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REDUCED RESPONSE OF RETINAL VESSELS TO FLICKER LIGHT STIMULATION IN DIABETIC PATIENTS WITHOUT RETINOPATHY

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Purpose. In healthy subjects, retinal stimulation with flicker light induces retinal vessel dilatation, via a still partially understood neurovascular mechanism. The aim of the study was to determine if this vasomotive response due to retinal neural cell stimulation is impaired early in diabetes, before the occurrence of diabetic retinopathy.
Methods. Twenty-eight patients with diabetes (17 patients with type 1 diabetes, 11 patients with type 2 diabetes) without diabetic retinopathy on fundus examination, and 28 age- and sex-matched healthy volunteers were included. The diameter of retinal arteries and veins was measured using the commercially available Zeiss Retinal Vessel Analyzer (RVA). During the examination, three periods of flicker light stimulation (530-600 nm, 12.5 Hz, 20 seconds) were performed. Flicker light-induced retinal arterial and venous responses were assessed using three different calculation methods (R1, R2, R3).
Results. The arterial response to flicker light was significantly reduced in diabetic patients compared with healthy volunteers (Student Test, $p < 10\text{-}4$, $p < 10\text{-}5$, $p < 0.001$, for R1, R2, R3, respectively). In healthy volunteers, flicker light stimulation increases arterial diameter by (mean ± SD) 9.39% ± 2.51%, 4.14% ±1.78%, and 4.91% ± 2.40%, for R1, R2, and R3, respectively, compared with 5.97% ± 2.89%, 1.88% ± 1.42%, and 2.92% ± 2.07%, for diabetic patients. Venous response was also decreased in diabetic patients compared with healthy volunteers (Student test, $p < 0.05$, $p < 0.01$, $p < 0.05$, for R1, R2, R3, respectively). In healthy volunteers, flicker light stimulation increases venous diameter (mean ±SD) by 5.90% ± 2.35%, 4.41% ± 2.21%, and 4.57% ± 2.02%, for R1, R2, and R3, respectively, compared with 4.23% ± 1.87%, 2.58% ± 1.86%, and 3.03% ± 1.79%, for diabetic patients.
Conclusions. Flicker light-induced retinal arterial and venous responses are reduced in diabetic patients without diabetic retinopathy. This decrease in retinal vasomotive response may be due to an early decrease of retinal vascular reactivity and/or retinal neural activity.

ATP- AND ADENOSINE-INDUCED RELAXATION OF PORCINE RETINAL ARTERIOLES DEPENDS ON PERIVASCULAR RETINAL TISSUE AND ACTS VIA AN ADENOSINE RECEPTOR

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Purpose. Disturbances in the tone regulation of retinal arterioles is assumed to be involved in the pathophysiology of diabetic retinopathy, an effect that may be related to disturbances in the metabolism of purinergic compounds and prostaglandins. However, it is unknown whether the perivascular retinal tissue is involved in these effects.
Methods. Adenosine and ATP induced vasodilation of porcine retinal arterioles were studied in a wire myograph before and after removal of the perivascular tissue. Additionally, the effect of adding the prostaglandin synthesis inhibitor ibuprofen was studied.

Results. Both adenosine and ATP induced relaxation of the studied arterioles. This effect depended on the perivascular tissue and could be blocked by antagonists, but only ATP induced relaxation was affected by ibuprofen.
Conclusions. The relaxation of porcine retinal arterioles induced by purinergic compounds is modulated by the perivascular retinal tissue. The disturbances in the purinergic metabolism observed in diabetes mellitus may contribute to the disturbances in retinal blood flow that lead to diabetic retinopathy. This reaction pattern depends on an interplay between the retinal blood vessel and the perivascular retina.

HIGH GLUCOSE CONDITIONED MATRIX ENHANCES APOPTOSIS OF HUMAN RETINAL PERICYTES

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Purpose. Capillary pericytes are selectively lost in diabetic retinopathy. We have reported reduced adhesion of bovine retinal pericytes (BRP) cultured on extracellular matrix (ECM) produced by human vascular endothelial cells (HUVEC) in high hexose concentrations, probably due to glycation of matrix proteins, but no changes in their apoptosis. Some observations suggest, however, that human and bovine pericytes may behave differently in experimental conditions mimicking the diabetic milieu. The aim of this study was to verify human retinal pericytes (HRP) behaviour, when cultured on altered ECMs.
Methods. Conditioned ECMs were obtained by growing HUVEC for 7 days in culture media containing normal (5.6 mmol/L) or high (28 mmol/L) D-glucose. Cells were then lysed and ECM fixed by NH4OH. HRP were cultured in normal or high glucose on these conditioned ECMs or plastic alone. Pericyte adhesion was evaluated after 12-18 hours. After 7 days of culture, cell proliferation was assessed by cell counts and BrdU incorporation. DNA fragmentation was evaluated by ELISA, as a marker of early apoptosis, and the expression of three genes involved in apoptosis, p53, Bax and Bcl-2, was determined by RT-PCR.
Results. HRP adhered less on high glucose-conditioned ECM and plastic than on normal glucose-conditioned ECM, while there were no significant differences, after 7 days, in their number, nor in DNA synthesis, when grown in physiological glucose. In contrast, DNA synthesis was impaired in HRP cultured in high glucose on the three different matrixes, in comparison with HRP cultured in normal glucose. Apoptosis was greatly enhanced by high glucose-conditioned matrix, both in HRP grown in normal and high glucose and this was confirmed by p53, Bcl-2 and Bax mRNA expression.
Conclusions. Human pericyte apoptosis seems to be strongly affected by matrix produced in high glucose. This behaviour is different from that observed with bovine pericytes, underlining the importance of establishing a cell model as similar as possible to the human diabetic eye.

INCREASED SHEDDING OF VASCULAR ENDOTHELIAL MICROPARTICLES IN PROLIFERATIVE DIABETIC RETINOPATHY

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Purpose. Diabetic retinopathy (DR), the main cause for visual loss in adults, is associated with vascular proliferation, oedema and capillary occlusions. We hypothesized that microparticles (MP), submicron membrane vesicles released following cell activation or apoptosis, accumulate in vitreous fluid from patients with DRP.
Methods and Results. 60 patients needing eye surgery were classed as non-diabetic (ND, n=26, 68±2 yrs) or diabetic (D, n=34, 60±2 yrs, 7.5±0.2% HbA1c, 28 with proliferative and 6 non-proliferative DR). Levels and cellular origins of MP in platelet-free plasma and cell-free vitreous fluid were analyzed by flow cytometry, using annexinV (AnnV) labelling as a marker of apoptotic origin and specific markers for platelet (CD41) and endothelial (CD144) origins. Plasma MP levels were not different in ND and D patients (1605 ± 309 vs 1561 ± 276 AnnV+MP/mL, 1265 ± 254 vs 843 ± 147 CD41+MP/mL, 198 ± 45 vs 291 ±129 CD144+MP/mL, respectively). However vitreous MP levels were all markedly increased in D compared with ND patients (131 ±41 vs 54 ± 24 AnnV+MP/mL, $p=0.035$; 94 ± 25 vs 31 ± 8 CD41+MP/mL, $p=0.018$; 197 ± 38 vs 63 ± 15 CD144+MP/mL, $p<0.001$, respectively). The ratio of vitreous to plasma MP levels indicates the importance of local formation versus potential plasma leakage of MP from microvessels in vitreous fluid. This ratio for CD144+MP was markedly greater than 1 in proliferative DR ($p=0.020$), clearly indicating local accumulation of endothelial MP. For all markers the ratio was increased in proliferative DR compared to ND.
Conclusions. Proliferative DR is associated with a specific ocular increase in MP shed from activated or apoptotic vascular endothelial cells.

DIFFERENTIAL ROLES OF CTGF AND VEGF IN ANGIOGENESIS AND FIBROSIS IN PROLIFERATIVE DIABETIC RETINOPATHY

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Purpose. Vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF) may be causal factors of neovascularisation and fibrosis in diabetic retinopathy (DR), but their relative contribution to angiogenesis and fibrosis is unknown. We hypothesised that there is an association of VEGF and CTGF levels in vitreous with retinal neovascularisation and/or fibrosis when there is a causal relation, and reduced CTGF expression limits (VEGF-induced) angiogenesis when angiogenesis is CTGF dependent.

Methods. VEGF and CTGF were measured by ELISA in 68 vitreous samples of patients with proliferative DR (PDR, n=32), macular hole (n=13) or macular pucker (n=23) and related to clinical data, including degree of intra-ocular neovascularisation and fibrosis. The effects of reduced CTGF gene expression on angiogenesis was investigated in heterozygous and homozygous CTGF knockout mice in oxygen-induced retinopathy, laser-induced choroidal neovascularisation and in an in vitro angiogenic assay in metatarsal explant cultures.

Results. In PDR patients but not the other patients, vitreous CTGF levels correlated significantly with degree of fibrosis and with VEGF levels, but not with neovascularisation, whereas VEGF levels correlated only with neovascularisation. The ratio of CTGF and VEGF was the strongest predictor of degree of fibrosis. In mice, CTGF deletion did not inhibit angiogenesis induced by hypoxia, wound healing or VEGF levels, respectively.

Conclusions. CTGF is primarily a pro-fibrotic factor in the eye and a shift in the balance between CTGF and VEGF levels causes the switch from angiogenesis to fibrosis.

ADVANCED GLYCATION END PRODUCTS CAUSE INCREASED CCN FAMILY AND EXTRACELLULAR MATRIX GENE EXPRESSION IN THE DIABETIC RODENT RETINA

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Purpose. Referred to as CCN, the family of growth factors consisting of cystein-rich protein 61 (CYR61, also known as CCN1), connective tissue growth factor (CTGF, also known as CCN2), nephroblastoma overexpressed gene (NOV, also known as CCN3) and WNT1-inducible signalling pathway proteins 1, 2 and 3 (WISP1, -2 and -3; also known as CCN4, -5 and -6) affects cellular growth, differentiation, adhesion and locomotion in wound repair, fibrotic disorders, inflammation and angiogenesis. AGEs formed in the diabetic milieu affect the same processes, leading to diabetic complications including diabetic retinopathy. We hypothesised that pathological effects of AGEs in the diabetic retina are a consequence of AGE induced alterations in CCN family expression.

Methods. CCN gene expression levels were studied at the mRNA and protein level in retinas of control and diabetic rats using real-time quantitative PCR, western blotting and immunohistochemistry at 6 and 12 weeks of streptozotocin-induced diabetes in the presence or absence of aminoguanidine, an AGE inhibitor. In addition, C57BL/6 mice were repeatedly injected with exogenously formed AGE to establish whether AGE modulate retinal CCN growth factors *in vivo*.

Results. After 6 weeks of diabetes, Cyr61 expression levels were increased more than threefold. At 12 weeks of diabetes, Ctgf expression levels were increased twofold. Treatment with aminoguanidine inhibited Cyr61 and Ctgf expression in diabetic rats, with reductions of 31 and 36%, respectively, compared with untreated animals. Western blotting showed a twofold increase in CTGF production, which was prevented by aminoguanidine treatment. In mice infused with exogenous AGE, Cyr61 expression increased fourfold and Ctgf expression increased

twofold in the retina.
Conclusions. CTGF and CYR61 are downstream effectors of AGE in the diabetic retina, implicating them as possible targets for future intervention strategies against the development of diabetic retinopathy.

VEGF-A INDUCES EXPRESSION OF PRO-FIBROTIC GROWTH FACTOR AND EXTRACELLULAR MATRIX GENES IN THE RETINA

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Purpose. Vascular endothelial growth factor-A (VEGF) causes increased vascular permeability and leukocyte adhesion in preclinical diabetic retinopathy (PCDR). Another hallmark of PCDR is thickening of the capillary basement membrane (BM). Recently, VEGF was shown to induce expression of pro-fibrotic genes such as transforming growth factor β1 (TGF-β1) and connective tissue growth factor (CTGF or CCN2) in cultured endothelial cells. Moreover, neutralization of VEGF prevented BM thickening in diabetic mice *in vivo*. Therefore, we hypothesize that VEGF directly contributes to BM thickening in the diabetic retina by inducing expression of pro-fibrotic growth factors and extracellular matrix (ECM) components.
Methods. Transcription and protein levels of ECM-related genes were evaluated in the rat retina after intravitreal VEGF injection by real-time quantitative PCR, Western blotting and immunohistochemistry, respectively. In addition, expression profiles of the same genes in response to VEGF stimulation were investigated in bovine retinal vascular cells *in vitro*.
Results. Intravitreal VEGF injection induced retinal transcription of CYR61 (CCN1), CTGF, TGF-β1, tissue inhibitor of metalloproteases-1 (TIMP-1) and fibronectin, and protein expression of CYR61, CTGF and fibronectin. In bovine retinal endothelial cells and pericytes stimulated by VEGF *in vitro*, gene expression profiles were similar to those in the intact retina *in vivo*.
Conclusions. VEGF induces pro-fibrotic growth factors and extracellular matrix genes in the retina *in vivo*, as well as in cultured retinal vascular cells *in vitro*. Our findings may have relevance for understanding the pathogenesis of preclinical DR, where early upregulation of VEGF may cause BM thickening by induction of ECM-related genes.

CROSSTALK BETWEEN TNF-α, NADPH OXIDASE, PKCβ 2, AND CORE 2 TRANSFERASE IN DIABETIC LEUKOCYTES

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Purpose. Increasing evidence suggests that chronic, subclinical inflammation plays an important role in diabetic retinopathy. We have recently reported that a glycosylating enzyme, core 2 β-1, 6-N-acetylglucosaminyltransferase (core 2 GlcNAc-T), is implicated in increased leukocyte-endothelial cell adhesion in retinopathy via an up-regulation mechanism controlled by tumour necrosis factor-alpha (TNF-α) (Ben-Mahmud et al., 2006). The aim of the present study was to elucidate the potential role of NADPH oxidase signalling pathway in the raised activity of core 2 GlcNAc-T in diabetic leukocytes. NADPH oxidase is the most important source of cellular reactive oxygen species (ROS) in leukocytes and blood vessels.
Methods. Human leukocytes (U937 cells) and a lymphoblastoid cell-line deficient in p47phox were cultured in RPMI medium containing norml (5.6 mM glucose). The cells were exposed to TNF-α (8 pg/mL) for 24 h in the presence and absence of (i) NADPH oxidase inhibitors, 30 μM apocynin and 1μM of scrambled and unscrambled gp91ds-tat (ii) 50 nM LY379196, a specific PKCβ 1/2 inhibitor and (iii) antioxidants, 15 mM N-acetyl cysteine (NAC, 15 mM) and 5 mM Tiron. NADPH oxidase activity was measured using cytochrome c reduction assay. PKCβ1/2 activity was measured using TruLight™ PKC-β1/2 assay kit (Calbiochem, UK).
Results. Compared to control medium, exposure to TNF-α (8pg/mL; 24h) raised core 2 GlcNAc-T activity in human leukocytes [1722 ± 255.3 (n = 10) vs 374 ± 80.3 (n = 10), $p<0.0001$] that was significantly reversed with apocynin and LY379196. These findings were further supported with (i) significant reversal of TNF-α-induced core 2 GlcNAc-T activity with unscrambled and not scrambled gp91ds-tat, a specific NADPH oxidase inhibitor; (ii) use of a lymphoblastoid cell-line deficient in p47phox, a major subunit of NADPH oxidase; and (iii) reversal with NAC and Tiron.
Conclusions. Our results demonstrate a novel signalling crosstalk between TNF-α, core 2 GlcNAc-T, NADPH oxidase and PKCβ1/2 in diabetic leukocytes.
The study was supported by EFSD/Servier.

THE ROLE OF ADVANCED STRUCTURAL AND FUNCTIONAL RETINAL TESTING IN THE DIAGNOSIS OF EARLY RETINOPATHY IN TYPE 1 DIABETES

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Purpose. To investigate early structural and functional retinal impairment in patients with type 1 diabetes (DM1).
Methods. Thirty long-term and well-controlled DM1 patients, without fluorescein angiographic signs of retinal vasculopathy, and 15 healthy control subjects, performed structural tests included peripapillary retinal nerve fiber layer (RNFL) thickness measurement by Scanning Laser Polarimetry (GDx VCC) and by Optical Coherence Tomography (OCT3), and macular thickness evaluation by OCT3. Functional tests included retinal sensitivity evaluations by white-on-white Humphrey visual Field Analyser (HFA), Frequency Doubling Technology (Humphrey Matrix) and MP1 Microperimetry.
Results. TSNIT average, superior and inferior RNFL thicknesses at GDx VCC were significantly reduced in DM1 respect to healthy subjects. All OCT-3 parameters were similar between groups. HFA pattern standard deviation, Humphrey Matrix mean deviation, and temporal and infero-temporal retinal sensitivity at MP1 were significantly reduced in DM1 compared to control group.
Conclusions. DM1 patients showed a specific reduction in RNFL thickness and retinal sensitivity, despite the presence of any retinal vasculopathy, suggesting that advanced structural and functional retinal testing may be useful in the diagnosis of early diabetic retinal impairment.

EFFECT OF INAPPROPRIATE INSULIN THERAPY IN TYPE 2 DIABETES ON DIABETIC RETINOPATHY PROGRESSION

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Purpose. Recent studies have demonstrated that good metabolic control (glycosylated haemoglobin (HbA_{1c}) level less than 7%) achieved with insulin therapy (IT) can delay the onset and progression of diabetic retinopathy (DR). Often IT is unavailable or unsuitably used, despite being listed by WHO as an essential drug. IT is indicated when insulin resistance is present, it happens when oral drugs become ineffective, and large daily doses of insulin (0.5-1.2 U/kg) may be needed (even more than 1.5 U/kg, at least initially) to overcome prevailing insulin resistance.
Methods. We observed 3 groups of patients with type 2 diabetes and indications for IT to value progression of DR in 3 year period. Patients from the first group (n=75) had indications for IT, but refused over 3 years. Patients from the second group (n=215) were switched to IT at the beginning of the study and continued IT for 3 years. Patients from the third group (62) were treated with IT for more than 4 years. All were examined at baseline and 1, 2 and 3 years. DR was graded by biomicroscopy using the ETDRS scale. At baseline patients had either no DR or nonproliferative DR (≤level 47). Duration of diabetes, HbA_{1c}, blood pressure, lipids, BMI, presence of nephropathy, neuropathy and insulin dose were recorded.
Results. We found high progression levels in all groups: 73.3% in the first, 60.9% in the second and 41.9% in the third. IT switch was made after 13.4 ±0.7 years of diabetes, medium daily dose of insulin was less than 0.4 U/kg. 3-year progression in all groups was associated with the following risk factors: HbA1C level, duration of diabetes, initial degree of retinopathy, systolic hypertension, high cholesterol level, high BMI level, age and sex ($p<0.001$).
Conclusions. Our research provides clear evidence of low effectiveness of IT in type 2 diabetes in real clinical practice. The delay of IT and low insulin dose leads to an uncontrolled course of diabetes and its complications. IT in real clinical practice does not prevent long-term complications of diabetes, including blindness.

COURSE OF DIABETIC RETINOPATHY AFTER SUCCESSFUL PANCREAS TRANSPLANTATION ACCORDING TO THE LEVEL OF DIABETIC RETINOPATHY AT THE TIME OF TRANSPLANTATION

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Purpose. To identify the potential long-term role of successful pancreas transplantation on the course of different levels of diabetic retinopathy (DR).
Methods. We retrospectively evaluated all our patients

who underwent combined kidney and pancreas transplantation (KPTx) or pancreas transplantation (PTx) and who had stable graft function for at least one year. Patients were divided into four groups according to the level of DR (modified ETDRS scale) at the time of transplantation. Blind patients were excluded. Besides these factors, we also assessed diabetic macular edema (DME), visual acuity (VA), the need for laser treatment (LT) and pars plana vitrectomy (PPV). Other parameters such as cataract progression and glaucoma were also evaluated. We took into account also other risk factors for the progression DR before and after TX, e.g.; duration of diabetes, nephropathy before TX, blood pressure (BP), dyslipidemia, etc.
Results. Out of 300 transplanted patients, 189 KPTx were included into the study (mean follow-up 89 months); 17 patients after PTx were followed for up to 31 months on average. At the time of Tx the distribution of patients between the various levels of DR was (KPTx, PTx): grade 0 (no retinopathy) 1, 4; I. (mild non-proliferative DR) 21, 6; II. (moderate NPDR) 53,4; III. (severe NPDR) 53, 1; IV. (proliferative DR) 61,2. DME was present in 38 KPTx and 0 PTx patients. Progression of DR was recorded predominately in the advanced levels (III – IV) of the KPTx group (35%), compared only one case in level IV in the PTx group. VA outcomes were similar in each groups. LT before and need for LT after Tx was in KPTx patients 65 and 38 respectively and in PTx 2 and 1. PPV before and after Tx was required in 22 and 1 patients respectively. Cataract surgery in 2 years after Tx was required in 17 KTPx patients and 1 PTx. Duration of diabetes before Tx was nearly 3x longer in KPTx patients, and these patients had a higher incidence of nephropathy and hypertension.
Conclusions. Transplantation does not have a dramatic effect on pre-established DR. In patients with advanced forms of DR transplantation is not able in itself to prevent deterioration. In contrast, worsening is not generally seen in earlier levels of DR.

INTERNAL QUALITY ASSURANCE IN A DIGITAL RETINAL PHOTOGRAPHIC SCREENING PROGRAMME FOR DIABETIC RETINOPATHY

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Purpose. To establish the level of inter-grader agreement between graders of digital retinal images acquired by a mobile retinal screening service
Methods. The retinal images of 835 type II diabetics were submitted for grading by up to 3 separate graders as recommended by the National Screening Committee on Diabetic Retinopathy (NSC) in the UK. Sensitivity and specificity levels were established for primary grading carried out by non-clinical personnel performing first stage grading. The results of the initial grader were masked when the same images were submitted to second and in some instances third line grading by an accredited optometric grader and medical ophthalmologist respectively. The sensitivity and specificity of initial grading (test grading) on all cases were calculated by reference to the final grading decision which was taken as the true grading for each case. Of those cases identified as having disease greater than minimal background diabetic retinopathy and hence requiring hospital referral, the decision as to priority of referral was based on strict agreed criteria and referrals were classified as either routine hospital or fast-track hospital referral. The levels of inter-grader agreement for those cases which were graded as either routine hospital referral or fast-track referral were subsequently calculated.
Results. The results for specificity and sensitivity were: number of patients with some disease at first level grade = 289, number of patients with some disease at final level grade (true +ve) = 204 (TP), number of patients with no disease at first level grade = 212, number of patients initially graded as disease that were subsequently graded as no disease (false +ve) = 85 (FP), number of patients who were graded as no disease at final grade (true-ve) = 266 (TN), number initially graded as no disease who subsequently were graded as disease (false-ve) = 8 (FN), sensitivity = TP/TP+FN = 204/204+8 = 204/212 = 96.2%, specificity = TN/TN+FP = 266/266+85 = 266/351 = 76%. The level of inter-grader agreement between either routine and fast-track referral based on those 104 cases requiring hospital referral for more than minimal retinopathy was 94%.
Conclusions. Trained accredited graders can be recruited from non-clinical personnel and achieve adequate grading standards to be useful in the establishment of a national retinopathy screening service.

REACHING THOSE WHO NEED IT THE MOST – DIABETIC RETINOPATHY SCREENING IN EAST LONDON

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Purpose. The population of patients with diabetes doubled since 1995 in Tower Hamlets (TH), an underprivi-

leged East London Borough where the estimated prevalence is now 6.1%. In addition, TH had the highest diabetes related mortality in the UK in 2001. It was believed that all diabetes related problems were exacerbated by cultural and language barriers as TH houses the largest Bengali population outside of Bangladesh. It was estimated that attendance at diabetic retinopathy screening DRS was only 30% in 2001.
Methods. In 2001, the TH Diabetes Team, including DRS, was formed to improve patient services. Systematic recruitment of staff and patients was moved forward by a partnership between TH and Moorfields Eye Hospital, London, UK. A team, comprising of a clinician, screeners and administrative personnel was formed to improve attendance in DRS. The accuracy of the database was determined first by cross-examining relevant hospital databases. Second, an educational campaign was carried out; this aimed at physicians, diabetologists and religious leaders of the community. Third, appointments were booked and patients were screened by Bengali-speaking staff to minimise the anxiety associated with screening. Furthermore, a second clinic in a geographically more convenient location was set up to facilitate take-up of services.
Results. The DRS database was found to be over 90% accurate. On days when Bengali-speaking administrators made bookings, the attendance rate increased dramatically (from 50% to 75%) this for follow-up patients was 90%. On hospital databases a further 202 patients were identified as participating in slit-lamp screening. Bengali speaking screeners at the second location brought the overall attendance rate to 70%.
Conclusions. A team approach coupled with administrative and educational actions was effective in raising participation in the TH DRS 72% of eligible patients screened to date. This was then within government guidelines for DRS in the UK. Further improvement is needed if current government guidelines are to be met.

VISUAL ACUITY IN DIABETICS AT FIRST SCREENING FOR EYE DISEASE DIABETIC RETINOPATHY SCREENING SERVICE FOR WALES (DRSSW)

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Purpose. Diabetic retinopathy is the third major cause for visual impairment in the UK and screening services attempt to reduce the incidence of severe blindness by early detection in this high risk population group.
Aims. The aims of this study were to measure visual acuity impairment in a cohort of diabetics at first presentation for screening at the Diabetic Retinopathy Screening Service for Wales (DRSSW) and to establish the causes thereof. A further aim was to estimate the numbers of visually impaired diabetics whose visual loss is remediable or preventable, to be able to project the impact of that workload on Ophthalmic Services.
Methods. Data was used from diabetics attending for their first screening at the DRSSW. After their photographs had been graded and data collated, an estimate of the prevalence and distribution of visual impairment was performed according to age and disease. Multiple regression analysis of risk factors for disease was done by statistical analysis to evaluate risk factors for visual impairment.
Results. Of the 27,178 diabetics, 4.4% (1,193) had moderate visual impairment and 1.4% (393) had severe visual impairment. Multiple logistic regression analysis of risk factors for visual impairment were female sex – Odds ratio (OR) 1.6, [95% confidence interval (CI) 1.4-1.8]; aged 65 years or older – OR 2.7 [95% CI 2.4-3.0]; proliferative diabetic retinopathy – OR 5.4, [95% CI 3.7-7.7] and diabetic maculopathy – OR 1.7 [95% CI 1.4-2.0]. The proportion of individuals who required eye care services for visual impairment was estimated at 6.3% (1,703).
Conclusions. With this analysis the DRSSW can provide projected numbers with regards to visual impairment in the diabetic population and the resulted impact of these on eye care services. With the incidence of diabetes rising, diabetic eye screening to optimise Health Care provision can aid future planning and cost structuring.

DIABETIC RETINOPATHY SCREENING WITH FUNDUS PHOTOGRAPHS: COMPARISON OF DIFFERENT APPROACHES

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Purpose. To analyse the ability to identify individual lesions and to determine clinical levels of diabetic retinopathy using non-mydriatic digital colour retinal images compared to Early Treatment Diabetic Retinopathy Study (ETDRS) seven standard 35-mm stereoscopic colour fundus photographs (ETDRS photos).
Methods. Sixty-six eyes of diabetic patients with type 1 or type 2 diabetes mellitus from a single center including the full spectrum of diabetic retinopathy were enrolled. Non-simultaneous 45°-field non stereoscopic digital colour images were taken from one central field and from three fields with a non-mydriatic fundus camera (Nidek Technologies, Albignasego, Italy) (1F-NM and 3F-NM images) before pupil dilation. The 3F-NM procedure for field location was au-

tomatically performed by the fundus camera. Following pupil dilation, standard 30° ETDRS photos were obtained with Topcon TRC50IA (Tokyo, Japan). NM images and ETDRS photos were graded on a lesion-by-lesion basis by two independent, masked readers to assess the ETDRS grading of the lesions, and the clinical severity of the disease according the International proposed five-stage disease severity Classification.
Results. Comparison of individual lesions among 1F-NM image or 3F-NM images and ETDRS photos revealed good agreement for hard exudates (k=0.74 and k=0.75 respectively); moderate agreement for haemorrhages and/or microaneurysms (k=0.49, k=0.60), cotton wool spots (k=0.41, k=0.49) and retinal new vessels (k=0.40, k=0.43). The agreement was fair for clinical significant macular edema (k=0.40, k=0.39). There was very high agreement between 3F-NM and ETDRS images for severe non-proliferative and proliferative diabetic retinopathy (k=0.81 and k= 0.82 respectively), while it was moderately good between 1F-NM and ETDRS images.
Conclusions. Undilated digital images using non-mydriatic cameras are becoming a new tool for the screening of diabetic retinopathy. The agreement appeared excellent for high risk diabetic retinopathy levels, while it was poor for the clinical significant macular oedema due to non-stereo technique. The automatic non-mydriatic system may be an effective tool for determining the level of the diabetic retinopathy and identifying the need for prompt referral to the ophthalmologist, even when applied as a telemedicine tool. It is still controversial if one 45° image instead of three fields images is adequate for diabetic retinopathy screening.

PROLIFERATIVE DIABETIC RETINOPATHY IS AN IMPORTANT PREDICTOR OF MORTALITY AMONG TYPE 1 DIABETIC PATIENTS

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Purpose. To evaluate the effect of diabetic retinopathy on 25-year survival among a population-based cohort of type 1 diabetic patients from the Danish County of Fyn.
Methods. In 1973 all type 1 diabetic patients from Fyn County, Denmark, with onset before the age of 30 as of July 1st 1973 were identified (n=727). In 1981-1982 573 of the 627 patients still alive and living in Denmark participated in a clinical examination where diabetic retinopathy was graded and other markers of diabetes measured. 25-years follow-up mortality was examined in 2006 and related to the baseline examination.
Results. Of the 573 patients participating in the baseline examination in 1981-1982 297 (51.8%) were still alive. 256 had died (44.7%). 3 had emigrated (0.5%) and 17 (3.0%) were unaccounted for because they had chosen not to provide data for scientific examinations. There was no difference in survival among males and females (p=0.52). Age- and sex-adjusted hazard ratios (HRs) of mortality were 1.01 (95 CI: 0.72-1.42) and 2.04 (1.43-2.91) for patients with non-proliferative and proliferative retinopathy at baseline compared to patients with no retinopathy, respectively. In a univariate model different risk factors measured at baseline were added to the above model. Adjusting for diabetes duration, smoking, HbA1c, systolic and diastolic blood pressure and BMI only changed HR marginally. After adjusting for proteinuria however, HR decreased to 1.49 (0.99-2.24). In a multivariate model including all above risk factors, HR among patients with proliferative retinopathy was no longer statistically significant but still remaining increased 1.48 (0.98-2.23).
Conclusions. Proliferative diabetic retinopathy is a predictor of mortality among type 1 diabetic patients. This association is partly explained by proteinuria but HR still remains increased after adjusting for proteinuria. Nonproliferative diabetic retinopathy at baseline did not affect survival among the type 1 diabetic patients in the current study and there was no difference in mortality between men and women.

DIABETIC MACULAR OEDEMA: EFFECTS OF CHANGES IN PLASMA OSMOLARITY ON THE RETINAL THICKNESS AS EVALUATED BY OCT

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Purpose. To examine if the osmotic Starling forces affect diabetic macular oedema by analysis of the effect of increasing the plasma osmolarity on the retinal thickness in clinically significant diabetic macular oedema (CSMO).
Methods. Prospective, paired, unmasked study. On two separate days, 14 patients with diabetic CSMO were randomised to an oral glycerol solution (0.57 g/mL) of 1.5 and 3 mL/kg body weight (maximum 250 mL). Plasma osmolality (p-OSM) and glycerol (p-GLY); and the primary effect parameter: the retinal thickness (RT) of the peak oedematous field on the retinal maps of the StratusOCT™ fast protocol, were monitored for the subsequent 180 min. The systemic blood pressure (BP),

intraocular pressure (IOP) and capillary glucose (CG) were also monitored over the same time interval.
Results. P-OSM and p-GLY correlated strongly (r=0.79, p<0.0001). Baseline p-OSM was 300 (4) mOsm/L (mean)(SD) for the low and 302 (8) mOsm/L for the high glycerol dose. The peak Δ p-OSM increased from 13 (9;17) mOsm/L (mean)(95% confidence limits, CL) at 60 min to 23 mOsm/L (20;27) mOsm/L at 120 min, respectively (p<0.0001). Baseline RT was 377 (73) (mean) (SD) and 373 (68) µm for the low and high dose, respectively. The maximal Δ RT of 7 µm (4;10 µm) (mean) (95% CL) (p=0.0002) after the low dose and 7 µm (3;12 µm) (p=0.006) after the high dose occurred in the interval from 20 to 30 min, where the dose effect of p-OSM had not yet become significant.
Neither BP, IOP nor CG interacted significantly with the thickness results (p>0.05).
Conclusions. Glycerol transiently reduces the peak RT in diabetic CSMO confirming the application of the osmotic Starling forces on diabetic macular oedema; however, no dose dependent effect was found.

ASSESSMENT OF DIABETIC MACULAR EDEMA: A COMPARISON OF DIFFERENT METHODS

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Purpose. To compare effectiveness of 35° stereo fundus photography, optical coherence tomography (OCT), confocal retinal tomography (Heidelberg retina tomography II – HRT II), fluorescein angiography (FA) with non-contact lens biomicroscopy for the diagnosis of diabetic macular edema (DME).
Methods. 136 patients (210 eyes) with DME, 30 diabetic patients without macular edema (54 eyes), 35 healthy subjects (67 eyes) were examined using with non-contact lens biomicroscopy, stereophotography (Topcon TRC-50IX fundus camera, Agfachrome 100 colour film), OCT (Stratus 3000, scan protocol «Macular Thickness»), HRT II (Macula Edema Module, version 1.6), FAG (Topcon TRC-50IX fundus camera, IMAGEnet 2000).
Results. In comparison to fundus biomicroscopy the following sensitivity and specificity were found: for OCT – 0.98 and 0.85, k – 0.82; for HRT II – 0.94 and 0.76, k – 0.71; for FAG – 0.90 and 0.92, k – 0.76 and for stereophotography – 0.85 and 0.89, k – 0.75 ($p < 0.001$) respectively. OCT and FAG were the optimal combination (OCT and FAG – sensitivity 0.98 and specificity 0.87, k – 0.84, $p < 0.001$; OCT and HRT II – 0.98 and 0.70, k – 0.69, $p < 0.001$; HRT II and FAG – 0.60 and 0.55, k – 0.60, $p < 0.001$, respectively). The agreement between methods was fair (OCT and FAG – k 0.56; OCT and stereophotography k - 0.59; FAG and stereophotography k – 0.46).
Conclusions. The best agreement with fundus biomicroscopy was shown by OCT. Combination of OCT and FAG is more informative for DME diagnosis, because it allows the assessment of morphological and physiological criteria of DME.

MULTIFOCAL ERG RESPONSE SEEMS TO IMPROVE IN AREAS TREATED WITH PHOTOCOAGULATION FOR DIABETIC MACULAR OEDEMA

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Purpose. To evaluate the local correspondence between multifocal electroretinogram (mfERG) response and retinal thickness assessed with OCT after focal laser treatment in patients with diabetic macular oedema.
Methods. Twelve diabetic patients (aged 60±14 years, diabetes duration 16 ± 8 years) treated with focal/grid photocoagulation for clinically significant macular oedema underwent mfERG and optical coherent tomography (OCT) before and three months after treatment. The fixation during mfERG recording was controlled using a fundus camera and illumination with infrared light from the recording electrode, with visualization of the hexagonal elements over the retina. The average thickness (µm) in any of the nine sectors, as defined by the ETDRS, which was treated with photocoagulation was measured. Amplitudes and implicit times were analyzed within corresponding areas on the mfERG.
Results. There was a borderline increase in mfERG amplitudes after photocoagulation; 20.4 ±7.5 vs 15.8 ±6.2 nV/deg^2; p=0.055, whereas no difference was seen in implicit time. OCT values in the treated regions were lower at follow-up 272 ±23µ vs. 327 ±79µ; p=0.013. No correlation was seen between the changes in mfERG response and changes in OCT values. The decrease in retinal thickness was correlated with the amount of laser spots given p=0.002.
Conclusions. Focal argon laser treatment is effective in reducing retinal thickness and there is a tendency toward improved retinal function in treated areas demonstrated by increased amplitudes on the mfERG.

OCT FEATURES DURING EVOLUTION OF SEROUS RETINAL DETACHMENT ASSOCIATED WITH DIABETIC MACULAR EDEMA

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Purpose. To analyse the evolution of serous retinal detachment (SRD) associated with diabetic macular edema (DME) using optical coherence tomography (OCT).
Methods. 64 eyes of 40 diabetic patients who had SRD associated with DME were studied retrospectively. All the patients had fluorescein angiography and repeated OCT3 examinations during follow-up. Foveolar neuroretinal thickness (NRT) and height of the SRD (HSD) were measured. The evolution of the OCT macular profiles was qualitatively analysed.
Results. Mean follow-up was 11.8 months. DME was focal in 10 eyes (15.6%), diffuse in 17 (26.6%) and both diffuse and focal in 37 (57.8%). Mean (+/-SD) initial VA, NRT and HSD were 0.35 (+/- 0.21), 346.88+/- 138.61 µm and 199.48+/-139.8 µm respectively . HSD was not correlated with VA (p=0.23) nor with NRT (p=0.31). In 9 eyes (14.1%), NRT above the SRD was normal. In eyes in which DME improved during follow-up (19 eyes), SRD disappeared before the maximal reduction of retinal thickness in 7 eyes (36.8%) and after or simultaneously in 12 (63.2%). In eyes in which DME worsened during follow up (45 eyes), the SRD disappeared in 15 (33.3%).
Conclusions. In this study, SRD height did not correlate with retinal thickening. The latter may appear before central neuroretinal thickening and disappear before or after its regression. Consequently, SRD does not seem to be related either to the severity of the DME nor to its reabsorption.

INTRAVITREAL TRIAMCINOLONE VERSUS LASER PHOTOCOAGULATION FOR DIABETIC MACULAR OEDEMA

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Purpose. To determine if repeated intravitreal triamcinolone improves best corrected visual acuity at 1 year compared to conventional laser therapy for persistent diabetic macular oedema.
Methods. This was a prospective randomised controlled clinical trial. 88 eyes with persistent clinically significant macular oedema after at least one prior laser photocoagulation. 43 patients were randomised to intravitreal triamcinolone and 45 to laser photocoagulation 4mg of 0.1mL intravitreal triamcinolone versus standardised ETDRS macular laser photocoagulation were given every 4 months for one year. The primary endpoint was the proportion of patients who improved by 15 ETDRS letters at 12 months. Secondary endpoints were the change in mean best corrected visual acuity at 12 months, difference in macular thickness and macular volume in TA vs laser groups and adverse event reporting in particular elevated intraocular pressure.
Results. Improvement in 15 or more ETDRS letters was seen in 2 out of 41 patients in the ivTA group (4.9%) and in 5 out of 41 (12.2%) patients in the laser group (p = 0.492). The mean Early Treatment of Diabetic Retinopathy Study (ETDRS) scores at baseline were 54.4 letters in the study group and 53.0 letters in the control group (p = 0.59). At 12 months the mean ETDRS scores were 54.5 and 54.6 respectively (p = 0.97). Optical coherence tomography showed a reduction in central macular thickness with triamcinolone of 82.0 µm and 62.3 µm with laser (p = 0.6) at 12 months. There was 1 case of sterile endophthalmitis. 22 out of 43 patients in the study group required ocular antihypertensives.
Conclusions. This study did not show any benefit from intravitreal triamcinolone for patients with persistent diabetic macular oedema compared to conventional laser therapy and its use is not recommended in routine clinical practice.

INTRAVITREAL BEVACIZUMAB (AVASTIN) FOR DIABETIC MACULAR EDEMA

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Purpose. To report the safety and efficacy of intravitreal injections of bevacizumab for the treatment of diabetic macular edema.
Methods. This prospective, non-comparative case series included 21 eyes of 21 consecutive patients with diabetic macular edema. Patients with macular edema, independently of the size and duration of edema, retinal thickness, visual acuity and type of diabetes were included. Among the exclusion criteria were any prior treatments (either macular laser or intravitreal triamcinolone) in the study eye within 6 months preceding enrolment, presence of non-perfusion for >1 disc area involving the foveal avascular zone, epiretinal membrane and significant media opacities. At each visit all patients underwent assessment of best corrected visual acuity (BCVA) with ETDRS-like charts, slit-lamp examination, intraoc-

ular pressure measurement, retinal thickness measurement using optical coherence tomography (OCT), fluorescein angiography and fundus biomicroscopy. Main outcome measures were occurrence of treatment-related ocular or systemic complications, mean change in BCVA, change in foveal thickness on OCT. All patients received at least one intravitreal injection of 1mg/0.04 mL bevacizumab (Avastin) on a monthly basis.

Results. All patients completed 3 months of follow-up. 16 patients (76%) received 3 injections, 3 patients (14%) and 2 patients (10%) received 2 and 1 injection respectively. All patients but two had undergone previous treatments, such as grid laser, full scatter panretinal photocoagulation and intravitreal injection of triamcinolone with no benefit or with recurrence of the edema. A total of 134 injections were performed with no evidence of systemic or ocular side effects. At baseline, mean BCVA was 59.4 ±14.2 ETDRS letters, ranging from 34 to 84, and mean central retinal thickness by OCT was 501 ±146 μm (range 321-721 μm). Mean BCVA at 4 months was 64.5 ±8.5 ETDRS letters: changes in visual acuity were not significant throughout follow-up. Mean retinal thickness decreased to 444 ±177 μm, 456 ±59 μm and 426 ±192 at 4, 8 and 12 weeks respectively. Anatomical improvement was sustained up to the 4th month and was statistically significant.

Conclusions. Preliminary, short-term results suggest that IVB provides morphological improvement with no significant adverse events in patients with diabetic macular edema. Decrease in mean retinal thickness was significant but it was not associated with an overall increase in mean BCVA, except for 3 patients with severe non proliferative diabetic retinopathy and moderate to marked peripheral retinal ischemia. This seems to suggest that in such patients VEGF may play a predominant role, compared to other mediators, in the genesis of the edema and its inhibition could provide both functional and anatomical improvement.

POSTERS

BASELINE DATA OF THE ÅRHUS PROSPECTIVE STUDY OF AUTOREGULATION IN DIABETIC RETINOPATHY

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Purpose. To study autoregulation of retinal arterioles in type 2 diabetic patients with mild diabetic retinopathy at baseline, and after 2 and 5 years to correlate changes in autoregulation with changes in retinopathy.
Methods. Sixty-five type 2 diabetic patients (mean age 57.2y, range: 43.9y - 65.3y) were examined. All patients had mild (1 to 4 dot and blots haemorrhages alone) retinopathy in at least one eye, had no other known systemic vascular or ocular diseases. All patients underwent a general ophthalmological examination including measurement of visual acuity, intraocular pressure, slit lamp examination, and fundoscopy. Subsequently, the Retinal Vessel Analyzer was used to measure the diameter response of a retinal arteriole at rest and during isometric exercise by lifting a hand weight. The systemic blood pressure was measured on the upper left arm at rest and during exercise.
Results. The visual acuity of the examined eye ranged between 0.6 and 1.2 (mean = 0.97). The mean intraocular pressure and mean blood glucose was 17.0 ±0.4 mmHg and 11.5 ±0.6 mmol/L. The mean systemic arterial blood pressure at rest was 101.7 ±1.4 mmHg and a significant increase of 24.8 ±1.8% was observed during isometric exercise ($p<0.0001$). The mean blood vessel diameter at rest was 116.8 ±1.9 AU (AU = arbitrary unit which approx. is equal to microns) and exercise induced a non-significant change in diameter of 0.1 ±0.4% ($p=0.79$). A considerable variation was observed in the diameter response among the patients (var = 9.6). However no significant correlation was found between the change in diameter and the change in MAP ($p=0.18$).
Conclusions. Type 2 diabetic patients with mild diabetic retinopathy have a diminished autoregulatory response in the retinal vessels, indicating that autoregulation is disturbed early in the disease process. Follow-up examination of the cohort to observe whether a further development of diabetic retinopathy is paralleled in changes in autoregulation will indicate whether these two parameters are related causally.

CONNECTIVE TISSUE GROWTH FACTOR (CTGF) IS NOT INVOLVED IN ANGIOGENESIS IN KNOCK OUT MOUSE MODELS

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Purpose. Connective tissue growth factor (CTGF) is a member of the CCN family of growth factors. CTGF is important in scarring, wound healing and fibrosis. It has also been implicated to play a role in angiogenesis besides vascular endothelial growth factor (VEGF). In the eye, angiogenesis and subsequent fibrosis are the main cause of blindness in diabetic retinopathy.
Methods. We have applied 3 different models of angiogenesis to homozygous CTGF-/- and heterozygous CTGF+/- mice to establish involvement of CTGF in neovascularisation. CTGF-/- mice die around birth. Therefore, embryonic CTGF-/-, CTGF+/- and CTGF+/+ bone explants were used to study *in vitro* angiogenesis and neonatal and mature CTGF+/- and CTGF+/+ mice were used in models of oxygen-induced retinopathy and laser-induced choroidal neovascularisation (CNV).
Results. Angiogenesis *in vitro* was independent of the CTGF genotype both in the presence and absence of VEGF. Oxygen-induced vascular pathology in the retinas as determined semi-quantitatively and laser-induced CNV as determined quantitatively were not affected by the CTGF genotype either.
Conclusions. Our data strongly suggest that down-regulation of CTGF levels does not affect neovascularisation in the eye and support that VEGF is the major inducer of angiogenesis under diabetic conditions.

RETINAL VESSEL SIGNS AND EARLY RETINOPATHY IN TYPE 1 DIABETES

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Purpose. To evaluate and grade arteriolosclerotic retinal vessel signs in the ocular fundus and to study their association with early DR in T1D.
Methods. This preliminary cross-sectional IDEAL substudy of the collaborative multicenter FinnDiane study comprised of 76 consecutive patients (58% men) aged 26 (SD 6), with T1D duration of 9 (2) yrs and age at onset 17 (SD 6). One macula and one optic disc centered 50-60º red-free fundus image was digitized. In patients with DR (45%) the more affected eye and in patients without DR a randomly selected eye was graded by J.P.K. and P.A.S. unaware of the patient characteristics.
The grading focused on: 1) arteriolar signs; 2) venular signs; 3) arteriovenous nickings (AVN: remoteness, arching, banking, compression and deviation) according to a classification based on early literature of vascular signs; 4) DR (a modified ETDRS classification); 5) AVN signs summed as the AVN risk sum (ANR); 6) all arteriolar, venular and nicking signs expressed as the arteriolosclerotic risk burden (ARB).
Results. Thirty-one patients (41%) had minimal to mild and 3 (4%) moderate DR. Arteriolar signs (sinusoidal elongation 74% (n=56), generalised 45% (n=34), and focal narrowing 3% (n=2), pronounced light streak 40% (n=30), straightening 1% (n=1) as well as venular signs (tortuosity 65% (n=49), minimal tortuosity 51% (n=39), tortuosity in macula 57% (n=43) and local narrowing 1% (n=1) were common in all 76 eyes. At least one AVN occurred in 96% of patients. ANR and ARB did not differ between patients with and without DR, although there was a trend of higher ARB in patients with DR (p=0.064). In a univariate regression analysis, ANR was associated with duration (r=0.263, p=0.022). ARB was associated with duration (r=0.262, p=0.022) and HDL cholesterol (r= 0.241, p=0.036).
Conclusions. These preliminary data show that early arteriolar and venular signs are common in T1D with short duration.

POSSIBLE INCREASED SEVERITY OF RETINAL VEIN OCCLUSION IN DIABETIC SUBJECTS

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Purpose. To report the evolution of retinal vein occlusion (RVO) in diabetic subjects.
Methods. The charts of 16 cases of RVO (10 central RVO, 6 branch RVO) in diabetic subject are reported.
Results. 11 patients developed chronic macular oedema. 4 patients developed new vessels, either preretinal or on the disc. Three of them had preretinal fibrovascular proliferation, which is highly uncommon in nondiabetic RVO. 14 had no or minimal diabetic retinopathy (DR) in the fellow eye.
Conclusions. RVO in diabetic patients appears associated with a high rate of chronic macular oedema and capillary nonperfusion. Moreover, diabetic-like complications such as fibrovascular proliferation may develop even in the absence of underlying DR, suggesting a reciprocal aggravation of diabetes and RVO. These findings may aid the understanding of microvascular remodelling following both RVO and DR, and the management of patients.

EFFECT OF LUTEIN IN THE RETINA OF DIABETIC MICE

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Purpose. Oxidative stress markers and functional tests were studied to evaluate early biochemical and functional changes in retina of diabetic mice after different periods of time. We also tested the effects of lutein treatment compared to insulin therapy.
Methods. Mice were rendered diabetic by alloxan injection and divided into subgroups: control, control + lutein, diabetic, diabetic + lutein, diabetic + insulin and diabetic + insulin + lutein. Treatments started on day 4 after alloxan injection and animals were sacrificed on days 7, 14 or 21. MDA concentration and GPx activity were measured as oxidative stress markers. Electroretinogram (ERG) was carried out to evaluate retinal function.
Results. We observed an increase in MDA concentration

and a decrease of GPx activity in the retina after 7 days of diabetes induction. This oxidative stress situation is better established after 2 and 3 weeks of diabetes. We also observed an impairment of retinal function since the first week of diabetes. This alteration was more evident after 3 weeks of diabetes induction. Lutein prevented all these changes even under hyperglycaemic conditions.
Conclusions. Although a proper glycaemic control is desirable to prevent the development of diabetic complications, it is not sufficient to prevent them completely. Therefore, lutein, a natural antioxidant without hypoglycaemic properties, could be an appropriate coadjuvant treatment for the changes observed in this study.
This work was supported by projects PI03/1710 from Fondo de Investigación Sanitaria and PRUCHB06/09 from Universidad CEU-Cardenal Herrera.

EFEECT OF DIABETES IN RAT RETINA AND LENS. TREATMENT WITH LUTEIN

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Purpose. As oxidative stress may play an important role in the pathogenesis of diabetes complications, the aim of this study was to study the status of the antioxidant defences in the retina and lens of diabetic rats after 3 months of hyperglycemia. We also investigated retinal function and assayed a treatment with the natural antioxidant lutein.
Methods. Rats were rendered diabetic by streptozotocin injection and divided into subgroups: control, control + lutein, diabetic, diabetic + lutein, diabetic + insulin and diabetic + insulin + lutein. Treatments started on day 4 after streptozotocin injection and were administered daily until the end of the experiment, 3 months of after diabetes induction. Antioxidant defences: GSH concentration and GPx activity were measured, and electroretinogram (ERG) was carried out to evaluate retinal function.
Results. GSH concentration was decreased in the retina and lens after 3 months of diabetes, in contrast, GPx activity was decreased in the retina but not in lens. We observed an impairment in the ERG of diabetic animals when compared to controls. The administration of insulin and lutein together was the only treatment able to recover to control values all the alterations observed, being the most efficient treatment.
Conclusions. Although a proper glycaemic control is desirable to prevent the development of diabetic complications, it is not sufficient to prevent them completely. Therefore, lutein, a natural antioxidant without hypoglycaemic properties, could be an appropriate coadjuvant treatment for the changes observed in this study.
This work was supported by projects PI03/1710 from Fondo de Investigación Sanitaria and PRUCHB06/09 from Universidad CEU-Cardenal Herrera.

MIXED MACULAR PATHOLOGY IN A DIABETIC PATIENT

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Purpose. We present a rare case of co-existing pathology of diabetic and bull's eye maculopathy. To our knowledge, only one similar case has been reported in the literature before.
Results. A 55 year old male was reviewed in the Medical Retinal clinic with bilateral moderate diabetic retinopathy and bilateral diabetic maculopathy with clinically significant macular oedema in the right eye. Visual acuities at the time were 6/6 bilaterally and the patient was asymptomatic. Fluorescein angiography (FA) revealed marked hypofluorescence in the central macula in both eyes and significant angiographic macular oedema in the right eye. The initial interpretation of the FA was enlarged foveal avascular zone in both eyes. Macular grid laser for the right eye was entertained but the patient was not keen to proceed. In further follow up, autofluorescence was performed which showed a distinct ring of increased autofluorescence surrounding an area of decreased autofluorescence. Electrodiagnostic tests were requested. Results revealed undetectable pERGs, diagnosing severe macular dysfunction.
Conclusions. Caution has to be taken when interpreting the clinical picture and fluorescein angiography in a diabetic patient, as coexisting pathology may go unnoticed. The fact that the bull's eye maculopathy acted as a barrier in the expansion of diabetic oedema in the fovea in this patient, is of interest and possible explanations are discussed in this paper.

REFRACTION IN PEOPLE WITH AND WITHOUT DIABETES OVER A 10 YEAR PERIOD

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PURPOSE. To examine the changes in refraction and refractive components for people with and without diabetes over a 10 year follow-up period.
METHODS. A longitudinal study of 21 twin pairs with at least one twin with Type 1 diabetes at baseline was performed in 1993 and 2003. At baseline, patients were from 12-39 years old. Refractometer- and keratometer-measurements were performed in cycloplegia. The spherical equivalent of refraction (refraction) and the radius of corneal curvature (CC) were calculated. Axial length (AL), anterior chamber depth (ACD) and lens thickness (LT) were measured with ultrasound biometry.
RESULTS. Refraction shifted in a myopic direction in both people with and without diabetes. The mean difference in refraction over 10 years was -0.40 D in people with diabetes (p=0.001) and -0.22 D for people without diabetes (p=0.069). Lens thickness increased with 0.52 mm (p<0.001) and 0.44 mm (p<0.001) in people with and without diabetes, respectively, and a corresponding decrease in anterior chamber depth of -0.20 mm (p<0.001) and -0.14 mm (p=0.018) was found. Axial length increased with 0.05 mm (p=0.161) and 0.12 mm (p=0.044). Corneal curvature radius increased with 0.05 mm (p<0.001) and 0.03 mm (p=0.045). The differences in change between the groups with and without diabetes were not statistically significant in any of the parameters mentioned.
CONCLUSIONS. This study suggests that the myopic changes in refraction over time regardless of diabetic status may be caused by increased thickness of the lens. In addition, the duration of diabetes might enhance these myopic changes in the lens. An important perspective of this study is the evaluation of anterior chamber depth when examining patients with diabetes, to examine whether an increased risk of angle-closure glaucoma is present.

EFFECT OF THE ORAL PROTEIN KINASE Cβ; INHIBITOR RUBOXISTAURIN ON VISUAL ACUITY IN THE PKC-DRS2 STUDY

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PURPOSE. Patients with advanced nonproliferative diabetic retinopathy (NPDR) are at increased risk of vision loss. We explored the impact of Ruboxistaurin, an oral PKC β; inhibitor, on different visual acuity outcome measures, and the need for focal photocoagulation (PC), compared to placebo, in addition to standard of care.
METHODS. The PKC-DRS2 study was a 36-month, double-masked, parallel, multi-center, phase 3 study. Patients were randomized to placebo (n=340) or 32 mg/d ruboxistaurin (RBX, n=345). Participants had moderately severe to very severe NPDR (ETDRS retinopathy score ≥47A and <53E), no prior panretinal photocoagulation, and a best-corrected visual acuity (VA) of ≥45 letters (~20/125, 0.16 or 6/40 Snellen) in a study eye. The primary objective was to assess the effect of RBX on the reduction of sustained moderate visual loss (SMVL: ≥15 ETDRS letter loss sustained over the last 6 months of the study).
RESULTS. In the PKC-DRS2 study, 5.5% of RBX patients experienced SMVL, compared to 9.1% of placebo patients (40% risk reduction, p=0.034). RBX eyes were more likely to gain 15 letters of VA (4.9% vs 2.4% placebo; p=0.027) and less likely to lose 15 letters (6.7% RBX vs 9.9% placebo, p=0.044). Compared to placebo, RBX also reduced sustained loss of 10 letters (9.9% vs 14.1%, p=0.043) and 5 letters (20.3% vs 26.5%, p=0.033). From baseline-to-endpoint (last observation carried forward), the mean change in VA was -0.8 vs -2.6 letters for the RBX and placebo groups, respectively (p=0.014). In eyes without focal PC prior to randomization, fewer RBX eyes required application of focal PC during the study (28.0%, RBX, vs 37.9% placebo; p=0.008).
DISCUSSION. In the PKC-DRS2 study, oral RBX reduced visual acuity loss and improved visual acuity more frequently than placebo over 36 months of treatment. RBX was also associated with less need for application of focal photocoagulation. These beneficial outcomes were evident in addition to standard of care.

SUSTAINED MODERATE VISUAL LOSS AS A PREDICTIVE ENDPOINT FOR VISION LOSS IN NONPROLIFERATIVE DIABETIC RETINOPATHY

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Purpose. Oral ruboxistaurin (RBX) has been demonstrated to reduce the occurrence of moderate vision loss (MVL: ≥15 ETDRS letter loss) in eyes with advanced nonproliferative diabetic retinopathy (NPDR). In order to determine whether sustained MVL is a more durable measure than single time-point MVL, we compared the occurrence of sustained (for 6 months) MVL and single time-point MVL within 2 yrs in regard to the presence of MVL sustained for 6 months at 3 yrs of study participation (endpoint SMVL).
Methods. The PKC-DRS2 was a prospective, 36-month, multi-center, parallel, placebo (PBO)-controlled, double-masked phase 3 clinical trial. Patients were randomized to receive RBX 32 mg/day (n=345) or PBO (n=340) once-daily orally. Eligible patients had type 1 or 2 diabetes and these 3 ocular characteristics in at least one eye: moderately severe to very severe NPDR, no previous panretinal photocoagulation, and best-corrected visual acuity (VA) score of ≥45 letters (~20/125, 0.16, 6/36 Snellen).
Results. RBX reduced endpoint sustained MVL by 40% (RBX: 5.5%, PBO: 9.1%, p=0.034). Among eyes with MVL at any single time-point visit before year 2, 23.8% had endpoint SMVL at yr 3 (RBX: 16.4%, PBO: 30.8%, p=0.058). However, among eyes with MVL lasting for at least 6 months before yr 2, 65.0% had endpoint SMVL at yr 3 (RBX: 64.0%, PBO: 66.7%, p=0.864).
Conclusions. Sustained MVL (MVL lasting for at least 6 months) is more predictive of subsequent vision loss than single time-point MVL in patients with moderate to severe NPDR. RBX appears to reduce the occurrence of sustained MVL in patients with single time-point MVL.

INTRAVITREAL APPLICATION OF TRIAMCINOLONE IN THE TREATMENT OF DIABETIC MACULAR EDEMA

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Purpose. To evaluate over a one year follow-up period, the efficacy of a 4 mg intravitreal triamcinolone (IVT) injection in patients with diabetes mellitus (DM) refractory to laser therapy.
Methods. The study group: 20 eyes of 20 patients (15 male, 5 female). The mean age was 61.5 years (29-76). The mean duration of DM in years was 14.5 (range 2-28). Twelve patients (60%) were treated with insulin, 8 patients (40%) were treated with oral antidiabetic drugs. In all patients, treatment with IVT injection was initiated 3 months after the last unsuccessful focal laser coagulation for diabetic macular edema (DME). IVT was performed as an outpatient procedure in aseptic conditions. Five days before IVT all patients underwent: biomicroscopic examination, color fundus photography, best-corrected visual acuity (BCVA) using EDTRS optotypes, macular thickness (MT) estimation using optical coherent tomography (OCT) and applanation intraocular pressure measurement. All these examinations were repeated 1, 3, 6, 9 and 12 months after IVT.
Results. BCVA mean was initially 0.17 ± 0.09 (range 0.08-0.4). It improved to 0.30 ± 0.17 (0.08-0.63) after 1 month, to 0.29 ± 0.16 (0.1-0.63) after 3 months and 0.22 ± 0.14 (0.05-0.5) after 12 months. Improvement of vision was significant in all follow-up months (month 1 p=0.001, month 12 p=0.038). MT decreased from the initial value of 506.2 ± 91.4 μm (range 389-719) to 238.8 ± 57.2 μm (159-352) after 1 month, 287 ± 125.6 μm (121-541) after 3 months and 362.4 ± 92.6 μm (211-569) after 12 months. The decrease in MT was significant in all follow-up months. In the first month p<0.0005 and in the 12 month p=0.001. The correlation coefficient between BCVA and MT was -0.467.
Conclusions. Intravitreal triamcinolone injection reduces MT and improves BCVA in patients suffering from DME refractory to laser coagulation. The best IVT effect was observed in the first 3 months after application. Within 12 months we noted a decrease in MT in 90% of patients and an improved visual acuity in 55% of patients.

DIABETIC MACULAR EDEMA TREATED WITH SUBTENON TRIAMCINOLONE ACETONIDE

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Purpose. To evaluate subtenon injection of triamcinolone acetonide (TA) for refractory laser treated diabetic macular edema (DME).
Methods. Prospective study, between June and December 2005, of subtenon injection of TA in refractory laser treated DME patients. One eye of each of 14 type 2 diabetic patients was studied. Ages ranged from 51 to 74 years (mean 61.4 years (SD=7.4), 42.86% male). Patients

underwent best-corrected Snellen visual acuity (VA), intraocular (IOP) measurement, slit lamp biomicroscopy, 'Stratus' OCT and a posterior subtenon injection of 40 mg TA. IOP was measured at months 1 and 2 and VA and OCT at month 3.
Results. No statistically significant difference was observed between pre- and post-treatment measurements of VA (p= 0.210) and macular thickness (p=0.198). No significant correlation was observed between delta of the VA and macular thickness (r = 0.318; p = 0.267). No statistically significant difference in IOP was observed between pre-treatment and months 1 or 2 (p= 0.152).
Conclusions. Macular thickness and VA remained stable after subtenon triamcinolone acetonide injections for refractory DME. Many studies are still required to establish better treatment results.

INTREAVITREAL BEVACIZUMAB (AVASTIN) INJECTION IN DIABETIC RETINOPATHY WITH DIFFUSE BREAKDOWN OF BLOOD RETINAL BARRIER

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Purpose. To evaluate the short-term anatomic and functional effects after intravitreal injection of Bevacizumab (Avastin; Genentech), in patients affected by a severe and rare form of diabetic retinopathy with diffuse breakdown of blood-retinal barrier and macular edema (diffuse diabetic capillaropathy).
Methods. This is a retrospective study of 4 patients affected by diffuse diabetic capillaropathy who were treated with intravitreal injection of Bevacizumab (1.25mL). The main outcome measurements were: visual acuity (VA), regression of new vessels and breakdown of blood-retinal barrier by fluorescein angiography, reduction of macular thickness at OCT (before, one week and one month after injection).
Results. At one week and one month after injection all patients demonstrated: improvement of VA, complete or partial regression in leakage due to breakdown of blood-retinal barrier and new vessels, reduction of macular thickness. No significant ocular or systemic adverse events were observed.
Conclusions. The number of patients was limited and the follow-up too short to make any treatment recommendations, but the good results suggest further study is needed.

CHANGES IN THE DIAMETER OF RETINAL VESSELS *IN VIVO* AFTER TOPICAL APPLICATION OF A PROSTAGLANDIN AGONIST AND A PROSTAGLANDIN SYNTHESIS INHIBITOR. A PILOT STUDY

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Purpose. Disturbances in retinal perfusion are believed to be involved in the pathophysiology of diabetic retinopathy. These disturbances may be due to changes in the basal diameter of retinal arterioles and to disturbances in the autoregulation of the diameter of these vessels when the blood pressure and the retinal metabolism changes. *In vitro* studies have shown that prostaglandins are involved in the tone regulation of retinal arterioles, but it is unknown whether this finding is relevant in clinical practise.
Methods. Three normal persons and three type 1 diabetic patients below the age of 30 years and with minimal diabetic retinopathy were studied. The persons were prescribed the prostaglandin agonist xalatan or the prostaglandin synthesis inhibitor voltaren for use twice every day for one week. The baseline diameter and the diameter change during isometric exercise (pressure autoregulation) of a retinal arteriole was measured before and at the end of the treatment period using the Retinal Vessel Analyser.
Results. In both normal persons and in patients with diabetic retinopathy xalatan induced a significant contraction (6.6 ±3.6 µm, n=3) while voltaren produced a significant dilation (5.7 ±2.3 µm, n=3) of the basal diameter of the measured retinal arteriole. The number of observations was too small to evaluate the effect of the treatment on retinal autoregulation.
Conclusions. Topical treatment with compounds interfering with the effect of prostaglandins may affect the diameter of retinal resistance vessels and consequently affect retinal blood flow. A prospective randomised study is being planned to assess intervention on the retinal prostaglandin metabolism can be used to modulate flow disturbances in diabetic retinopathy.

CORRELATION BETWEEN MICROPERIMETRY, OPTICAL COHERENT TOMOGRAPHY FINDINGS AND BEST-CORRECTED VISUAL ACUITY OF LASER PHOTOCOAGULATION FOR DIABETIC MACULAR OEDEMA

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Purpose. To compare the changes in macular sensitivity (microperimetry), macular thickness and best-corrected visual acuity (BCVA) in patients with diabetic macular oedema after laser photocoagulation.
Methods. Retrospective review of 8 consecutive patients (11 eyes, 4 males and 4 females), average age 63.5 (44-77) with macular oedema in diabetic retinopathy (8 eyes with focal exudative macular oedema and 3 eyes with diffuse exudative macular oedema). Patients undergoing retinal photocoagulation with argon laser wave length 532 nm, spot 100-200 µm, exposure time 0.1 s, energy 160-420 mW. All included eyes underwent functional and morphologic examination of the macula. Logarithm of the minimum angle of resolution (logMAR) BCVA was evaluated by means of an ETDRS chart. Foveal thickness was measured by Stratus OCT. Lesion-related macular sensitivity and retinal fixation were investigated with an advanced, automatic microperimeter. Main outcome measures were mean retinal sensitivities within the central 6° area. Results were quantified before and 6 months after treatment.
Results. Mean OCT foveal thickness ± SD significantly decreased from 424 ±72 µm (range 292-599) to 340 ±58 µm (range 267-640). logMAR BCVA improved in 45.4% (5) eyes, was unchanged in 36.4% (4) eyes and decreased in 18.2% (2) eyes. Mean central 6° retinal sensitivity ±SD decreased after treatment by 91% eyes to -4.85 ±2.64 [(range -3.25-(-8.0 dB)], while improving in one eye to +0.5 dB.
Conclusions. Changes after treatment of macular oedema may be better documented by adding macular sensitivity mapping by microperimetry. Decreased retinal sensitivities are related to the effect of laser photocoagulation, do not correspond with final BCVA and are towards compared with final reduced macular oedema measured by OCT.

INCIDENCE, PROGRESSION AND RISK FACTORS FOR DIABETIC RETINOPATHY IN A DANISH DIABETES MANAGEMENT PROGRAMME

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Purpose. To evaluate the incidence of and risk factors for development and progression of diabetic retinopathy in a clinic-based photographic diabetes management programme.
Methods. Longitudinal observational study including 729 type 1 (T1DM) and 577 type 2 (T2DM) diabetic patients with at least one follow-up examination in the management programme between 1997 and 2001. Retinopathy was evaluated from two 60° retinal photographs.
Results. Of the 378 T1DM patients without retinopathy at baseline, 121 developed some retinopathy, an incidence rate of 129.2 per 1,000 person-years (PY). The respective figure in T2DM was 103.4 per 1,000 PY. The incidence rate of progression of retinopathy from a level of mild, moderate or severe non-proliferative retinopathy at baseline was 176.6 (175.9), 209.8 (217.7), 222.4 (177.2) per 1,000 PY in T1DM and T2DM patients (in brackets), respectively. No statistically significant difference in the incidence rate was observed between T1DM and T2DM patients at any level of retinopathy ($p<0.05$). Poisson regression showed that duration of diabetes (incidence rate ratio (IRR)=1.04), BMI (IRR=1.09), HbA1c (IRR=1.20) and increased urinary albumin excretion rate (IRR=1.61) was independently associated with development of retinopathy in patients with T1DM. In patients with T2DM, HbA1c (IRR=1.13) was associated with progression of retinopathy.
Conclusions. The incidence rates of retinopathy were comparable to results from recent European studies using similar photographic methods. Risk factors for development and progression of retinopathy over a short follow-up period were similar to known long-term risk indicators. Incidence and progression of retinopathy was similar among patients with T1DM and T2DM.

DIABETIC RETINOPATHY IN OUTPATIENTS WITH TYPE 2 DIABETES: CLINICAL AND EPIDEMIOLOGICAL FEATURES

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Purpose. To estimate the prevalence of diabetic retinopathy (DR) and associated risk factors in outpatients with type 2 diabetes in a representative area of Northern Italy.
Methods. A sample of 466 consecutive type 2 diabetics (236 M, 230 F, age 64.6 ±8.5 yr) (out of a total of 2850 subjects) was studied. Patients underwent fundus ophthalmoscopic examination through dilated pupils and, when suitable, fluorescein angiography; other clinical and laboratory examination were also performed.
Results. 20% of patients showed DR (17% background, 3% proliferative). Sex distribution, age, body mass index, fibrinogen, triglycerides, total and HDL cholesterol were similar in patients with and without DR; whereas known duration of diabetes, HbA1c and fasting glycaemia were significantly higher in patients with than without DR (respectively p=0.003; p=0.008; p=0.03). DR frequency was significantly higher in hypertensives than normotensives (p=0.00007), as well as in insulin-treated vs in non insulin-treated patients (p=0.0003).DR frequency was similar in smokers and in non-smokers, and no relation with albuminuria excretion levels was found. The frequency of coronary heart disease and peripheral diabetic neuropathy was similar in patients with and without DR, whereas peripheral artery disease was significantly more frequent in the former than in the latter (p=0.002). Duration of diabetes, glycaemic control, hypertension, insulin therapy and peripheral vascular disease maintained the above observed significant differences also considering the subgroups with background and proliferative DR with respect to patients without DR.
Conclusions. The results confirm the importance of the role of duration of diabetes in the development of DR, and show its association with some potentially modifiable factors (glycaemic control and hypertension), as well as with some indicators of more severe diabetic disease (insulin therapy and other vascular complications).

PLASMA HAPTOGLOBIN MAY SIGNAL AN INCREASED RISK OF DEVELOPING PROLIFERATIVE DIABETIC RETINOPATHY IN TYPE 1 DIABETES

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Purpose. Screening for diabetic retinopathy is important for preventing visual loss secondary to the disease. An optimisation of the screening intervals requires increased knowledge of individual risk factors for development of vision threatening retinopathy. In addition to known risk factors such as age, diabetes type, duration, blood pressure, and HbA1c it is likely that genetic factors expressed in the proteom may also play a role. We have previously shown a differential expression of different albumin fractions in proliferative diabetic retinopathy, but a detailed analysis of the albumin free fraction of the plasma is lacking.
Methods. Blood samples from 10 type 1 diabetic patients with proliferative diabetic retinopathy and ten matched patients with no retinopathy was analyzed. The samples were centrifuged and the supernatant was depleted for albumin and immunoglobulins. The remaining plasma proteins were separated by high resolution two-dimensional gel electrophoresis (2D-PAGE). The gels were silver stained and protein spots were defined by Melanie II software. The proteins that differed most between the patients with proliferative retinopathy and controls were extracted, trypsin-digested, and identified by mass spectroscopy.
Results. Approximately 650 protein spots were detected on each gel. Among these there was a significant differential expression of haptoglobin in the plasma of patients with proliferative diabetic retinopathy.
Conclusions. There is differential expression of plasma haptoglobin in type 1 diabetes patients without retinopathy and matched patients with proliferative diabetic retinopathy. This is similar to what has previously been found in patients with diabetic nephropathy. Analysis of plasma haptoglobin may perhaps help identifying patients at risk of developing proliferative diabetic retinopathy in type 1 diabetes.

EXPERIMENTAL MODEL FOR THE SCREENING OF THE DIABETIC RETINOPATHY IN LAZIO REGION. PILOT STUDY

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Purpose. Diabetic retinopathy (DR) screening and treatment represent the medical procedure with the highest Quality Adjusted Life Year (QALY) benefit. Implementation of DR guidelines of care leads to a substantial reduction of vision loss and costs for the management of the disease. The importance of detecting clinically important lesions of retinopathy is to facilitate the timely administration of treatment strategies to prevent vision loss.
Methods. Lazio region with the G.B. Bietti Eye Foundation-IRCCS collaboration promoted a pilot study to assess the effectiveness of an experimental model for the screening of DR in Lazio region. Patients with a diagnosis of diabetes mellitus and with an age >12 years will be enrolled in the screening program.
Diabetological centres screening activity represent the first level of the program that will be provided using a non-mydriatic fundus camera. Digital images will be transferred on-line to the reading centre located in the G.B. Bietti Eye Foundation-IRCCS and graded. Patients will then be referred to the second level as necessary for full ophthalmological examination and onward for treatment if required within a third level structure.
Results and conclusions. The screening program characteristics will be described in details.