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A nationwide cross-sectional study of retinopathy and microalbuminuria in young Norwegian Type 1 (insulin-dependent) diabetic patients

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Summary. A nationwide cohort of Type 1 (insulin-dependent) diabetic patients was studied to determine the prevalence of retinopathy and microalbuminuria and to evaluate the association to various risk factors. Of 600 subjects with mean age of 19.8 years (range 8.0–30.3) and a mean duration of diabetes of 10.5 years (range 6.2–17.3), 371 (60 %) volunteered for a clinical examination which included fundus photography, timed overnight urine samples for albumin excretion rate, measurement of arterial blood pressure and determination of HbA_{1c}. Retinopathy was found in 122 of 371 patients (32.8 %), in 3 of 41 (7.3 %) patients aged less than 13 years. The youngest subject with retinopathy was 9.6 years old. Microalbuminuria was found in 44 of 351 patients (12.5 %), in 1 of 41 (2.4 %) patients aged less than 13 years. The youngest subject with microalbuminuria was 11.5 years old. Mean HbA_{1c} was 8.6 % (normal range 4.5–6.1 %). Patients with retinopathy had significantly higher mean age ($p = 0.0001$), longer mean duration of diabetes ($p = 0.0001$), higher mean HbA_{1c} ($p = 0.009$), and higher mean arterial blood pressure ($p = 0.0001$) compared to patients without retinopathy. In microalbuminuric patients HbA_{1c} ($p = 0.0001$) and mean arterial blood pressure ($p = 0.01$) were significantly higher compared to non-microalbuminuric patients, but there was no difference in age or diabetes duration. In a multiple logistic regression model, age, HbA_{1c}, duration of diabetes and mean arterial blood pressure were found to be significantly associated with retinopathy, while HbA_{1c}, mean arterial blood pressure and onset before 13.0 years of age were found to be associated with microalbuminuria. The prevalence of retinopathy and microalbuminuria was relatively low. Both retinopathy and microalbuminuria were strongly associated with blood glucose control and developed at prepubertal age in some patients. The findings indicate that more intense optimization of blood glucose control in children and adolescents with Type 1 diabetes is warranted.

Key words: Type 1 (insulin-dependent) diabetes mellitus, retinopathy, microalbuminuria, risk factors, adolescents, blood pressure, puberty.

Few population-based studies of microvascular complications, including retinopathy, nephropathy and neuropathy, of Type 1 (insulin-dependent) diabetes mellitus have been published, despite an increasing interest in their epidemiology and pathogenesis. Diabetic retinopathy is still a leading cause of vision impairment in young and middle-aged people [1]. Guidelines for screening have recently been developed for use in European countries [2] to detect patients at risk while they can still be effectively treated. Microalbuminuria has been established as a significant predictor of diabetic nephropathy [3, 4], and cardiovascular mortality is closely associated with the presence of proteinuria [5]. The association between blood glucose control and the incidence and progression of diabetic retinopathy is well established [6–9], but the role of hyperglycaemia as a risk factor for microalbuminuria is more controversial [10–13].

Studies on screening for diabetic retinopathy have been published from Iceland [14], USA [15] and Denmark [16]. The overall prevalence of retinopathy in these studies, based on different grading procedures, varied from 34 to 71 %, and there was a consistent association with duration of diabetes, age and HbA_{1c}.

Studies from Sweden [17], Denmark [18], Norway [19] and USA [20] reported a prevalence of persistent microalbuminuria of 15–59 % in selected groups of children and adolescents with Type 1 diabetes, and additionally 9 % of the patients in the USA study had proteinuria. However, in a nationwide screening for microalbuminuria among children and adolescents in Denmark [21], microalbuminuria was found in only 4.3 % of the patients.

A higher prevalence of retinopathy in patients with age at diagnosis of 13 years or above has been reported [22], and other authors have suggested that the contribution of

Table 1. Demographic characteristics of the total cohort of Type 1 (insulin-dependent) diabetic patients diagnosed 1973–1982 with age at onset 0–14 years ($n = 1914$)

	n	%
Sex		
Male	1040	54.3
Female	874	45.7
Year of birth		
1958–1962	17	9.4
1963–1967	617	32.2
1968–1972	733	38.3
1973–1977	321	16.8
1978–1981	64	3.3
Age at onset		
0–4 years	343	17.9
5–9 years	696	36.4
10–14 years	875	45.7

diabetes developing during the prepubertal years to the risk of diabetic complications is minimal [23].

The purpose of the present study was to determine the prevalence of retinopathy and microalbuminuria nationwide in a young cohort of Type 1 diabetic patients in Norway and to evaluate the association of various risk factors to the development of microvascular complications. The study meets the need for a population-based study on the combined prevalence of the major complications to Type 1 diabetes and their risk factors.

Subjects and methods

All new cases of Type 1 diabetes in the age group 0–14 years were reported through a nationwide incidence survey in Norway during 1973–1982. This cohort of 1,914 diabetic subjects comprised the main body of the Norwegian Diabetes Register and ascertainment was nearly 100% complete [24]. Table 1 shows the demographic characteristics of the cohort.

Data from the Norwegian Diabetes Register on the subjects in the 1973–1982 cohort were linked with the National Person Register of Norway to classify each subject as alive, dead or emigrated. Addresses for those patients alive and still residing in Norway were obtained.

Twenty-two subjects had died, 10 subjects had emigrated and 14 subjects could not be unequivocally identified within the National Person Register. The remaining 1,868 subjects were eligible to participate in the study.

Randomly, 600 subjects were selected on a nationwide basis for a cross-sectional study on diabetic complications, i.e. retinopathy and microalbuminuria. A computer-generated code was used for the random assignment of the subjects. The 600 selected diabetic patients were invited by letter to take part in a clinical examination in a hospital in their home county. The team of examiners visited selected hospitals in all 19 counties in Norway, bringing equipment to perform the examination according to the standardized procedures. Two or three weeks before the visit, the patients in the region received supplies and detailed information on how to perform two overnight urine collections at home and information on the exact time and place for the examination.

The subjects underwent the following procedures:

1. Arterial blood pressure was measured twice in the sitting position after 15 min rest with a standard mercury sphygmomanometer, cuff size 9 cm in patients below 12 years of age and 12 cm in patients of 12 years or above. Diastolic pressure was recorded at the disappearance of the Korotkoff sounds (phase 5). Mean arterial blood pressure (MAP) was calculated with the formula: [systolic blood pressure + ((systolic pressure-diastolic pressure)/3)].

2. Fundus photography was performed in mydriasis (tropicamid) by a nonmydriatic 45° Canon camera (45NM-CR), using a 35 mm film. Two photographs were taken of each fundus, and the one with the best quality was selected for retinopathy reading. A "standard" fundus photograph was produced by centering the photograph at half way between the fovea and the temporal edge of the optic disc.

3. Blood was collected using venepuncture and was analysed for HbA_{1c}, total cholesterol and triglycerides.

4. The patients brought to the examination two overnight timed urine specimens collected at home.

5. Data concerning glycated Hb taken prior to the study (1985–1989) were collected for patients where we had access to their hospital record or to records via a computerized hospital laboratory system.

Of 600 patients 371 volunteered for the examination. Only two patients were excluded because of unreadable photographs. All fundus photographs were read, without knowledge of the subjects identity, by an ophthalmologist (O.B.-H). In brief: in assessing retinopathy, a magnifying grid was applied directly onto the negative film and microaneurysms and haemorrhages were counted as "red spots". The mean from both eyes were used in each subject and the definition of retinopathy was a score of one or more definite red spots. Hard exudates and cotton-wool spots were assessed as present or not present. The method is described in a previous paper, and the intra-observer variation was studied (concordance rate 93%) [25].

All blood samples and urine specimens were analysed in the Department of Clinical Chemistry, Aker University Hospital. HbA_{1c} was analysed by an HPLC-method in a "Diamat"-machine (Biorad, Richmond, Calif., USA; normal range HbA_{1c} 4.3–6.1%, interassay coefficient of variation 3%).

Complete urine collection (two samples) were obtained from 351 patients. The albumin concentration was measured by immunoturbidimetry, and albumin excretion rate (AER) was calculated on the basis of concentration, collection time and volume. Upper level of normal for AER was 15 μg/min, which is an accepted cut-off level for defining microalbuminuria [26], and also used as the upper limit of normal in our laboratory. Patients with an AER above 15 μg/min in one or two urine specimens repeated the urine collections. The criteria for microalbuminuria was set to AER greater than 15 μg/min in at least two out of three consecutive urine collections.

Any method used between 1985 and 1989 for measurement of glycated Hb was considered acceptable, and we obtained recorded measurements for a total of 291 of the invited 600 subjects, of which 200 were subjects who did attend (participants) and 91 subjects who did not attend the examination (non-participants). These analyses had been performed at different laboratories with different methods and different ranges for normal values. We performed recalculation of the glycated Hb to a "p_{mean}" with the following formula: [glycated Hb (%) × 100/local laboratory upper normal value = p_{mean}]. The p_{mean} values were only used to evaluate the representativeness of the participants. The glycated Hb values used in the univariate analyses and multiple regression models, are the cross-sectional results.

No assessment of pubertal stage was done during the clinical examination. The age at onset for each subject was recorded in the register and in the analyses on effect of age at onset, 13.0 years was used in both sexes as the cut-off point.

Statistical analysis

Two-sided chi-square, Wilcoxon two sample and Kruskal-Wallis tests [27, 28] were used to measure the association between the different variables. The level of significance used was 0.05. SAS soft-

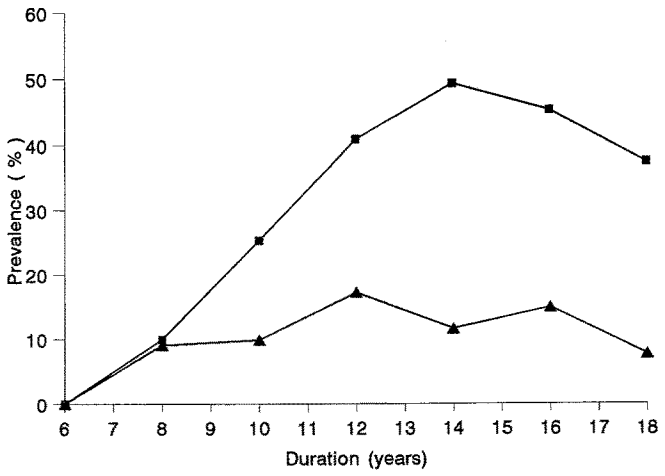

Fig. 1. Prevalence (%) of retinopathy ■—■ and microalbuminuria ▲—▲ by duration of Type 1 (insulin-dependent) diabetes mellitus

ware was used in these analyses [29, 30]. BMDP stepwise logistic regression program [31] was used with the maximum likelihood method for entering and removing terms at each step. p values for entering and removing terms were 0.10 and 0.15, respectively.

Results

When compared to the total recruitment cohort, the participants were slightly younger (18.3 ± 4.9 vs 19.8 ± 4.5 years; $p = 0.0001$) and had a slightly shorter diabetes duration (10.1 ± 2.9 vs 10.5 ± 2.8 years; $p = 0.01$), but the participants were representative regarding sex (male:female ratio 1.17 vs 1.25; NS) and the proportion of individuals with onset before 13 years of age (319 of 371 vs 1,580 of 1,914, NS).

To evaluate whether the 371 examined patients were representative of the population under study, the recorded values for glycated Hb measured between 1985–1989 from 200 of the 371 participants were compared with values from 91 of the 229 non-participants. The patients who volunteered for the study had slightly better blood glucose control (calculated p_{mean} units = 134.9 ± 22.8 units) compared to the group who did not participate (p_{mean} = 144.5 ± 27.5 units; $p = 0.004$).

Retinopathy (microaneurysms and haemorrhages) was found in 122 (32.8%) of 371 patients. The distribution of the microaneurysm count were as follows: less than 10, 73 of 122 patients (59.8%); 10–29, 34 of 122 patients (27.9%); 30 or more, 15 of 122 patients (12.3%). Hard exudates were found in 30 (8.1%) patients, and two patients also had cotton-wool spots. Proliferative retinopathy was not observed. Retinal photocoagulation (laser) had been performed in three patients; quantification of their retinopathy was not possible.

Figure 1 demonstrates the increasing prevalence of retinopathy by duration of diabetes from 10% after 8 years duration to 49% after 14 years. The youngest subject with retinopathy was 9.6 years old and retinopathy was found in three out of 45 subjects (6.7%) below 13 years of age.

The characteristics of the patients with retinopathy compared to those without retinopathy is found in Table 2. The patients with retinopathy had significantly higher mean age, longer mean duration of diabetes, higher HbA_{1c} at the time of examination and higher MAP compared to patients without retinopathy. A significantly higher proportion of subjects with onset before 13.0 years of age among patients with retinopathy was not seen compared to those without retinopathy.

In Table 3 the results of the multiple logistic regression analysis show the four risk factors that were significantly associated with retinopathy: age, HbA_{1c}, duration of disease and MAP. Onset before 13.0 years of age and sex showed no significant association with retinopathy in the model.

AER was greater than 15 μg/min in 44 of 351 patients (12.5%) (persistent microalbuminuria). The distribution of AER values was as follows: 15.1–49.9 μg/min: 31 of 44 patients (70.5%); 50.0–99.9 μg/min 7 of 44 patients (15.9%); above 100 μg/min 6 of 44 patients (13.6%). The prevalence of microalbuminuria increased with duration of diabetes from 9% of the patients after 8 years duration up to 18% after 12 years (Fig. 1). The youngest patient with microalbuminuria was 11.5 years old and only one of 43 patients (2.3%) below 13 years of age had microalbuminuria. One patient (0.3%) with a diabetes duration of 7 years had proteinuria (AER greater than 200 μg/min).

The characteristics of the microalbuminuric patients compared to those without microalbuminuria are demonstrated in Table 4. Microalbuminuric patients had a significantly higher HbA_{1c} and mean arterial blood pressure, and there was a significantly higher proportion of subjects with onset before 13.0 years of age among patients with microalbuminuria compared to those without microalbuminuria. No significant difference was found regarding mean duration of diabetes or age.

For microalbuminuria, HbA_{1c}, MAP and onset before 13.0 years of age were significantly associated in the logistic regression model, and no significant association was found for age, duration of diabetes or sex (Table 5).

Retinopathy was found in a significantly higher proportion of patients with microalbuminuria compared to patients without microalbuminuria (27 of 44 [61.4%] vs 87 of 303 [28.4%]; $p < 0.0001$).

Table 2. Characteristics of the Type 1 (insulin-dependent) diabetic patients with retinopathy compared to patients without retinopathy

	Retinopathy	No retinopathy	p value
n	122 (32.9%)	249 (67.1%)	
Mean age (years)	21.4 ± 4.4	18.1 ± 5.1	0.0001
Mean duration of diabetes (years)	12.2 ± 2.5	10.4 ± 3.0	0.0001
HbA_{1c} (%)[a]	9.3 ± 2.1	8.6 ± 1.8	0.009
MAP (mm Hg)	99.6 ± 12.7	91.1 ± 14.1	0.0001
Onset before 13.0 years of age	102/122 (83.6%)	217/249 (87.2%)	NS

[a] Normal range 4.5–6.1%
MAP, Mean arterial blood pressure

Table 3. Logistic regression for factors associated with retinopathy

	Coefficient	Standard error	*p* value
Age[a]	0.1284	0.0339	0.0001
HbA_{1c}	0.3335	0.0726	0.0000
Disease duration	0.1651	0.0526	0.0015
MAP	0.0347	0.0102	0.0005
Constant	–11.4150	1.5130	

[a] Variables are listed in the order that they entered the regression model. Onset before puberty and sex were not selected by the stepwise procedure for entry into the model.
MAP, Mean arterial blood pressure

Table 4. Characteristics of Type 1 (insulin-dependent) diabetic patients with microalbuminuria compared to patients without microalbuminuria

	Microalbuminuria	No microalbuminuria	*p* value
n	44 (12.5%)	307 (77.5%)	
Mean age (years)	20.5 ± 3.7	19.0 ± 5.2	NS
Mean duration of diabetes (years)	11.3 ± 2.7	10.9 ± 3.0	NS
HbA_{1c}[a] (%)	9.8 ± 1.9	8.7 ± 1.9	0.0001
MAP (mm Hg)	99.5 ± 14.0	93.0 ± 14.2	0.01
Onset before 13.0 years	43/44 (97.7)	256/303 (84.5%)	0.02

[a] Normal range 4.5–6.1%
MAP, Mean arterial blood pressure

Table 5. Logistic regression for factors associated with microalbuminuria

	Coefficient	Standard error	*p* value
HbA_{1c}[a]	0.2756	0.0847	0.0011
MAP	0.0297	0.0124	0.0163
Onset before 13.0 years	1.7140	1.0350	0.0326
Constant	–8.9241	1.7860	

[a] Variables are listed in the order that they entered the regression model. Age, disease duration, diastolic blood pressure and sex were not selected by the stepwise procedure for entry into the model.
MAP, Mean arterial blood pressure

Mean ± SD systolic blood pressure in the total group of participants was 122.2 ± 17.5 mm Hg (range 85–180) with corresponding diastolic pressure 79.8 ± 13.9 mm Hg (range 40–120). Calculated MAP was 93.4 ± 14.8 mm Hg. By using proposed standards for upper normal systolic and diastolic blood pressure defining "significant hypertension" in three different age groups (10–12 years greater than 125/82, 13–15 years greater than 135/85 and 16–18 years greater than 141/81) [32], we found a prevalence of elevated blood pressure in these groups of 13.6% (6 of 45), 23.9% (11 of 46) and 21.3% (17 of 79), respectively. In subjects over 18 years of age, the World Health Organization definition of hypertension was used (systolic blood pressure above 160 or diastolic pressure above 95 mm Hg or both) [33], for which 27 [14.8%] of the 183 subjects over 18 years fulfilled the criteria. Patients in the microalbuminuric group did not have significantly higher prevalence of hypertension compared to the non-albuminuric group (12 of 44 vs 50 of 307; $p = 0.1$).

The mean HbA_{1c} ± SD among the 351 examined patients with HbA_{1c}-measurements was 8.6 ± 1.9% (normal range 4.5–6.1%) with a median of 8.6% and range from 5.0 to 14.9%. There was a statistically significant difference in HbA_{1c} between the three different age groups; children (less than 13 years) 9.1 ± 1.6%, adolescents (13–18 years) 9.2 ± 2.1%, adults (≥ 19 years) 8.6 ± 1.8%; ($p = 0.006$, $df = 2$, Kruskal-Wallis test).

Discussion

A selection of a representative sample of patients is crucially important in prevalence studies on diabetic complications. In the present study the randomly selected sample of 600 patients was representative of the total 10-year cohort of diabetic patients regarding place of residence, gender, age and diabetes duration. This was not necessarily the case for blood glucose control, as it could be expected that diabetic patients with poor blood glucose control were under-represented among the 371 participants. Data concerning HbA_{1c} or HbA_1 during the 5-year priod prior to the study were available for 200 of 371 participants and 91 out of 229 non-participants, and we found that participants were apparently in slightly better blood glucose control. Furthermore, the participants were slightly younger and had slightly shorter disease duration than the total group. Thus, our results may be biased towards more favourable results than the true prevalence of microvascular complications in the diabetic population under study.

The present nationwide study has revealed a prevalence of diabetic retinopathy of 32.8% in a cohort of Type 1 diabetic patients aged 8–30 years. This overall prevalence corresponds well to other studies within the same range of age and diabetes duration [18, 34, 35]. The diagnosis of retinopathy is based on two non-stereo photographs of the posterior pole. Recent studies show that this method is efficient in detecting retinopathy in diabetic patients [36, 37], and the risk for missing patients with only peripheral retinal changes is probably small. However, in our study retinopathy was seen in younger patients than previously published [18, 38]. Admittedly, the three of the 41 patients below 13 years with retinopathy only had a few microaneurysms. The data suggest that the risk of retinopathy below 13 years of age is low, but these findings do indicate the first signs of microvascular complications in these patients which should be considered for determination of therapy.

Surprisingly, in this sample of Type 1 diabetic patients with a diabetes duration up to 17 years, no patients with proliferative retinopathy were found. Three patients previously treated with photocoagulation might, however, have had proliferative retinopathy.

Patients with retinopathy had higher HbA_{1c}, age, diabetes duration and MAP, and the same factors came

out as significantly associated with retinopathy in the regression model, and blood glucose control (HbA_{1c}) was most strongly related to retinopathy. Based on the assumption that one single HbA_{1c} measurement is representative of the patients' long-term blood glucose levels, these results suggest a strong relationship between hyperglycaemia and prevalence of non-proliferative retinopathy.

The overall prevalence of microalbuminuria in the present study was lower than that reported for selected patient groups [17, 18, 39] but higher than reported in the Danish nationwide study [21]. The Danish survey used comparable methods to ours regarding the cut-off level for defining elevated AER (20 μg/min), but the average age and duration of disease was shorter compared to our sample (15.0 vs 19.8 years and 6.5 years vs 10.5 years, respectively). The role of age and diabetes duration as risk factors for microalbuminuria has been debated and remains controversial, and in this study an association could not be found.

Regarding other risk factors for microalbuminuria, we found a strong association with blood glucose control (HbA_{1c}) in the univariate analysis and in our logistic model. The blood glucose control in our group was slightly better (HbA_{1c} mean 8.9%, median 8.6%) compared to the Danish patients (median HbA_{1c} 9.6%), which might give a lower number of microalbuminuric patients. In the Pittsburgh study [20], the frequency of microalbuminuria was similar to our study, but a considerable number of patients had overt nephropathy. This difference remains unexplained and is apparently not the result of poorer blood glucose control in the Pittsburgh patients, since they had a mean $HbA_1 \pm SD$ of 10.4 ± 1.8 (normal range 5.2–7.8) (T. Orchard, personal communication).

The results regarding risk factors found to be associated with microalbuminuria support the hypothesis that microalbuminuria and eventually progression to overt nephropathy is a late diabetic complication dependent on blood glucose control, but also related to other, non diabetes-related factors, i. e. genetic factors.

Studies on microvascular complications in relation to puberty, have reported a higher prevalence in pubertal than in prepubertal individuals [17, 22], and the risk of both retinopathy and nephropathy have been reported as higher in subjects with onset in pubertal years [34, 40]. Based on the assumption that 13.0 years of age is "before puberty" in both sexes in this sample, our study does not support the hypothesis that risk of non-proliferative retinopathy is related to onset before or after puberty. The "cut-off-age" of 13.0 years probably led to an overestimation of the number of children with onset before puberty in our data [41] and possibly a bias toward no effect. The data regarding microalbuminuria shows a higher prevalence of microalbuminuria among patients with onset before 13.0 years of age, and 43 of 44 cases with microalbuminuria had onset of diabetes before 13 years. Our logistic model also suggests an influence of onset before 13.0 years of age adjusted for blood glucose control and it could be speculated that the presence of a diabetic metabolism as the hormonal levels change in puberty might have an effect on the development of renal changes.

The blood pressure results should be interpreted with great caution because of the lack of a comparable control group, and also because the blood pressure was only measured on one occasion. However, the estimated prevalence of hypertension of 16% is within the same range as other studies [42, 43]. Surprisingly, 50 of 62 patients with apparent hypertension in our study did not have microalbuminuria. This is compatible with the hypothesis that hyperinsulinaemia may induce sodium retention and raise blood pressure [44].

Our data show that retinopathy and microalbuminuria develop during prepubertal age in some patients, and this fact indicates that intense optimization of blood glucose control in children and adolescents with Type 1 diabetes is warranted.

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