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Different risk factors of microangiopathy in patients with Type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study

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Abstract

Aims/hypothesis. To identify factors associated with early development of and late protection from microvascular complications in subjects with Type I (insulin-dependent) diabetes mellitus.
Methods. The frequency of microvascular complications and their relation to risk factors were studied in 300 Type I diabetic subjects with short duration of disease (≤ 5 years) compared with 1062 subjects with long duration (≥ 14 years). Microvascular disease was defined as the presence of either retinopathy (assessed from centrally-graded retinal photographs) or urinary albumin excretion rate of more than 20 μg/min.
Resu1ts. The prevalence of microvascular disease was 25 % in the short duration group. In the long duration group 18 % had no evidence of microvascular complications. In the short duration group factors associated with early development of complications were cigarette smoking and a family history of hypertension. Subjects free of microvascular complications in spite of long duration of diabetes had better glycaemic control, lower blood pressure, better lipid profile and lower von Willebrand factor levels.
Conclusion/interpretation. At the early stages of Type I diabetes, cigarette smoking and genetic susceptibility to hypertension are important risk factors for microvascular complications. At a later stage, additional risk factors are poorer glycaemic control, higher blood pressure, and an unfavourable lipid profile possibly associated with endothelial dysfunction. Many of these factors are amenable to long-term intervention which should be started as soon as possible in the course of the disease. [Diabetologia (2000) 43: 348–355]

Keywords Microvascular complications, retinopathy, nephropathy, hypertension, lipids, lipoproteins, smoking, endothelial dysfunction, von Willebrand factor.

In diabetic patients morbidity and mortality are mainly related to the presence of late complications, namely macro- and microangiopathy. The pathogenesis of microangiopathy is being extensively studied and evidence linking the degree of glycaemic control with the development of microangiopathy has been accumulated over the last 20–30 years [1–6], while evidence is also increasing for some genetic predisposition [7–10].

In Type I diabetic patients both the Stockholm Diabetes Intervention Study and the Diabetes Control and Complications Trial (DCCT) showed that glycaemic control is an important determinant of both the development and progression of diabetic microangiopathy [4, 5]. The United Kingdom Prospective Diabetes Study (UKPDS) has also confirm-

* See Appendix for complete list of participating centres
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Abbreviations: CVD, Cardiovascular disease; DD, diabetes duration; DM, diabetes mellitus; vWF, von Willebrand factor; WHR, waist to hip ratio.

ed the relation between glycaemic control and the development of microangiopathy in Type II (non-insulin-dependent) diabetic patients and moreover has documented the aggravating role of increased blood pressure [6, 11]. The results of these studies, however, possibly represent a general trend with many individual exceptions. It is well known that, irrespective of the quality of the glycaemic control, only 30–40 % of Type I diabetic patients eventually develop clinical nephropathy and retinopathy occurs in 80–100 % of subjects after 20 years of diabetes [12–16]. Various complications may be related differently to glycaemic control and other factors possibly have a role in this interaction or even act independently. There is increasing evidence for a genetic predisposition to diabetic microangiopathy. Data relating microangiopathy to various *HLA* genotypes are contradictory [17–21]. Type I diabetic patients with nephropathy, however, have more often a parental history of hypertension [22–26] and show higher velocity of sodium/lithium countertransport in red cells, a heritable feature [27], supporting the hypothesis of a genetic susceptibility to this complication. Finally in the EURODIAB IDDM Complications Study, Type I diabetic patients show an association of the albumin excretion rate with a diastolic blood pressure greater than 75 mm Hg, but only if they also have retinopathy [28]. Thus it appears that abnormal renal vulnerability to blood pressure exists only in those prone to the development of retinopathy. Therefore, the complexity of the interaction between metabolic control, genetic predisposition and other factors in the development of microangiopathy is apparent. The comparison of Type I diabetic patients who develop microangiopathy very early in the course of diabetes with those who after a long duration of diabetes remain totally free from microangiopathy could clarify the differing vulnerability to complications.

Therefore, it was our aim to study Type I diabetic patients with a short (≤ 5 years) and long (≥ 14 years) duration of diabetes (DD) from the EURODIAB cohort to identify factors associated with the early development or late protection or both from diabetic microangiopathy.

Subjects and methods

The EURODIAB IDDM Complications Study is a cross-sectional study designed to measure the prevalence of diabetic complications in Type I diabetic patients and investigate their relation with various risk factors. Type I diabetes was defined as diabetes onset before age 36 years and continuous treatment with insulin initiated less than 1 year from diagnosis. Duration of diabetes was at least 1 year. Details of the study design have already been published [14]. In summary, 3250 Type I diabetic patients were randomly selected from 31 clinics in 16 European countries, and the sample was stratified by sex, three age groups and three diabetes duration groups. Albumin excretion rate was calculated from a timed 24-h urine collection. Urinary albumin was measured in a central laboratory by an immunoturbidometric method using goat anti-human, albumin antiserum and human serum albumin standards. Microalbuminuria was defined as AER above 20 μg/min and less than 200 μg/min; macroalbuminuria as AER at or above 200 μg/min. Retinopathy was assessed by retinal photographs (two precisely defined 45° fields in each eye) taken after pupil dilatation, graded centrally against standard photographs (EURODIAB Hammersmith System) and classified as none, background or proliferative [29]. The value of HbA_{1c} (normal range 2.9–4.8 %) was measured centrally by an enzyme immunoassay (Dako Ltd., Ely, UK) using a monoclonal antibody raised against HbA_{1c}, [30]. Plasma fibrinogen, von Willebrand factor (vWF) and serum lipids were measured in central laboratories using methods described previously [31, 32]. Blood pressure was measured in the sitting position with the Hawksley random zero sphygmomanometer and the mean of two consecutive measurements was calculated. Diastolic pressure was recorded at the disappearance of sound (phase V). Hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher, or if the subject was taking antihypertensive drugs. The diagnosis of cardiovascular disease (CVD) was based on a positive history of heart attack, angina pectoris, stroke or coronary artery bypass graft and/or an abnormal resting ECG suggestive of probable or possible ischaemia according to the Minnesota Code [31, 33]. Severe hypoglycaemia was defined as at least one episode in the last year requiring the help of another person. Severe ketoacidosis was defined as at least one episode in the last year requiring hospital admission. For our analysis nephropathy was designated as AER above 20 μg/min (micro- or macroalbuminuria) and retinopathy as the presence of any retinal lesion. Of the 3250 Type I diabetic patients there were 300 with a duration of diabetes shorter than 5 years and 1062 with diabetes longer than 14 years. Of the 300 patients with a short duration of diabetes 75 (45 men and 30 women), had retinopathy and/or nephropathy (Group A), while 225, (116 men and 109 women), had neither retinopathy nor nephropathy (Group B). Of the 1062 patients with a long duration of diabetes 872, (437 men and 435 women) had retinopathy and/or nephropathy (Group C), whereas 190 (81 men and 109 women) had neither complication (Group D). In Groups B and D, namely those without complications, there were no patients with systemic or autonomic neuropathy.

Statistical analysis. Analysis of covariance was used to adjust means for age and duration and to assess statistical differences between adjusted means for duration (short/long) and microangiopathy (absent/present) groups. For categorical variables the chi-square test was used to assess differences in proportions of those in the duration/microangiopathy groups. Because of the skewness of the distributions of fasting triglyceride, fibrinogen and von Willebrand factor, the log transforms of these variables were used throughout all statistical analysis and geometric means presented.

Results

The prevalence of microangiopathy, i.e. retinopathy or nephropathy or both, in the Type I diabetic patients with a duration of diabetes of 5 years or less was 25 %, 75/300 (Table 1). Of these, 55 had only microalbuminuria, 12 only retinopathy, while 8 had

Table 1. Distribution of Type I diabetic patients studied according to sex, duration of diabetes and the presence of retinopathy and/or nephropathy

	Short DD Microangiopathy Group A $n = 75$	Short DD No Microangiopathy Group B $n = 225$	Total	Long DD Microangiopathy Group C $n = 872$	Long DD No Microangiopathy Group D $n = 190$	Total
Men	45 (28%)	116	161	437	81 (17%)	518
Women	30 (22%)	109	139	435	109 (20%)	544
Total	75 (25%)	225	300	872	190 (18%)	1062

Table 2. Comparison of age and duration adjusted means of continuous variables between groups with and without microangiopathy in Type I diabetic patients with short and long duration of diabetes

	Short DD Microangiopathy Group A $n = 75$	Short DD No Microangiopathy Group B $n = 225$	Long DD Microangiopathy Group C $n = 872$	Long DD No Microangiopathy Group D $n = 190$
BMI, kg/m2	23.0	22.4	24.0[a]	23.5
Waist/Hip Ratio (WHR)	0.84	0.82	0.85[b]	0.83
Systolic BP, mm Hg	118	116	127[c]	120
Diastolic BP, mm Hg	75	73	78[c]	73
Insulin, U/day	42.6[a]	38.1	46.0	44.6
Insulin/kg body weight	0.63	0.58	0.68	0.69
HbA_{1c} %	6.84	6.51	6.68[c]	6.03
Total cholesterol, mmol/l	5.27	5.04	5.54[c]	5.19
Fasting triglyceride, mmol/l[d]	1.02	0.87	1.04[c]	0.84
HDL cholesterol, mmol/l	1.49	1.48	1.50	1.55
LDL cholesterol, mmol/l	3.32	3.17	3.49[a]	3.26
Fibrinogen, g/l[d]	2.96	3.10	3.34[b]	3.05
von Willebrand factor, U/ml[d]	1.16	1.04	1.10	1.08

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$, [d] geometric means

both. The prevalence was a little higher among men 45/161 (28%) than women 30/139 (22%) but this difference was not significant. On the other hand the percentage of patients without microangiopathy among those with a duration of diabetes of 14 years or more was 190/1062 (18%) and no difference was noted between men and women, 81/518 (17%) and 109/544 (20%) respectively.

Between those with (Group A) and those without (Group B) microangiopathy and short diabetes duration (Table 2) only the total daily dose of insulin differed significantly, being higher in the group with microangiopathy, 42.6 vs 38.1 U/day ($p < 0.05$). The degree of glycaemic control did not differ significantly, although HbA_{1c} was slightly higher in those with microangiopathy, 6.84 vs 6.51%. Between the two Groups (C and D) with a long duration of diabetes (Table 2), most variables studied were significantly different. Those with microangiopathy had higher BMI 24.0 vs 23.5 ($p < 0.05$), WHR 0.85 vs 0.83 ($p < 0.01$), systolic 127 vs 120 mm Hg and diastolic blood pressure, 78 vs 73 mm Hg ($p < 0.001$ for both), cholesterol 5.54 vs 5.19 mmol/l ($p < 0.001$), fasting triglyceride 1.04 vs 0.84 mmol/l ($p < 0.001$), LDL cholesterol 3.49 vs 3.26 mmol/l ($p < 0.05$), fibrinogen concentrations 3.34 vs 3.05 g/l ($p < 0.01$) and HbA_{1c} 6.68 vs 6.03% ($p < 0.001$).

Patients with a short duration of diabetes and microangiopathy (Group A) compared with those without (Group B) after age and duration adjustment (Table 3), had a higher prevalence of cardiovascular disease, 15 vs 7% ($p < 0.05$), of current smoking, 43 vs 29% ($p < 0.05$) and a more frequent family history of hypertension, 49 vs 33% ($p < 0.05$). Patients with a long duration of diabetes and microangiopathy (Group C), compared with those without (Group D), after age and duration adjustment, had higher prevalence of hypertension, 38 vs 17% ($p < 0.001$) and cardiovascular disease, 12 vs 6% ($p < 0.05$).

Patients with an early development of microangiopathy (Group A) compared with those protected from microangiopathy (Group D), after a long duration of diabetes (Tables 4 and 5), had a lower insulin dose 0.58 vs 0.72 U/kg body weight and a higher systolic blood pressure 121 vs 117 mm Hg ($p < 0.05$), cholesterol 5.5 vs 5.1 mmol/l ($p < 0.001$), triglyceride 1.10 vs 0.83 mmol/l ($p < 0.001$), LDL cholesterol 3.57 vs 3.15 mmol/l ($p < 0.05$), vWF 1.24 vs 1.04 U/ml ($p < 0.05$) and HbA_{1c} 6.84 vs 6.07% ($p < 0.01$). Patients with early microangiopathy had a lower prevalence of severe hypoglycaemia 19 vs 38% ($p < 0.01$), but a higher prevalence of cardiovascular disease, 15 vs 6% ($p < 0.05$) and current smoking, 43 vs 28% ($p < 0.05$). The above mentioned differences showed

Table 3. Comparison of categorical variables between groups with and without microangiopathy in Type I diabetic patients with short and long duration of diabetes, *n* (%)

	Short DD Microangiopathy Group A *n* = 75	Short DD No Microangiopathy Group B *n* = 225	Long DD Microangiopathy Group C *n* = 872	Long DD No Microangiopathy Group D *n* = 190
Severe hypoglycaemia	14 (19)	36 (16)	307 (35)	72 (38)
Severe ketoacidosis	7 (9)	16 (7)	45 (5)	10 (5)
Frequency of injection, per day				
1	8 (4)	3 (4)	25 (3)	8 (4)
2	36 (48)	103 (46)	361 (41)	79 (42)
3	36 (48)	110 (49)	423 (49)	83 (44)
Hypertension	10 (13)	21 (9)	334 (38)[b]	32 (17)
Cardiovascular disease	11 (15)[a]	16 (7)	104 (12)[a]	12 (6)
Current smoking	32 (43)[a]	64 (29)	266 (31)	54 (28)
Ex-smoking	10 (23)	35 (22)	207 (34)	39 (29)
Father with diabetes (DM)	8 (11)	19 (9)	98 (11)	22 (12)
Mother with DM	8 (11)	15 (7)	105 (12)	20 (11)
Father and/or mother with DM	16 (22)	34 (16)	187 (22)	39 (21)
Family history of hypertension	31 (49)[a]	64 (33)	347 (45)	80 (48)

[a] $p < 0.05$, [b] $p < 0.001$

Table 4. Comparison of the age adjusted means of continuous variables between those with short duration of diabetes and microangiopathy (Group A) and those with long duration and no microangiopathy (Group D)

	Total		Men		Women	
	Short DD Microangiopathy Group A *n* = 75	Long DD No Microangiopathy Group D *n* = 190	Short DD Microangiopathy Group A *n* = 45	Long DD No Microangiopathy Group D *n* = 81	Short DD Microangiopathy Group A *n* = 30	Long DD No Microangiopathy Group D *n* = 109
Duration	5.0[c]	18.8	4.6[c]	18.7	5.4[c]	18.9
BMI, kg/m2	23.5	23.2	23.2	23.4	23.8	23.1
Waist/Hip Ratio (WHR)	0.85	0.82	0.88	0.87	0.81	0.79
Systolic BP, mm Hg	121[a]	117	122	122	119	114
Diastolic BP, mm Hg	76	73	77	75	73	71
Insulin, U/day	39.8	46.8	41.7	55.2	37.6	40.3
Insulin/kg body weight	0.58[b]	0.72	0.58[a]	0.77	0.59[a]	0.68
HbA_{1c} %	6.84[b]	6.07	6.99[b]	5.97	6.61	6.15
Total cholesterol, mmol/l	5.5[c]	5.1	5.5[b]	4.9	5.6[a]	5.2
Fasting triglyceride, mmol/l[d]	1.10[c]	0.83	1.26[b]	0.84	0.92	0.82
HDL cholesterol, mmol/l	1.52	1.52	1.41	1.38	1.67	1.63
LDL cholesterol, mmol/l	3.57[a]	3.15	3.58	3.11	3.55	3.19
Fibrinogen, g/l[d]	3.02	3.05	2.88	2.94	3.35	3.13
Von Willebrand factor, U/ml[d]	1.24[a]	1.04	1.23	1.05	1.29	1.03

[a] $p < 0.05$, [b] $p < 0.01$, [c] $p < 0.001$, [d] geometric mean

the same trends when looked at separately in each sex, although, for some of them, statistical significance was not reached.

Discussion

This is the largest cross-sectional study examining Type I diabetic patients with a very early development of microangiopathy and those that were free of it after a duration of diabetes of 14 years or more. Previous reports on subsets of patients who remained virtually free of complications after a long duration of diabetes had studied small numbers of patients, had used relatively inaccurate methods of assessing diabetic complications and in most cases had lacked comparable control groups [15, 16, 34–36]. Moreover, no study had focused on the subset of patients with very early development of complications as a comparative group.

Our study included a much greater number of patients and used standardized and validated methodology for the assessment of complications, such as colour retinal photographs for the detection of retinopathy and testing for microalbuminuria to detect early renal involvement. Due to the accurate and sensitive methodology used, some patients in this study that were positive for complications would have been

Table 5. Comparison of categorical variables between those with short duration of diabetes and microangiopathy (Group A) and those with long duration and no microangiopathy (Group D), *n* (%)

	Total		Men		Women	
	Short DD Microangiopathy Group A *n* = 75	Long DD No Microangiopathy Group D *n* = 190	Short DD Microangiopathy Group A *n* = 45	Long DD No Microangiopathy Group D *n* = 81	Short DD Microangiopathy Group A *n* = 30	Long DD No Microangiopathy Group D *n* = 109
Severe hypoglycaemia	14 (19)[b]	72 (38)	7 (16)[b]	33 (41)	7 (23)	39 (36)
Severe ketoacidosis	7 (9)	10 (5)	4 (9)	2 (3)	3 (10)	8 (7)
Frequency of injection, per day						
1	3 (4)	8 (4)	3 (7)	2 (3)	0 (0)	6 (6)
2	36 (48)	79 (42)	22 (49)	39 (48)	14 (47)	40 (37)
3	36 (48)	83 (44)	20 (44)	36 (44)	16 (53)	47 (43)
Hypertension	10 (13)	32 (17)	8 (18)	13 (16)	2 (7)	19 (17)
Cardiovascular disease	11 (15)[a]	12 (6)	6 (13)	5 (6)	5 (17)	7 (6)
Current smoking	32 (43)[a]	54 (28)	19 (42)	22 (27)	13 (43)	32 (29)
Ex-smoking	10 (23)	39 (29)	5 (19)	21 (36)	5 (29)	18 (23)
Father with diabetes (DM)	8 (11)	20 (12)	6 (13)	8 (10)	2 (7)	14 (13)
Mother with DM	8 (11)	20 (11)	6 (13)	7 (9)	2 (7)	13 (12)
Father and/or mother with DM	16 (22)	39 (21)	12 (27)	14 (17)	4 (14)	25 (24)
Family history of hyertension	31 (49)	80 (48)	21 (54)	28 (39)	10 (42)	52 (55)

[a] $p < 0.05$, [b] $p < 0.01$

classified as free of complication in previous studies. We have documented the presence of microalbuminuria or retinopathy or both very early in 25% of the patients, whereas it was previously generally believed that microangiopathy does not appear until at least 5 years after diagnosis of Type I diabetes [37]. On the other hand, 18% of Type I diabetic patients with a mean duration of diabetes of almost 19 years still remain free of any complication. The relation of poor glycaemic control to the development of microvascular complications in Type I diabetic patients has been clearly shown in prospective studies and randomized controlled trials of intensive insulin therapies [3–5]. In our cross-sectional study, in the short duration groups, HbA_{1c} was not different between those with and those without microangiopathy (Groups A and B). This is possibly due to limitations in the use of a single HbA_{1c} measurement to characterize long-term glycaemic control.

The higher prevalence of hypertension in the parents of patients in Group A may represent a genetic predisposition to develop microalbuminuria very early. In two studies, parents of proteinuric Type I diabetic patients were found to have significantly higher blood pressure than matched control subjects [22, 38], a finding not confirmed by another study [39]. The genetically determined high rate of red cell sodium-lithium counter transport is associated with the risk of essential hypertension in non-diabetic patients [40] and has been found in Type I diabetic patients with proteinuria and their parents [27, 41]. Thus a familial predisposition to raised blood pressure has been suggested as a possible contributing factor to the susceptibility for diabetic nephropathy [23, 24]. Furthermore, the higher prevalence of CVD in those with early microangiopathy (Group A) suggests a parallel evolution of micro- and macroangiopathy in these patients, which is supportive of the suggestion that increased urinary albumin excretion reflects a more generalized endothelial dysfunction [31,42–44].

We also show an association of current cigarette smoking with microangiopathy in the subset of patients with early complications (Group A) compared with those without (Group B). The association of smoking with the development of microangiopathy is not clear. Analysis of the entire EURODIAB cohort with respect to smoking has shown a clear association of current smoking with AER, the prevalence of microalbuminuria and retinopathy [45]. Previous studies have produced conflicting results, some of them showing a strong relation between smoking and microvascular complications [46–49] and others no relation at all [50–54]. The above discrepancies may be due to some studies failing to distinguish between current and ex-smokers, considering them as one group, or failing to take into account the possible effect of smoking on glycaemic control [48, 55, 56]. Moreover, recent studies show that advanced glycation endproducts accumulate both in the serum and LDL of smokers and possibly contribute to the development of complications [57, 58].

Thus, even during the first 5 years after the diagnosis, signs of microangiopathy appear in one of four Type I diabetic patients and seem to be related to a family history of hypertension, which cannot be treated, but also to cigarette smoking, which can and should be treated effectively at this early stage.

In the groups with long duration of diabetes glycaemic control becomes an important risk factor for microangiopathy, but risk factors for macrovascular

disease such as serum lipids and fibrinogen are also associated with microvascular complications. The effect of fibrinogen may be indirect through platelet activation and increased aggregability, increased blood viscosity and blood hypercoagulability [59]. Involvement of those abnormalities in the pathogenesis of diabetic nephropathy has been postulated and thus may explain the observed relation of increased fibrinogen with microangiopathy [60, 61].

The comparison of the two groups representing the "extremes" of the spectrum of the development of microangiopathy (Groups A and D) shows that patients free from microangiopathy and long duration of diabetes have lower blood pressure, better glycaemic control, better lipid profile, and lower vWF levels. They also have less CVD and a lower prevalence of smoking. The better glycaemic control is associated with the use of more insulin per kilogram of body weight and twice as frequent severe hypoglycaemic episodes, a finding similar to that in the intensive treatment group of the DCCT [5]. The lower level of vWF indicates better endothelial function in this group, with possible beneficial effects both on macro- and microangiopathy [32]. Studies in Type II diabetic patients have shown that increased levels of vWF are associated with microalbuminuria and the development of renal lesions [62]. Smoking emerges as risk factor of microangiopathy only in the short duration group but its possible effect on the development of microangiopathy in patients with long duration of diabetes may be masked by a stronger influence of other risk factors. The effect of smoking is not mediated through a vWF increase, since no relation was found between the two in the EURODIAB cohort [32].

In conclusion, when microangiopathy develops early in the course of Type I diabetes, it is possibly related to different risk factors than when it develops later. With a short duration of diabetes the main factors associated with the early development of microangiopathy are smoking and a family history of hypertension. On the other hand, with a long duration of diabetes glycaemic control is a risk factor, while factors usually related to macroangiopathy become important also for microangiopathy. These cross-sectional findings from the EURODIAB IDDM Complications Study need to be confirmed by prospective follow-up, which is currently under way. Nevertheless, this study confirms that smoking, lipid abnormalities and raised blood pressure are important and treatable risk factors for microangiopathy and should be actively managed.

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