Age-Corrected Empirical Genetic Risk Estimates for First-Degree Relatives of IDDM Patients

HARTMUT TILLIL AND JOHANNES KÖBBERLING

SUMMARY

The families of 554 type I (insulin-dependent) diabetics were genetically analyzed according to probands' sex and age at onset applying a modification of Strömgren's method of age correction. Lifetime recurrence risk of type I diabetes (risk up to age 80 yr) for first-degree relatives in three consecutive generations was calculated. The overall risk (±1 SE) for siblings was 6.6 ± 1.1% and for children was 4.9 ± 1.7%. The similar risks among siblings and children argue against a simple autosomal recessive trait. The results do not permit a conclusion about a distinct mode of inheritance. Regardless of age at onset, offspring of male probands always had a higher risk than offspring of female probands. Among all probands, fathers were significantly more often affected with type I diabetes (about twice) than mothers (4.1 ± 0.9 vs. 1.7 ± 0.6%, respectively). The risk for further siblings of the proband was significantly increased in the presence of a type I diabetic parent (25.2 ± 10.3 vs. 5.8 ± 1.0% for remaining probands), indicating a nonrandom clustering of type I diabetes in families. Younger age at onset (<25 yr) was not associated with an increased risk to siblings. Type II diabetes was not more frequent among parents and siblings of type I diabetics than in the general population. The calculated risk estimates are of practical value in genetic counseling and are important for genetic models concerning type I diabetes.

***Diabetes* 36:93–99, 1987**

Type I and type II diabetes are etiologically distinct entities (1). There is no doubt that type I diabetes has a hereditary basis (1), although environmental factors probably play an important role in the pathogenesis (2). Twin studies (3) and family studies (4) have revealed the lower genetic determination of type I diabetes compared with that of type II diabetes. In the last decade, knowledge of genetics (5), immunogenetics (5), and immunology (6) in type I diabetes has accumulated and sophisticated genetic models have been applied to type I diabetes (7–9), but the mode of inheritance remains unclear. By HLA typing of families with at least two diabetic children, a single autosomal recessive or a single autosomal dominant mode of transmission has been excluded (10–13). Subclassifications of type I diabetes were proposed, assuming genetic heterogeneity (14). Because there is still a lack of markers for the genotype predisposing to type I diabetes (15) and because the mode of inheritance is still unknown, empirical genetic risk estimates have to be applied for genetic counseling. However, there are only a few studies that give appropriate age-corrected risk estimates separately for type I and type II diabetes (16–21). In most studies, risk estimates were not given for all first-degree relatives. In this study of 551 families ascertained through at least one proband with type I diabetes, age-corrected empirical risk estimates throughout life for parents, siblings, and children were calculated with respect to sex and age at diagnosis of the probands.

From the Department of Internal Medicine, University of Göttingen, Federal Republic of Germany.
Address reprint requests to Dr. H. Tillil, Department of Medicine (Endocrinology), Box 435, University of Chicago School of Medicine, 5841 South Maryland Avenue, Chicago, IL 60637.
Received for publication 15 March 1986 and in revised form 19 May 1986.

METHODS

Proband recruitment. Five hundred fifty-four type I diabetic patients irrespective of age at onset served as probands and fulfilled the following criteria for inclusion into our study: *1*) insulin therapy within half a year after diagnosis and ever since and *2*) normal weight or <20% overweight (Broca index = 100%) before diagnosis. Periods of ketonuria or ketoacidosis, especially at diagnosis or before insulin therapy was started, were not regarded as a prerequisite for entrance into the study, because type I diabetes is often diagnosed in an early (nonketotic) stage.

The probands were recruited from two diabetic hospitals (Diabetic Outpatient Clinic, University of Göttingen, *N* = 202; Diabetic Hospital, Bad Lauterberg im Harz,

TABLE 1
Sex distribution of probands according to age at onset

Probands	Age at diagnosis (yr) <25	≥25	Total
Female	341	83	424
Male	75	55	130
Total	416	138	554

N = 76) and from an earlier study (18) that was devoted to the calculation of the risk of diabetes for children (no analysis for parents and siblings) of insulin-treated diabetic mothers (232 female probands published, 44 female probands later ascertained). Because there is selection in favor of female sex among the probands (Table 1), the families of male and female probands were analyzed separately. The preponderance of women was lower among probands diagnosed after age 25. Twenty-three (4.2%) probands were diagnosed at age 40 or later (mean 51.7 yr, range 40–71 yr).

From 1978 to 1982, 551 families were ascertained through a single proband with the exception of 3 families with two independently ascertained probands. The daughter of a proband and a granddaughter of a proband were also independently ascertained as probands; two probands were married. The 278 probands from the diabetic hospital and the diabetic outpatient clinic were personally interviewed according to their diabetes history and to their family history of diabetes; the respective data of the remaining 276 female probands [ascertainment described previously (18)] were obtained by a questionnaire and, if necessary, were verified or corrected by contacting the relatives themselves or their doctors. Age at diagnosis refers to the age at which diagnosis was first made by a physician. Only siblings and children beyond the age of 1 mo (30 days) were included in the analyses. The probands were divided into two groups according to age at diagnosis (<25 or ≥25 yr) (Table 1), because the inheritance patterns of type I diabetes with onset later in life are not well known.

Recurrence risk to relatives. A modification of Strömgren's method of age correction (4,18,22,23) yielding the theoretical risk of developing diabetes until a certain age was used. Strömgren's method presumes that it is known how the risk of becoming affected before a certain age increases during the period of manifestation and that the risk, apart from a factor of proportion, increases in this manner in the group to be investigated.

It was shown by Gamble (24) in an epidemiological study of childhood diabetes (age at onset before age 16) that the distribution of age at onset in the diabetic siblings is similar to that in the general population.

Published data from other groups were used as basis for the calculation of the frequency of type I and type II diabetes among relatives.

An unselected age at onset distribution of type I diabetic patients from London (newly diagnosed patients at Kings College Hospital between 1965 and 1968) given by Gamble and Taylor (Fig. 1 in ref. 25) and the mean age distribution of the population of the Federal Republic of Germany between 1965 and 1968 (26) were used. For type II diabetes, age-related incidence figures from Edinburgh given by Falconer et al. (Fig. 10 in ref. 27) served as basis for the calculations. The diabetic patients in the study by Falconer et al. (27) were not differentiated into type I and type II diabetes. From these data the age-related relative risk up to an age of 80 yr was calculated separately for type I and type II diabetes (Tables 2 and 3). First-degree relatives were counted with the weights derived from Table 2 or 3 to yield the age-reduced total number of relatives. The number of diabetic relatives divided by the age-reduced total number of relatives yields the age-corrected risk, which is the theoretical risk of becoming diabetic to age 80, i.e., the prev-

TABLE 2
Strömgren's method of age correction for type I diabetes

1	2	3	4	5	6	7	8	9
N	Age group	a_N	b_N ($\times 10^6$)	$c_N = a_N/b_N$	Relative risk d_N (%)	Cumulative relative risk $e_N = \Sigma d_N$ (%)	$\bar{e}_N$ (%)	Correction factor
1	0–4	8	5.064	1.58	4.84	4.84	4.8	0.0240
2	5–9	11	4.585	2.40	7.35	12.19	12.2	0.0850
3	10–14	25	4.009	6.24	19.11	31.30	31.3	0.2175
4	15–19	14	3.858	3.63	11.11	42.41	42.4	0.3685
5	20–24	11	3.878	2.84	8.70	51.11	51.1	0.4675
6	25–29	9	4.944	1.82	5.57	56.68	57.6	0.5435
7	30–34	10	4.187	2.39	7.32	64.00	63.0	0.6030
8	35–39	5	3.933	1.27	3.89	67.89	67.8	0.6540
9	40–44	5	3.842	1.30	3.98	71.87	72.3	0.7005
10	45–49	6	3.123	1.92	5.88	77.75	76.9	0.7460
11	50–54	5	3.356	1.49	4.56	82.31	81.4	0.7915
12	55–59	3	3.926	0.76	2.33	84.64	85.8	0.8360
13	60–64	5	3.616	1.38	4.23	88.87	90.3	0.8805
14	65–69	7	2.920	2.40	7.35	96.22	95.0	0.9265
15	70–74	1	2.060	0.49	1.50	97.72	98.7	0.9685
16	75–79	1	1.339	0.75	2.30	100.02	100.0	0.9935
Total		126	58.640	32.66	100.02			

Col. 3, a_N, age-at-onset distribution of type I diabetics given by Gamble and Taylor (25).
Col. 4, b_N, average age structure of population of Federal Republic of Germany between 1965 and 1968 (26).
Col. 6, d_N (%) = $c_N \times 100\%/\Sigma c_N$.
Col. 8, smoothed representation of values of col. 7 according to graph.
Col. 9, factor of age correction for relatives in respective age group.

TABLE 3
Strömgren's method of age correction for type II diabetes

1	2	3	4	5	6
N	Age group	Incidence c_N	Relative risk d_N (%)	Cumulative relative risk $e_N = \Sigma d_N$ (%)	Correction factor
1	25–29	0.47	1.46	1.46	0.0073
2	30–34	0.61	1.90	3.36	0.0241
3	35–39	0.84	2.61	5.97	0.0467
4	40–44	1.29	4.01	9.98	0.0798
5	45–49	2.00	6.22	16.20	0.1309
6	50–54	2.70	8.40	24.60	0.2040
7	55–59	3.90	12.13	36.73	0.3067
8	60–64	4.65	14.46	51.19	0.4396
9	65–69	5.10	15.86	67.05	0.5912
10	70–74	5.25	16.32	83.37	0.7521
11	75–79	5.35	16.64	100.01	0.9169
Total		32.16	100.01		

Col. 3, C_N, age-related incidence figures given by Falconer et al. (27).
Col. 4, d_N (%) = $c_N \times 100\%/\Sigma c_N$.

alence of diabetes on the assumption that all relatives will reach the age of 80 (approximate lifetime risk). The result is thereby independent of the actual age of the probands and their relatives. The method gives no information about the percentage of diabetic relatives at the time of interview. For a newborn the risk R of becoming affected by age a can be calculated by multiplying the total risk by the proportion of the total lifetime risk that that age contributes to the lifetime risk. The respective values are given in Table 2 or 3. If the individual is at age $a1$ and is still unaffected, the relative risk of still becoming affected by age $a2$ depends on being unaffected at age $a1$ and is given by $(R2 - R1)/(100\% - R1)$, where $R1$ and $R2$ are the unconditional relative risks at ages $a1$ and $a2$, respectively.

For evaluation of the Strömgren method, the overall risks of type I diabetes for parents, siblings, and children were also calculated with the life-table method according to Nyholm and Helweg-Larsen (28,29), because the morbid risk as calculated by the life-table method is only based on the age distribution and the age-at-onset distribution of the relatives themselves. In this procedure, individuals are considered lost to follow-up at ages equal to their current age. The risks are cumulative up to specific ages. The curve generated by connecting all cumulative risk estimates is referred to as the risk curve (Fig. 1). In most studies the risk to siblings is calculated as the frequency of type I diabetes among all siblings of the index cases, i.e., the proband exclusion method. Because in this study three families were ascertained through two probands, Weinberg's (30) proband method was used; i.e., these three families were counted twice.

Statistical analysis. The conventional χ^2-test was used to test the statistical significance of results (31). The α-error for statistical significance was set as 0.05 (respective $\chi^2 = 3.84$). The age-adjusted numbers of relatives were used for the calculation of the χ^2-values.

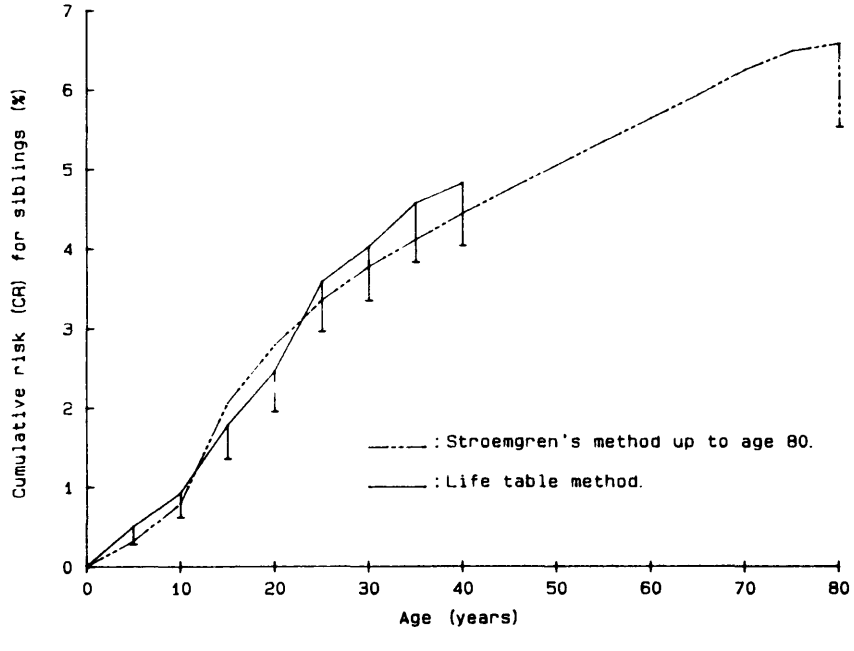

FIG. 1. Risk curves (*vertical bar* = −1 SE) of type I diabetes for siblings of all probands with type I diabetes using modified Strömgren method and life-table method of age correction.

TABLE 4
Age-corrected empirical risk estimates of type I diabetes up to age 80 for first-degree relatives of probands with type I diabetes

Probands' age at onset	Parents	Siblings	Children
<25 yr	2.2 ± 0.6% [15/811 (689.9)]	6.9 ± 1.3% [28/718 (404.2)]	5.6 ± 2.8% [4/414 (71.2)]
≥25 yr	4.9 ± 1.4% [12/272 (246.8)]	5.8 ± 1.8% [11/264 (189.8)]	4.3 ± 2.2% [4/235 (93.1)]
Total	2.9 ± 0.6% [27/1083 (936.6)]	6.6 ± 1.1% [39/982 (594.0)]	4.9 ± 1.7% [8/649 (164.3)]

Strömgren's method and Weinberg's proband method used to determine risk. Estimates ±1 SE. Totals (before and after age correction) given in brackets.

RESULTS

The age-corrected risk estimates of type I diabetes for parents, siblings, and children as calculated by the Strömgren method up to age 80 (nearly lifetime risk) are given in Table 4. For example, the 718 siblings of probands diagnosed before age 25 were reduced to 404.2 siblings after age correction. Twenty-eight siblings in 27 families (three of them counted twice) had type I diabetes. Without age correction, the risk of type I diabetes among siblings was 3.9 ± 0.7% (28/718); after age correction this increased to 6.9 ± 1.3% (28/404.2), which is the prevalence of type I diabetes on the assumption that all siblings will live to 80 yr. For siblings there was no statistically significant difference between the two age groups. Among the 42 siblings of the 23 probands with age at onset ≥40 yr (age-corrected number of siblings, 34.3), one brother had type I diabetes (age-corrected risk up to age 80, 2.9%). Age at onset of this brother was 12 yr; the respective proband was diagnosed at age 46. This difference of 34 yr was the greatest observed in diabetic sibling pairs in this study. For siblings of all probands the age-corrected risk is 6.6 ± 1.1%; up to age 25 the risk is 3.4% (recalculated from Tables 2 and 4). Siblings always had a slightly but not significantly higher risk than children.

As with siblings, no significant difference for children between the two age groups of probands was found. For children of all probands the age-corrected lifetime risk is 4.9 ± 1.7%; up to age 25 yr the risk is 2.5%.

Probands whose spouses also had type I diabetes were excluded from the calculation of the risk for children in Tables 4–6. This was the case in four female probands and one male proband who is married to one of these four female probands. According to Weinberg's proband method, this family with a nonaffected child was counted twice. Of six children of conjugal diabetic parents, two had developed type I diabetes. Thus, the risk for children of parents conjugal for type I diabetes seems to be markedly increased. The age at onset of the two diabetic children was 5 and 7 yr; age at onset of their four diabetic parents was higher, between 12 and 19 yr. Regardless of the spouses', diabetic status, the overall risk for children was 6.1 ± 1.9% [10/655 (165.1)].

Parents of probands diagnosed before age 25 had a significantly lower risk than parents of probands with age at onset ≥25 yr (χ^2 = 4.69). No parent was diagnosed before age 20 (see also Table 6). Parents of probands diagnosed before age 25 had a significantly lower risk than siblings (χ^2 = 15.25) but not than children (χ^2 = 3.15). Among parents of all probands, fathers [4.1 ± 0.9%; 19/534 (461.6)] were significantly (χ^2 = 4.95) more frequently affected than mothers [1.7 ± 0.6%; 8/549 (475.0)].

The joint effects of the probands' sex and age at diagnosis are shown in Table 5. In male probands standard errors were high because of the small number of relatives. The risks of type I diabetes in parents as in siblings of male and female

TABLE 5
Age-corrected empirical risk estimates of type I diabetes up to age 80 for first-degree relatives of male and female probands with type I diabetes

Probands' sex and age at onset	Parents	Siblings	Children
Female	1.9 ± 0.6% [11/666 (570.9)]	6.0 ± 1.4% [20/580 (331.6)]	4.4 ± 2.5% [3/395 (68.2)]
<25 yr			
≥25 yr	6.7 ± 2.1% [10/164 (149.8)]	7.2 ± 2.5% [8/155 (111.1)]	3.6 ± 2.5% [2/150 (55.7)]
Total	2.9 ± 0.6% [21/830 (720.7)]	6.3 ± 1.2% [28/735 (442.8)]	4.0 ± 1.8% [5/545 (123.9)]
Male	3.4 ± 1.7% [4/145 (119.0)]	11.0 ± 3.9% [8/138 (72.6)]	33.4 ± 33.4% [1/19 (3.0)]
<25 yr			
≥25 yr	2.1 ± 1.5% [2/1098 (97.0)]	3.8 ± 2.2% [3/109 (78.7)]	5.4 ± 3.8% [2/85 (37.4)]
Total	2.8 ± 1.1% [6/253 (215.0)]	7.3 ± 2.1% [11/247 (151.2)]	7.4 ± 4.3% [3/104 (40.4)]

Strömgren's method and Weinberg's proband method used to determine risk. Estimates ± 1 SE. Totals (before and after age correction) given in brackets.

TABLE 6
Age-corrected empirical risk estimates of type I diabetes (up to certain ages) for first-degree relatives of all probands with type I diabetes

Cumulative risk	Parents	Siblings	Children
5		0.5 ± 0.2% (5)	0.5 ± 0.3% (3)
10		0.9 ± 0.3% (4)	1.0 ± 0.4% (2)
15		1.8 ± 0.4% (8)	
20		2.5 ± 0.5% (6)	
25	0.2 ± 0.1% (2)	3.6 ± 0.6% (9)	1.9 ± 1.0% (1)
30	0.8 ± 0.3% (7)	4.0 ± 0.7% (3)	
35	1.5 ± 0.4% (7)	4.6 ± 0.8% (3)	3.7 ± 2.1% (1)
40		4.8 ± 0.8% (1)	6.4 ± 3.4% (1)
45	2.0 ± 0.4% (5)		
50	2.3 ± 0.5% (3)		
55	2.4 ± 0.5% (1)		
60	2.7 ± 0.5% (2)		

Life-table method and Weinberg's proband method used to determine risk. Estimates ± 1 SE. Number of diabetic relatives diagnosed in respective age interval in parentheses.

probands were about equal. The higher risk of children of male probands was not statistically significant ($\chi^2 = 0.76$). Except for parents, there were only minor differences between siblings and children of female probands with different age at onset. Parents and siblings of female probands with age at onset ≥25 yr had a higher risk than parents and siblings of male probands with age at onset ≥25 yr, but the differences were not statistically significant ($\chi^2 = 2.71$ and 0.97, respectively). Regardless of age at onset, children of male probands always had a higher risk than children of female probands, but this difference was only significant in children of male probands diagnosed under age 25 ($\chi^2 = 4.57$). The total number of children of male probands, however, was very small. Also, parents and siblings of male probands diagnosed under age 25 had a higher risk than parents and siblings of female probands diagnosed under age 25, but the differences were not statistically significant ($\chi^2 = 0.95$ and 2.36, respectively).

If in addition to the proband, regardless of age at onset, a parent also had type I diabetes ($N = 25$), the age-corrected risk for siblings increased to 25.2 ± 10.3% (6/23.8) compared with 5.8 ± 1.0% (33/569.6) among siblings of the remaining probands ($\chi^2 = 10.54$), except for one proband with conjugal type I diabetic parents [uncorrected risks 14.6 ± 6.0% (6/41) vs. 3.5 ± 0.6% (33/940), respectively]. Twenty of the 25 families were informative; i.e., the proband had at least one sibling. Each of the 20 families was ascertained through only one proband. In one family the father and all three children (single-proband family) had type I diabetes. In one proband with a diabetic sibling, one of two children of the respective proband had type I diabetes. Transmission of type I diabetes through three consecutive generations was not observed.

Table 6 shows the cumulative risk of type I diabetes up to certain ages (in intervals of 5 yr) separately for parents, siblings, and children of all probands as calculated by the life-table method. In Fig. 1 the risk curves for siblings calculated by Strömgren's method and by the life-table method are compared. The two risk curves were nearly equal up to age 40.

The age-corrected risk of type II diabetes from age 25 to age 79 among parents and siblings is given in Table 7. None of the diabetic relatives was diseased before age 25. There was no significant difference among parents or siblings of the two age groups. Also, no significant difference was found between parents and siblings of each age group and of all probands. No child with type II diabetes has been found.

DISCUSSION

This hospital-based family study of 554 type I diabetic patients is the first study in which the lifetime recurrence risk for first-degree relatives in three consecutive generations was calculated. Presumably no selection favoring ascertainment of multiplex families was made. We think that on the basis of the two criteria of inclusion for type I diabetes, only a few patients might have been misclassified. Patients with idiopathic diabetes diagnosed before age 25 (or even before age 40) have a very high a priori probability to type I diabetes (32). Green and Hougaard (33) reported that in 576 of 577 patients characterized by having diagnosed diabetes before age 30, virtually no endogenous insulin production was left as assessed by C-peptide level in a clinical follow-up examination.

From the overall risks for parents, siblings, and children (Tables 4 and 6), one cannot conclude a mode of inheritance. However, the risks for parents, siblings, and children of probands diagnosed at age 25 or later are not significantly different from each other; thus, they are compatible with a simple autosomal dominant mode of inheritance with highly reduced penetrance. In this material, however, direct transmission of type I diabetes through three consecutive generations was not observed. The slightly higher risk in siblings compared with children does not favor simple autosomal recessive inheritance, which has been widely touted in the literature (34–37) but might be explained by a biparental contribution of genes predisposing to type I diabetes. This hypothesis was tested by Weitkamp (38) on the basis of pooled HLA family data. In families with a diabetic parent and two haploidentical diabetic children, their common haplotype was inherited more often than expected from the nondiabetic parent. Assuming a biparental influence on the inherited susceptibility to type I diabetes, however, one would expect a more pronounced difference in the risk figures between siblings and children.

TABLE 7
Age-corrected empirical risk estimates of type II diabetes up to age 80 for first-degree relatives of probands with type I diabetes

Probands' age at onset	Parents	Siblings
<25 yr	15.5 ± 2.1% [52/809 (336.5)]	9.6 ± 5.6% [3/500 (31.1)]
≥25 yr	9.6 ± 2.4% [18(16*)/272 (166.5)]	10.2 ± 4.2% [6/237 (59.0)]
Total	13.5 ± 1.6% [70(68*)/1081 (503.0)]	10.0 ± 3.3% [9/737 (90.1)]

Strömgren's method and Weinberg's proband method used to determine risk. Estimates ± 1 SE. Totals (before and after age correction) given in brackets.
*Parents diagnosed before age 80.

To approach the mode of inheritance, the segregation ratio should be known according to the parents' disease status. The results showed clustering of diabetes in certain families, i.e., a nonrandom distribution of type I diabetes in families, which points against a simple autosomal dominant transmission of type I diabetes with highly reduced penetrance. Similar calculations were performed in two studies from the United States (20,21). Chern et al. (21) found no difference between the group of probands with one affected parent and the group with no affected parents. They made no correction for families ascertained through more than one proband. The uncorrected Li-Mantel estimate (39) of 15.6% for siblings of probands with one type I diabetic parent in the Pittsburgh study (20) is in good accordance with the respective value of 14.6% calculated in this study. The Li-Mantel estimates (under incomplete ascertainment) given in the Pittsburgh study should be regarded with caution, because the number of single proband families (Table 4 in ref. 20) was given as the number of sibships with only one affected member (used under complete ascertainment) instead of the number of families with only one index proband as proposed by Davie (39).

The tendency of aggregation of type I diabetes in families of female probands with onset after age 25 gives support to a subclassification of type I diabetes proposed by Cudworth and Wolf (14) that says that type I diabetes in middle-aged females belongs to an autoimmune type and shows a familial aggregation of autoimmune diseases.

The tendency that children of male probands have a higher risk than children of female probands was also found in a study of Warram et al. (40), who gave two possible explanations for this observation. One reason can be the lower frequency of recombination between linked loci in men than in women. In view of the concept that type I diabetes is the expression of a combination of several alleles in the HLA region, such a specific combination is more likely to be inherited from an affected father than an affected mother. The other, nongenetic possibility may be selective loss of fetuses that are genetically susceptible to type I diabetes or, alternatively, the protection of fetuses from the subsequent manifestation of type I diabetes by exposure to a diabetic mother during gestation. One way to test the latter hypothesis is to calculate the risk in children separately for those born before and after onset of diabetes in the mother. In this study, only five diabetic children (except for the two diabetic children with conjugal diabetic parents) were born to diabetic mothers, too few to test this hypothesis. Probably this question can only be answered in a multicenter study; such an investigation is complicated by the fact that the disease can be initiated some years before its clinical manifestation (41). One reason for the difference between children of male and female probands could also be an effect of small numbers. For both hypotheses raised by Warram et al. (40) the risk for parents of male and female probands should be equal, as should the risk for siblings. One would expect more fathers to be affected than mothers. All these were found in this study. In a recent study by Dahlquist et al. (42) it was approximately twice as common that a parent with type I diabetes was a father than a mother.

The risk for children of conjugal diabetic parents seems to be markedly increased. Further studies to investigate this are necessary but are difficult to design because of selection bias favoring diabetic children. Such a study can be best performed if a central diabetes register is available as in the German Democratic Republic; thus ascertainment is nearly complete. Using complex segregation analysis, Green (19) calculated a risk estimate of 39.0% (from birth to age 70) for children of conjugal type I diabetic parents. This estimate of 39.0% is within the range of the uncorrrected estimate of 33.3% (2/6) calculated in this study.

The chance of type I diabetics having children was small in the first decades of this century. Thus, there is little chance of ascertaining probands with type I diabetic parents, especially those with diabetic mothers. The lower risk of type I diabetes among parents of probands diagnosed before age 25 compared with probands with diagnosis after age 25 and the lower risk among mothers compared with fathers thus might be an effect of selection.

A significantly higher risk for siblings of probands diagnosed before age 10 was described by Chern et al. (21). In our study a higher risk (not significant) was found (Table 5) only for siblings of male probands with onset below age 25.

Regardless of parental diabetic status, the risk for siblings (6.6% among all siblings) can be calculated according to the degree of HLA haplotype identity between proband and diabetic sibling (Table 3 in ref. 43). The risk of 15.5% for HLA-identical siblings is ~3 times higher than for HLA haploidentical (4.9%) and ~13 times higher than for HLA-nonidentical siblings (1.2%). This fact was one reason to perform follow-up studies of healthy siblings of type I diabetics as, for example, in the Barts-Windsor study (41,44). The HLA haplotype distribution according to parental diabetic status and the number of affected siblings was analyzed by pooled data by Weitkamp (38), and we believe that this subject should be followed further. These data are important for genetic counseling, because experience shows that healthy siblings of type I diabetics constitute a considerable part of the clientele of genetic counseling centers.

The two risk curves for siblings in Fig. 1 as calculated by the Strömgren method and the life-table method were very much the same, and despite the small numbers, there was also good accordance for children (not shown). The similarity of the two risk curves for siblings can be taken as proof for the age-correction curve of this study (column 8, Table 2), which was derived by Strömgren's method. Fig. 1 shows that the risk estimate for siblings up to age 80 is a reliable estimate of the lifetime risk. An estimate of the lifetime risk could not have been calculated by the life-table method in this material. The fact that no parent had developed diabetes before age 20 (Table 6) indicates that the Strömgren method, even when using reliable incidence estimates, should be applied with caution if the relative morbid risk in relatives does not correspond to the relative risk among probands or in the general population, whether this is an effect of selection or due to other reasons.

The risk of type II diabetes for parents and siblings was not significantly different from the risk of ~11% in the general population as calculated earlier by us (4). This again shows the genetic independence of the two major types of idiopathic diabetes. In two other studies the risk of type I diabetes for siblings was higher if one parent had developed type II diabetes (20,21). This observation can be explained

by an etiological interrelationship between type I and type II diabetes as well as by a higher awareness of diabetes in multiplex families. We favor the latter possibility, and if it were true, the prevalence of diabetes among parents before onset of diabetes in the second child should be lower than after onset of diabetes in the second child. We have not analyzed our data in this direction until now.

Before studying the formal genetics of type I diabetes, more studies should be performed to receive suitable genetic baseline data and to look for genetic heterogeneity or to better define subtypes of type I diabetes (45).

ACKNOWLEDGMENTS

We thank Prof. Dr. B. Willms, Fachklinik für Diabetes und Stoffwechselkrankheiten, Bad Lauterberg im Harz, FRG, for allowing us to study patients under his care.

This work was supported by Grant Ko-457/13-3 from the Deutsche Forschungsgemeinschaft (DFG).

REFERENCES

1. Köbberling J, Tillil H: Genetic factors in the etiopathogenesis of type I and type II diabetes mellitus. In *Diabetes Mellitus: Etiopathogenesis and Metabolic Aspects*. Vol. 4. Belfiore F, Galton DJ, Reaven GM, Eds. Basel, Karger, 1984, p. 1–11 (Frontiers in Diabetes)
2. Vague P: Environmental factors in the pathogenesis of insulin-dependent and noninsulin-dependent diabetes. In *Diabetes Mellitus: Etiopathogenesis and Metabolic Aspects*. Vol. 4. Belfiore F, Galton DJ, Reaven, GM, Eds. Basel, Karger, 1984, p. 12–25 (Frontiers in Diabetes)
3. Barnett AH, Eff C, Leslie RDG, Pyke DA: Diabetes in identical twins. A study of 200 pairs. *Diabetologia* 20:87–93, 1981
4. Köbberling J, Tillil H: Empirical risk figures for first degree relatives of non-insulin dependent diabetics. In *The Genetics of Diabetes Mellitus*. Köbberling J, Tattersall RB, Eds. London, Academic, 1982, p. 201–209
5. Köbberling J, Tattersall RB, Eds.: *The Genetics of Diabetes Mellitus*. London, Academic, 1982
6. Irvine J: *Immunology of Diabetes*. Edinburgh, Teviot, 1980
7. Hodge SE: A three-allele model for heterogeneity of juvenile onset insulin-dependent diabetes. *Ann Hum Genet* 43:399–412, 1980
8. Spielman RS, Baker L, Zmijewski CM: Gene dosage and susceptibility to insulin-dependent diabetes. *Ann Hum Genet* 44:135–50, 1980
9. Thomson G: A two locus model for juvenile diabetes. *Ann Hum Genet* 43:383–98, 1980
10. Walker A, Cudworth AG: Type I (insulin-dependent) diabetic multiplex families: mode of genetic transmission. *Diabetes* 29:1036–39, 1980
11. Svejgaard A, Ryder LP: HLA genotype distribution and genetic models of insulin-dependent diabetes mellitus. *Ann Hum Genet* 45:293–98, 1981
12. Rotter JI: The modes of inheritance of insulin-dependent diabetes mellitus or the genetics of IDDM, no longer a nightmare but still a headache. *Am J Hum Genet* 33:835–51, 1981
13. Rotter JI, Anderson CE, Rubin R, Congleton JE, Terasaki PI, Rimoin DL: HLA genotypic study of insulin-dependent diabetes: the excess of DR3/DR4 heterozygotes allows rejection of the recessive hypothesis. *Diabetes* 32:169–74, 1983
14. Cudworth AG, Wolf E: The genetic susceptibility to type I (insulin-dependent) diabetes mellitus. *Clin Endocrinol Metab* 11:389–408, 1982
15. Rotter JI, Rimoin DL: Diabetes mellitus: the search for genetic markers. *Diabetes Care* 2:215–26, 1979
16. Degnbol B, Green A: Diabetes mellitus among first- and second-degree relatives of early onset diabetics. *Ann Hum Genet* 42:25–34, 1978
17. Gottlieb MS: Diabetes in offspring and siblings of juvenile- and maturity-onset-type diabetics. *J Chronic Dis* 33:331–39, 1980
18. Köbberling J, Brüggeboes B: Prevalence of diabetes among children of insulin-dependent diabetic mothers. *Diabetologia* 18:459–62, 1980
19. Green A: Empirical risk estimation for relatives of insulin-dependent diabetics: theoretical considerations and practical applications. In *The Genetics of Diabetes Mellitus*. Köbberling J, Tattersall RB, Eds. London, Academic, 1982, p. 21–26
20. Wagener DK, Sacks JM, La Porte RE, MacGregor JM: The Pittsburgh study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. *Diabetes* 31:136–44, 1982
21. Chern MM, Anderson VE, Barbosa J: Empirical risk for insulin-dependent diabetes (IDD) in sibs: further definition of genetic heterogeneity. *Diabetes* 31:1115–18, 1982
22. Stroemgren E: Zum Ersatz des Weinbergschen "abgekürzten Verfahrens." Zugleich ein Beitrag zur Frage von der Erblichkeit des Erkrankungsalters bei der Schizophrenie. *Z Gesamte Neurol Psychiatr* 135:784–97, 1935
23. Köbberling J: Untersuchungen zur Genetik des Diabetes mellitus. Eine geeignete Methode zur Durchführung von Alterskorrekturen. *Diabetologia* 5:392–96, 1969
24. Gamble DR: An epidemiological study of childhood diabetes affecting two or more siblings. *Diabetologia* 19:341–44, 1980
25. Gamble DR, Taylor KW: Seasonal incidence of diabetes mellitus. *Br Med J* 3:631–33, 1969
26. Statistisches Bundesamt Wiesbaden: *Fachserie A, Bevölkerung und Kultur. Gesundheitswesen. 1965–1968*. Ser. 7. Stuttgart-Mainz, FRG, Kohlhammer
27. Falconer DS, Duncan LJP, Smith C: A statistical and genetical study of diabetes. I. Prevalence and morbidity. *Ann Hum Genet* 34:347–69, 1971
28. Nyholm M, Helweg-Larsen HF: On the computation of morbid risk (disease expectancy). *Acta Genet* 5:25–38, 1954
29. Grunnet J: Heredity in diabetes mellitus. A proband study. *Opera Domo Biol Hereditar Hum Univ Hafniensis* 39:1–128, 1957
30. Weinberg W: Mathematische Grundlage der Probandenmethode. *Z Ind Vererbungsl* 48:179–228, 1927
31. Kollegium Biomathematik NW: *Biomathematik für Mediziner*. Berlin, Springer-Verlag, 1975
32. Tillil H, Köbberling J: A statistical method to assign individual diabetic patients to IDDM or NIDDM (Abstract). *Excerpta Med Int Congr Ser* 577:70, 1982
33. Green A, Hougaard P: Epidemiological studies of diabetes mellitus in Denmark. 4. Clinical characteristics of insulin-treated diabetes. *Diabetologia* 25:231–34, 1983
34. Rubinstein P, Ginsberg-Fellner F, Falk C: Genetics of type 1 diabetes mellitus: a single, recessive predisposition gene mapping between HLA-B and GLO. *Am J Hum Genet* 33:865–82, 1981
35. Dunsworth TS, Rich SS, Morton NE, Barbosa J: Heterogeneity of insulin-dependent diabetes—new evidence. *Clin Genet* 21:233–36, 1982
36. Rotter JI, Anderson CE, Rubin R, Congleton JE, Terasaki PI, Rimoin DL: HLA genotypic study of insulin-dependent diabetes: the excess of DR3/DR4 heterozygotes allows rejection of the recessive hypothesis. *Diabetes* 32:169–74, 1983
37. Williams RC: Has the recessive hypothesis for susceptibility to insulin-dependent diabetes mellitus been firmly and unequivocally rejected? *Diabetes* 32:774–76, 1983
38. Weitkamp LR: HLA and disease: predictions for HLA haplotype sharing in families. *Am J Hum Genet* 33:776–84, 1981
39. Davie AM: The "singles" method for segregation analysis under incomplete ascertainment. *Ann Hum Genet* 42:507–12, 1979
40. Warram JH, Kro!ewski AS, Gottlieb MS, Kahn CR: Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med* 311:149–52, 1984
41. Gorsuch AN, Spencer KM, Lister J, McNally JM, Dean BM, Bottazzo GF, Cudworth AG: The natural history of type 1 (insulin-dependent) diabetes mellitus: evidence for a long pre-diabetic period in type I (insulin-dependent) diabetes mellitus. *Lancet* 2:1363–65, 1981
42. Dahlquist G, Blom L, Holmgren G, Hägglöf B, Wall S: Epidemiology of diabetes in Swedish children aged 0–15 years: a 6-year prospective study (Abstract). *Diabetologia* 27:266A, 1984
43. Bertrams J, Sodomann P, Gries FA, Sachsse B, Jahnke K: Die HLA-Assoziation des insulinpflichtigen Diabetes mellitus, Typ I. *Dtsch Med Wochenschr* 106:927–32, 1981
44. Rosenbloom AL, Hunt SS, Rosenbloom EK, Maclaren NK: Ten-year prognosis of impaired glucose tolerance in siblings of patients with insulin-dependent diabetes. *Diabetes* 31:385–87, 1982
45. Diabetes Epidemiology Workgroup, National Conference on Diabetes: Research needs in the epidemiology of diabetes. *Am J Epidemiol* 113:105–12, 1981