SCIENTIFIC REPORT

The North Jutland County Diabetic Retinopathy Study (NCDRS) 2. Non-ophthalmic parameters and clinically significant macular oedema

L L Knudsen, H-H Lervang, S Lundbye-Christensen, A Gorst-Rasmussen

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See end of article for authors' affiliations

Correspondence to: L L Knudsen, Department of Ophthalmology, Aarhus University Hospital, Aalborg Sygehus Syd, Hobrovej 18–22, DK-9100 Aalborg, Denmark; u19204@aas.nja.dk

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Background: The influence of non-ophthalmic parameters on the prevalence of clinically significant macular oedema has not been unambiguously established. The present study was initiated with the aim of 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. The association between the presence of clinically significant macular oedema and blood pressure, HbA1c, BMI, age, onset of diabetes, duration of diabetes, blood-pressure-reducing medication, lipid-lowering medication, neuropathy and urinary albumin excretion was explored using multiple logistic regression analysis.
Results: We found no significant association between the presence of clinically significant macular oedema and any of the examined parameters in type 1 diabetic subjects. In type 2 diabetic subjects, the duration of diabetes, HbA1c, neuropathy and increased urinary albumin excretion was significantly associated with the presence of clinically significant macular oedema.
Conclusions: The risk factors for clinically significant macular oedema differ in type 1 and type 2 diabetic subjects and can account only in part for this manifestation.

Diabetic maculopathy is a leading cause of visual acuity reduction and blindness.[1–3] The understanding of possible risk factors is therefore of interest, and a number of large-scale studies have explored the subject. Some studies suggest an association with metabolic regulation and other non-ophthalmic parameters[4 5] while others disprove these results.[6 7] The risk factors and causes of the diabetic maculopathy therefore still remain unclear.[8]

Recently, a large-scale cross-sectional study from the county of North Jutland explored the prevalence of proliferative retinopathy and clinically significant macular oedema (CSMO).[9] The prevalence of proliferative retinopathy was reported to be reduced to less than a tenth of that of previous studies, possibly as a result of improved blood glucose regulation.[9] Still, the prevalence of CSMO was reported to be relatively high and possibly increased, although the regulation of blood glucose had improved.[9] The present study was initiated to explore the influence from non-ophthalmic risk factors on the prevalence of CSMO in the present population.

MATERIAL AND METHODS

In the period 1 April 2000 to 30 April 2004, 656 subjects with type 1 diabetes and 328 subjects with type 2 diabetes underwent diabetic retinopathy screening in the county of North Jutland. The type 1 diabetic subjects were almost exclusively from larger Aalborg (an urban area in the County of North Jutland), representing 70–75% of all adult type 1 diabetic subjects in this region. The type 2 diabetic subjects were enrolled from the entire County of North Jutland mainly due to poor regulation of diabetes. These individuals accounted for less than 5% of registered type 2 diabetic subjects in the County. The over-riding participants were Caucasians.

Diabetic retinopathy screening

The method has previously been described[9] and is briefly summarised as follows. First, a standardised visual acuity was measured using a decimal progression scale. Second, the retina was photographically recorded using a digital camera (Zeiss DSC 420 resolution 1524×1012). One photo was centred at the macular region, and the other included the optic disc and the nasal part of the retina. Simultaneously, a number of selected non-ophthalmic parameters, as indicated below, were registered. Third, the digitised retinal recordings and registered non-ophthalmic parameters were electronically transferred to the Department of Ophthalmology for additional evaluation. Fourth, the retinal recordings were examined on a high-resolution screen (Nokia 446 PRO) for lesions in the macular region. In cases of any detectable pathology in the macular region, subjects were called for a clinical examination (22% of all subjects) to determine the presence of CSMO. If a subject failed to appear, they were summoned again, resulting in a 100% participation.

Definition of diabetes type

In the study, we defined type 1 and type 2 diabetes as follows:

- type 1 diabetes: diabetic subjects less than 30 years of age at diagnosis, usually normal or underweighted at diagnosis or with a history of keto-acidosis
- type 2 diabetes: diabetic subjects aged above 30 years at diagnosis, normally overweight at diagnosis and without a history of keto-acidosis

Non-ophthalmic parameters

The recorded non-ophthalmic parameters and their methods of measurement are described below:

- regulation, blood pressure and DM status: HbA1c (%), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), mean arterial blood pressure (mm Hg), neuropathy (±) and u-alb excretion (normal/micro-alb/proteinuri)

Abbreviation: CSMO, clinically significant macular oedema

- person characteristics: age (years), height (m), weight (kg), body mass index (BMI) (kg/m^2)
- characteristics of diabetes: duration of diabetes (years), age of DM-start (years)
- medication: insulin (±), oral antidiabetics (±), diet only (±), blood-pressure-reducing medication (±), lipid-lowering medication (±); median and inter-quartile range for continous parameters are displayed in table 1.

Definition of CSMO

The presence of CSMO was established from a clinical three-dimensional evaluation of the macular region using the ETDRS criteria.[10]

Data analysis

Data were composed from several sources. Typing errors and mismatch of cases were controlled for by visual inspection of scatter plots and and by validation of selected cases. Multiple logistic regressions were used for the calculation of prevalence, odds ratios and confidence intervals adjusted for various parameters. To avoid possible bias, the statistical analysis only included clinically significant macular oedema on the right eye. The statistical analysis was carried out using SPSS 12.0.2 for Windows and R R.2.1.1.[11]

RESULTS

The crude prevalence of CSMO was 9.6 (7.9 to 11.6)% for all diabetic subjects, 7.9 (6.1 to 10.3)% for type 1 and 12.8 (9.6 to 16.9)% type 2 diabetic subjects.

Among type 1 diabetic subjects, the presence of CSMO was not significantly associated with any of the examined parameters. An additional subdivision into prepuberty (<15 years) and postpuberty (≥15 years) onset revealed no differences between these two groups.

Among type 2 diabetic subjects, the presence of CSMO was significantly associated with the duration of diabetes ($p = 0.035$; adjusted (for age, duration of diabetes, blood pressure, BMI and HbA1c) OR = 1.05, HbA1c ($p = 0.036$; adjusted OR = 1.26) and neuropathy ($p = 0.047$; adjusted OR = 2.60). Additional sub-analyses among patients with registered nephropathy revealed that microalbuminuria influenced the prevalence of CSMO insignificantly ($p = 0.92$; adjusted OR = 1.06), while proteinuria influenced it significantly ($p = 0.004$; adjusted OR = 5.18). Systolic blood pressure ($p = 0.063$; adjusted OR = 1.02) and blood-pressure-reducing medication ($p = 0.068$; adjusted OR = 2.59) were found to be close to the 5% confidence limit.

DISCUSSION

The presence of CSMO was not found to be associated with any of the examined parameters among type 1 diabetic subjects. In type 2 diabetic subjects, it was associated with the duration of diabetes, HbA1c, neuropathy and proteinuria. The study thus suggests differences between type 1 and type 2 diabetic subjects with respect to the presence and risk factors for CSMO. However, a selection bias among the type 2 diabetic subjects might be present. The study also suggests that the present risk factors account for only a minor fraction of subjects with CSMO.

The metabolic control of diabetic subjects has generally been improved to date, and these subjects also comprise the present population.[9] Still, the prevalence of CSMO in the present study was found to be relatively high and possibly increased compared with previous studies. A multiple regression analysis of the present data revealed no significant influence of HbA1c in type 1 diabetic subjects and a significant but modest increased risk (26%) among type 2 diabetic subjects. The blood pressure did not influence the presence of CSMO significantly in any group of diabetic subjects. Consequently, the influence of regulatory parameters on the presence of CSMO in the present population was limited and could only account for a small number of these cases. However, it should be noted that the present population was relatively well regulated. Less well-regulated diabetic subjects could still have a significant increased risk for CSMO.

The potential advantages of a very tight regulation have previously been discussed. The present study results suggest that such additional improved regulation will have little additional benefit on the presence of CSMO. The identification of additional risk factors should have a high priority in future studies.

In the light of the present study, the causes of the development of CSMO therefore still remain unclear, but at least two possibilities seem plausible: previous glycaemic malregulation or genetic factors.

It is well documented that the function of various organic systems is influenced by previous malregulation, which makes it obvious to suspect such an association. It is also well known

Table 1 Crude and corrected odds ratios (OR) among type 1 and type 2 diabetic subjects for age, duration of diabetes, blood pressure, BMI and HbA1c

	Crude OR	Corrected OR†	Corrected OR‡
Type 1			
Age	1.02* (1.00; 1.05)	1.01 (0.98; 1.04)	1.01 (0.98; 1.04)
Duration of diabetes	1.03** (1.01; 1.06)	1.03 (1.00; 1.06)	1.03 (1.00; 1.06)
Blood pressure			
Diastolic	1.03 (1.00; 1.06)	1.03 (1.00; 1.06)	1.03 (1.00; 1.07)
Systolic	1.01 (1.00; 1.03)	1.00 (0.99; 1.02)	0.99 (0.97; 1.02)
Mid	1.02 (1.00; 1.05)	1.02 (0.99; 1.05)	1.02 (0.99; 1.05)
BMI	0.97 (0.89; 1.05)	0.98 (0.90; 1.06)	0.96 (0.88; 1.05)
Hb1Ac	1.16 (0.93; 1.44)	1.15 (0.91; 1.44)	1.13 (0.89; 1.43)
Type 2			
Age	1.04* (1.00; 1.07)	1.02 (0.99; 1.05)	1.01 (0.97; 1.04)
Duration of diabetes	1.07** (1.03; 1.11)	1.06** (1.02; 1.10)	1.05* (1.00; 1.10)
Blood pressure			
Diastolic	1.01 (0.97; 1.04)	1.01 (0.97; 1.04)	0.98 (0.93; 1.02)
Systolic	1.02** (1.01; 1.04)	1.01 (1.00; 1.03)	1.02 (1.00; 1.05)
Mid	1.03 (1.00; 1.05)	1.02 (0.99; 1.05)	1.01 (0.98; 1.04)
BMI	1.03 (0.98; 1.08)	1.04 (0.99; 1.09)	1.04 (0.98; 1.09)
Hb1Ac	1.31** (1.07; 1.60)	1.29* (1.05; 1.60)	1.26* (1.01; 1.58)

*Significant at the 0.05 level. **Significant at the 0.01 level.
†Corrected for age and duration of diabetes; ‡corrected for all other variables.

Table 2 Median, interquartile range and max/min values among type 1 and type 2 diabetic subjects for age, duration of diabetes, blood pressure, HbA1c and BMI

	Type 1				Type 2			
	Median	Interquartile range	Min	Max	Median	Interquartile range	Min	Max
Age at entry	37.3	19.0	17.0	79.0	58.1	15.0	18.0	83.0
Duration of diabetes	17.6	16.0	1.0	58.0	8.0	11.0	0.0	48.0
Blood pressure								
Systolic	130.0	20.0	75.0	220.0	140.0	25.0	100.0	205.0
Diastolic	80.0	15.0	50.0	110.0	80.0	15.0	55.0	110.0
Mid	96.7	14.0	58.3	140.0	101.0	13.3	73.3	136.3
HbA1c	8.3	1.6	5.1	13.9	8.1	2.3	4.8	15.2
Body Mass Index	24.1	4.5	13.7	41.3	29.7	8.3	14.2	58.8

Table 3 Crude and corrected odds ratios (OR) among type 1 and type 2 diabetic subjects for blood-pressure-reducing medication, lipid-reducing medication neuropathy and nephropathy

	Crude OR	Corrected OR†	Corrected OR‡
Type 1			
Blood-pressure-lowering medication	2.03** (1.13; 3.64)	1.60 (0.85; 3.01)	1.34 (0.70; 2.56)
Lipid-lowering medication	0.26 (0.04; 1.90)	0.15 (0.02; 1.14)	0.18 (0.02; 1.40)
Neuropathy	0.82 (0.28; 2.35)	0.42 (0.14; 1.34)	0.39 (0.12; 1.24)
Nephropathy			
Micro	2.24* (1.02; 4.92)	1.95 (0.61; 4.09)	1.93 (0.83; 4.50)
Macro	1.89 (0.63; 5.69)	1.48 (0.47; 4.66)	1.26 (0.37; 4.28)
Type 2			
Blood-pressure-lowering medication	3.19** (1.47; 6.90)	2.52* (1.10; 5.77)	2.36 (0.94; 5.92)
Lipid-lowering medication	1.09 (0.53; 2.23)	1.02 (0.48; 2.16)	0.96 (0.43; 2.15)
Neuropathy	3.48** (1.72; 7.018)	2.53* (1.20; 5.323)	2.26* (1.01; 5.045)
Nephropathy			
Micro	1.59 (0.61; 4.09)	1.36 (0.52; 3.58)	1.06 (0.37; 3.01)
Macro	7.50** (2.90; 19.38)	6.58** (2.42; 17.89)	5.18** (1.71; 15.68)

*Significant at the 0.05 level; **significant at the 0.01 level.
†Corrected for age and duration of diabetes; ‡corrected for age, duration of diabetes, blood pressure, BMI and Hb1Ac.

that the thickness and the composition of basement membranes in several organic systems differ in diabetic subjects. These changes in the basement membranes are, in general, the result of the surrounding cells and their function, thus suggesting some genetic influence. In the future, we will focus on previous regulation and possible genetic risk factors.

Authors' affiliations

L L Knudsen, Department of Ophthalmology, Aarhus University Hospital, Aalborg Sygehus Syd, Aalborg, Denmark
H-H Lervang, Department of Medical Endocrinology, Aarhus University Hospital, Aalborg Sygehus Syd, Aalborg, Denmark
S Lundbye-Christensen, A Gorst-Rasmussen, Department of Mathematical Sciences, Aalborg University, Aalborg Øst, Denmark

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