Risk Factors for Development of Diabetic Nephropathy and Retinopathy in Jewish IDDM Patients

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Risk factors associated with diabetic microvascular complications, with special reference to ethnic origin, were looked for in 231 young Jewish insulin-dependent diabetes mellitus (IDDM) patients with duration of diabetes ≥10 yr. Median age at diagnosis of diabetes was 9.2 yr (range 0.04–26.2 yr), and median duration of the disease was 15.3 yr (range 10.0–37.2 yr). Sixty-three percent of the patients were Ashkenazi Jews, and 37% were non-Ashkenazi Jews. HbA_1 was evaluated every 3 mo in the last 10 yr of follow-up, and albumin excretion rate was tested in three 24-h urine collections. Direct and indirect ophthalmoscopy was performed every year since diagnosis of diabetes, and if retinal pathology was suspected, color photographs were taken. Microalbuminuria was detected in 31% and macroalbuminuria in 7% of the patients. Nonproliferative and proliferative retinopathy was found in 44 and 12% of the patients, respectively. On logistic regression analysis, two variables were significantly and independently associated with diabetic nephropathy—non-Ashkenazi origin and mean HbA_1 values over the first 5 of 10 yr of follow-up. Variables significantly and independently related to diabetic retinopathy were non-Ashkenazi origin, mean HbA_1 values over the last 10 yr of follow-up, and duration of diabetes. Because non-Ashkenazi Jews in Israel are of lower socioeconomic status than Ashkenazi Jews, we stratified our patients according to their socioeconomic parameters, median HbA_1 values, and duration of diabetes. Non-Ashkenazi patients were at a higher risk to develop complications in all strata. We further stratified patients into four quartiles according to mean HbA_1 values; there was a steep increase in the risk to develop macroalbuminuria in the 4th quartile of HbA_1 (odds ratio [OR] 4.3 vs. 1.2 in the 3rd quartile) and proliferative retinopathy (OR 13.0 in the 4th quartile of HbA_1 vs. 2.8 in the 3rd quartile). We conclude that non-Ashkenazi Jewish IDDM patients are at significant risk to develop microvascular complications, independent of their glycemic control, duration of diabetes, and socioeconomic status. Careful follow-up and special efforts toward improving glycemic control should be focused on high-risk subgroups of patients. *Diabetes* 40:204–10, 1991

Microvascular complications are an integral part of the natural history of insulin-dependent diabetes mellitus (IDDM), but their pathogenesis has not been fully elucidated (1). Diabetic nephropathy eventually affects ~40% of all IDDM patients (2), microalbuminuria heralding the subsequent development of frank proteinuria (3–5). Both microalbuminuria (5) and macroalbuminuria (2,6) are rare in the first 5 yr after onset of diabetes. The incidence of nephropathy increases thereafter, and the peak in the second decade of the disease is followed by a decline (2,6). The prevalence of diabetic retinopathy increases unremittingly over the years, and after 20 yr of diabetes, all patients are affected to some extent (7,8).

Considerable evidence implicates poor glycemic control in the pathogenesis of both retinopathy (9–14) and nephropathy (6,13,14), but there is no full explanation for the variations in susceptibility to microvascular complications. The question of whether ethnic origin influences the prevalence of microvascular diabetic complications has been debated (15). In a study in England (16), diabetic nephropathy was found to be more common among Asian than among white diabetic patients, and in the United States, diabetic end-stage renal disease and diabetic retinopathy have been reported to be more common in patients of Mexican origin than in non-Hispanic whites (17,18). The incidence of end-stage

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renal disease is also higher in black diabetic than white diabetic patients in the U.S. (19).

Because the incidence of juvenile IDDM is higher among juveniles of Ashkenazi origin than among non-Ashkenazi Jews in Israel (20), we undertook to assess the prevalence of microalbuminuria, macroalbuminuria, and retinopathy in a group of 231 Ashkenazi and non-Ashkenazi Jewish IDDM patients with early onset of diabetes, who had been followed in our center for at least 10 yr. We looked for significant and independent factors influencing the rate of diabetic microvascular complications, with special reference to ethnic origin.

RESEARCH DESIGN AND METHODS

The study included all Jewish patients attending our center who had early-onset IDDM before 30 yr of age with a duration of diabetes of ≥10 yr (n = 231). Each year, our center admits ~60% of the newly diagnosed juvenile diabetic patients in Israel and functions as a primary, secondary, and tertiary care clinic. Patients are not referred to other clinics when they reach adulthood, unless they specifically wish to make the transfer. The patients are seen routinely at 3-mo intervals. At that time, each patient is evaluated and counseled by a physician, a nutritionist, and a member of the psychosocial team (21). Blood for HbA_1 has been taken routinely at each follow-up visit since March 1978. Each patient had undergone a yearly ophthalmological examination since diagnosis. Urine testing for albumin excretion rate was performed during the years 1987–1989. Eight patients did not complete evaluation for albumin excretion rate.

Retinopathy status was assessed as follows. Direct and indirect ophthalmoscopy was performed in every patient by a retinal specialist after dilation of pupils. When retinal pathology was suspected, stereoscopic color photographs of seven standard fields were obtained. These were graded according to a variation (22) of the modified Airlie House classification (23), with grades >1 and ≤5 being classified as nonproliferative retinopathy and grades ≥6 as proliferative retinopathy (22). Each eye was graded lesion by lesion and field by field and then classified according to this assessment. Grading was done by a retinal specialist who had been blinded as to the glycemic control and other clinical parameters of the patient. The value used for analysis in this study was the maximal grade of retinopathy in the worse eye recorded for each patient during follow-up.

Assessment of albuminuria was performed as follows. The albumin excretion rate was measured in three 24-h urine collections with a radioimmunoassay technique (24). The mean value of the three determinations was used for the statistical analysis in this study. In our laboratory, the upper limit of normal is 21.5 mg/24 h (mean ± SD normal values 11.6 ± 4.7 mg/24 h). Microalbuminuria was therefore defined as values in the range of 22–300 mg/24 h and macroalbuminuria as albumin excretion >300 mg/24 h.

HbA_1 values were measured with ion-exchange chromatography (Isolab, Akron, OH). For each patient, we computed the mean value of HbA_1 over the last 10 yr of follow-up (10-yr HbA_1). This 10-yr period was further divided into two intervals, and the HbA_1 was computed over the first 5 yr (5-yr HbA_1).

Ethnic origin was determined according to criteria similar to those of Goodman (25). Patients whose families originated from Europe (excluding Bulgaria and Greece), USSR, and U.S. were classified as Ashkenazi Jews, and those originating from Iraq, Iran, Syria, Turkey, Egypt, Afghanistan, India, North Africa, Bulgaria, Greece, and Yemen were classified as non-Ashkenazi Jews. Ten patients were of mixed origin. The exclusion of those patients did not alter the results of the data analysis, and they were finally classified according to the origin of their paternal grandfather.

To assess socioeconomic status (SES), three parameters were used: *1*) housing density, expressed as persons per room (26); *2*) family income, divided into two categories: equal or above the median income per family in Israel and below the median (27); *3*) father's education, whether equal, below, or above eight grades of schooling (28).

For univariate analysis, we used the χ^2-test to look for statistical significance of the contingency tables. Because

TABLE 1
Characteristics of patients without albuminuria versus patients with microalbuminuria or macroalbuminuria

	No albuminuria	Microalbuminuria	Macroalbuminuria	P
n	135	72	16	
Age at study (yr)*	26.2 (11.8–43.0)	24.2 (13.1–42.3)	27.3 (19.4–41.6)	>0.1
Male (n %)	42	50	44	>0.1
Non-Ashkenazi (n %)	29	43	69	0.005
Age at diagnosis (yr)*	9.4 (0.04–26.2)	8.9 (0.9–26.0)	9.9 (3.5–25.6)	>0.1
Duration of diabetes (yr)*	15.3 (10.0–37.2)	15.0 (10.0–30.2)	15.8 (10.0–35.9)	>0.1
10-yr HbA_1 (%)*	10.1 (7.0–14.1)	10.3 (7.2–14.7)	11.8 (9.7–16.2)	0.0003
5-yr HbA_1 (%)*	10.6 (6.1–18.3)	10.7 (7.4–17.3)	13.3 (9.4–17.1)	0.0003
Retinopathy (n %)				
Nonproliferative	46	46	20	0.0001
Proliferative	6	14	73	
Family income <national median (n %)	14	23	57	0.001
Father's education ≤8 grades (n %)	24	25	64	0.02
Housing density (persons/room)*	1.3 (0.7–3.7)	1.7 (0.7–3.7)	1.8 (0.7–6.4)	0.06

HbA_1, glycosylated hemoglobin.
*Values given as median with range in parentheses.

most continuous variables were not normally distributed, they were analyzed for statistical significance by the Kruskal-Wallis test. The values of the continuous variables are given as median and range. The risk to develop complications associated with the levels of each risk factor is expressed as odds ratio (OR) with 95% confidence intervals (95% CI). The ORs of non-Ashkenazi versus Ashkenazi patients to develop complications were corrected for confounding variables (socioeconomic parameters, HbA_1 values, and duration of diabetes) by the Cochran-Mantel-Haenszel (CMH) statistic (29). To determine which risk factors are independently and significantly related to complications, we did a stepwise logistic regression analysis (30). The regression parameters were used to compute adjusted OR and 95% CI for each risk factor finally included in the model.

RESULTS

Included in the study were 231 patients (105 males, 126 females) with median age 25.5 yr (range 11.8–43.0 yr). Median age at diagnosis of IDDM was 9.2 yr (0.04–26.2 yr), and median duration of disease was 15.3 yr (10.0–37.2 yr). One hundred forty-six (63%) patients were Ashkenazi Jews, and 85 (37%) were non-Ashkenazi. Microalbuminuria was detected in 72 patients (31%) and macroalbuminuria in 16 patients (7%). Nonproliferative retinopathy was found in 101 patients (44%), and proliferative retinopathy was found in 28 patients (12%).

Factors related to proteinuria. The values for various parameters in patients with no proteinuria, microalbuminuria, and macroalbuminuria are shown in Table 1 and Fig. 1. The median 5-yr HbA_1 was 13.3% in patients with macroalbuminuria vs. 10.7 and 10.6% in patients with microalbuminuria and those without albuminuria, respectively ($P = 0.0003$; Fig. 1). Non-Ashkenazi Jews constituted 69% of all patients with macroalbuminuria and 43% of those with microalbuminuria but only 29% of the patients without proteinuria ($P = 0.005$). The families of patients with albuminuria had a significantly lower income, less education, and higher housing density. There was no significant difference between groups with regard to duration of diabetes (Table 1).

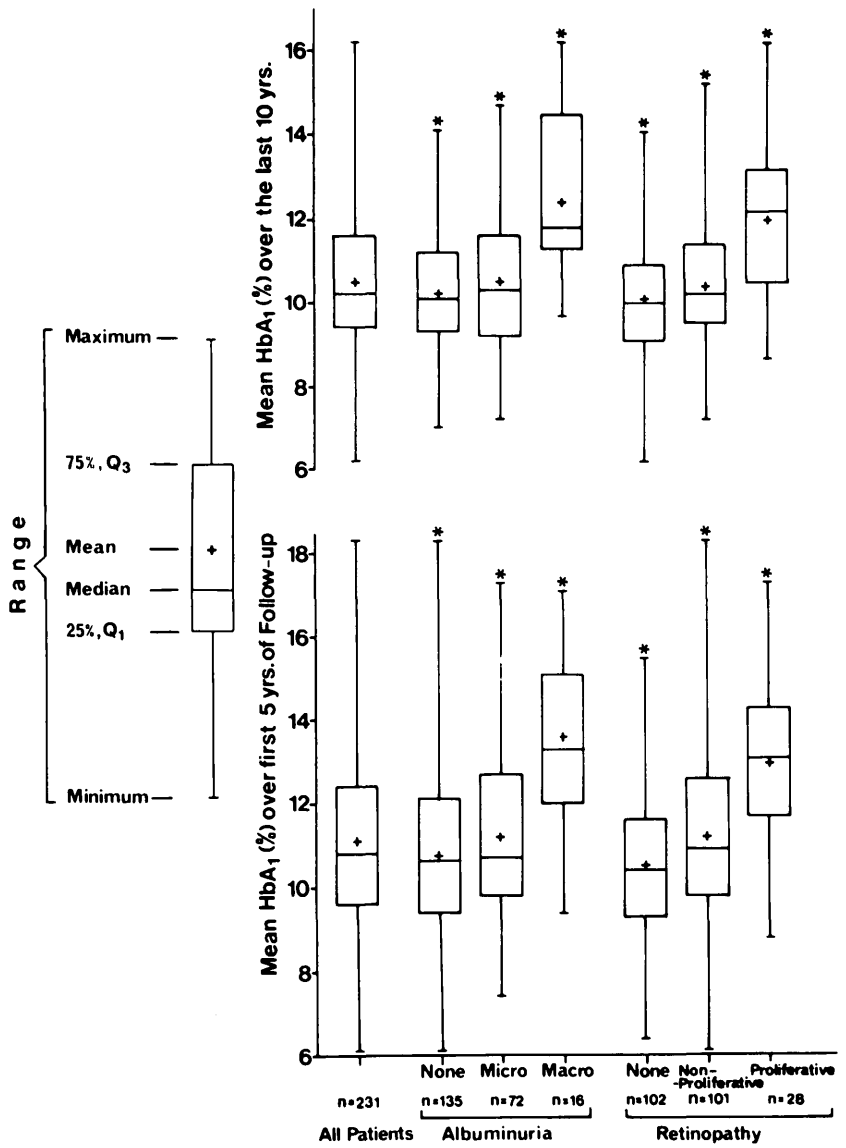

FIG. 1. HbA_1 during first 5 yr of follow-up and HbA_1 during last 10 yr of follow-up in insulin-dependent diabetes mellitus patients with and without retinopathy and nephropathy. Q, quartile. *$P < 0.001$.

To assess the risk for albuminuria associated with each of these factors, we computed the crude ORs for any albuminuria (microalbuminuria and macroalbuminuria) and for macroalbuminuria alone (Table 2). The OR for non-Ashkenazi versus Ashkenazi Jews for any albuminuria was 2.0 and for macroalbuminuria 3.8. The OR for macroalbuminuria increased gradually to 2.5 in the 4th quartile of mean 5-yr HbA_1 compared with the 1st quartile. This was in contrast to the rise to 4.3 observed in the 4th quartile for macroalbuminuria. Similar results were obtained over the quartiles for 10-yr HbA_1 (data not shown).

Patients with a lower SES were at a higher risk for developing any albuminuria and macroalbuminuria (Table 2). To test whether the association of ethnic origin and albuminuria is independent of other factors, we computed the OR for developing albuminuria in non-Ashkenazi versus Ashkenazi Jews in subgroups stratified by the median value of 5-yr HbA_1 and by the socioeconomic variables (Table 3). Non-Ashkenazi Jews were at a higher risk for developing albuminuria in all strata and when corrected for the confounding factors by the CMH statistic (OR > 1). The ORs of non-Ashkenazi versus Ashkenazi Jews to develop any albuminuria were 1.7 (0.8–3.8) in patients with mean 5-yr HbA_1 below median, and 2.3 (1.1–5.0) for mean 5-yr HbA_1 above median. The ORs to develop macroalbuminuria were 1.0 (0.9–1.2) and 7.6 (1.6–36.4), respectively.

We looked for independent and significant correlates to albuminuria by performing a stepwise logistic regression analysis. Two models were tested, one having any albuminuria and the other macroalbuminuria as the dependent variable. The independent variables initially entered into the analysis were ethnic origin, 5-yr HbA_1, 10-yr HbA_1, duration of diabetes, and socioeconomic data. Two factors were found to be significantly and independently related to albuminuria in both final models: 5-yr HbA_1 (adjusted OR 1.3, 95% CI 1.1–1.5 for any albuminuria; and adjusted OR 1.8, 95% CI 1.1–3.1 for macroalbuminuria) and non-Ashkenazi origin (adjusted OR 1.9, 95% CI 1.1–3.4 for any albuminuria and adjusted OR 2.9, 95% CI 1.0–8.6 for macroalbuminuria).

TABLE 2
Crude odds ratio for developing any albuminuria and for developing macroalbuminuria alone

	Any albuminuria	Macroalbuminuria
n	88	16
Ashkenazi*	1	1
Non-Ashkenazi	2.0 (1.2–3.5)	3.8 (1.3–10.7)
Quartiles (Q) of 5-yr HbA_1 (%)		
Q 1 (<9.6)*	1	1
Q 2 (≥9.6 and <10.8)	2.1 (1.0–4.4)	0.2 (0.0–3.4)
Q 3 (≥10.8 and <12.4)	1.1 (0.5–2.3)	1.2 (0.2–6.1)
Q 4 (≥12.4)	2.5 (1.2–5.3)	4.3 (1.2–15.3)
Income		
≥Average*	1	1
<Average	2.2 (1.1–4.4)	5.3 (1.9–15.3)
Father's education		
>8 Grades*	1	1
≤8 Grades	1.3 (0.7–2.6)	5.2 (1.6–16.8)
Housing density (persons/room)		
≤Median*	1	1
>Median	2.1 (1.2–3.8)	1.9 (0.7–5.5)

Ninety-five percent confidence intervals are given in parentheses.
HbA_1, glycosylated hemoglobin.
*Reference category.

TABLE 3
Odds ratios for developing albuminuria in non-Ashkenazi versus Ashkenazi Jews corrected for confounding factors

Confounding factor	Any albuminuria	Macroalbuminuria
5-yr HbA_1	2.0 (1.1–3.5)	3.3 (1.1–10.5)
Income	1.4 (0.7–2.7)	3.1 (0.9–10.8)
Father's education	1.6 (0.8–3.2)	4.3 (1.1–17.3)
Housing density	1.6 (0.8–3.0)	4.6 (1.1–19.3)

Odds ratios were derived from the Cochran-Mantel-Haenszel statistic. Ninety-five percent confidence intervals are given in parentheses.

Factors related to retinopathy. The median 10-yr HbA_1 in patients with proliferative retinopathy was 12.2 vs. 10.2% in patients with nonproliferative retinopathy and 10% in those without retinopathy (P = 0.0001) (Fig. 1). Sixty-eight percent of the patients with proliferative retinopathy, 34% of those with nonproliferative retinopathy, and only 28% of the patients without retinopathy were non-Ashkenazi Jews (P = 0.0001). Patients with proliferative retinopathy and patients with nonproliferative retinopathy had a longer median duration of IDDM (16.2 and 17.6 yr, respectively) than patients without retinopathy (median duration 12.9 yr) (P = 0.0001). Only 25% of patients with proliferative retinopathy were males compared to 47% of patients with nonproliferative retinopathy and 50% of patients without retinopathy (P = 0.06). Patients with retinopathy had SES significantly lower than patients without retinopathy (Table 4).

Non-Ashkenazi Jews were at higher risk than Ashkenazi Jews for developing both any retinopathy (OR 1.9) and proliferative retinopathy (OR 4.4). The risk for any retinopathy increased through the quartiles of 10-yr HbA_1 from an OR of 1.8 in the 2nd quartile to an OR of 3.2 in the 4th quartile. The risk for proliferative retinopathy increased steeply to an OR of 13 in the 4th quartile (Table 5). Table 5 further details the ORs across the quartiles of duration of disease and in accordance with the socioeconomic factors.

The patients were stratified according to the median value of 10-yr HbA_1, the median duration of diabetes, and the socioeconomic data. Non-Ashkenazi Jews were at a greater risk for developing any retinopathy and proliferative retinopathy in all subgroups and when corrected for the confounding factors by the CMH statistic (Table 6). The ORs of non-Ashkenazi versus Ashkenazi Jews to develop any retinopathy were 1.7 (0.7–4.0) in patients with mean 10-yr HbA_1 below median, and 1.8 (0.9–3.9) for mean 10-yr HbA_1 above median. The ORs to develop proliferative retinopathy were 2.2 (0.4–14.0) and 3.7 (1.3–10.3), respectively.

To look for independent and significant correlates with retinopathy, we tested two models by a stepwise logistic regression analysis, one having any retinopathy as the dependent variable and the other proliferative retinopathy. The independent variables initially entered into the analysis were ethnic origin, 10-yr HbA_1, 5-yr HbA_1, duration of diabetes, age at study, sex, and socioeconomic variables. Three factors were included in the final models as significantly and independently predicting both any retinopathy and prolif-

TABLE 4
Characteristics of patients without retinopathy compared with patients with nonproliferative retinopathy or proliferative retinopathy

	No retinopathy	Nonproliferative retinopathy	Proliferative retinopathy	*P*
n	102	101	28	
Age at study (yr)*	22.7 (11.8–37.5)	27.4 (15.7–43.0)	25.7 (18.2–41.4)	0.01
Males (*n* %)	50	47	25	0.06
Non-Ashkenazi (*n* %)	28	34	68	0.0001
Age at diagnosis (yr)*	8.2 (0.04–26.2)	10.2 (1.0–26.0)	9.6 (3.5–16.4)	>0.1
Duration of diabetes (yr)*	12.9 (10.0–30.2)	17.6 (10.0–33.0)	16.2 (10.0–37.2)	0.0001
10-yr HbA_1 (%)*	10.0 (6.2–14.1)	10.2 (7.2–15.2)	12.2 (8.7–16.2)	0.0001
5-yr HbA_1 (%)*	10.4 (6.4–15.5)	10.9 (6.1–18.3)	13.1 (8.8–17.3)	0.0001
Family income				
<National average (*n* %)	13	17	58	0.0001
Father's education				
≤ 8 Grades (*n* %)	20	28	54	0.01
Housing density				
(persons/room)*	1.3 (0.7–4.7)	1.4 (0.7–3.7)	2.0 (1.0–6.4)	0.007

*Values given as median with range in parentheses.

erative retinopathy: non-Ashkenazi origin (adjusted OR 2.3, 95% CI 1.2–4.6 for any retinopathy; and adjusted OR 7.2, 95% CI 2.7–19.3 for proliferative retinopathy), 10-yr HbA_1 (adjusted OR 1.8, 95% CI 1.4–2.3 for any retinopathy; and adjusted OR 1.9, 95% CI 1.4–2.5 for proliferative retinopathy), and duration of diabetes (adjusted OR 1.2, 95% CI 1.1–1.4 for any retinopathy; and adjusted OR 1.2, 95% CI 1.1–1.3 for proliferative retinopathy).

Dropouts and deaths. Ninety-nine patients that fulfilled the inclusion criteria were lost to follow-up and are not included in the 231 patients described above. The characterization of these patients is important in assessing whether the above results may have been the influence of selective loss of follow-up. Their median age at diagnosis of diabetes was 10.1 yr (0.8–24.0), and their median duration of follow-up was 10.2 yr (1.7–28.1). Fifty-nine (60%) of the patients were Ashkenazi Jews, and 40 (40%) were non-Ashkenazi. Median duration of follow-up of the Ashkenazi and non-Ashkenazi patients in this group was similar (10.3 vs. 10.0 yr, respectively). Data concerning the degree of diabetic retinopathy were available in 57 of the 59 Ashkenazi (97%) and 38 of the 40 non-Ashkenazi (95%) patients. Of the Ashkenazi patients, 74% did not have signs of retinopathy, 21% had nonproliferative retinopathy, and 5% had proliferative retinopathy. The percentages in the non-Ashkenazi patients were 63, 24, and 13%, respectively.

Eight patients died before entering the study; four of them were Ashkenazi Jews. The cause of death was related to diabetes in two patients: diabetic ketoacidosis in an Ashkenazi Jew and diabetic end-stage renal disease in a non-Ashkenazi patient. Two deceased Ashkenazi patients had nonproliferative retinopathy. One deceased non-Ashkenazi patient had nonproliferative retinopathy, and another had proliferative retinopathy.

TABLE 5
Odds ratios for developing any retinopathy and proliferative retinopathy according to 10-yr HbA_1, duration of diabetes, ethnic origin, and socioeconomic factors

	Any retinopathy	Proliferative retinopathy
n	129	28
Ashkenazi	1	1
Non-Ashkenazi	1.9 (1.1–3.3)	4.4 (2.0–9.7)
Quartiles (Q) of 10-yr HbA_1 (%)		
Q 1 (<9.4)*	1	1
Q 2 (≥9.4 and <10.2)	1.8 (0.9–3.9)	1.6 (0.3–9.6)
Q 3 (≥10.2 and <11.6)	1.7 (0.8–3.5)	2.8 (0.6–13.7)
Q 4 (≥11.6)	3.2 (1.5–6.9)	13.0 (3.6–46.5)
Quartiles of duration of diabetes (yr)		
Q 1 (≥10 and <12.4)*	1	1
Q 2 (≥12.4 and <15.3)	2.8 (1.3–6.0)	1.6 (0.4–5.8)
Q 3 (≥15.3 and <18.8)	3.0 (1.4–6.5)	2.8 (0.9–9.3)
Q 4 (≥18.8)	10.5 (4.6–23.8)	2.0 (0.6–7.1)
Income		
≥Average*	1	1
<Average	2.4 (1.2–4.9)	7.8 (3.5–17.2)
Father's education		
>8 Grades*	1	1
≤8 Grades	2.0 (1.0–4.0)	3.5 (1.5–8.3)
Housing density		
≤Median*	1	1
>Median	1.3 (0.8–2.4)	4.0 (1.8–8.6)

Ninety-five percent confidence intervals are given in parentheses.
*Reference category.

TABLE 6
Odds ratios for developing retinopathy in non-Ashkenazi versus Ashkenazi Jews corrected for confounding factors

Confounding factor	Any retinopathy	Proliferative retinopathy
10-yr HbA_1 (%)	1.8 (1.0–3.1)	3.4 (1.4–8.0)
Duration of diabetes (yr)	2.4 (1.3–4.2)	5.2 (2.3–12.0)
Income	1.5 (0.8–2.9)	2.0 (0.7–5.4)
Father's education	1.5 (0.8–3.0)	4.1 (1.2–13.4)
Housing density	2.0 (1.0–3.7)	2.7 (1.1–6.8)

Odds ratios were derived from the Cochran-Mantel-Haenszel statistic. Ninety-five percent confidence intervals are given in parentheses.

DISCUSSION

A major finding in this study was the association between ethnic origin and diabetic microvascular complications. About one-third of our patients were non-Ashkenazi Jews, the same proportion as in a large cohort of Israeli Jewish patients with early-onset IDDM (20). The percentage of dropout patients was 29%, and the percentage of deceased patients was 2%. However, the dropout patients probably did not introduce a bias into our study. The percentage of non-Ashkenazi patients and the ratio of non-Ashkenazi versus Ashkenazi Jews in patients with retinopathy were similar in the study and dropout groups.

Non-Ashkenazi Jews constituted two-thirds of the patients with macroalbuminuria and proliferative retinopathy. This correlation was highly significant and independent of other variables on logistic regression analysis. When the patients were stratified according to the risk factors significantly associated with albuminuria and retinopathy, the non-Ashkenazi Jews were found to be at higher risk to develop complications in every stratum. The risk for the development of macroalbuminuria and proliferative retinopathy was especially high in the non-Ashkenazi Jews with poor glycemic control. This finding implies an interaction between ethnic origin and glycemic control.

Because non-Ashkenazi Jews are of lower SES than Ashkenazi Jews in Israel (26–28), we tested whether the complications are independently associated with ethnic origin and not through SES. Both the stratified analysis and the logistic regression analysis showed the independence of ethnicity as a risk factor for complications. None of the socioeconomic factors emerged as a significant and independent correlate to microvascular complications. The relationship between SES and complications in the univariate analysis is probably determined through the ethnic origin. An association between ethnic origin and complications was shown in Mexican Americans and American blacks with non-insulin-dependent diabetes (NIDDM) (17–19) and Asian diabetic patients in England (16). In two studies this association was independent of glycemic control (16–18). In the Mexican Americans, the association was independent of SES (17,18), and a low SES by itself was not related to retinopathy (31). It is intriguing, however, that, in these four studies (from the U.S., England, and Israel), the ethnic group with the highest complication rate also was of lower SES.

Our finding of an association between ethnic origin and microvascular complications is one in a series of observations that implicate constitutional or genetic factors in the pathogenesis of diabetic complications. Sequist et al. (32) have shown that diabetic nephropathy occurs in familial clusters. Patients with nephropathy have also been found to have higher values than control subjects for lithium-sodium countertransport (33,34), a marker thought to be genetically determined (30).

We did not find a significant correlation between diabetic nephropathy and duration of diabetes, probably because, in our group of patients, the duration of diabetes was by definition ≥10 yr, and the median duration was 15.3 yr. Thus, as a whole, this group of patients was assessed for albuminuria past the peak incidence rate of nephropathy (2,6), and most of the susceptible patients had probably already developed microalbuminuria. In contrast, we found a significant correlation between diabetic retinopathy and duration of diabetes in both the univariate and multivariate analyses. The prevalence of diabetic retinopathy increased unremittingly over the years, and thus a correlation could be demonstrated even in this group of patients with duration of diabetes >10 yr (7,8).

Poor glycemic control was significantly associated with a higher prevalence of diabetic nephropathy and retinopathy, and this association was independent of any other variables. The risk to develop any degree of albuminuria or any retinopathy increased moderately and almost linearly over the quartiles of HbA_1. There was a steep increase in the OR for macroalbuminuria, from 1.2 in the 3rd quartile of HbA_1 to 4.3 in the 4th quartile. The increase was even steeper for proliferative retinopathy, from 2.8 in the 3rd quartile to 13.0 in the 4th quartile. Similar findings regarding proliferative retinopathy have been reported by Janka et al. (9). This steep increase supports the hypothesis that proliferative retinopathy is more strongly related to the exposure to extremely high blood glucose values than to the cumulative effect of mild or moderate hyperglycemia (1). From our data, such a relationship can be postulated for macroalbuminuria as well.

In the final logistic models, 10-yr HbA_1 was found to be an independent correlate to retinopathy, and 5-yr HbA_1 was an independent correlate to nephropathy. This difference may be accidental, or it may indicate that poor glycemic control in the early years of diabetes is crucial for the development of nephropathy. The risk to develop retinopathy is influenced by glycemic control at a constant rate over the years. The difference in the time course for developing albuminuria and retinopathy may have a bearing on this observation.

In conclusion, in our patients, the association between the duration of diabetes and microvascular complications was compatible with the time course already described (1). Glycemic control was significantly related to diabetic microvascular complications. A steep increase in the risk to develop albuminuria and proliferative retinopathy was found in the 4th quartile of HbA_1 and in the non-Ashkenazi patients with poor glycemic control. Special efforts should be made to improve glycemic control in those subgroups. Non-Ashkenazi Jews were of a greater risk to develop severe microvascular complications. Further investigation is necessary to search for the pathophysiological mechanisms underlying this association.

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REFERENCES

1. Krolewski AS, Warram JH, Rand LI, Kahn R: Epidemiologic approach to the etiology of type I diabetes mellitus and its complications. *N Engl J Med* 317:1390–98, 1987
2. Andersen AR, Sandahl Christiansen J, Andersen JK, Kreiner S, Deckert T: Diabetic nephropathy in type I (insulin dependent) diabetes: an epidemiologic study. *Diabetologia* 25:496–501, 1983
3. Mathiesen ER, Oxenboll B, Johansen K, Svendsen PA, Deckert T: Incipient nephropathy in type I (insulin dependent) diabetes. *Diabetologia* 26:406–40, 1984
4. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin dependent patients. *N Engl J Med* 311:89–93, 1984
5. Close CF, MCS group: Sex, diabetes duration and microalbuminuria in type I (insulin dependent) diabetes mellitus (Abstract). *Diabetologia* 35:508A, 1987
6. Krolewski AS, Warram JH, Christlieb AR, Busick EJ, Kahn CR: The changing natural history of nephropathy in type I diabetes. *Am J Med* 78:785–94, 1985
7. Klein R, Klein BEK, Moss SE, Davis MD, De Mets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 102:520–26, 1984
8. Burger W, Hovener G, Dusterhus R, Hartmann R, Weber B: Prevalence and development of retinopathy in children and adolescents with type I (insulin dependent) diabetes mellitus: a longitudinal study. *Diabetologia* 29:17–22, 1986
9. Janka HU, Warram JH, Rand LI, Krolewski AS: Risk factors for progression of background retinopathy in long-standing IDDM. *Diabetes* 38:460–64, 1989
10. Groop LC, Teir H, Koskimies S, Groop P-H, Matikainen E, Verkkala E, Scheinin T, Kontiainen S, Teppo A-M, Tolppanen E-M, Tallgren LG: Risk factors and markers associated with proliferative retinopathy in patients with insulin-dependent diabetes. *Diabetes* 35:1397–403, 1986
11. Weber B, Burger W, Hartmann R, Hovener G, Malchus R, Oberdisse U: Risk factors for the development of retinopathy in children and adolescents with type I (insulin dependent) diabetes mellitus. *Diabetologia* 29:23–29, 1986
12. Rand LI, Krolewski AS, Aiello LM, Warram JH, Baker RS, Maki T: Multiple factors in the prediction of risk of proliferative diabetic retinopathy. *N Engl J Med* 313:1433–38, 1985
13. Johnsson S: Retinopathy and nephropathy in diabetes mellitus: comparison of the effects of two forms of treatment. *Diabetes* 9:1–8, 1960
14. Pirart J: Diabetes mellitus and its degenerative complications: a prospective study of 4400 patients observed between 1947 and 1973. *Diabetes Care* 1:168–88, 252–63, 1978
15. West KM: *Epidemiology of Diabetes and Its Vascular Lesions*. New York, Elsevier, 1978, p. 420–22
16. Samanta A, Burden AC, Feehally J, Walls J: Diabetic renal disease: differences between Asian and White patients. *Br Med J* 293:366–67, 1986
17. Pugh JA, Stern MP, Haffner SM, Eifler CW, Zapata M: Excess incidence of treatment of end stage renal disease in Mexican Americans. *Am J Epidemiol* 127:135–44, 1988
18. Haffner SM, Fong D, Stern MP, Pugh JA, Hazuda HP, Patterson JK, Van Heuven WAJ, Klein R: Diabetic retinopathy in Mexican Americans and non-Hispanic whites. *Diabetes* 37:878–84, 1988
19. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM: Disparities in incidence of diabetic end stage renal disease according to race and type of diabetes. *N Engl J Med* 321:1074–79, 1989
20. Laron Z, Karp M, Modan M: The incidence of insulin-dependent diabetes mellitus in Israeli children and adolescents 0–20 years of age—a retrospective study 1975–1980. *Diabetes Care* 8 (Suppl. 1):24–28, 1985
21. Laron Z, Galatzer A, Amir S, Gil R, Karp M, Mimouni M: A multidisciplinary, comprehensive, ambulatory treatment scheme for diabetes mellitus in children. *Diabetes Care* 2:342–48, 1979
22. Klein R, Klein BEK, Magli YL, Brothers RJ, Mauer SM, Moss SE, Davis MD: An alternative method of grading diabetic retinopathy. *Ophthalmology* 93:1183–87, 1986
23. Diabetic Retinopathy Study Research Group: Report 7: a modification of the Airlie-House classification of diabetic retinopathy. *Invest Ophthlamol Visual Sci* 21:210–26, 1981
24. Christensen C, Orskov C: Rapid PEG radioimmunoassay for quantification of pathological microalbuminuria. *Diabetic Nephrop* 3:92–94, 1984
25. Goodman RM: *Genetic Disorders Among the Jewish People*. Baltimore, MD, Johns Hopkins Univ. Press, 1979, p. 1–26
26. Housing Density in Israel 1980. *Monthly Bull Stat* (Israel) 32 (Suppl.):1–60, 1981
27. Income Surveys, 1983. *Monthly Bull Stat* (Israel) 35 (Suppl.):121–54, 1984
28. Families in Israel 1980. *Monthly Bull Stat* (Israel) 32 (Suppl.):31–70, 1981
29. SAS User's Guide: *Statistics. Version 5 Edition*. Cary, NC, SAS Inst., 1985, p. 420–32
30. Harrell FE: The LOGIST procedure. In *SUGI Supplemental Library User's Guide. Version 5 Edition*. Cary, NC, SAS Inst., 1986, p. 269–93
31. Haffner SM, Hazuda HP, Stern MP, Patterson JK, Van Heuven WAJ, Fong D: Effect of socioeconomic status on hyperglycemia and retinopathy in Mexican Americans with NIDDM. *Diabetes Care* 12:128–34, 1989
32. Sequist ER, Goetz F, Rich S, Barbosa J: Familial clustering of diabetic kidney disease: evidence for genetic susceptibility to diabetic nephropathy. *N Engl J Med* 320:1161–65, 1989
33. Krolewski AS, Canessa M, Warram JH, Laffel LMB, Christlieb AR, Knowler WC, Rand LI: Predisposition to hypertension and susceptibility to renal disease in insulin dependent diabetes mellitus. *N Engl J Med* 318:140–45, 1988
34. Mangili R, Bending JJ, Scott G, Li LK, Gupta A, Viberti GC: Increased sodium-lithium countertransport activity in red cells of patients with insulin dependent diabetes and nephropathy. *N Engl J Med* 318:146–50, 1988