retina obtained using widefield OCTA (PLEX Elite) is particularly relevant to identify NPDR progression and discriminate ETDRS 35 (mild NPDR) from ETDRS 43-47 (moderate and moderately severe NPDR).

Combination of Ultra-widefield Colour Fundus Photography and Optical Coherence Tomography Angiography Identify Different Subtypes of Non-proliferative Diabetic Retinopathy

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DESIGN. Cross-sectional observational study.
PURPOSE. To identify changes in central vascular density using Optical Coherence Tomography Angiography (OCTA) in diabetic patients with and without peripheral lesions identified on ultra-widefield fundus photographs (UWF-FP).
METHODS. A cross-sectional observational study in patients with Type II diabetes. All patients underwent UWF 200° examinations with OPTOS California (Optos, Dunfermline, UK) and 3×3 mm acquisitions with CIRRUS™ HD-OCT 5000 with AngioPlex® OCT Angiography (ZEISS, Dublin, CA, USA). UWF images were graded based on the presence and location of retinal lesions: A-eyes without lesions; B-eyes with lesions inside the 7-ETDRS fields; C-eyes with lesions inside and outside the 7-ETDRS fields; and D-eyes with peripheral lesions only (outside 7-ETDRS fields). OCTA metrics like foveal avascular zone, vessel density (VD) and perfusion density (PD) were computed with Carl Zeiss Meditec Density Exerciser (version:10.0.12787).
RESULTS. 729 diabetic eyes were observed. 131 (18%) presented visible lesions in UWF-FP, while 598 (82%) showed no visible lesions. According to the location of retinal lesions, 26 (19.9%) showed only lesions inside the 7-ETDRS fields, 46 (35.1%) presented visible lesions inside and outside the 7-ETDRS fields and 59 (45%) presented visible lesions only in the peripheral retina (outside the 7-ETDRS fields). OCTA metrics calculations were performed in all eyes with lesions ($n = 131$) and in a sample of eyes without lesions ($n = 124$). VD and PD values on SD-OCTA were significantly decreased in all groups when compared with an age matched healthy population ($p < 0.001$). The group with lesions both inside and outside the 7-fields ETDRS area showed the most significant decrease of VD and PD ($p < 0.001$).
CONCLUSIONS. Central retinal VD and PD show microvascular changes in all eyes with diabetes type 2 including eyes without visible lesions or with visible lesions only in the periphery of the retina. These findings suggest the relevance of OCTA to identify macular microvascular changes in the initial stages of DR and confirm that there are different subtypes of DR, confirming the value of OCTA and widefield imaging for their characterization.

The Dipeptidyl Peptidase 4 (DPP-4) Inhibitor, Sitagliptin, Exerts Direct Anti-inflammatory Effects on Microglial Cells

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DESIGN. We demonstrated that neuroinflammation-mediated by microglia has a major contribution for retinal dysfunction/degeneration. We also reported that the inducible nitric oxide synthase (iNOS) has a key role in blood-retinal barrier (BRB) breakdown triggered by diabetes. Sitagliptin is an oral drug for type-2 diabetes. By inhibiting dipeptidyl peptidase 4 (DPP-4), sitagliptin stimulates insulin release. In diabetic animal models, we found that sitagliptin prevents BRB dysfunction, nitrosative stress and the increase in pro-inflammatory mediators.
PURPOSE. We evaluated whether sitagliptin is able to directly inhibit microglia reactivity.
METHODS. Retinal primary mixed cell cultures and organotypic cultures from Wistar rats, and cultures of the BV-2 microglia cell line were exposed, respectively, to 1microg/mL, 3microg/mL or 0.1microg/mL lipopolysaccharide (LPS), for 24 h, in the absence or presence of 200microM sitagliptin. iNOS immunoreactivity was quantified in CD11b-positive cells. Nitrites were measured by the Griess reaction. Changes in microglia morphology were assessed in organotypic cultures. In BV-2 cells, the expression of DPP-4 was assessed by RT-PCR and Western Blot (WB). The protein levels of iNOS, IL-1 beta and TNF-alpha were assessed by WB. The phagocytic efficiency was determined using fluorescent microbeads.
RESULTS. Exposure of primary and organotypic cultures to LPS significantly increased iNOS immunoreactivity in CD11b-positive cells. Sitagliptin significantly inhibited iNOS immunoreactivity in both cell cultures by 63.6% and 48.1%, respectively. In primary cultures, sitagliptin inhibited the levels of nitrites. LPS changed the morphology of microglia, becoming more amoeboid. Sitagliptin prevented those morphologic changes. BV-2 cells expressed DPP-4. LPS enhanced the levels of iNOS, IL-1 beta and TNF-alpha in BV-2 cells. Sitagliptin inhibited those increases to $39.9 \pm 6.3\%$, $47.2 \pm 8.1\%$ and $34.0 \pm 7.2\%$, respectively, comparing to LPS condition. Sitagliptin also reduced the LPS-induced increase in phagocytic efficiency of BV-2 cells by approximately 40%.
CONCLUSIONS. Sitagliptin exerts direct anti-inflammatory effects on microglial cells. BV-2 cells express DPP-IV, but additional experiments are needed to prove whether the effects of sitagliptin are completely mediated by DPP-4 blockade. Altogether, these results suggest that sitagliptin can potentially be used in retinal pathologies characterized by microglia-mediated neuroinflammation.

Mirna-124 Prevents Rat Diabetic Retinopathy by Inhibiting the Microglial Inflammatory Response

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DESIGN. Wistar rats were induced diabetes by streptozotocin (STZ) injection. Diabetic rats were intravitreally injected with miR-124 mimic or miR-124 inhibitor. Diabetic retinopathy was evaluated on vasculature and neuroretinal function. The effect of miR-124 replacement on glial activation and inflammatory responses was assessed both in vitro and in vivo.
PURPOSE. MicroRNA (miR)-124 is a short non-coding RNA abundant in the central nervous system (CNS). It inhibits retinal microglial activation and alleviates vasoregression in a neurodegenerative rat model. The aim of the present study was to determine whether miR-124 affects vascular and neural damages in the early diabetic retina.
METHODS. Eight-week-old male Wistar rats were induced diabetes by a single intraperitoneal injection of STZ (35 mg/kg BW). Diabetic rats were intravitreally injected with 25 pmol of miR-124 mimic (DC + 124), or miR-124 inhibitor (DC + inh) or solvent (DC). Retinal morphometry was analyzed at 24 weeks. miR-124 distribution was detected by in situ hybridization (ISH) and Müller glial activation was assessed by GFAP immunofluorescence (IF). Microglial activation was evaluated by Iba1-IF. Neuroretinal function was analyzed by ERG. The motility of miR-124 transfected BV2 microglial cells was examined by wound healing assay. The downstream signals of miR-124 regulation were evaluated by qPCR and immunostaining.
RESULTS. miR-124 treatment reduced AC formation by 63% and pericyte loss by 24% in comparison to non-treated diabetes group ($p < 0.001$). miR-124 blunted Müller glial- and microglial activation in diabetic retinae and ameliorated neuroretinal function. The retinal expression of inflammatory factors including Tnf-α, Il-1β, Cd74, Ccl2, Ccl3, Vcam1, Tgf-β1, Arg1, and Il-10 was reduced in the group with exogenous miR-124 introduction. The elevated mobility of microglia upon high glucose exposure was normalized by miR-124. The expression of the transcription factor PU.1 and lipid raft protein Flot1 was downregulated by miR-124 both in vivo and in vitro.
CONCLUSIONS. miR-124 prevents vasoregression and glial activation, improves neuroretinal function, and

modulates microglial activation and inflammatory responses in diabetic rats. Hence, miR-124 intervention at early stage might prevent progression of diabetic retinopathy.

Tear Fluid Proteins Analysis from Donors with Diabetes and Diabetic Retinopathy (DR)

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DESIGN. This was a cross-sectional, non-interventional study approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (CHUC; Coimbra, Portugal) with identification CHUC-059-18. All participants provided informed consent after being briefed of the purposes of the study, design, and possible complications. The study adhered to the Declaration of Helsinki. Participants included patients with T2D, without or with diabetic retinopathy (NPDR or PDR), and healthy subjects (control group) aged 40-75 years old. A total of 54 T2D patients, who had been diagnosed for over 5 years and were on insulin therapy and/or oral antidiabetic agents, were included: 13 without DR, 25 with NPDR, and 16 with PDR. The control group included 12 healthy subjects. All participants, including those in the control group and patient groups, underwent an ophthalmic examination.
PURPOSE. Tear fluid biomarkers can offer a non-invasive approach for identifying diabetic patients at higher risk of developing DR or experiencing disease progression. In this study, we examined the tear fluid of individuals without diabetes, diabetic patients without DR, and diabetic patients with either NPDR or PDR to identify potential biomarkers for diagnosis and stage of DR.
METHODS. Tear fluid samples were collected from 12 healthy individuals and 54 Type 2 Diabetes (T2D) patients using Schirmer test strips and analysed using mass spectrometry (MS)-based shotgun proteomics and bead-based multiplex assay. Tear fluid-derived small extracellular vesicles were also analysed using transmission electron microscopy, Western Blotting, and nano tracking.
RESULTS. Proteomics analysis showed differentially expressed proteins in tear fluid of NPDR and PDR patients when compared to controls. Data is available on ProteomeXchange under PXD033101. Multicomparison analyses found significant changes in 32 proteins, most associated with oxidative stress and small extracellular vesicles. T2D patients with NPDR have higher concentrations of IL- 2/-5/-18, TNF, MMP-2/-3/-9 compared to controls. PDR patients have higher concentrations of IL-5/-18 and MMP-3/-9 and lower IL-13 concentrations compared to controls.
CONCLUSIONS. The results indicate changes in the protein profile of tear fluid in diabetic patients with retinopathy. The promising biomarkers identified will require further validation in a larger patient cohort.

Variations in Genetic Profile as Predictors of Anti-VEGF Treatment Response in Conditions with Macular Oedema

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DESIGN. Genome wide association study (GWAS) of patients with macular oedema treated with anti-VEGF.
PURPOSE. Intraocular anti-VEGF therapies are currently the primary treatment for retinal conditions with vascular leakage and/or macular oedema, but there is significant variability in how well they work for different patients. This study aimed to identify genetic factors that may influence the effectiveness of anti-VEGF treatment for ME.
METHODS. We performed a GWAS using the Infinium® Global Screening Array of Illumina on 3 well-characterized cohorts of 606 patients with diabetic macular oedema (DMO), retinal vein occlusion (RVO) and neovascular age-related macular degeneration (nAMD) treated with bevacizumab or ranibizumab, with visual acuity (VA) and anatomical optical coherence tomography (OCT) parameters as outcomes.
RESULTS. GWAS meta-analysis for change in VA after 6 months of anti-VEGF treatment for the combined cohorts resulted in 135 variants of which 6 with a p-value < 1x 10-6. GWAS meta-analysis for change in retinal thickness after 6 months of anti-VEGF treatment for the combined cohorts resulted in 586 variants of which 45 with a p-value < 1x 10-6.
CONCLUSIONS. Our GWAS meta-analysis identified several genetic variants that may be associated with functional or anatomical response to anti-VEGF treatment in patients with retinal conditions with vascular leakage and/or MO. These findings may help to identify genetic markers that can predict treatment response, or uncover new pathways involved in vascular leakage and MO.

Differential Pattern of Biomarkers Between an Early and Advance Stage in T1DM Patients with Diabetic Retinopathy

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DESIGN. Inflammatory phenomena are present in the development of diabetes, and therefore in the appearance and progression of diabetic retinopathy (DR). In addition, in patients with Type 1 diabetes mellitus (T1DM) there are alterations in the innate immune system that can enhance rapid DR progression. The rupture of the blood retail barrier (BRB) allows the exchange of these inflammatory mediators between the retina and the circulatory system. The use of SD-OCT has facilitated the assessment of DR progression, however the association between SD-OCT parameters and serum biomarkers could help determine DR progression in a personalized way.
PURPOSE. The goal of this study is to determine the relationship between the SD-OCT parameters detected in the retina and serum inflammatory mediators in T1DM patients in two different steps of disease as an early prognostic biomarker for DR.
METHODS. A total of 44 patients were divided in two groups: Early (from 2 to 5 years) and Advance (> 5 years) with T1DM diagnosis without other immunological or neurological diseases where included in the study. We analysed the relationships of spectral-domain (SD) OCT parameters, angiography and foveal avascular zone (FAZ) with serum biomarkers (48 cytokines multiplex panel (Bio-Rad)), in two different DR progression groups.
RESULTS. Retinal thickness mRNFL in early group showed a strong positive correlation with serum IL-8 ($r = 0, 928$; $p = 0.008$) and negative correlations with IL-17 ($r = -0.9$; $p = 0.037$). In the case of the advanced group, the mRNFL thickness shows a negative correlation with serum IL-2Ra ($r = -0.900$; $p = 0.003$). Furthermore, in the advanced group angiography determinations correlated in a negative way with: ZAF ($r = -0.362$; $p = 0.049$), serum MIP-1b ($r = -0.722$; $p = 0.028$) and TNF-a ($r = -0.670$; $p = 0.048$). The advanced group also showed a positive correlation between angiography parameters and serum IL-1Ra ($r = 0.88$; $p = 0.021$). Finally, ZAF determinations correlated with TNF-a ($r = 0.9$; $p = 0.037$) and IL-9 ($r = 0.9$; $p = 0.037$) in the advanced group.
CONCLUSIONS. In early stages of T1DM, there is an association between alterations determined by SD-OCT and serum IL-8 and IL-17 levels. However, in advanced stages, the events detected by SD-OCT are related to IL-2Ra, as well as vascular and foveal alterations.

Automated Discrimination Between Eyes with Mild and Moderate Nonproliferative Diabetic Retinopathy

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DESIGN. 2-year prospective longitudinal study
PURPOSE. Manual ETDRS grading of 7-field colour fundus photography (CFP) is time-consuming. It is highly relevant to identify the eyes at risk of developing severe NPDR. We compare the performance of several CFP, optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) metrics for the automated discrimination of eyes classified as ETDRS 35 or ETDRS 43-47.
METHODS. Imaging data from 93 eyes (66.51 ± 6.97 years), 64 with ETDRS 35 and 29 with ETDRS 43-47 acquired during the baseline of the CORDIS cohort study (NCT03696810) were used in this study. OCT and OCTA data were acquired using CIRRUS™HD-OCT5000 with AngioPlex®OCTA (protocol angiography 3×3 mm) and the CFPs using a Topcon TRC 50DX. The performance of 18 metrics was evaluated. Vessel density (VD), perfusion density (PD) and abnormal intercapillary spaces (AIS) were measured based on the OCTA and retinal thickness metrics were measured using the OCT. Associated with AIS, two metrics were measured, the total area of the AIS and the number of abnormal areas (nAIS). All the OCTA metrics were measured in the superficial capillary plexus (SCP), deep capillary plexus (DCP) and full retina (FR). The microaneurysm turnover (MAT) was computed using the RetmarkerDR® (2-field CFP). Additional CFP were used to compute the MAT at a 6- and at 12 months interval. Logistic regression models were used to discriminate between the ETDRS groups. The performance metric was the area under the receiver operating characteristic (AUC) measured using a 5-folder cross-validation approach. The Mann-Whitney U test was used to study the statistical significance difference between the ETDRS groups.
RESULTS. The best combination of features, which was found using the forward feature selection method, includes

the 6 months MAT, the PD and VD in the DCP and the nAIS in the DCP and in the FR. With these 5 features, the AUC was equal to 0.82 ± 0.10 (mean $\pm$ std). The best individual metric was the 6 months MAT (p-value $<$ 0.05) with the value of AUR equal to 0.79 ± 0.1.

CONCLUSIONS. The results support that metrics obtained from non-invasive imaging methods at the central retina can be used for automated ETDRS classification of eyes with NPDR, identifying the eyes at risk for progression to severe NPDR.

Rate and Predictors of Misclassification of Diabetic Macular Edema as Detected by the Artificial Intelligence Eyeart System

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DESIGN. Cross-sectional study of prospectively enrolled patients

PURPOSE. To estimate the sensitivity, specificity, and misclassification rate of the EyeArt Artificial Intelligence (AI) system in the diagnosis of diabetic macular edema (DME) and to identify factors associated with true and false positives.

METHODS. Cross-sectional study of prospectively enrolled patients aged $\geq$18 years who had diabetes mellitus (DM). Participants underwent 2-field fundus photography (macula centered, disc centered) with a true-color confocal camera (iCare DRSplus, CenterVue, Padua, Italy). The presence of intraretinal or subretinal fluid on spectral-domain optical coherence tomography (SD-OCT) (Spectralis, Heidelberg Engineering, Heidelberg, Germany) was used as the gold standard. Sensitivity and specificity and their 95% confidence intervals (CIs) were estimated with generalized estimating equations (GEEs). Predictor variables associated with true and false positives were explored with logistic regression models.

RESULTS. 298 eyes of 154 patients were included. Sixty-four patients (44.4%) had DME in either eye based on SD-OCT examination, for a total of 92 eyes (31%). The sensitivity for DME detection was 82.61% (95% CI 72.37-89.60), and the specificity was 84.47% (95% CI 78.34-89.10%). The misclassification rate at the patient-level comparison was 16.1%, accounting for a test accuracy of 84%. Younger age ($p = 0.01$), shorter DM duration ($p = 0.006$), presence of hard exudates ($p = 0.005$), and microaneurysms ($p = 0.002$) were predictive of true positives. Longer DM duration ($p = 0.01$), worse DR severity ($p = 0.008$), the presence of hard exudates ($p < 0.001$), microaneurysms ($p < 0.001$), and an epiretinal membrane ($p = 0.06$) were predictive of false positives. A higher CMT was also associated with a higher risk of false positives ($p = 0.04$).

CONCLUSIONS. The AI system had good sensitivity and specificity for DME detection. The presence of macular lesions, such as microaneurysms, hard exudates, or epiretinal membrane, increased the sensitivity but also the false positive rate. Further eye examinations, such as SD-OCT, are needed for therapeutic management.

Adaptive Comparative Judgement as A Basis for A Machine Learning Algorithm for Diabetic Retinopathy Screening

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DESIGN. A machine learning development study

PURPOSE. To introduce a novel method of training a machine learning algorithm for diabetic retinopathy (DR) screening based on adaptive comparative judgement.

METHODS. This method involves pairwise comparisons of 2 colour fundus photographs; the artificial intelligence (AI) uses convolutional neural networks to learn and decide which of two images has the more severe DR. In total, the AI was trained using 28,000 images to generate 1.8 million pairs. The algorithm was validated and tested on the DDR database. We randomly selected 1399 cases to match the relatively high prevalence of DR in China based on the 2019 epidemiological study in China by Cui et al. Each new image was compared with a set of 140 curated images ranked in severity. The results were analysed using Gaussian Bayes Inferences, then ranked and classified into 3 categories: (1) no or mild non-proliferative DR (NPDR) (2) Moderate NPDR and (3) Severe NPDR or Proliferative DR.

RESULTS. For detection of severe NPDR and proliferative DR, the sensitivity was 0.97 (95% CI: 0.95 to 1.00) and specificity was 0.88 (95% CI: 0.86 to 0.90), the PPV was 50.5% and NPV was 99.6%. For detection of moderate NPDR, the sensitivity was 0.90 (95% CI: 0.87 to 0.93) and specificity was 0.90 (95%CI: 0.88 to 0.92), the PPV was 74.9% and NPV was 96.5%. One major novel finding is that the errors in judgement made by the AI algorithm is normally distributed around the threshold rank.

CONCLUSIONS. ACJ confers 3 advantages: firstly, the risk of disease can be assessed as a continuum through ranking, secondly, the uncertainty of the AI is associated with difficulty of the ranking and lastly, each result can be traced back to the comparisons allowing human users to question the judgement of the AI. Practically, this

system of ranking is a paradigm shift, enabling flexible thresholds for detection that is safe yet efficient. Depending on the prevalence, we believe the AI can safely screen 70% to 80% of the images with minimal human intervention.

Associations Between Serum Inflammatory Mediators and Spectral-domain (SD) Oct Parameters in T1 Diabetes Mellitus and Multiple Sclerosis Patients

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DESIGN. Type 1 diabetes mellitus (T1DM) and multiple sclerosis (MS) are chronic organ-specific diseases that share several etiological and pathological features than expected between two autoimmune diseases. Previous works have described the relation between T1DM and MS, due to the similarities in immunological, genetics and inflammatory factors present in both of them. However, the mechanism behind their co-occurrence remains unclear. Current concepts for measuring neuroinflammation and neurodegeneration upon diagnosis include optical coherence tomography (OCT), neurofilament light chain (NfL) and biomarkers from biological fluids. In meta-analysis studies, the pattern of cytokines altered during DR in the vitreous humor has been determined, which can contribute to study the same cytokine profile and the existing correlation in serum samples and retinal affectation. And there is an association between T1DM and MS due to the disruption of Blood Retinal Barrier (BRB) that could contribute to the progression of diseases.
PURPOSE. The aim of this study was to establish the relation between the alterations detected in the retina and blood markers in DR and MS as possible early biomarkers
METHODS. A total of 99 patients (63 T1DM/36 MS) and 29 healthy controls with >2 years from diagnosis without other immunological or neurological diseases were included in the study. We analysed the relationships of spectral-domain (SD) OCT parameters with serum biomarkers (48 cytokines Multiplex Panel (Bio-Rad) and ELISA) and with the progression of T1DM and MS
RESULTS. Spearman test revealed a correlation between mRNFL thickness and several citokines: IL-8 ($r = 0, 928$; $p = 0.008$), IL-17 ($r = 0.900$; $p = 0.03$) in T1DM; IL-7 ($r = 0{,}812$; $p = 0.04$) in MS and IL2Ra (T1DM, $r = -0{,}900$; $p = 0.03$; MS, $r = -0{,}900$; $p = 0.03$) in both of them. The NfL levels were significant elevated in T1DM and MS groups compared to control.
CONCLUSIONS. During an early stage of T1DM and MS, inflammatory phenomena occur that affect the retina and cause BRB rupture that allows extravasation of inflammatory mediators into the bloodstream. There is an association between the appearance of retinal alterations and the detection in serum of cytokines associated with neuroinflammatory processes that occur during T1DM and MS.

The Navisight Study: An Investigation into the Peripheral Retina in Diabetes and Navigating the Built Environment

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DESIGN. Prospective Observational
PURPOSE. To investigate the impact of peripheral retinal pathology and visual function on independent navigation of the built environment
METHODS. Participants with varying levels of diabetic retinopathy (DR) and retinitis pigmentosa (RP) were recruited and completed a clinical visit and short walk of 1 mile. Participants discussed confidence, anxiety and difficulty during the walkaround. The clinical visit included quality of life questionnaires, diabetes distress scales, retinal imaging and visual function testing. The Boston Grid was used to grade Optos widefield retinal images. Retinal grading and visual function results were compared with confidence, difficulty and anxiety levels during the walkaround.
RESULTS. Thirty-three participants attended – 22 (66.7%) had diabetes and 11 (33.3%) RP. Most (69.7%) were male, and the mean age was 49 (range 18-76). Many (72.7%) had type 1 diabetes, 22.7% had type 2 diabetes and 1 was in diabetes remission. Diabetes duration ranged from 2-67 years (mean 25). Fifteen eyes had no DR, 25 had mild-severe DR and 3 had proliferative DR. Fifteen eyes had laser treatment, 1 eye was blind. Results showed people with treated DR had significantly lower quality of life ($p = 0.021$) than those without treated DR. Grading showed both RP and treated DR had similar areas of retinal pathology. Despite this, only 1 participant with diabetes stated that towns and cities were difficult to navigate. In contrast over 60% with RP felt they were difficult to navigate which significantly reduced confidence ($p = 0.006$) and increased difficulty ($p = 0.000$). Despite most people with diabetes anticipating no issues during the walkaround some later stated issues with visual field

loss. The most common issues were bollards, pavement issues, street cafés, parked cars, and street furniture.
CONCLUSIONS. Despite similar levels of peripheral pathology those with treated DR did not have the same difficulty navigating the built environment as those with RP. Despite this some later stated issues with visual field during the walkaround. This further shows the importance of making streetscapes more accessible for all, especially those with visual impairment.

Inter-observer Reliability of Counting Retinal Microaneurysms and Haemorrhages in Elderly with Diabetes

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DESIGN. Cross-sectional retrospective cohort study
PURPOSE. To investigate if quantifying retinal microvascular lesions is a reliable outcome measure in elderly.
METHODS. Fundus photographs from all patients with type 2 diabetes, age ≥80 years, visiting the screening program 2008 in Region Värmland Sweden, n = 668, were reviewed. Inclusion criteria were mild/moderate diabetic retinopathy (DR) according to the International Diabetic Retinopathy Severity Scale. Exclusion criteria were hard exudates within two disc-diameters, and microaneurysms or haemorrhages within one-disc diameter, from the centre of the macula. Two observers counted microaneurysms and haemorrhages independently. Outcome measures were the total sum of microaneurysms and the total sum of haemorrhages per patient. Correlation, agreement and reliability between the counts of the observers was assessed. Analyses microaneurysm counts utilized all included patients while analyses of haemorrhages those with at least moderate DR in one eye.
RESULTS. In total 101 patients met the inclusion/exclusion criteria, median age 82 years and 50.5% were of female sex. Moderate DR in at least one eye was present in 59 patients. In all patients the number of microaneurysms ranged from 1-82, and among patients with at least moderate DR the haemorrhages ranged from 1–29. For microaneurysm count the Pearson correlation coefficient was 0.896 $p < 0.001$ and intraclass correlation coefficient (ICC) was 0.944 (95% CI 0.917–0.962) between the two observers. For haemorrhage count the Pearson correlation coefficient was 0.897 $p < 0.001$ and ICC was 0.94 (95% CI: 0.893–0.965) between the two observers.
CONCLUSIONS. Retinal microaneurysm count and haemorrhage count was assessed with excellent reliability. The results suggests that retinal microvascular lesions in elderly with diabetes can be manually quantified but the usefulness of such measures needs further evaluation.

Abnormal Retinal Fluid in Eyes with Diabetic Macular Edema

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DESIGN. 2-year prospective longitudinal study
PURPOSE. To characterize the occurrence of center-involved macular edema (CIME) in different diabetic retinopathy (DR) risk phenotypes in type 2 diabetes (T2D) and the presence of abnormal retinal fluid accumulation identified by optical coherence tomography leakage (OCT-Leakage).
METHODS. A prospective longitudinal cohort study (CORDIS, NCT03696810) was conducted with 3 annual visits (baseline, one- and two-year). Ophthalmological examinations included visual acuity, colour fundus photography (CFP), optical coherence tomography (OCT) and OCT-Angiography (OCTA). Only risk phenotypes B (increased CRT) and C (ischemia, decreases in VD ≥ 2 SD of healthy population) were included.
Seven-field ETDRS grading was performed. OCT data was analyzed with OCT-Leakage, a novel patented technique by AIBILI for noninvasive assessment of abnormal accumulation of fluid in the retina through low optical reflectivity ratios (LOR).
RESULTS. Of the 122 T2D individuals that completed the study, 65 eyes (53%) were classified as phenotype B and 57 (47%) eyes as phenotype C. During the 2-year period of follow-up, 23 eyes (19%) developed CIME and 2 (2%) clinically significant macular edema (CSME). Phenotype B was preferentially associated with the development of CIME (31%) in comparison with phenotype C (5%). Patients that developed CIME showed a progressive increase in CRT (β=23.705 μm, $p < 0.001$) and LOR changes (β=0.018, $p < 0.001$) with time when compared to patients that did not. This difference remains statistically significant when controlling for age, sex, diabetes duration and HbA1c. Changes in time for CRT, over the two-year period of follow-up, are associated with longitudinal changes in LOR ratios (β=114.831, $p < 0.001$) and with

longitudinal changes in VD and PD in the deep capillary plexus (VD: β=2.642, p = 0.001; PD: β=130.415, p = 0.004). LOR increases are associated with BCVA loss (p = 0.052).
CONCLUSIONS. CIME may occur in both risk phenotypes and in different ETDRS levels. LOR changes were identified in eyes with CIME. There was a clear association between CRT changes and changes in the deep retinal capillary plexus. LOR changes were associated with BCVA loss.

Non-invasive Characterization of Intraretinal Microvascular Abnormalities with Widefield Swept Source Octa Imaging

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DESIGN. Cross sectional, observational
PURPOSE. To explore the use of non-invasive methods such as Wide-Field Swept-Source optical coherence tomography angiography (SS-OCTA) to identify and characterize intra-retinal microvascular abnormalities (IRMA) in severe non proliferative diabetic retinopathy (PDR) or PDR patients.
METHODS. 26 eyes from type 2 diabetes individuals were imaged with 7-Fields Colour Fundus Photography (CFP) and SS-OCTA Zeiss PlexElite 9000 using Wide-Field Angio 15 × 9 mm protocols. Regions suspicious for IRMA were first identified in CFP and then searched in SS-OCTA co-locations on the Superficial Capillary Plexus (SCP) and Vitreous-Retina Interface (VRI) slabs. When detected, presence of surrounding capillary non-perfusion, overlayed flow, hyperreflective dots in inner retina, protrusion of inner limiting membrane (ILM) and breach of ILM with or without breach of posterior hyaloid (PH) were analysed. Fluorescein angiography (FA) was used to confirm the presence of new vessels.
RESULTS. Of the total number of IRMAs identified by SS-OCTA (n = 69), 80% (n = 55) were located in non-perfused areas with 73% (n = 40) showing some degree of flow. 82% (n = 56) were confirmed within ILM without breaching PH, while 14% (n = 10) seem to cause an ILM protrusion with detectable flow in both SCP and VRI slabs. Only 4% (n = 3) were identified as new vessels on OCTA due to its location above PH and detection in the VRI slab. All these proliferation loci showed leakage on FA.
CONCLUSIONS. Wide-Field SS-OCTA images are a valuable tool to identify IRMA and early stages of vascular neo-proliferation, allowing an improved characterization of these vascular lesions and offering an accurate non-invasive alternative to FA for its detection.

Clarus (or Wide-field Fundus Imaging) Improves Etdrs Grading with Classic 7-Fields Fundus Photographs

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DESIGN. Cross-sectional, observational study
PURPOSE. To analyse and compare grading of Diabetic Retinopathy (DR) severity level using standard 30° ETDRS 7-fields photography and Clarus 500TM wide-field imaging system (2-fields).
METHODS. A cross-sectional analysis of retinal images of patients with diabetes type 2 (n = 109 eyes). All patients underwent 7-fields colour fundus photography (CFP) at 30° on a standard Topcon TRX-50DR® camera and ultra-wide field (UWF) images at 133° on CLARUS 500TM by an automatic montage of two 90° images (nasal and temporal) (Carl Zeiss Meditech, USA). Seven-fields photography's were graded by two graders, according to the Early Treatment Diabetic Retinopathy Study (ETDRS). For CLARUS UWF images, a 7-fields grid was applied using a CLARUSTM software viewer, and the same ETDRS grading procedures were performed inside that area only. Grading of DR severity level was compared between these two methods to evaluate the agreement between both imaging techniques.
RESULTS. Images from 109 diabetic eyes were considered for analysis. According to the 7-fields 30° images, 9 eyes were considered DR severity level 10-20, 54 eyes were considered level 35, 30 eyes level 43, 12 eyes level 47, 3 eyes level 53 and 3 eyes level 61. The same DR severity level was achieved with CLARUS 500TM UWF images in 61% of the cases. However, 37 eyes (34%) showed a worse DR level with UWF images, mostly due to a better visualization of haemorrhages (increasing their severity) and a higher detection of intraretinal microvascular abnormalities (IRMA). Only 5% (n = 5) of the cases showed a decrease in severity level with CLARUS 500TM system, mainly due to the presence of artifacts in the montage junctions of the 2 images (blurred zones) and presence of cortical cataracts.
CONCLUSIONS. The UWF CLARUS 500TM system showed a substantial agreement with standard 30° seven-

fields CFP in all ETDRS levels. However, CLARUS images showed a superior ability to detect IRMA and to evaluate haemorrhages severity demonstrating that UWF systems can be used to grade ETDRS severity level more accurately.

Diabetic Retinopathy Progression Among Children and Young Adults with Type 1 Diabetes in India

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DESIGN. Observational follow-up study
PURPOSE. Diabetic retinopathy (DR) can lead to vision impairment and blindness if not detected and treated early. This study aims to evaluate the rates of DR progression or regression among children and young adults with Type 1 diabetes mellitus (T1DM) in India.
METHODS. Children and young adults with T1DM were screened for DR between 2020-2022 at the Hirabai Cowasji Jehangir Medical Research Institute, India. Baseline and follow-up fundus images were captured using a Forus Health 3netra classic digital non-mydriatic fundus camera, with a duration of one year between visits. They were then sent to the Belfast Ophthalmic Reading Centre for grading by an experienced grader and ophthalmologist. DR severity was graded according to the UK's DR classification scale. Two main outcomes were considered (at least one step change in DR severity): 1) Overall DR Progression (in at least one eye); and 2) Overall DR regression (in at least one eye). Data was analysed using descriptive statistics and the Mann-Whitney U test was used to compare differences between groups.
RESULTS. Among the 348 children and young adults (2.4-23.6 years) included in the analysis, 188 (54.02%) were female. Of these, 18 (5.17%) had DR progression and 11 (3.16%) had DR regression. None of the participants included in the study progressed to develop sight-threatening DR. The mean age of participants with no DR progression was 12.8 years (SD: 4.3 years) compared to 15.5 years (SD: 3.3 years) with DR progression, ($P < 0.05$). The mean duration of diabetes for those with DR progression was 9.5 years (SD: 3.6) compared to 7.3 years (SD: 4.0), ($P < 0.05$).
CONCLUSIONS. To date, limited studies on DR progression among children and young adults are available. This study highlights that few children and young people had DR progression after one year. Although the numbers are small, it is evident that duration of diabetes and increasing age are correlated with DR progression. Collecting more longitudinal data among children and young adults is recommended for the future. This will allow us to evaluate and predict future DR progression trends.

The Relationship Between Visual Function and Severity of Diabetic Retinopathy

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DESIGN. Systematic review and meta-analysis
PURPOSE. To establish the relationship between the presence and severity of diabetic retinopathy (DR), and visual function.
METHODS. A systematic literature review was conducted using MEDLINE, CINAHL, EMBASE and Web of Science. Selected studies included adult participants with DR and visual function recorded using the Visual Function Questionnaire-25 (VFQ-25) composite score or its subscales. A score of 0 represents the lowest and 100 the best possible visual function. Analysis 1 included studies with a group of participants with no DR. This group was selected as the referent to which we compared scores of participants with DR, grouped according to DR severity. For Analysis 2, we pooled VFQ-25 scores from all studies within categories of DR severity and compared these groups. DR was classified as (i) non-proliferative DR (NPDR), (ii) Any DR (studies combining scores for participants with NPDR and advanced DR) and (iii) Advanced DR (proliferative DR and/or diabetic macular oedema). Analyses were performed using fixed effects meta-analysis. [PROSPERO ID CRD42021293544]
RESULTS. 35 studies reported data on VFQ-25 composite scores. Analysis 1 consisted of 8 studies including 1138 participants with DR and 347 participants without DR. Compared to those with no DR, VFQ-25 composite score was 3.8 (95% CI 1.0, 6.7) points lower in NPDR, 12.5 (95% CI 8.5, 16.5) lower in Any DR and 25.1 (95% CI 22.8, 27.2) lower in Advanced DR ($P < 0.001$). There was a variation across VFQ-25 subscales depending on DR severity, though general vision, near vision and colour vision had significantly lower scores across all groups with DR compared to no DR. Analysis 2 consisted of all 35 studies including 6351 participants with DR. The results were strongly supportive of Analysis 1. The mean VFQ-25 composite score was 91.8 (95% CI 91.0, 92.7)

for NDPR, 76.5 (95% CI 75.8-77.1) for Any DR and 73.2 (95% CI 72.6, 73.7) for Advanced DR ($P < 0.001$).
CONCLUSIONS. Visual function declines with the presence and increasing severity of DR. Therapies which prevent the development or progression of DR, even before advanced stages, may improve visual function and quality of life.

Follow-up and Management of Diabetic Patients with Neovascular Glaucoma Referred from the Northern Ireland Diabetic Eye Screening Programme in 2015-2016

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DESIGN. Retrospective observation study
PURPOSE. Software for recording the diabetic retinopathy (DR) grade was introduced to the Diabetic Eye Screening Programme for Northern Ireland (DESPNI) in 2015. Proliferative DR (PDR) is a common complication of both type 1 and 2 diabetes. A further complication of diabetes in the eye is neovascular glaucoma (NVG), indicating severe ocular ischaemia. This is a rare but sight threatening complication of diabetes and must be treated promptly in order to save useful vision.
METHODS. All patients referred to hospital eye services (HES) by DESPNI for PDR in one or both eyes in 2015-2016 were included. Subsequently we identified all patients who were diagnosed with neovascular glaucoma at the time of the first HES review. Visual acuity at first HES appointment and most recent visual acuity, treatment regime and complications were recorded.
RESULTS. There were 13 patients with neovascular glaucoma at the time of DESPNI referral (7 male, 6 female; average age 64 years, average duration of diabetes 21 years at time of screening, 4 Type 1 and 9 Type 2 patients). Of 13 patients, 3 had bilateral NVG. Altogether, these patients represent 1.4% of all PDR referrals of 950 patients. Mean visual acuity of affected eyes at presentation was 1.3 LogMAR with no significant visual improvement at follow-up, but 8 eyes retained useful vision (better than or equal to 1.00 LogMAR). Four patients are now deceased. Twelve eyes received pan retinal laser photocoagulation (PRP), 3 had anti-VegF injections, one had cyclodiode laser, 2 underwent trabeculectomy, and one was enucleated. All patients received topical pressure lowering drops during their management.
CONCLUSIONS. NVG is a rare but sight threatening complication in diabetes. Intense monitoring and prompt treatment is required in order to save useful vision. Treatment options vary. According to the Royal College of Ophthalmologists' guidelines, PRP is the first line treatment and should be used if possible. Anti-VegF injections, cycloablative laser, pressure lowering surgery such as trabeculectomy with input from glaucoma specialists are also indicated in many patients.

Introduction of Virtual Eye Clinics to Reduce Delayed Follow up Waiting Times Following Covid-19 Pandemic

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DESIGN. Retrospective observational study.
PURPOSE. To reduce delayed follow up of patients in the Hospital Eye Service.
METHODS. Clinics were set up with Ophthalmic technicians who imaged using Optos widefield photography, 2 $\times 45°$ digital colour photography and Triton OCT of each eye. 800 patients were invited and 488 attended the clinic.
RESULTS. Clinics were commenced in Feb 2021 which were 2 half day clinics each week. In the following 11 months, 488 attended the clinic, out of which 63 attended the clinic more than once. 138 of these patients were referred for further management to subspecialty clinics. The remaining were followed up in virtual eye clinics. A further total of 91 patients needed intervention in some form. 31 eyes in 21 patients needed macular laser. 23 eyes in 19 patients needed intravitreal injections of a VEGF inhibitor. 44 eyes in 36 patients needed panretinal photocoagulation. 3 patients needed pars plana vitrectomy and 7 were listed for cataract surgery.
CONCLUSIONS. The virtual eye clinics were introduced keeping in mind the backlog of patients during the Covid 19 pandemic and with the aim of reducing delays in follow up of patients in the Hospital Eye Service while maintaining social distancing and reduced times in the hospital. These clinics helped in streamlining patients who needed further management and the ones who could be followed up in Virtual Eye clinics routinely.

Economic Impact of Fenofibrate Among the Chinese Patients with Diabetic Retinopathy

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DESIGN. Secondary analysis based on clinical trial results (ACCORD Eye study, FIELD study) and literature review on cost and epidemiological data.
PURPOSE. To estimate the economic impact of fenofibrate use for preventing disease progression in Chinese patients with diabetic retinopathy (DR).

METHODS. For a cohort of patients with diabetes mellitus (DM) and mean age 50, a 30 year cost comparison between fenofibrate addition and no addition was simulated using a Markov model. Six health states were modelled in the Markov model: normal, non-proliferative DR (NPDR), proliferative DR (PDR), diabetic macular edema (DME), severe vision impairment (SVI) with bilateral best corrected visual acuity < 6/60, and death. Normal status assumed to require screening for DR and NPDR patients were assumed to require regular follow-up observations. Considering the available dosage form of fenofibrate in China, fenofibrate cost was estimated as 200 mg/day. Discount rate of 3% was applied for the more than 12 months future cost items. An exchange rate of 1 USD = 7 CNY was applied to convert the Chinese cost items to USD.
RESULTS. China has more than 100 million patients with DM. Out of this, 21.6% of patients have any DR. DM patients in rural area have significantly higher rate of DR (OR = 1.22, $p < 0.01$). From the current literature in China, annual treatment cost for PDR was reported as 137.6 USD/year (photocoagulation) and that of DME was 1,741.46 USD/year (intravitreal anti-vascular endothelial growth factor therapy). For the SVI cost, it was estimated as 3,600 USD/year including indirect cost of productivity loss. However, adding fenofibrate to the Chinese patients with DM which reduces the DR progression, the net cost/ 30 year was estimated as 831.78 USD per patient after discounting.
CONCLUSIONS. Even for a developing country with a large population of diabetic patients and a large at-risk population of diabetic retinopathy, like China, it is recommended to add fenofibrate to the existing regimen for diabetes (DM). Since the 30-year net cost of DM by adding fenofibrate is substantially on the lower side compared to the higher yearly cost of currently available treatments.

Visual Function and Quality of Life in People with Diabetic Retinopathy: Insights from the Lens Trial

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DESIGN. Cross-sectional analysis
PURPOSE. Previous research shows that visual function is reduced in people with non-proliferative diabetic retinopathy (NPDR) compared to those with no DR. However, there is limited information available about how visual acuity and other variables affect visual function and quality of life (QoL) in DR. We investigated these questions in a trial population with NPDR.
METHODS. Lowering Events in Non-proliferative retinopathy in Scotland (LENS) is a randomised double-blind placebo-controlled trial investigating the effect of fenofibrate on the progression of DR in participants with mild to moderate NPDR (defined as bilateral ETDRS 20-35; or unilateral/bilateral ETDRS 43; or unilateral/bilateral hard exudates within 1-2 disc diameters of the fovea centre) (NCT03439345, ISRCTN15073006). The trial is embedded within Scotland's diabetic eye screening program. At the LENS screening visit, visual function (using the VFQ-25 questionnaire) and QoL (using the EQ-5D instrument) were recorded. Eligible participants with NPDR then entered a 2-month active run-in period (receiving fenofibrate) prior to randomisation.
RESULTS. 1633 participants were screened for LENS, of whom 1484 entered the run-in period and 1151 were randomised. VFQ-25 and EQ-5D forms are available for approximately 1400 participants who entered the run-in phase. Of these people, about 30% had type 1 diabetes, 70% were men, mean duration of known diabetes was 18 (SD 10) years, mean age was 60 (SD 13) years and mean HbA1c was 67 (SD 16) mmol/mol. The mean best corrected visual acuity in the better eye was 0.04 (SD 0.14) LogMAR and 15% had subnormal vision (defined as best corrected visual acuity >=0.3 on LogMAR scale) in at least one eye. Cross-sectional analyses are underway using multivariate regression model to explore the relationships between visual function and (i) key variables including age, sex, duration of diabetes, type of diabetes, visual acuity, DR grading and HbA1c (ii) QoL, and these results will be presented at the conference.
CONCLUSIONS. Analyses in LENS trial participants will provide insights into visual function in various groups of people with NDPR and will improve our understanding of the relationship between visual function and QoL.

A Pilot Study of Implementing Diabetic Retinopathy Screening in the Region of Oslo, Norway: Baseline Results

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DESIGN. Cross-sectional pilot study
PURPOSE. To gain insight into the baseline parameters of a population with diabetes mellitus (DM) included in diabetic retinopathy (DR) screening at the Oslo University Hospital (OUH), Oslo, Norway.
METHODS. This was a cross-sectional pilot study on a cohort of adult patients (>18 years) with type 1 or 2 DM (T1D and T2D). The study included 180 eyes of 90 patients. Best corrected visual acuity (BCVA), blood pressure (BP), heart rate (HR), intraocular pressure (IOP), height and weight were measured. HbA1c, total serum cholesterol,

urine -albumin, -creatinine and -albumin-to-creatinine ratio (ACR) were collected as well as baseline parameters like socio-demographic parameters, medication and previous screening history. Colour fundus photographs were obtained and graded by two experienced ophthalmologists according to the International Clinical Disease Severity Scale for DR.
RESULTS. The study included 180 eyes of 90 patients; 12 (13.3%) had T1D and 78 (86.7%) had T2D. In the T1D group, 5 patients (41.7%) had no DR and 7 (58.3%) had some degree of DR, while in the T2D group 60 patients (76.9%) and 18 patients (23.1%), respectively. None of the patients had proliferative DR. Of the 43 patients not included at time of DM diagnosis (not included within 1 year for T1D and within 5 years for T2D), only 5.7% of the patients with T2D and 37.5% of the patients with T1D had previously undergone screening according to the Norwegian Guidelines. Univariate analysis for age, HbA1c, urine albumin-to-creatinine ratio, duration of diabetes found significant difference in the odds ratio for DR in the study population. For the T2D group alone, significant difference was found in the odds ratio for DR regarding HbA1c, BMI (body mass index), urine creatinine and duration of DM. The analysis also showed more than 3 times higher odds for DR in the T1D group versus the T2D group.
CONCLUSIONS. This study shows the importance of implementing a systematic DR screening program in the Oslo region. Only 11.6% of the patients not included at diagnosis were followed-up as recommended by the Norwegian Guidelines. A proper and systematic DR screening may reduce the chance for DR to develop and progress.

Associations Between Metabolic and Structural Retinal Parameters and Depression Score in Individuals with Type 2 Diabetes

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DESIGN. Cross-sectional

PURPOSE. Ischemic cerebrovascular micro-vasculopathy may be causally related to geriatric depressive symptoms. The present study aimed to examine whether retinal metabolic or vascular parameters, reflecting indirectly early cerebral pathology are associated with depression in individuals with type 2 diabetes.
METHODS. We performed a cross-sectional study at the Department of Ophthalmology, Odense University Hospital, with individuals recruited from the Funen Diabetes Database between 25 November 2020 and 25 February 2022. We included individuals of 65 years or more with type 2 diabetes for five years duration or longer, and excluded individuals with known or previous retinal disease beside diabetic retinopathy (DR), history of stroke or neurodegenerative disease, or media opacities precluding retinal imaging. We evaluated retinal metabolism by retinal oximetry and measured structural retinal parameters in fundus photographs and OCT-angiography. Depression was measured with the Self-rated Inventory of Depressive Symptomatology questionnaire (IDS-SR-30) with scores ≥ 18 indicating depression. If eligible, both eyes were included in the analysis. We performed mixed regression model analysis with cluster robust standard error applying a crude and a multivariable model adjusting for age, sex and presence of DR.
RESULTS. We included 134 individuals with type 2 diabetes. Median (interquartile range) age and duration of diabetes were 72 (69-76) and 19 (13-23) years, and 70% were male. Overall, 22% had IDS-SR-30 scores ≥ 18, indicating depression. Individuals with depression had higher retinal arteriolar oxygen saturation in the lower temporal quadrant (89.1% vs. 86.2%, $p = 0.035$) and a higher retinal venular oxygen saturation in the upper nasal quadrant (62.7% vs. 58.9%, $p = 0.048$) after adjustment of age, sex and DR. We did not find any differences in the overall retinal arteriolar (91.0% vs. 91.0%, $p = 0.96$) or venular oxygen saturation (57.7% vs. 54.9%, $p = 0.52$) and the groups did not differ according to retinal vascular caliber, tortuosity, density or fractal dimension.
CONCLUSIONS. We found some retinal metabolic but no vascular differences in those with elevated depression scores. Thus, our findings only partly support the notion that retinal vascular factors may be indicative of depression.

Performance of "Treat and Extend" Anti-VEGF Therapies (Aflibercept, Ranibizumab) Used for Diabetic Macular Oedema in West of Scotland at 1 Year

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DESIGN. Retrospective case note review. Data collected from real world patients. No exclusions were made for ocular co-morbidities, retinopathy status or modifiable risk factors. The time period of collection occurred during the COVID 19 pandemic; which was a substantial factor affecting the delivery of our service.
PURPOSE. To compare visual acuity (BCVA) and central macular thickness (CMT) outcomes of anti-VEGF therapies subgroups prescribed as "treat and extend"
METHODS. We identified 94 eyes; median age 63.7 years (range 44.3 - 83.3). The sample comprised 3 sub-groups based on original prescribed loading doses; 33 eyes were prescribed Aflibercept monthly for 4 months (A4), 29 eyes Aflibercept for 3 months (A3) and 14 eyes Ranibizumab for 3 months. (R3) All groups subsequently received an average of 3 further injections
RESULTS. A4 subgroup report a + 13.8 letter BCVA and -99.4 micron CMT reduction at 1 year compared to base line. A3 subgroup report a + 6.7 letter BCVA and -63.9 micron CMT improvement. R3 subgroup report a + 9.3 letter BCVA and -93.6 micron CMT improvement. Subgroups A4 & R3 maintain BCVA between treat-extend decision and 1 year (+8.8 letters, + 6.4 letters respectively). Subgroup R3 report a vision loss (-7.1 letters BCVA) between treat-extend and 1 year. All groups report anatomical increase in CMT between treat-extend decision and 1 year.
CONCLUSIONS. There is no national or local consensus in Scotland when prescribing first time IVT for centre – involving diabetic macular oedema. Variation and clinical uncertainty exists between guidance from governing bodies, manufacturers recommendations, European societies and clinical studies. Our sample demonstrates superior functional and anatomical outcomes at 1 year from loading with 4 monthly Aflibercept injections, then extending with 3 further injections. The BCVA results compare favourably to DRAKO study at 1 year.

Is Diabetic Retinopathy Screening Worthwhile Among People First Diagnosed with Diabetes at Older Ages? Cohort Study of Norfolk Diabetic Retinopathy Screening Programme

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DESIGN. Cohort study
PURPOSE. The United Kingdom's Diabetic Eye Disease Screening Programme offers screening to every UK resident over age 12 with diabetes. People first diagnosed with diabetes at older ages are more likely to die and therefore may be less likely to benefit from screening and treatment. To inform decisions about whether diabetic eye screening should consider age at diagnosis of diabetes, we investigated the probability of receiving treatment according to age at diagnosis.
METHODS. This was a cohort study of participants in the Norfolk Diabetic Retinopathy Screening Programme from 2006 to 2017, with individuals' programme data linked to hospital treatment and death data recorded up to 2021. We estimated and compared the probability and annual incidence of receiving retinal laser photocoagulation or intravitreal injection, and of death, in age groups defined by age at first screening episode. Statistical survival analyses included Cox and competing risks regression. We also estimated and compared screening costs per person treated in different age groups.
RESULTS. The probability, incidence and hazard of death increased with increasing age, while the probability, incidence and hazard of both treatments decreased with increasing age. The estimated cost of screening per person who received either or both treatments was £18,608 among all participants, increasing with age up to £21,721 in those aged 70-79 and £26,214 in those aged 80-89. Among those who died after treatment, median survival from first treatment to death was 8.7 in those aged 70-79 and 10.0 in those aged 80-89.
CONCLUSIONS. Diabetic retinopathy screening is less effective and less cost effective with increasing age, because of the competing risk of death before participants develop sight-threatening diabetic retinopathy (STDR) and can benefit from treatment. This suggests that implementing an upper age limit for the screening programme or more aggressive risk stratification in older age groups may be appropriate.

The Effects of Reminder and Information Letters on Non-attendance to A Diabetic Retinopathy Screening Clinic for Pregnant Patients

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DESIGN. This was a retrospective comparative analysis of pregnant patients who missed one or more Diabetic Retinopathy Screening (DRS) appointments.
PURPOSE. Sight-threatening diabetic retinopathy may be asymptomatic. Pregnancy is known to accelerate diabetic retinopathy. Regular attendance to a DRS programme during pregnancy is essential to detect and manage retinal pathology. This audit aims to review whether sending a reminder and information letter to pregnant women due to attend DRS has any impact on nonattendance rates.

METHODS. The groups were divided into those who did not receive a reminder or information letter between April and August 2019, and those who received a letter one week prior to their appointment between April & October 2022. A subset of this patient cohort was defined as never-attenders.
RESULTS. In 2019, 92 out of 277 patients (33%) did not attend their scheduled appointments. Following the introduction of a reminder and information letter in 2022, 18 out of 86 patients did not attend (21%). This finding achieved statistical significance ($p < 0.02$). The mean ages of the two cohorts were 34 and 32 years respectively. Reminder and information letters did not show any statistically significant impact on reducing the rate of never attendance.
CONCLUSIONS. The positive impact of both patient education and reminding our patients of their appointments is clearly demonstrated in this audit. Improved attendance rates benefit our patients' ocular health and allow for better allocation of healthcare resources. We also identified a subset of patients who did not attend DRS, further analysis of this group is warranted to identify potential barriers to patient engagement with DRS.

Prevalence and Severity of Retinopathy and Maculopathy in People with Diabetes Mellitus before and After Hospital Admission Due to Covid-19 in the First Wave of the Pandemic (March-June 2020)

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DESIGN. Retrospective analysis
PURPOSE. To assess prevalence and severity of retinopathy and maculopathy pre and post hospital admission for COVID-19 treatment in the first wave of the pandemic
METHODS. Retrospective analysis of medical records on the Northern Ireland Diabetic Eye Screening System was conducted on 72 patients who had been admitted for treatment of COVID-19 in the first wave of the pandemic (March–June 2020). Data were collected on age, gender, retinopathy and maculopathy grades pre and post hospital admission, and deceased status
RESULTS. Out of 72 patients, 23 had pre- and post-COVID screening grades. Forty patients had died, 13 of which were due to COVID (3 deceased patients had pre- and post- retinopathy grades). Twenty-two patients had not attended a pre- or post- visit, or were medically unfit, 2 were not on the Optomize system. Those with pre- and post- grades had a mean age of 66 (40-92), were 70% male, and had a mean diabetes duration of 8 years, those without had a mean age of 79 (49-95), 47% male, and diabetes duration of 12 years.
Of the 23 patients with both grades, 1 had ungradable images, out of 22 gradable patients, 18 (82%) had no change in retinopathy (R) or maculopathy (M) grade, 3 (14%) had 1 step retinopathy progression (1 in both eyes), and 2 (9%) had progressed to maculopathy in both eyes. Those with no progression had a mean of 3 years between screenings compared to 2.3 for those who had progressed
CONCLUSIONS. Admission to hospital with COVID-19 did not appear to result in a higher retinopathy or maculopathy progression rate for surviving patients. However it is impossible to rule out worsening in those who died or did not attend for a follow-up screening. It is also possible that retinopathy could have worsened and resolved before post-COVID screening.

The Role of Regular Screening Program and the Involvement of International Organizations for the Successful Implementation of The Project

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DESIGN. Education in diabetic eye disease
PURPOSE. Diabetic Retinopathy is one of the main causes of blindness in industrialized nations. At the time of diabetes diagnosis there may already be a high prevalence of diabetes related conditions, such as obesity, hypertension, cardiovascular disorders, retinopathy and neuropathy. To reduce visual impairment, regular annual examination of the eye, as well as regular diabetes control, lipid, microalbuminuria and BP monitoring are necessary. In Georgia, the situation is worse in rural and remote high mountain areas as there is no access to specialized care. Although remedial work is ongoing, sustainability is low.
METHODS. Our group of endocrinologist, ophthalmologists and educators is working on organising regular screening program in rural Georgia, which include: 1) Registration of patients, collecting baseline information and preparing individualised care-plans for each patient; 2) Screening for diabetic retinopathy (DR) and providing education, clinical and laboratory tests and physical examination; 3) Establishing network of ophthalmology clinics, polyclinics and diagnostic centres; 4) Preparation of educational materials for patients, general practitioners, ophthalmologists and other allied healthcare providers; 5) providing a 5-days education course on DM and its complications for patients; 6) providing training courses for

all healthcare providers; 7) Establishing patient follow-up; 8) Post-education patient testing and laboratory tests.
RESULTS. The Project is the first wide-scale screening program for DR in rural regions of Georgia. It is aimed at creating right approach to diabetes mellitus and its complications, their timely prevention, screening and treatment.
CONCLUSIONS. The project carried out to demonstrate that regular screening and good control of metabolic parameters and education increases awareness of people with diabetes, their relatives, health care providers and whole society; will prevent or slow down progression of late diabetes complications development and improve the quality of lives of people with DM.

Prevalence of Diabetic Retinopathy and Related Risk Factors in Diabetic Patients Tirana District / Albania

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DESIGN. Diabetic Retinopathy (DR) is a serious and frequent complication of diabetes and it is often present at the time of the diagnosis of type 2 diabetes. The complications remain largely preventable with screening, followed when required by proper interventions' therapy.
PURPOSE. To define the prevalence of DR in a group of T2DM patients living in Tirana district; to analyse the clinical features associated with this complication in the examined group.
METHODS. We included in the study T2DM patients living in Tirana district, member of Albanian Diabetes Association who have >5 years of T2DM diagnosis. The eye examinations were performed by certified ophthalmologists, as part of an awareness program for eye complications in people with diabetes, supported by Bayer office in Albania. In total, we included 250 patients type 2 diabetes mellitus.
RESULTS. Altogether, 227 patients were examined, mean age of 62.5 ± 11.6 years, 126 males (55.5%). Diabetes duration was 9.6 ± 7.8 years, mean HbA1c of $7.8 \pm 1.4\%$, mean BMI 28.9 ± 5.1 kg/m2, 87 (38.3%) were on insulin therapy. DR was present in 59 (26%) of the patients, and 15% have diabetic macular oedema. Only 56 (24,7%) of the patients have been examined with OCT. The multivariate analyses revealed that significant DR predictors for were diabetes duration ($p = 0.0001$ OR = 4.36), poor metabolic control as HbA1c > 8% ($p = 0.0015$ OR = 3.02), insulin treatment (OR = 4.24) and blood pressure ≥150/95 mm Hg ($p = 0.002$ OR = 2.45). There was a good correlation between DR and nephropathy. The other features such as BMI, coronary artery disease, or HTA treatment were univariate predictors of diabetic retinopathy, but they lost significance in multivariate analyses.
CONCLUSIONS. Our study showed that DR remains one of the most frequent complications of diabetes. Those with type 2 diabetes with poor metabolic control, longer diabetes duration, nephropathy, uncontrolled HTA, and on insulin treatment are more prone to develop DR.

Lipid Metabolism Biomarkers in Diabetic Retinopathy in Patients with Type 1 Diabetes Mellitus

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DESIGN. Cross-sectional study
PURPOSE. The aim of the study was to analyse the association between DR in patients with type 1 diabetes mellitus (T1DM), lipid biomarkers and highlight possible correlation.
METHODS. A total of 72 T1DM patients were included in this study. The enrolled participants were assigned into three groups, based on the results of fundus photographs as following: 1st group - no DR, 2nd group - non-proliferative diabetic retinopathy (NPDR), and 3rd group - proliferative diabetic retinopathy (PDR). Serum lipids: triglycerides (TG), total cholesterol (TC) and lipoprotein (a) (Lp (a)) were measured at the baseline.
RESULTS. The data revealed no difference in TG serum levels in patients of the 1st and 2nd groups. The increase of TG serum levels was identified with the progression of the DR in the 3rd group (+121%, $p = 0.018$). TC also rose in patients in the 3rd study group (+19%, $p > 0.05$ compared to the 1st and 2nd study groups). An increase of Lp (a) was highlighted with the evolution of DR: in the 2nd group (+73%, $p > 0.05$) and in the 3rd group (by about 320%, $p = 0.019$) compared to 1st study group. The correlation analysis revealed a weak positive correlation between the grade of DR and Lp (a) levels ($rs = 0.319$, $p = 0.006$), and TG ($rs = 0.239$, $p = 0.043$).
CONCLUSIONS. Our study showed statistically significant changes of TG and Lp (a) levels correlated with the DR grade and a non-significant increase in TC level in T1DM patients. Our data indicate a likely involvement of lipid metabolism disorders in the progression of DR.

Assotiation Between Ganglion Cell-Inner Plexiform Layer in Type 2 Diabetes Without and with Retinopathy and its Correlated Systemic Risk Factors

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DESIGN. Cross-sectional observational study.
PURPOSE. This study aimed to evaluate the thickness of ganglion cell-inner plexiform layer (GCL-IPL), a marker of retinal neurodegeneration, in patients with type 2 diabetes mellitus (T2DM) without diabetic retinopathy (DR) and with nonproliferative DR (NPDR) using the optical coherence tomography (OCT) and to determine its correlated risk factors.
METHODS. This cross-sectional study included 50 eyes of 25 T2DM with a median age of 64 years and a median diabetes duration of 13 years. Complete diabetes, nephrological and ophthalmological examination was performed, including colour fundus photography according to the EURODIAB methodology and OCT of the macula to evaluate the thickness of GCL-IPL. Patients with proliferative DR and diabetic macular oedema were not included in the study.
RESULTS. Fifty eyes were divided into group 1 (no DR; n = 34) and group 2 (NPDR; n = 16). Group 2 had significantly longer diabetes duration ($p = 0.042$), higher glycated haemoglobin (HbA1c) ($p = 0.002$), and lower GCL-IPL ($p = 0.027$) than group 1. GCL-IPL was negatively associated with DR ($p = 0.024$), diabetes duration ($p = 0.042$), systolic blood pressure ($p = 0.016$), HbA1c ($p = 0.043$), and albumin/creatinine ratio ($p = 0.007$) while positively with estimated glomerular filtration rate (eGFR) ($p < 0.001$). The best model for predicting GCL-IPL ($R2 = 0.232$) obtained from stepwise regression included only eGFR.
CONCLUSIONS. GCL-IPL was significantly reduced in T2DM patients with NPDR and correlated with longer diabetes duration, poor glycaemic control, hypertension, and coexistent diabetic nephropathy.

Optimal Choice of Gas or Silicone Tamponade for Surgical Treatment Advanced Stages of Proliferative Diabetic Retinopathy Patients

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DESIGN. Vitreoretinal surgery using various types of tamponade in severe, high risk proliferative diabetic retinopathy (PDR).
PURPOSE. Comparative analysis of effectiveness of silicone and gas tamponade in surgery for advanced stages of PDR.
METHODS. 320 operated patients (320 eyes) with stages 4 and 5 of PDR (ETDRS classification, 1991). The ages ranged from 18 to 82 years; 82 patients had type 1 diabetes and 238 patients had type 2 diabetes. All patients underwent 25G vitrectomy with removal of the vitreous body and fibrovascular membranes. In 198 eyes, gas tamponade was used (Group 1); in 122 eyes - silicone tamponade was needed (Group 2). Both groups were comparable in terms of severity of PDR, age and gender. In preoperative period, the stages of panretinal photocoagulation (PRP) were performed in 30 eyes of patients of the 1st group and in 23 eyes of the 2nd group.
RESULTS. In the postoperative period, preretinal haemorrhages were found both in Groups 1 and 2 (59 and 53 eyes, respectively). In Group 1, these were always combined with haemophthalmos; in the Group 2, silicone oil tamponade allowed for further PRP. On the 5-7th day, haemophthalmos occurred in 59 eyes of Group 1, PRP was performed in 27 eyes (13.6%). In Group 2, there were no cases of haemophthalmos, allowing PRP treatment in 89 patients (72.9%). After 6 months, diffuse haemophthalmos occurred in 71 eyes of the Group 1, in 46 eyes of them repeated endovitreal interventions with silicone tamponade were performed; in 17 eyes, the presence of epiretinal membranes in the posterior pole was noted, in 8 eyes there was recurrent retinal detachment. In Group 2 by 6 months, there were no cases of haemophthalmos, recurrent retinal detachment were in 3 eyes, epiretinal membranes formed in 5 eyes.
CONCLUSIONS. In our setting and in cases of very severe PDR, silicone tamponade was the preferred method in surgical treatment of severe stages of PDR.

Detection of Early Worsening of Diabetic Retinopathy in Diabetic Pregnant Women Using Oct Angiography

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DESIGN. During pregnancy, patients with diabetes mellitus (DM) may develop diabetic retinopathy (DR) or show DR progress and/or macular oedema. Timely diagnosis of these conditions in pregnant women with DM determines management options in patients: with early worsening of retinopathy - monitoring and correction of glycaemia, in some patients laser photocoagulation of the retina might be required.

PURPOSE. To investigate the possibility of OCT-A for the differential diagnosis of early worsening of DR and incident DR in pregnant women with DM.
METHODS. 24 pregnant women with type 1 diabetes were examined, average age was 29.1 ± 4.7 years, average duration of diabetes was 11.1 ± 8.4 years; 15 (63%) were had well controlled diabetes. OCT-A examination was carried out in each trimester and 3 months after delivery. The criteria for DR worsening during pregnancy was the growth of retinal nonperfusion zones during pregnancy and/or the regression of DR after childbirth. DR progression was determined by the expansion of retinal nonperfusion zones on OCT-A, the increase in vascular abnormalities, the increased presence of retinal haemorrhages, cotton-wool like foci, macular oedema, and neovascularization.
RESULTS. DR was detected in 14 pregnant women (58%). of these, 9 progressed. In 3 patients, macular oedema developed in both eyes during pregnancy: in a patient with severe non-proliferative DR oedema was focal and resolved after birth. In 2 patients with proliferative DR the maculopathy was diffuse and did not resolve after childbirth.
CONCLUSIONS. Progression of DR in pregnant women with DM is common, and many changes will not resolve, therefore careful examination and timely treatment is required in every case.

Long-Term Results of Drainage Surgery of Neovascular Glaucoma in Patients with Diabetes Mellitus

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DESIGN. Diabetes mellitus (DM) is one of the leading medical and social problems in the world. Diabetic retinopathy (DR) is one of the most prevalent complications of DM. Secondary neovascular glaucoma (NG) is a manifestation of the terminal stage of proliferative DR.
PURPOSE. Assessment of patients with DM in the late (10-15 years) postoperative period after NG drainage surgery, analysis of IOP characteristics, the presence of pain and any intraocular complications.
METHODS. 160 patients (164 eyes) operated from 2006 to 2022 inclusive were included in this study. Drainage surgery was performed on all of them (Ahmed's valve – 152 eyes and 12 eyes – Molteno valve). The average age of patients was 69.4 + 3.0 years, the duration of diabetes was 17.2 + 4.5 years, the level of glycated haemoglobin before surgery was 9.8 + 1.6%. The postoperative follow-up group included 52 patients 10-15 years of follow-up.
RESULTS. After surgery, pain was not reported by any of the 52 patients after the post-operative period. At the end of the long-term follow-up, the following complications were present: corneal vascularisation in 11 patients (21.2%), corneal epithelial-endothelial dystrophy in 9 patients (17.3%), phtysis bulbi in 8 patients (15.4%) and anophthalmos in 3 patients (5.8%). The last 3 patients were referred for cosmetic eye prosthetics.
CONCLUSIONS. Appropriate valve surgery allows patients to be pain-free and allows for most patients to remain in cosmetically acceptable state.