exhibited more dysuria, but the urethral syndrome was not associated with any increase in psychiatric morbidity.

When no infection is found doctors may be more likely to regard patients' emotions as the cause rather than the effect of the condition.[18] Our findings indicate that patients with the urethral syndrome are no more neurotic than those with significant bacteriuria and that both groups require tolerance of the distress engendered by their conditions.

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Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study

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Abstract

***Objective*—To study insulin dependent diabetic patients for change in non-proliferative retinopathy and its relation to glycaemic control and to various clinical background data.**

***Design*—Prospective study with follow up for seven years.**

***Setting*—Outpatient departments of university hospitals.**

***Main outcome measures*—Glycated haemoglobin concentration; degree of retinopathy.**

***Results*—Retinopathy worsened by an overall increase in counts of microaneurysms and haemorrhages from 17 (SD 25) to 45 (58) ($p=0\cdot005$). Intensified insulin treatment and home blood glucose monitoring improved concentrations of glycated haemoglobin (HbA_1) from 11·2% (2·2%) at the start of the study to a mean of 9·5% (1·5%) over the seven years of the study ($p<0\cdot0001$). A mean value for HbA_1 >10% was associated with an increased risk of progression of retinopathy and a mean value <8·7% was associated with a diminished risk. Multiple regression analysis identified four independent variables as indicative of outcome of retinopathy after seven years: HbA_1 value at baseline; the change in HbA_1 from start to the mean level through the seven years; duration of diabetes; and retinopathy at start. Age, blood pressure, and urinary albumin excretion were not related to the presence or progression of retinopathy.**

***Conclusion*—Secondary intervention by long term lowering of glycated haemoglobin has a beneficial impact on non-proliferative retinopathy. A four factor regression model can determine patients at high risk of severe retinopathy.**

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Introduction

An accumulation of data suggests an association between hyperglycaemia and the incidence and progression of diabetic retinopathy.[1-9] Intervention studies, in which attempts have been made to lower mean blood glucose levels give conflicting results regarding beneficial effects on progression of retinopathy[10-20]—but they have all studied the patients for only a short period, up to three years.

The severity of retinopathy is related mainly to the duration of diabetes. Exposure to various factors in diabetes can be characterised by intensity, duration, and cumulative dose (intensity times duration).[21] The results obtained in a well designed study may depend on a cumulative dose being reached through sufficient duration of the study. This is illustrated by our study, in which the same patients were examined by identical tests at intervals for seven years.

The Oslo study was originally designed as a prospective, randomised study of the effects of insulin pumps, multiple insulin injections, and conventional treatment with insulin.[22-27] Results after two years showed marginal beneficial effect of intervention on progression of retinopathy.[25] This effect was not evident after three to four years,[26] even though assessment was performed according to both the mode of insulin treatment and the mean blood glucose concentration. After seven years' follow up, however, the long term beneficial effects of improved glycaemic control were evident. The present paper determines the change in retinopathy after seven years, examines relevant clinical variables, identifies four independent risk factors, and presents a long term regression model for severity of non-proliferative retinopathy.

Patients and methods

Forty five insulin dependent diabetic patients were included in the Oslo study seven years ago. Inclusion criteria and background clinical data have been described previously.[22-27]

Table I shows background data relevant to the current paper at the start of the study and after seven years. At baseline, the 21 men and 24 women averaged 26 (range 18-36) years and had had diabetes for 13 (6-23) years. They had no clinical signs of systemic hypertension, nephropathy, or neuropathy;

patients with proliferative retinopathy had not been included. Visual acuity was 20/20 in all eyes, except in two patients (20/25 in one eye each). No deterioration of visual acuity occurred in any patient throughout the study.

TABLE I—*Clinical characteristics of 45 diabetic patients at baseline and after seven years' follow up. Values are mean (range)*

	Baseline	After seven years	p Value
Age (years)	26 (18-36)	33 (25-43)	
Duration (years)	12·8 (6-23)	19·7 (13-31)	
Systolic blood pressure (mm Hg)	125 (110-160)	131 (105-165)	0·002
Diastolic blood pressure (mm Hg)	81 (70-95)	81 (60-100)	0·86
Urinary albumin excretion (mg/24 h)	20·0 (2-525)	53·0 (1-409)	0·5
Severity of retinopathy*	17 (0-154)	45 (0-200)	0·005

*Counts of microaneurysms and haemorrhages (both eyes).

Before starting the study the participants had been using two daily injections of insulin. The original design randomised patients to insulin pumps (continuous subcutaneous insulin infusion), multiple injections (four to six times daily), and conventional insulin treatment (twice daily); there were 15 patients in each group.[22,23] After 41 months of the study[26,27] multiple injections with an insulin pen became very popular in Norway. We decided to change the protocol, now allowing each patient to choose the mode of insulin treatment. At seven years 10 patients used insulin pumps; 29 used multiple injections (regular insulin before meals and isophane insulin at bedtime) delivered by an insulin pen; and six patients used conventional treatment (regular insulin and isophane insulin twice daily). Glycaemic control was estimated every second month by determining the concentration of "stable" haemoglobin A_1 (by the agar gel electrophoresis method; normal range (2 SD) 5·4-7·6%).[28] During the last two years high performance liquid chromatography (Diamat) was used, with the same normal range (coefficient of variation <3%).

Throughout the study each of the 45 patients had had a total of 11 eye examinations at intervals of no more than one year. Fundus colour photography was performed, and retinopathy was assessed by a masked counting of microaneurysms and haemorrhages ("red spots"). The individual retinopathy score was obtained by the counts from a 30° standard field photograph of both eyes. Details of variability and concordance are described elsewhere.[26]

Transient proliferative retinopathy developed in a 22 year old woman after six months[29] and in a 23 year old woman after six years. As spontaneous regression occurred photocoagulation treatment was not performed. In a 30 year old man fibrovascular proliferative retinopathy (mean concentration of glycated haemoglobin (HbA_1) over seven years 13·5%) was detected at the seven year eye examination. He received laser treatment after completing the protocol.

Blood pressure (mm Hg) was measured at the time of the eye examination by auscultation after five minutes' rest in the seated position. Microalbuminuria was determined by immunoturbidometry in a 24 hour urine collection (mg/24 h) within two months of the eye examination.

A two tailed Wilcoxon signed rank test was used to compare values at baseline and after seven years. Correlation was performed by Spearman's method. Multivariate regression analysis was used for identifying independent variables for development of retinopathy. As all variables except microaneurysms and haemorrhages had a nearly normal distribution, in the multivariate analysis we used parametric statistics after logarithmic transformation of microaneurysms and haemorrhages. Parametric statistics were used in this analysis as appropriate non-parametric multivariate methods were not available. The level of significance was 5%.

Results

Clinical data at the start of the study and after seven years' follow up are presented in tables I and II. In the 45 patients systolic blood pressure rose significantly (p=0·002), overall retinopathy worsened (p=0·005), and, of course, age and duration of diabetes increased by seven years. One patient received antihypertensive drugs during the last four years of the study. Details of changes in urinary albumin excretion rate (table I) will be described elsewhere.

The mean concentration of HbA_1 was significantly reduced in participants in the study: 11·2% (SD 2·2%); range 7·5-18·9%) at the start, compared with 9·5% (1·5%; 7·3-13·2%) after seven years, a change of 1·7% (2·0%; −3·1-7·1%, p<0·0001). The concentration did not drift upwards when, after 41 months of strict randomisation,[26] treatment was allocated according to patients' preference. The differences in glycaemic control between the three modes of insulin treatment during the first 41 months seem to have been sustained through the rest of the study. The seven year mean HbA_1 concentrations, according to the original randomisation ("intension to treat") were 9·1% (1·1%) in the group treated by insulin pump; 9·3% (1·4%) in the group treated by multiple injections; and 10·4% (1·5%) in the group given conventional insulin treatment. The mean HbA_1 values during the months preceding the eye examination at 41 months were 9·1%, 9·3%, and 10·5% respectively.

The mean (SD) counts of microaneurysms and haemorrhages in all 45 patients were 17·1 (25) at start and 44·7 (58) after seven years (p=0·005) (tables I and II). We grouped patients according to mean HbA_1 concentration over seven years to show the progression of retinopathy (table III). Cut off points of 9% and 10% were chosen before the relation between HbA_1 concentration and retinopathy was analysed. A mean value of HbA_1 above 10% was associated with increased risk of progression of retinopathy (p=0·014) and with greater retinopathy at seven years (p=0·009). Plots of the relation between retinopathy (progression and at endpoint) and HbA_1 concentration suggested an exponential relation between the two variables. No true thresholds were observed at which there was a definite increase in progression or below which the patient was protected. However, in the 15 (34%) patients with a seven year mean HbA_1 concentration below 8·7% there was no severe progression of retinopathy (10 patients developed fewer than 10 microaneurysms and haemorrhages and five patients fewer than 40) or severe retinopathy at seven years (11 patients had fewer than

TABLE II—*Severity of diabetic retinopathy at baseline and at seven years. Figures are numbers of patients*

	No of microaneurysms and haemorrhages			
	0	0-20	21-50	>50
At baseline	7	25	12	1
After seven years	5	17	12	11

TABLE III—*Severity of retinopathy at baseline and after seven years in patients grouped according to mean blood glucose concentrations*

	Blood glucose concentration		
	<9·0% (n=20)	9·1-10·0% (n=13)	>10·1% (n=12)
Mean (SD) microaneurysms and haemorrhages:			
At baseline	11·8 (14·8)	24·7 (40·8)	17·6 (16·2)
After seven years	25·5 (43·1)	41·1 (58·7)	80·5 (66·7)
Change	13·8 (39·5)	16·4 (56·6)	62·8 (65·8)*

*p=0·014 compared with patients with HbA_1 <10·0%.

TABLE IV—*Correlation of retinopathy and clinical data at baseline and at seven years and predictive value of baseline data for retinopathy at seven years*

	Baseline	At seven years	Predictive value
Age (years)	$r=0{\cdot}08$ ($p=0{\cdot}61$)	$r=-0{\cdot}08$ ($p=0{\cdot}59$)	$r=-0{\cdot}08$ ($p=0{\cdot}59$)
Duration (years)	$r=0{\cdot}36$ ($p=0{\cdot}01$)	$r=0{\cdot}31$ ($p=0{\cdot}04$)	$r=0{\cdot}36$ ($p=0{\cdot}02$)
Urinary albumin excretion (mg/24 h)	$r=0{\cdot}02$ ($p=0{\cdot}92$)	$r=0{\cdot}22$ ($p=0{\cdot}14$)	$r=0{\cdot}03$ ($p=0{\cdot}87$)
Systolic blood pressure (mm Hg)	$r=-0{\cdot}03$ ($p=0{\cdot}79$)	$r=0{\cdot}04$ ($p=0{\cdot}80$)	$r=0{\cdot}01$ ($p=0{\cdot}96$)
Diastolic blood pressure (mm Hg)	$r=0{\cdot}14$ ($p=0{\cdot}35$)	$r=0{\cdot}10$ ($p=0{\cdot}51$)	$r=-0{\cdot}04$ ($p=0{\cdot}78$)

TABLE V—*Results of multivariate regression analysis with logarithm of counts of microaneurysms and haemorrhages (red spots) as dependent variable*

	Regression coefficient (95% confidence interval)	p Value
Constant term	−2·66 (−2·97 to −2·35)	<0·001
Glycated haemoglobin (%):		
Mean at baseline	0·36 (0·06 to 0·66)	0·027
Difference between baseline and mean for seven years	−0·35 (−0·68 to −0·02)	0·041
Duration of diabetes (years before start of study)	0·009 (0 to 0·018)	0·044
Severity of retinopathy at baseline (log of counts of red spots)	0·35 (0·02 to 0·68)	0·046

TABLE VI—*Counts of microaneurysms and haemorrhages at seven years in four risk groups (45 patients divided by quartiles) determined by summing four independent variables: blood glucose concentration at baseline and change in HbA_1 concentration from baseline to mean through seven years; duration of diabetes; and retinopathy at baseline. Numbers are percentage chance of individual diabetic patient having more than specified number of microaneurysms and haemorrhages after seven years*

Risk groups	>10 microaneurysms and haemorrhages	>30 microaneurysms and haemorrhages	>50 microaneurysms and haemorrhages
I	30	20	0
II	58	25	0
III	92	25	25
IV	100	91	73

25 microaneurysms and haemorrhages and four had fewer than 40).

Transient worsening of retinopathy (development of cotton wool spots at start of the study (at three to six months)) occurred in 15 patients, all of whom were being treated with insulin pumps and multiple injections.[22,23] We examined possible negative long term effects of this worsening. The 15 patients who developed cotton wool spots did not have a different retinopathy outcome at seven years than the 30 who did not.

Clinical background data (table I) were tested for possible relations to retinopathy at baseline and at seven years and for the ability to predict degree of retinopathy at seven years (table IV). The duration of diabetes was correlated with the severity of retinopathy at baseline ($p=0{\cdot}01$) and at seven years ($p=0{\cdot}04$) and was a predictive risk factor for retinopathy after seven years ($p=0{\cdot}02$). The severity of retinopathy was not correlated to age, blood pressure, or kidney function, and patients with the most retinopathy at baseline were more likely to have more severe retinopathy seven years later ($r=0{\cdot}41$; $p=0{\cdot}005$) (data not shown).

Table V shows four independent variables related to severity of retinopathy at seven years. Retinopathy was not correlated to the baseline HbA_1 value ($r=0{\cdot}22$; $p=0{\cdot}14$; data not shown). Given the notion that HbA_1 concentration at baseline could be indicative of glycaemic control in the preceding years of diabetes, this value was included in a multiple regression analysis. Further, the fact that significant improvement in glucose control was obtained for a period of seven years, as compared with HbA_1 concentration at baseline, initiated an analysis of individual changes of HbA_1 from baseline to the mean value through seven years. The HbA_1 value at baseline, the change in HbA_1 concentration, the duration of diabetes, and the retinopathy at baseline were all independent variables.

To evaluate the relative influence of these four variables on severity of retinopathy after seven years the results of the current study were used to produce a regression model (table V). This model explained 34% of the variability in number of microaneurysms and haemorrhages after seven years. The relative influence of each variable is shown by equating the effects of the variables on the progression of retinopathy through seven years. The severity of retinopathy at seven years was reduced to the same extent by a baseline HbA_1 concentration of 10% rather than 11%; a reduction of baseline HbA_1 concentration of 11% to a mean over seven years of 10%; 38 months' shorter duration of diabetes at baseline; or 10 microaneurysms and haemorrhages at baseline rather than 28.

An earlier regression model had included the treatment code (the initial randomised mode of insulin treatment), but this variable did not contribute significantly ($p>0{\cdot}5$) to outcome of retinopathy after seven years.

Individual diabetic patients could be characterised by a relative risk "index" for developing severe retinopathy at seven years. This index was calculated for each patient by summing the four variables in table V. The 45 patients were assigned to four groups according to risk by using the regression model. This formed the basis of a risk model for predicting the level of retinopathy after seven years (table VI).

Discussion

The most important finding of the present study is that long term lowering of blood glucose concentration retards the progression of diabetic retinopathy. Secondary glycaemic intervention has a beneficial effect on established retinopathy, even in subjects who have had diabetes for up to 23 years. This study also indicates that hyperglycaemia plays an important part in the pathogenesis of diabetic retinopathy.

Relations between blood glucose concentration and retinopathy were assessed by three separate methods: the predictive value of the baseline concentration of glycated haemoglobin, the impact of treatment over seven years, and the grouping of subjects according to mean HbA_1 concentration over the seven years. The HbA_1 value at inclusion may, in a sense, represent glycaemic control during the preceding years. The multiple regression analysis gives support to this assumption: patients with higher HbA_1 values at inclusion had greater retinopathy seven years later. This agrees with the four year results of the Wisconsin epidemiological study, in which the progression of retinopathy was associated with a single measurement of glycated haemoglobin.[5] In the present study the "predictive" impact of the HbA_1 concentration at inclusion was statistically detectable, in spite of intervention, as improved glycaemic control through the next seven years. This reflects the long term relation between glycaemic control and retinopathy and explains, in part, the difficulty in finding this relation in previous studies.[12-19,22,23,25,26]

Because it has been claimed that inherent characteristics determine both HbA_1 concentration and the development of diabetic retinopathy we studied the metabolic intervention in each subject as individual changes from the baseline value to the mean vaue for HbA_1 over seven years. The overall glycaemic control improved from an average HbA_1 concentration of 11·2% to 9·5%, and this change proved to be an independent variable determining severity of retinopathy. It is of interest that a patient's mean HbA_1 concentration was not correlated with the duration of diabetes, the duration being a well established risk factor. This further supports the independence of high blood glucose concentration as a risk factor and, most importantly, as a risk factor accessible to intervention.

Long term (seven year) blood glucose concentrations

above 10% were associated with a significantly increased risk of progression to severe non-proliferative retinopathy, although no obvious increment was found at this level. The 10% threshold has, however, been associated with an increased risk for proliferative retinopathy on the basis of six year HbA_1 data.[8] Other reports have shown no threshold value in the relation of progression of retinopathy and HbA_1.[4 20]

The number of microaneurysms and haemorrhages at baseline was an independent risk factor for more severe retinopathy seven years later. This accords with a population based study in Wisconsin which found that the microaneurysm count at baseline predicted the four year progression of retinopathy.[30] This long term prediction was independent of the starting level of glycated haemoglobin, as in the present study; we also found that it was independent of seven years' improvement in glycaemic control. Short term effects may, however, be different. Kohner and Dollery found no difference in the formation and disappearance of microaneurysms in patients with mild or severe retinopathy who had conventional insulin treatment; they analysed the turnover per month.[31] Worsening of retinopathy, seen after the initiation of tight glycaemic control in the Kroc collaborative study[14] and the present study,[23] seemed to occur as often in patients with mild retinopathy as in patients with more severe retinopathy. This emphasises the need for careful matching of baseline levels of retinopathy in any comparative clinical trial.

Neither age, blood pressure, nor urinary albumin excretion were correlated with retinopathy at baseline or at seven years. These variables had no predictive ability in selecting patients at high risk of severe retinopathy seven years later.

The role of blood glucose in the incidence and progression of retinopathy is pathogenetically complex. The present study shows that long term improved control retards progression of retinopathy after seven years, but short term rapid lowering of blood glucose concentrations may transiently worsen retinopathy,[13 14 22 23 32] affecting the severity of retinopathy for at least a year.[23] This emphasises the critical need for closely monitoring both retinopathy and blood glucose; single cross sectional associations may be misleading. Furthermore, the course of the disease before patients entered the study may have had a considerable impact on the end results. This has previously been shown by Engerman and Kern: good glycaemic control from the start of diabetes inhibited development of retinopathy in dogs but was less efficient in inhibiting retinopathy if good control had been preceded by a long period of poor control.[33]

The present study has identified clinical variables that characterise the severity of retinopathy after secondary intervention by intensified insulin treatment. Four risk factor can be applied to individual patients to calculate the probability of increased severity of retinopathy. A risk index for retinopathy has been derived by modelling the intensity, duration, and cumulative dose of each factor, and the informative value of the model should be superior to the clinical use of a single risk factor such as duration of diabetes. The practical value of the present model has to be tested in future studies on different populations of diabetic patients.

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