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PAPERS

VASOMOTION IN LARGE RETINAL ARTERIOLES IN HEALTHY SUBJECTS AND IN PATIENTS WITH DIABETIC RETINOPATHY

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PURPOSE. Retinal hyperperfusion due to disturbed tone regulation in retinal arterioles is assumed to be a key factor in the development of diabetic retinopathy. The disturbed tone regulation involves changes in pressure autoregulation, but it has been suggested that disturbances in retinal vasomotion may also be involved. The purpose of the present study was to compare vasomotion in large retinal arterioles from normal subjects with that of type 2 diabetic patients with mild to moderate stages of diabetic maculopathy using the retinal vessel analyzer (RVA, Imedos, Germany).
METHODS. Eighteen type 2 diabetic patients and sixteen normal subjects were studied. The diabetic patients consisted of patients with mild to moderate maculopathy, but none with CSMO or PDR.
The diameter changes of a retinal arteriole were measured continuously over a 3-minute period at a first order retinal arteriole using the RVA. The diameter changes were analyzed by Fourier transformation and the significant peaks in the frequency domain between 1 to 10 cycles/min was found using Fisher's test. The occurrence or not of significant frequency peaks among the two groups was tested using the Chi-square test. The significant frequencies found in the two groups were compared using an independent samples t-test.
RESULTS. Significantly fewer diabetic patients had an identifiable peak as compared to normal subjects (7 out of 18 diabetic patients vs. 3 of 16 normal subjects, p=0.03). Among the persons in whom identifiable peaks were found there was a significant difference between the vasomotion frequency in normal subjects (3.4±1.5 cycles/min) and in diabetic patients (1.8±0.7 cycles/min), p=0.01.
CONCLUSIONS. The occurrence and the frequency of retinal vasomotion is significantly decreased in type 2 diabetic patients with mild retinopathy. This suggests that changes in vasomotion occur at an early stage in diabetes and may be involved in the vascular disturbances observed in diabetic maculopathy.

TWO TYPES OF CALCIUM OSCILLATIONS IN RETINAL VASCULAR SMOOTH MUSCLE CELLS MAY BE INVOLVED IN THE REGULATION OF RETINAL PERFUSION

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PURPOSE. Retinal hyperperfusion secondary to disturbances in the tone regulation of retinal arterioles are assumed to be key elements in the pathogenesis of diabetic retinopathy. The disturbed tone regulation is assumed to involve several mechanisms, including rhythmic oscillations in the tone of retinal resistance vessels termed vasomotion. Previous studies suggest that vasomotion is controlled by oscillations in the intracellular calcium concentration ([Ca2+]i), but evidence of oscillations of [Ca2+]i in individual retinal smooth muscle cells to support this hypothesis is sparse.
METHODS. Nine porcine retinal arterioles with an inner diameter of approximately 150 microns were mounted in a small-vessel myograph for isometric tone measurements. The myograph was mounted in a confocal laser microscope and the vessels were incubated with the fluorescent dye Calcium-green. After cumulative addition of the prostaglandin analogue U46619 (10-10 M to 10-6 M in five steps) [Ca2+]i was measured in two minute periods during addition in at least four vascular smooth muscle cells in each vessel.
RESULTS. In four of the vessels where [Ca2+]i could be observed in individual vascular smooth muscle cells two types of local changes in [Ca2+]i were observed: 1) Slow [Ca2+]i oscillations (0.41±0.03 min-1, n=8 cells in 2 vessels) that occurred synchronously in all cells and associated with changes in tone. 2) Fast (2.6±0.55 min-1 at 10-10 M U46610, and 7.6±1.71 min-1 at 10-6 M U46610, ($p<0.05$), n= 17 cells in 4 vessels) transient elevations in [Ca2+]i that occurred asynchronously in the smooth muscle cells and were unassociated with the tone changes.
CONCLUSIONS. Two types of oscillations in [Ca2+]i with possible different roles for the regulation of vascular tone can be observed in retinal vascular smooth muscle cells. These changes in [Ca2+]i may constitute possible targets for pharmacological intervention in retinal diseases characterized by hyperperfusion, such as diabetic retinopathy.

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INCREASING MYOGENIC RESPONSE WITH DECREASING DIAMETER IN RETINAL ARTERIOLES

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Purpose. Diabetic retinopathy is accompanied by disturbances in retinal autoregulation so that an increase in the blood pressure does not lead to a compensatory decrease in the diameter of retinal resistance arterioles. It is assumed that the capacity of retinal arterioles to initiate this response varies along the vessel, but this variation has not been studied in detail.
Methods. Ten healthy young volunteers aged 22-33 years were subjected to diameter measurement of four segments of a retinal arteriole using the Retinal Vessel Analyzer (RVA) during rest and during an increase in the mean systemic arterial blood pressure (MAP) induced by isometric exercise. The diameter response during the increase in MAP was compared to the diameter of the arterioles during rest for the four segments.
Results. The isometric exercise induced a significant contraction of the studied vessel segments of averagely 2.5%±0.4 ($p<0.0001$, n=40). There was a significant negative correlation between the baseline diameter of the studied vessel segments and the diameter change induced by isometric exercise ($p=0.04$).
Conclusions. The diameter response of retinal arterioles secondary to an increase in the arterial blood pressure increases with decreasing diameter of the vessel. The results indicate that the distal retinal arterioles are important sites for the regulation of retinal blood flow and possible sites of disturbed autoregulation in retinal vascular diseases such as diabetic retinopathy.

DISTURBANCES IN PRESSURE AUTOREGULATION AND METABOLIC AUTOREGULATION INTERACT IN RETINAL FLOW DISTURBANCES IN DIABETIC RETINOPATHY

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Purpose. Retinal hyperperfusion due to impaired autoregulation is believed to be involved in the pathophysiology of diabetic retinopathy. However, the contribution of different types of autoregulation to this response is unknown. Autoregulation is adjustments of the diameter of resistance vessels in order to ensure a balanced blood supply to the tissue during changes in blood pressure (pressure autoregulation) and during changes in metabolism (metabolic autoregulation).
Methods.Twenty type 2 diabetic patients with minimal retinopathy and twenty age (58.4±0.2 years) and sex matched normal persons were examined. Using the Retinal Vessel Analyzer the diameter response was measured after an increase in the blood pressure induced by lifting a 2 kg hand weight, after an increase in the retinal metabolism induced by light flicker at 8 Hz, and after simultaneous exposure to the two experimental conditions.
Results. The baseline diameter of the studied vessels was 120±3.5 microns. The increased blood pressure induced by lifting a hand weight resulted in a significant ($p=0.02$) contraction of retinal arterioles in normal subjects (preserved pressure autoregulation as compared to no diameter response in diabetic patients). The flicker light induced a significant dilation of retinal arterioles in normal subjects ($p<0.001$), whereas this response was absent in diabetic patients. In normal subjects the flicker induced vasodilation was not affected by a simultaneous increase in the blood pressure. However, in diabetic patients the flicker induced vasodilation was normalized by a simultaneous increase in the blood pressure ($p=0.02$)
Conclusions. Diabetic patients have impaired diameter response to both an increase in arterial blood pressure induced by isometric exercise (impaired contraction) and an increase in retinal metabolism induced by light flicker (impaired dilation). However, the interaction between these two types of autoregulation is complex. During special conditions the combined action of the two types of impaired autoregulation may result in a normalization of retinal blood flow. This may be used to design strategies for normalizing retinal blood flow in diabetic patients.

THE APOPTOTIC RESPONSE OF RETINAL PERICYTES TO INTERMITTENT HIGH GLUCOSE: A COMPARISON BETWEEN BOVINE AND HUMAN MODELS

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Purpose. The loss of pericytes in retinal microvessels is one of the earliest events in diabetic retinopathy, but the exact mechanism has not yet been elucidated. To investigate the pathophysiological roles of pericytes, primary bovine or rat cells have been used so far in *in vitro* studies, but preliminary observations suggest that human and bovine retinal pericytes may behave quite differently in experimental conditions designed to mimick the diabetic milieu. The aim of this study was to verify whether the periodic vs continuous exposure to high glucose may have different effects on human (HRP) and bovine retinal pericyte (BRP) apoptosis.
Methods. Both BRP and HRP were grown in normal or high glucose for 7 days and then exposed to a rapid depletion of glucose to physiological concentrations for 24/48/72h. DNA fragmentation was evaluated by ELISA, as a marker of early

apoptosis. In parallel, the expression of two genes involved in apoptosis, bax and p53, was determined by RT-PCR.
Results. Stable high glucose induced apoptosis in BRP, but not in HRP. However, apoptosis in BRP seemed to regress after glucose depletion, while it was enhanced in HRP exposed to intermittent, rather than constant, high glucose concentration. In particular, an increase in HRP apoptosis was shown 48h after glucose depletion and confirmed at 72h. After 48h glucose depletion, Bax was expressed in BRP as well as in cells grown in basal conditions, while in HRP there was a clear over-expression. p53 mRNA was unchanged in both cell types.
Conclusions. Human and bovine retinal cells show different behaviour when grown in constant rather than intermittent high glucose. BRP, more rapidly subjected to high glucose damage, seem to be able to recover when cultured in a normal milieu. HRP, on the other hand, show a resistance to constant high glucose, while are highly subject to fluctuations from high to low glucose levels. This suggests that variability in glycemic control can play a major role in developing diabetic retinopathy.

MICROGLIAL CHANGES OCCUR WITHOUT NEURAL CELL DEATH IN SHORT TERM DIABETIC RETINOPATHY

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Purpose. Very early neuroglial changes were observed in the retina of diabetic patients and animal models prior to a major vascular change. To further assess the sequence of these neuroglial changes, they were examined in alloxan-induced diabetic mice.
Methods. Diabetes was triggered by an alloxan injection in C57/Bl6 mice subsequently receiving daily insulin injections. Diabetic and control animals were weighted and their blood glucose level measured every week.They were investigated by electoretinographic recordings and scanner laser ophthalmoscope (SLO) examination at 15 days, 1 month and 3 months after the onset of diabetes. Induction of diabetes was attested by glucose in theurine, a 3-fold increase in blood glucose level, weight loss and an increase in glycated hemoglobin.
Results. After 3 months of diabetes, the electroretinogram b/a wave amplitude ratio was reduced at the highest light intensities while oscillatory potentials were delayed. Retinal fundus and vessels remained unchanged during the study. No cell apoptosis was detected in vertical and horizontal sections of the retina with TUNEL or immunocytochemistry for the active caspase 3. No increase in GFAP immunostaining indicative of a glial reaction was present in Müller glial cells. By contrast, microglial cells had changed morphology and their dendrites exhibited reduced lengths.
Conclusions. These results indicated that the microglial reaction is a very early event in the progression of diabetic retinopathy which would occur with the early electroretinographic modifications. Furthermore, the absence of apoptotic cells contrasting with a previous study on streptozotocin-induced diabetic mice is consistent with an insulin neuroprotection.

GLYCATION END PRODUCTS (AGE) AND DIABETIC RETINOPATHY

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Purpose. The role of glycation end products (AGEs) in the development of diabetic microvascular complications (retinopathy and glomerulopathy) has been evidenced by *in vitro* studies, and in animal models. *in vitro* studies have shown that AGEs induce apoptosis and/or activation of vascular and perivascular cells. After binding to the RAGE receptor, CML-protein induces VEGF secretion, increasing vascular permeability and stimulating neo-angiogenesis, two mechanisms involved in diabetic retinopathy. The present study aimed at defining relations between circulating AGEs and adhesion molecules in type 2 diabetic patients with and without diabetic retinopathy.
Aims. To examine potential relations between AGE (carboxymethyl-lysine-albumin: CML-HSA) serum levels, and markers of endothelial activation: Macrophage Colony Stimulating Factor (M-CSF), and Vascular Cell Adhesion Molecule (VCAM-I).
Methods. CML-HSA, M-CSF, and VCAM-I were assessed by ELISA in 40 patients with type 2 diabetes, and in 55 age and sex-matched non-diabetic controls.
Results. CML-HSA serum levels were significantly increased in diabetic patients compared to controls (40.0 ± 4.7 vs 7.9 ± 0.7 pmol/mg protein, respectively; $P < 0.001$). Plasma concentrations of M-CSF and VCAM-1 were significantly higher in diabetic patients with retinopathy and increased urinary albumin excretion (M-CSF: 2158 ± 428 pg/mL); VCAM-I: 552 ± 65 ng/mL). Patients with creatinine clearance less than 80 mL/min were excluded, as CML-HSA excretion rates parallels creatinine one's.
Discussion. Increased in vivo circulating M-CSF concentrations in the presence of high CML-HSA levels in diabetic patients, as well as increased *in vitro* M-CSF production in response to cellular stimulation by CML-HSA suggest that AGEs may play a role in

attraction of monocytes. These results are in agreement with experimental evidence, and strongly support the participation of AGEs in diabetic microangiopathy.

THE EFFECT OF HYPOXIA AND HYPEROXIA ON THE SLOW MULTIFOCAL ELECTRORETINOGRAM AND MUTIFOCAL OCILLATORY POTENTIALS IN DIABETIC PATIENTS WITHOUT RETINOPATHY

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Purpose. To compare the effect of hypoxia and hyperoxia on the multifocal electroretinogram (mfERG) in patients with type 1 diabetes without retinopathy and in healthy subjects. Methods. In 8 eyes of 8 type 1 diabetic patients without retinopathy and 10 eyes of 10 non-diabetic subjects multifocal electroretinography (mfERG) was recorded at three levels of oxygenation: hypoxia induced by 10% oxygen and 90% nitrogen breathing, hyperoxia induced by 100% oxygen breathing and normoxia induced by room air breathing. MfERGs were recorded using the Veris 5 system. An array of 61 hexagons was displayed at a frame rate of 75 Hz and three dark frames were inserted between each m-sequence step.
Results. In diabetic patients hyperoxia significantly increased mfERG amplitudes in the central retina (0-2 degrees of eccentricity) by 15.1% ($p = 0.008$). In healthy subjects, hyperoxia induced no change in mfERG amplitude (0.9%, $p > 0.05$). Both in diabetic and healthy subjects hyperoxia tended to increase mfERG amplitudes at higher eccentricities to roughly the same magnitude ($p > 0.05$). In diabetic patients without retinopathy hypoxia reduced mfERG amplitudes in the central retina (0-2 degree) by 15.2% ($p > 0.05$) and in the more peripheral retina by 12.5 - 19.4 % ($p > 0.05$). In non-diabetic controls, hypoxia reduced central mfERG amplitudes by 38.5% ($p < 0.0001$) and peripheral amplitudes by 17.8 - 26.8% ($p < 0.01$).
In both diabetic patients and healthy controls mfERG implicit times were unaffected by changes in arterial oxygen tension.
Conclusions. Our results indicate that diabetes without diabetic retinopathy is associated with significant changes in retinal metabolism, as assessed by the ability of the retina to produce electroretinographic potentials. In conjunction with previous studies of the role of glucose, these results indicate a crucial role for changes in substrate supply and utilization in the retina during hyperglycemia with potential implications for the development of diabetic microangiopathy in the retina. The relative insensitivity of diabetic patients to hypoxia is consistent with previous reports of attenuation of amplitude during hypoxia in hyperglycemic cats compared to euglycemic cats.

MECHANISM FOR DIURNAL VARIATION IN CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA

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Purpose. To investigate the role of gravity as well as of a series of other systemic factors in the diurnal variation of clinically significant macular edema (CSME).
Methods. Ten eyes of 10 diabetic subjects with CSME underwent 4 OCT measurements of macular thickness with the Stratus OCT at 9:00 AM, 12:00 AM, 3:00 PM and 6:00 PM on two different days, during which the patients were in the upright and recumbent position, respectively. For the “recumbent position” measurements, the patients were admitted to the hospital the night before, so that they would remain recumbent throughout the day. Clinical evaluations at study entry included HbA1c, urinary albumin and serum creatinine. Refractions and ETDRS visual acuity measurements were also taken prior to each OCT measurement. Variation in blood pressure, body temperature, plasma glucose, renin, aldosterone and cortisol levels were measured for correlation with macular thickness.
Results. Macular thickness decreased in all cases over the course of the day. However, the decrease was significantly greater for the “upright position” measurements (mean ± SD of the relative decrease: 20 ± 7% in the upright position and 6 ± 5% in the recumbent position measurements). Visual acuity improved by at least 1 ETDRS line over the course of the day in 3 eyes in the upright measurements and only in 1eye in the recumbent position measurements. There were no changes in refractive errors over the course of the study in any of the study eyes. No apparent association between systemic factors, diurnal blood pressure variation and change in foveal thickening could be observed.
Conclusions. This study supports the hypothesis that gravity and hydrostatic pressure play a major role in determining time-related shifts in CSME and suggests that CSME formation may be explained, at least in part, by the forces of Starling’s law.

SHORT-TERM EFFECTS OF INTRAVITREAL TRIAMCINOLONE ON RETINAL VASCULAR LEAKAGE AND TRUNK VESSELS DIAMETERS IN DIABETIC MACULAR EDEMA

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Purpose. To assess retinal vascular permeability and vessel diameter changes after intravitreal triamcinolone acetonide injection (IVTA) in eyes with persistent foveal thickening after photocoagulation for diabetic clinical significant macular edema (CSME).

Methods. Blood-retinal barrier permeability as measured by vitreous fluorometry, artery and venous vessel diameter at one or both temporal vascular arcades measured on fundus photography, retinal thickness measured by optical coherence tomography. Seven patients with type 2 diabetes and CSME (primary eye: mean foveal thickness 478µm, range 277 µm to 749 µm) were examined immediately before and 1 week after intravitreal injection of triamcinolone acetonide 2 mg. Designed as an open-label interventional case series using the fellow eye as untreated control.
Results. When compared to baseline values, we observed one week after IVTA that blood-retinal barrier permeability had decreased to 27.2 ± 3.6% ($p < 0.0001$), retinal artery diameter had decreased to 94.9 ± 0.02% ($p = 0.05$), retinal vein diameter had decreased to 89.2 ± 0.03% ($p = 0.02$) and foveal thickness had decreased to 68.7 ± 6.9% ($p=0.004$). Visual acuity improved 7.4 ± 2.2 letters ($p=0.01$). No significant change was observed in control eyes except that mean visual acuity deteriorated 2.6 ± 0.9 letters ($p=0.03$). Changes in permeability were closely correlated to changes in retinal thickness ($R=0.84$) and venule diameter ($R=0.93$), in treated eyes.
Conclusions. Intravitreal injection of triamcinolone acetonide in eyes with diabetic macular edema is followed by a marked reduction in retinal vascular leakage. The concomitant reduction in retinal vessel caliber suggests that the retinal hemodynamic is altered by triamcinolone acetonide

IMPAIRED RETINAL AUTOREGULATION IN SMALL RETINAL ARTERIOLES BEFORE AND AFTER FOCAL LASER TREATMENT FOR DIABETIC MACULOPATHY

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Purpose. To study how an acute increase in the arterial blood pressure affects the diameter response of retinal arterioles supplying 1) areas without oedema and 2) areas with focal diabetic macular oedema before and after focal laser treatment.
Methods. The Retinal Vessel Analyzer (RVA) was used to study the diameter response of retinal arterioles in seventeen diabetic patients after an increase in the arterial blood pressure induced by isometric exercise. In each patient a study arteriole supplying a focal area of macular oedema as well as a control arteriole supplying a retinal area without retinopathy lesions was selected, and the diameter response of these vessels was determined immediately before, and one hour and three months after focal laser photocoagulation in the oedema area.
Results. An impaired diameter response was found in both study arterioles and control arterioles before focal laser photocoagulation. The treatment induced regression of the focal oedema ($p<0.0001$), but did not affect the diameter response in the arteriole supplying the oedematous area ($p=0.85$).
Conclusions. Impairment of the diameter response in small arterioles from diabetic patients does not reflect the regional distribution and dynamics of retinopathy lesions. Other factors than disturbed pressure autoregulation are probably involved in generating flow disturbances and oedema in diabetic maculopathy.

RISK FACTORS FOR PROGRESSION TO PHOTOCOAGULATION OF CLINICALLY SIGNIFICANT MACULAR EDEMA OF TYPE I DIABETIC PATIENTS PHOTOSCREENED AT STENO DIABETES CENTER

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Purpose. To investigate the risk factors for photocoagulation due to clinically significant macular edema (CSME) in type 1 diabetic patients screened at Steno Diabetes Center (SDC) from 1988 until November 2005.
Methods. The patients are photoscreened at SDC. 2784 patients with more than 0.5 year of follow-up and a total of 22188 patient years at SDC were included. Mean follow-up was 7.95 years. Based on indirect sign of CSME (hard exudates, visual acuity), patients are referred for further diagnosis at Herlev Hospital and in case of CSME treated with photocoagulation. The risk factors for progression to macular photocoagulation were analyzed with a Cox model including time dependent HbA1c and blood pressure.
Results. Mean baseline HbA1c was 8.58% (SD1.4) and mean baseline blood pressure 134/79 mm Hg (SD 20/10). The change during follow-up was below 5%. 366 patients were registered with the event of macular photocoagulation due to CSME. Duration of diabetes and HbA1c and systolic blood pressure measured regularly at follow-up visits were all significant risk factors in the Cox model. Baseline HbA1c and the change of HbA1c since last visit were also significant if substituted for HbA1c as measured during follow-up. Baseline, but not follow-up diastolic blood pressure was significant. Nephropathy and neuropathy were also significant with a hazard ratio of 4.1 for nephropathy compared to no nephropathy and 2.9 for neuropathy compared to no nephropathy.
Conclusions. Based on a large photo-screened population, the duration of diabetes, follow-up HbA1c and systolic blood pressure are significant risk factors. Also, recent changes in HbA1c were significant underlining the importance of HbA1c in this population of patients closely monitored at the Steno Diabetes Center.

DIABETIC MACULAR EDEMA: A NEW STAGING BASED ON ENHANCED OCT

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Purpose. To evaluate the pattern and stages of involvement of different retinal layers in diabetic macular edema.
Methods. 20 patients with macular edema of different degrees of severity were examined with Optical Coherence Tomography (OCT). Retinal maps and multiple line scans were performed and the multiple line scans were averaged with specialized software.
Results. The outer nuclear layer and/or Henle's layer is the first affected layer in the early stage of macular edema although the source of leakage is microaneurisms in the inner retinal layers. Cyst formation of the outer nuclear layer and/or Henle's layer follows the steadily increasing retinal thickness of this layer. Inner nuclear layer affection might be coincident or following the cyst formation of the previous stage. In severe edema the next stage is serous detachment of the neuroretina. In all stages of development of macular edema the external limiting membrane was visible and seemed intact.
Conclusions. Macular edema progression could be related to and following the build up of leaked proteins anterior to the external limiting membrane, which acts as a barrier to large molecules. The late stage serous detachment of the neuroretina is probably related to water overload which exceeds the RPE capacity for active transport of water from the retina to the choroid.

EFFECT OF THE ORAL PKC ß INHIBITOR RUBOXISTAURIN ON VISION LOSS IN PATIENTS WITH DIABETIC RETINOPATHY: THE PKC-DRS2 STUDY RESULTS

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Purpose. Patients with advanced nonproliferative diabetic retinopathy (NPDR) are at increased risk of vision loss. The PKC-DRS2 study evaluated the effect of ruboxistaurin (RBX) mesylate, an oral protein kinase C ß; inhibitor, on sustained moderate visual loss (SMVL; ≥ 15ETDRS letter loss sustained for the last 6 months of the study) and visual acuity (VA).
Methods. The PKC-DRS2 study was a 36-month, randomized, double-masked, parallel, multi-center, phase 3 study. Patients (n=340, placebo; n=345, RBX) had moderately severe to very severe NPDR (ETDRS retinopathy score >47A and <53E), no prior panretinal photocoagulation, and a best-corrected VA of ≥ 45 letters (~6/38 Snellen) in at least one eye.
Results. RBX 32 mg/day reduced the occurrence of SMVL by 40% compared to placebo (from 9.1% to 5.5%, p=0.034). After 12 months of therapy, mean VA was higher in RBX eyes compared to placebo, and RBX-treated eyes lost almost 2 letters less vision from baseline to endpoint (-2.6 letters, placebo vs. -0.8 letters, RBX; p=0.012). With RBX treatment, 4.9% of eyes gained ≥15 letters in VA (vs. 2.4% placebo eyes, p=0.027) and fewer RBX eyes lost ≥15 letters (6.7% vs. 9.9%, p=0.044). Compared to placebo, clinically significant macular edema greater than 100 microns from the center of the macula was 24% less likely to progress to the center of the macula in the RBX group (67.6% vs. 51.7%, p=0.017). Adverse events and discontinuations between treatment groups were similar.
Conclusions. Compared to placebo, RBX was well-tolerated, reduced SMVL and had a positive effect on VA in patients with advanced NPDR.

PREDICTIVE FACTORS FOR ANATOMIC RESPONSE AFTER INTRAVITREAL TRIAMCINOLONE INJECTION FOR DIFFUSE DIABETIC MACULA EDEMA

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Purpose. To study which factors influence anatomical and functional results after intravitreal triamcinolone for diffuse diabetic macular edema (DME).
Methods. We retrospectively reviewed the data of 74 eyes of 74 patients which received intravitreal injection of triamcinolone for diffuse diabetic macular edema refractive to laser photocoagulation. Endpoint was visual acuity and measurement of central macular thickness of less than 300µm at 6 months post-injection. Baseline systemic and ocular data were collected. Data analyzed at one, three and six months included visual acuity, intraocular pressure and central macular thickness. Multivariate stepwise logistic regression was performed.
Results. Average pre-op logMAR VA was 0.90 ± 0.34, IOP was 16.72 mmHg ± 2.9 and mean central macular thickness was 546 µm ± 135.7 measured by OCT. Values at 6 months were 0.78 ± 0.34, 17.1 mmHg ±4.0, and 397 µm ±152.0 respectively.
Increased IOP at month 1 was significantly (p=0.013) and positively correlated with having CMT<300µm at 6 months. Presence of arterial hypertension was significantly (p=0.012) and negatively correlated with having CMT<300µm at 6 months. We did not find any correlation between visual acuity after injection and preoperative factors.
Conclusions. Hydrostatic pressure within retinal capillaries

and intraocular pressure may play a role in the pathophysiology of DME. In our study, increased IOP at one month post-triamcinolone injection, and absence of arterial hypertension at baseline may be predictive of a more prolonged effect of intravitreal triamcinolone for treatment of diffuse DME. Indeed, due to Starling's Law, vascular fluid tends to exit capillaries in case of systemic hypertension, while ocular hypertension has the opposite effect.

PROGRESSION OF MACULAR EDEMA IN DIABETIC PATIENTS

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Purpose. To investigate whether permeability or early retinal thickness changes are predictive of progression of diabetic macular edema as evaluated by the need for photocoagulation for vision-threatening macular edema.
Methods. Forty-four patients with diabetes and diabetic macular edema were followed for four years using vitreous fluorometry, OCT, and fundus photography. In this exploratory study, data is analyzed from baseline, 12 months, 18 months and 40 months to evaluate if any of the parameters differed between eyes that eventually underwent photocoagulation (progressing eyes) and those eyes that did not receive photocoagulation therapy (stable eyes). The patients were involved in a multicenter study exploring the effect of ruboxistaurin on macular edema.
Results. The only baseline parameter that differed significantly between stable and progressing eyes was blood-retinal barrier permeability ($p = 0.01$), the difference being present throughout the study. With time, retinal thickness also changed and a statistically significant difference was seen at 18 months. No significant effect was seen of visual acuity or retinal trunk vessels diameters or with regard to treatment with ruboxisturin.
Conclusions. The progression towards clinically significant macular edema requiring photocoagulation is preceeded by an increase in blood-retinal barrier permeability. The early increase in permeability is not accompanied by a similar increase in retinal thickness, the appearance of this characteristic being delayed by at least 18 months.

DOES HETEROPLASMY IN BLOOD LEUCOCYTES EXPLAIN RETINAL, RENAL AND CARDIOVASCULAR MANIFESTATIONS IN MIDD (MATERNALLY INHERITED DIABETES AND DEAFNESS)?

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MIDD, due to point mtDNA 3243 mutation, associates diabetes mellitus, neurosensory deafness, pattern dystrophy, and neuromuscular manifestations.
Purpose. To examine the potential role of heteroplasmy in mitochondrial manifestations and in development of diabetic complications.
Methods.Heteroplasmy was prospectively assessed in peripheral leucocytes from 113 patients with MIDD (46 men, 66 women), mean age (±SD): 48.8 ± 11.3 years, mean diabetes duration: 11.1 ± 9.2 years, mean HbA1c: 7.6 ± 1.6%. Neurosensory deafness was present in 93% patients, pattern dystrophy in 77%, and cardiomyopathy in 41%. Increased urinary albumin excretion (> 30 mg/24h) was present in 43%, chronic renal failure (CRF) in 14%. Renal manifestations are the consequence in MIDD of mitochondrial nephropathy. Neuromuscular manifestations were present in 24.3%. Among long-term diabetic complications, diabetic retinopathy was observed in 15/105 cases (14%) (non proliferative in 8, preproliferative or proliferative in 3, and maculopathy in 4), and macrovascular disease in 21%.
Results. Heteroplasmy levels decreased with age ($p<0.0001$). We observed a positive correlation between heteroplasmy levels and HbA1c ($p=0.02$), and a negative correlation between heteroplasmy levels and age of onset of diabetes ($p=0.0006$). No difference in heteroplasmy levels was present between MIDD patients with and without retinopathy. Higher levels of heteroplasmy were observed in patients with mitochondrial nephropathy (27.5 ± 26% vs 15.2 ± 12.2%, respectively, $p=0.016$), and in patients with neuromuscular manifestations (23.1 ± 23.9% vs 15.8 ± 10.4%, respectively, $P=0.05$). No difference was observed between patients with and without cardiomyopathy (15.9 ± 10.8% vs 17.0 ± 14.2%, respectively, $p=0.77$).
Conclusions. These results suggest that heteroplasmy levels are associated with a greater severity of diabetes, indicated by an earlier age of onset, and by a more severe chronic hyperglycemia. A higher frequency of mitochondrial neuromuscular and renal involvement is associated with higher heteroplasmy levels.

THE INFLUENCE OF DIABETES MELLITUS ON THE OPTICAL ABERRATIONS OF THE HUMAN EYE

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Purpose. The refractive error of the eye is usually described only by sphere and cylinder. Various other optical errors (higher order optical aberrations) are generally not taken into consideration, although they are known to affect visual acuity.
The purpose of this study is to examine the influence of diabetes mellitus on these optical aberrations of the human eye using aberrometry, which provides a complete description of all optical errors of the eye.
Methods. One hundred and thirteen subjects with diabetes mellitus (type 1: 50 subjects; type 2: 63 subjects) were measured using the IRX3 aberrometer. Subjects that suffered from cataract or any other ocular pathology were excluded. In order to obtain pupil dilation and paralysis of accommodation 5% phenylephrine and 1% cyclopentolate eye drops were administered. Higher order aberrations were determined by calculating root-mean-square values (RMS). The results were compared to data of 109 healthy eyes obtained from literature (Porter, Guirao, Cox and Williams, JOSA A, 2001).
Results. Sphere and cylinder were similar in diabetic and healthy eyes ($p = 0.31$ and $p = 0.58$). However, in subjects with diabetes RMS values were significantly higher (0.50 µm ± 0.02 µm) than in healthy subjects (0.39 µm ± 0.02 µm; $p = 0.0002$). Among these higher order aberrations, trefoil and spherical aberration in particular differed significantly between the two groups ($p < 0.0002$ and $p = 0.0004$).
Conclusions. The results of this study show that although diabetes mellitus does not influence sphere and cylinder, it does significantly increase the higher order optical aberrations. Consequently, this affects visual acuity in patients with diabetes. Furthermore, in clinical practice clear imaging of retinal pathology may be complicated as well. The increase of higher order optical aberrations is possibly due to lens shape alterations in diabetes mellitus.

THE PREVALENCE OF DIABETIC RETINOPATHY IN PATIENTS WITH UNDIAGNOSED TYPE 2 DIABETES IN DENMARK. ADDITION STUDY DENMARK

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Purpose. To estimate the prevalence of diabetic retinopathy in patients with undiagnosed type 2 diabetes in Denmark.
Methods. As part of the Anglo-Danish-Dutch study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care" (ADDITION study), 12,708 patients were screened for diabetes mellitus in general practise, among whom 670 persons with type 2 disease underwent a general physical examination including measurement of HbA1c and blood pressure. Additionally, an ophthalmological examination was performed including fundus photography for retinopathy grading.
Results. Forty-five (6.8%) of the examined patients had some retinopathy of which the majority was minimal. No patients had severe non-proliferative or proliferative diabetic retinopathy. There was no significant difference between age, sex, and visual acuity among patients with and patients without retinopathy. However, the patients with retinopathy had significantly higher HbA1c, systolic, and diastolic blood pressure than the patients without retinopathy.
Conclusions. Patients with undiagnosed diabetic retinopathy have a low prevalence of diabetic retinopathy and no vision threatening lesions. Screening for diabetic retinopathy should be focussed on those patients who have already been diagnosed with type 2 diabetes during routine clinical practice.

DIABETIC BLINDNESS SIGNIFICANTLY REDUCED IN THE WARMIA AND MAZURY REGION OF POLAND: SAINT VINCENT DECLARATION TARGETS ACHIEVED.

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Purpose.To verify if we have achieved the target of Saint Vincent Declaration concerning the reduction of diabetes-related blindness in the Warmia and Mazury Region, Poland?
Methods. A register of WHO-defined blindness due to diabetes was conducted in the Warmia and Mazury Region between 1989 and 2004. The incidence rate of blindness as the number of new cases/100,000 diabetic population/year and 100,000 total population/year was estimated for 3 sub-periods differing in political-economic systems and diabetes care delivery: 1989-1994, 1995-1999 and 2000-2004.
Results. The major cause of blindness among 280 diabetic patients was diabetic eye disease (97%). Out of 70 patients with Type 1 diabetes, 53% had lost vision due to proliferative diabetic vitreoretinopathy, 20% due to neovascularisation with glaucoma, while clinically significant macula edema and cataract associated with proliferative diabetic vitreoretino-pathy or clinically significant macula edema predominated among 210 patients Type 2 diabetes. Incidence rate of blindness due to diabetes in diabetic population ranged from 102.4/100,000 (CI:65.7-139.0) to 13.3/100,000 (3.8-24.9). Incidence rate of blindness due to Type 1 diabetes ranged from

1.3/100,000 (CI:0.5-2.2) to 0.1/100,000 (CI:-0.1-0.4). Incidence rate of blindness due to Type 2 diabetes was variable in the first sub-period, but then decreased by 19% each year from 3.9/100,000 (CI: 2.5-5.3) to 0.7/100,000 (CI:0.1-1.2); p<0.001.
Conclusions.The Saint Vincent Declaration target of reducing diabetes–related blindness by one third appears to have been achieved in the Warmia and Mazury Region.

MULTIFOCAL ERG (mfERG) IN PATIENTS WITH DIABETES MELLITUS AND AN ENLARGED FOVEAL AVASCULAR ZONE (FAZ)

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Purpose. To study the relationship of an enlarged foveal avascular zone (FAZ) and retinal function assessed with multifocal electroretinography (mfERG) in diabetic patients with normal visual acuity.
Methods. Twenty-six diabetic patients (aged 50 ± 15 years, diabetes duration 22 ± 7 years) with an enlarged FAZ (largest diameter >650mm) measured in fluorescein angiograms (FA) underwent mfERG. The largest FAZ diameter the FAZ area, as well as the adjacent perifoveal intercapillary area (PIA), was calculated in the FA. The eyes had either no retinopathy, or background retinopathy, and no eye had previously been treated with photocoagulation.
Results. The mean FAZ diameter for all eyes was 0.91 ± 0.23 µm and the mean FAZ area (including PIA) 0.91± 0.17 mm^2. There was a significant correlation between increasing FAZ diameter and increasing implicit time in the three innermost circles of the first order kernel of the mfERG; p=0.025, p=0.001, p=0.001, respectively. An increasing summed area (FAZ and PIA) was correlated to an increasing implicit time in the two innermost rings of the mfERG; p=0.003 and p=0.023, respectively. No correlation was seen between the ischemic areas and the mfERG amplitudes.
Conclusions. In eyes with normal visual acuity an enlarged foveal avascular zone, a sign of macular ischemia, is correlated with a prolonged implicit time in the mfERG. This indicates that diabetic retinopathy alters neuronal function before reducing visual acuity.

INFLUENCE OF METABOLIC CONTROL IN ALTERATIONS OF RETINAL THICKNESS IN TYPE 2 DIABETIC PATIENTS WITH MILD NONPROLIFERATIVE RETINOPATHY

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Purpose. Diabetic retinopathy in type 2 diabetes may induce visual loss and the most frequent cause is macular oedema. Metabolic control has been shown to influence the ocular disease progression. To evaluate influence of metabolic control in the alterations occurring in macular thickness in eyes of type 2 diabetic patients with initial stages of retinopathy.
Methods. Thirty five type 2 diabetic patients, with mild nonproliferative retinopathy were observed every 6 months for a 2 year follow-up period, by performing a metabolic and systemic control with analysis of HbA1c, lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) and blood pressure. The mean age at inclusion was 55.1 ±6.0 years and the duration of their diabetes was 9.1 ±4.8 years. Complete ophthalmological examinations were performed on each visit, and the retinal thickness was evaluated with the RTA (Retinal Thickness Analyzer, Talia Technologies). A reference map of retinal thickness (RT) was used to analyse areas of abnormal values (mean ± SD).
Results. The patients were grouped according to the level of metabolic control during the follow up period: group 1 (n=23) – good metabolic control (HbA1c < 7%) and group 2 (n=12) – poor metabolic control (HbA1c > 7%). Hemoglobin A1c values were evaluated using a moving average. No statistical differences were found regarding age, known duration of diabetes, lipid profile or blood pressure between the 2 groups. The values of RT were analysed and compared between the 2 groups.
Total volume of abnormal RT was significantly increased in group 2 at V18 (p=0.034) and V24 (p=0.026) when compared with group 1. There was significant increase in the total volume from V0 to V24 when we considered all the 35 type 2 diabetic patients (p=0.05). There was a significant increase in the fovea from V0 to V24 on group 2 (p=0.015).
Conclusions. This study showed that poor metabolic control (HbA1c > 7%) correlates with increases in retinal thickness. These changes were even more apparent in the fovea, the area of fine visual acuity.

POSTERS

PROTEOME PROFILING DIABETIC PLASMA AND IDENTIFICATION OF MARKER PROTEINS FOR PROLIFERATIVE RETINOPATHY - A PILOT STUDY

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Purpose. Screening for diabetic retinopathy is important for preventing visual loss secondary to the disease. An optimization 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 therefore identified plasma proteins differentially expressed in five type 1 diabetic patients (diabetes duration > 30 years) without retinopathy, and five matched patients with proliferative retinopathy.
Methods. On the basis of venous blood samples the 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 were most altered in expression comparing proliferative retinopathy and controls were extracted, trypsin-digested, and identified by mass spectroscopy.
Results. Approximately 500 protein spots were detected on each gel. Six proteins, pro-apoliproprotein A, apoliproprotein A, histidine-rich glycoprotein precursor, and 3 specific albumin homolog fragments were identified to be highly upregulated in patients with proliferative retinopathy as compared to reference diabetic patients without retinopathy.
Conclusions. There is differential expression of plasma proteins in type 1 diabetes patients without retinopathy and matched patients with proliferative diabetic retinopathy. Proteomic analysis of plasma samples may help defining the individual risk profile for developing vision threatening diabetic retinopathy and thereby optimizing the examination interval for patients enrolled in screening for diabetic retinopathy.

OPHTHALMIC PARAMETERS AND THE PRESENCE OF CLINICALLY SIGNIFICANT MACULAR OEDEMA

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Purpose. The influence of ophthalmic parameters on the prevalence of clinically significant macular oedema (CSME)was explored for clarification.
Methods. This cross-sectional study comprised 656 type 1 and 328 type 2 diabetic subjects undergoing retinopathy screening in the County of North Jutland, Denmark. The association between CSME and ocular parameters (microaneurysms, haemorrhages, soft exudates, hard exudates and visual acuity) was explored using logistic regression analysis.
Results. Among type 2 diabetic only hard exudates was found associated to CSME. The Odds-ratio was increased 19 % for each additional hard exudate. Among type 1 diabetic subjects hard exudates (26%), microaneurysms (13 %) and visual acuity (-5.1 %) was significantly associated to the presence of CSME. The parenthesis indicate changed odds-ratio for one additional manifestation.
Conclusions. Hard exudates are the single most important ophthalmic risk factor for the presence of CSME.

NON-OPHTHALMIC PARAMETERS AND THE PRESENCE OF CLINICALLY SIGNIFICANT MACULAR OEDEMA

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Purpose.The influence of non-ophthalmic parameters on the prevalence of clinically significant macular oedema (CSME) was explored for clarification.
Methods.This cross-sectional study comprised 656 type 1 and 328 type 2 diabetic subjects undergoing retinopathy screening in the County of North Jutland, Denmark. The association between the prevalence of CSME and blood-pressure, HbA1c, age, onset of diabetes and duration of diabetes was explored using logistic regression analysis.
Results. Among type 1 diabetic subjects the duration of diabetes influenced the prevalence of CSME significantly for post-puberty onset subjects. For pre-puberty onset subjects the prevalence was not influenecd by the duration of diabetes. The diastolic blood-pressure also influenced the prevalence of CSME among all type 1 diabetic subjects. Among type 2 diabetic subjects the prevalence of CSME was influenced by duration of diabetes, systolic blood-pressure and HbA1c.
Conclusions. Pre- and post-puberty onset type 1 diabetic subjects seem to differ with respect to risk for CSME. The examined non-ophthalmic risk factors only give evidence for a minor fraction of the subjects that developed CSME.

RESULTS OF LASER TREATMENT FOR EXUDATIVE DIABETIC MACULAR EDEMA

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PURPOSE. To assess the effectiveness of retinal laser photocoagulation in exudative diabetic macular edema.
METHODS. This study included 60 patients (30 males and 30 females), 104 eyes with type I and II diabetes mellitus, average age 62.5 (30-86), the duration of DM 17.5 years (2-32), maximal blood glucose 6.8-23 mmol/L (13.2), minimal blood glucose 2.8-13.2 mmol/L (7.4). 54% of patients were treated with insulin, 58% had arterial hypertension. Patients undergoing retinal photocoagulation with argon laser wave length 532 nm, spot 100-200 μm, time of exposition 0,1 s, energy 160- 420 mW. Macular edema was assessed using slit-lamp biomicroscopy, compared colour fundus photography. The efficacy of laser treatment was checked by measuring BCVA on Snellen optotypes. Follow-up time was 6- 24 months.
RESULTS. BCVA remained stable in 51%, BCVA improved in 17.3%. Stabilization of diabetic macular edema in 88.5%, worsening in 11.5%.
CONCLUSIONS. Laser photocoagulation exerts a significant stabilizing effect on exudative diabetic macular edema course and therefore on visual function.

AMBLYOPIA SEEMS TO LIMIT THE DEVELOPMENT OF DIABETIC RETINOPATHY COMPARED TO NORMAL EYES

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PURPOSE. To study the difference of retinopathy in amblyopic eyes and normal eyes.
METHODS. This was a database study using the Steno Diabetes Centre Eyeclinic database. The degree of retinopathy was graded using the EyeCare grading system, counting the number of microaneurysms, flameshaped haemorrhages, soft and hard exudates, proliferations, and laser treatment.
RESULTS. The total number of patients who had amblyopia and difference in vision between the two eyes of more than 0.5 on the Snellen Chart was 34 in the database containing approximately 5000 patients. The normal eye had, even though non-significant, more diabetic retinopathy when compared to the amblyopic eye (Wilcoxon p=0.065).
CONCLUSIONS. It seems that there is a trend towards lesser retinopathy in the amblyopic eye, when compared to the normal eye. This finding could suggest that a possible limited metabolic stress in the amblyopic eye could limit the development of diabetic retinopathy.

DIABETIC RETINOPATHY IN THE CZECH REPUBLIC – WHERE IS THE TRUTH?

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PURPOSE. The aim of our study was to compare the official data from the government Institute for Health Information and Statistics with our own investigations through the Czech Diabetological and Vitreoretinal Society.
METHODS. We compared the data about diabetic complications and treatment of diabetic retinopathy (DR) from official statistical sources with our statistical survey.
RESULTS. In the year 2004, from 10.2 million people in the Czech Republic, the official statistics give 712,079 diabetic patients. From those, (males/females respectively) 6.7% / 6.5% had type 1 diabetes; type 2 - 91.9 % / 92.2%, while 1.4% / 1.3% had secondary diabetes. DR affects 84,077 individuals, 22 % with proliferative DR, 3 %, i.e. 2364 patients are blind because of DR. However, the total number of patients with any form of diabetic retinopathy may be spuriously low, due to probable inaccuracy of data reported from individual outpatient clinics. In a survey done by the Czech Diabetes Society in 2002, which included a random sample of 3626 diabetic patients from 89 out-patient clinics, presence of retinopathy was reported in 19% of patients and proliferative retinopathy in 13.9% of those with retinopathy. According to the Czech Vitreoretinal Society survey, all ophthalmologists (the approximate number in the Czech Republic is 800) perform basic screening. Fourteen centers with laser are engaged in treatment of DR. However, the total number of laser workplaces must be higher. In 2004, 20263 laser photocoagulations were performed for DR, which shows 15% increase in contrast with the year 2003. On the contrary, pars plana vitrectomy for diabetic complications decreased from 1284 operations to 1166. The explanation for this decrease maybe not only imprecise statistical workout but also financial demands.
CONCLUSIONS. Comparison of two statistical sources points to inaccuracy of official data. Most probably, it is not a problem specific only to the Czech Republic. We indicate to following different sources to attain precise data.

LACK OF CORRELATION BETWEEN RETINOPATHY LESIONS IN LOCALIZED AREAS OF THE FUNDUS AND KNOWN RISK FACTORS FOR PROGRESSION OF THE DISEASE

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Previous studies have shown that the progression of diabetic retinopathy to vision threatening lesions may be related to the development of retinopathy lesions in specific retinal areas. The purpose of the present study was to study whether the occurrence of retinopathy in these retinal areas are related to known risk factors for progression of retino pathy in type 2.

Methods. Three-hundred-and-seventy-seven randomly selected patients with diagnosed type 2 diabetes were examined with measurement of blood pressure, hemoglobin A1c, cholesterol, and were subjected to a full eye examination including fundus photography. The fundus photographs were digitized, and using a computer-assisted technique retinopathy lesions were quantified in the macular area, around the vascular arcades and in the retinal periphery. Only the number of microaneurysms/hemorrhages was sufficient for statistical analysis.

Results.The patients with retinopathy had significantly longer diabetes duration, and higher blood pressure and HgbA1c than patients without retinopathy, but in the patients with retinopathy there was no correlation between these risk factors and the overall number of microaneurysms/haemorrhages or the number of these lesions in the studied localized areas of the fundus.

Conclusions. Future improvements in grading systems for diabetic retinopathy should focus on a quantification of the overall number and dynamics of retinopathy lesions in the early stages of retinopathy and the regional distribution and dynamics of lesions in more advanced stages of retinopathy.

GEOMETRY OF RETINAL VESSELS AND DIABETIC RETINOPATHY - A FOLLOW-UP STUDY

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Purpose. The purpose of this study was to investigate the geometric arrangement of the retinal vessels and examine if there was an association with development and progression of diabetic retinopathy over a 10-year period in a cohort of people with type 1 diabetes.

Methods. 25 type-1 diabetic and 14 non-diabetic individuals were followed from 1993 to 2003 as part of a twin study. Retinopathy was graded from retinal colour images in 1993 and 2003. The retinal images were digitized and geometric parameters; diameter, arterio-venous ratio, branching angle, length/diameter ratio, tortuosity index and expansion factor were measured using a validated, purpose-written measurement programme.

Results. There was a statistically significant change in retinopathy level in the follow-up period. Additionally, a significant (p=0.001) association between HgA1c in 1993 and level of diabetic retinopathy in 2003 was found. No association was found between the measured geometric parameters at baseline and level of retinopathy 10 years later. Further, geometric parameters of the retinal vessels did not change significantly over a 10 year period in any of the two groups, nor were there any significant differences between the groups.

Conclusions. The study confirmed a strong association between glycemic control and progression of retinopathy. However, no association between the geometric parameters at baseline in 1993 and progression of retinopathy over 10 years until 2003 was found.

CORRELATION BETWEEN METABOLIC CONTROL AND PROGRESSION OF DIABETIC RETINOPATHY

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PURPOSE. It is well recognised that the level of metabolic control is a major risk factor for development of diabetic retinopathy (DR). However there is clearly great individual variation in the presentation and course of DR. Follow up studies of the initial stages of DR have identified three major phenotypes of DR, according to the risk of retinopathy progression: A- characterised by slow progression, and the other two: B- or "leaky" type, and C- or "ischemic" type characterised by more rapid progression (Lobo et al). A prospective two year follow up study of mild non proliferative DR was analysed to evaluate the relationship between metabolic control and the different patterns of DR.

METHODS. Thirty five type 2 diabetic patients were followed during a 2 year period, and evaluated at 6-month intervals. At each visit metabolic and systemic control was assessed with HbA1c, lipid profile (total cholesterol, LDL, HDL and triglycerides) and blood pressure. Ophthalmological exams were performed to characterise the retinopathy progression patterns (fundus photography, fluorescein angiography, retinal leakage analysis, retinal thickness analysis).The mean age at inclusion was 55.1 ± 6.0 years and the known duration of their diabetes was 9.1 ± 4.8 years.

RESULTS. The patients were grouped according to the level of metabolic control during the follow up period: group 1 (n=23) – good metabolic control (HbA1c < 7%) and group 2 (n=12) – poor metabolic control (HbA1c > 7%). HbA1c values were evaluated using a moving average. No statistical differences were found regarding age, known duration of diabetes, lipid profile or blood pressure between the 2 groups. Fifty percent of patients of group 1 were classified as belonging to phenotype A, 33% as type B and 17% as type C. Sixty five percent of the patients of group 2 were classified as belonging to the phenotype A, 22% as type B and 13% as type C. No differences in the distribution of the retinopathy phenotypes were found between the two groups.

CONCLUSIONS. Ophtalmological characterisation of different retinopathy progression patterns obtained on a 2 year follow up period appears to be largely independent of level of metabolic control. Both Ophthalmologists and Endocrinologists working in close cooperation are needed to adequately manage diabetic retinopathy.