Equal Incidence of Adult-Onset Diabetes among Ancestors of Juvenile Diabetics and Nondiabetics

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Summary. The families of 118 ketosis-prone, insulin-requiring diabetic children who were diagnosed before age sixteen years and the families of 108 nondiabetic children with a family history of no individuals diagnosed as diabetic prior to age thirty years were interviewed. The incidence of individuals diagnosed as diabetic after age forty-five among 423 grandparents of the diabetic children (0.078) was not significantly different from that among 395 grandparents of the children in whose families there were no childhood diabetics (0.071). This is interpreted as evidence that juvenile and adult-onset diabetes are

under different genetic control. More families of diabetic children agreed to participate in the survey and they reported twice the incidence of adult-onset diabetes among non-relatives than did families of nondiabetic children. It is hypothesized that the results of a diabetes interview survey can depend on the participants' awareness of diabetes and willingness to cooperate with the investigator.

Key words: Juvenile diabetes, adult-onset diabetes, genetic heterogeneity, multifactorial inheritance, incidence, relatives, non-relatives, awareness, cooperation.

The question of whether the genetic control of juvenile diabetes is the same as that in adult-onset diabetes is still unsettled. Recently two groups of investigators who attempted to answer this question by comparing the heritability of liability to diabetes among the relatives of diabetics and nondiabetics came to essentially opposite conclusions [1, 2]. In 1969 Simpson concluded that juvenile and adult-onset diabetes are genetically different [1], while Smith, Falconer and Duncan concluded in 1972 that the two disorders have the same, or a very similar causation [2]. The use of the heritability of liability method is based on the assumption that diabetes is a multifactorially inherited disease [3]. However, Rimoin has presented extensive evidence to suggest that diabetes is a heterogeneous group of disorders and not primarily a single disease which is multifactorially inherited [4], so the heritability of liability method may not be valid when applied to diabetes. Furthermore, any evidence which suggests that juvenile diabetes is under different genetic control than adult-onset diabetes is evidence that diabetes is not necessarily a multifactorially inherited disease. Köbberling [5] and Lestrade *et al.* [6] have recently presented such evidence. Köbberling found that the incidence of juvenile diabetes was twenty-five times higher among siblings of juvenile diabetics than among siblings of adult-onset diabetics [5]. Lestrade *et al.* found that the frequency of non-insulin-deficient diabetes among the parents and grandparents of insulin-dependent diabetics was equal to that among the parents and grandparents of nondiabetics [6]. Both Köbberling and Lestrade concluded from their results that there is heterogeneity between juvenile and adult-onset diabetes.

In the present study, an attempt is made to determine whether the genetic control of juvenile diabetes

is different from that of adult-onset diabetes by using a less theoretical approach than the heritability of liability method. It is hypothesized that if juvenile and adult-onset diabetes are controlled entirely, or in part, by the same gene(s), then the incidence of adult-onset diabetes should be greater among the ancestors of juvenile diabetics than among the ancestors of nondiabetics. If this is not true, then this is evidence in favour of genetic heterogeneity.

A secondary purpose of this study was to determine whether the results of a diabetes interview study could be biased by a greater awareness of diabetes among families of diabetic children compared to families of nondiabetic children.

Materials and Methods

The medical records of 173 diabetic patients and 170 surgery patients were obtained from the medical record department of Children's Hospital. Each diabetic had been admitted to the hospital during the years 1965 to 1971. Control patients were selected by choosing every tenth patient admitted to the hospital for minor surgery during 1970. All diabetic and control patients were from Buffalo, New York or its suburbs. The same format was used each time by a single observer, to interview the parents, once and only once, about diabetes and factors associated with diabetes in their families.

To increase the probability that all diabetic probands in the study were true juvenile diabetics, and not merely children with adult-onset diabetes [7], each diabetic patient selected was prone to ketosis, took insulin, and was younger than sixteen years when diagnosed. Since it is unlikely that all diabetic children

with Down's syndrome, certain syndromes of dwarfism or cystic fibrosis are true juvenile diabetics [4, 8, 9], any proband with a serious disorder other than diabetes was excluded from the study. To reduce the incidence of genes which could lead to juvenile diabetes among the families of the controls, any family of a nondiabetic proband with an individual diagnosed as diabetic before the age of thirty years was excluded from the study.

Juvenile diabetes is uncommon among American Negroes and Indians, but adult-onset diabetes in these two populations is at least twice as common as in American whites [10–13]. Including Negro or Indian probands in a study consisting largely of whites could lead to artifactually high values for the incidence of

survey, if they had the genotype for adult-onset diabetes. Some individuals who are diagnosed as diabetic at an age of thirty to forty years clinically resemble juvenile diabetics and could be true (genetic) juvenile diabetics [14]. Therefore, grandparents diagnosed as diabetic before age forty-five years were excluded from the final statistical analysis to increase the probability that those included would be true adult-onset diabetics.

To determine whether families of diabetic children are more aware of diabetes than families of nondiabetic children, the parents of both groups were asked whether they had been checked for diabetes and whether they knew of non-relatives who were diabetic.

Conventional chi-square and Student's unpaired *t*-tests were used for statistical analysis.

Table 1. *Selection of probands*

Probands	Diabetic	Non-diabetic
Total	173	170
Unable to contact	15	7
Not contacted because . . .		
Not entirely of European descent	12	23
Adult-onset diabetic	6	—
Disease or syndrome which is sometimes associated with diabetes	9	5
Total contacted	131	135
Excluded from study as a result of questioning because . . .		
Refused to be interviewed	2	17
Unable to answer most questions	4	2
Consanguinity	5 ^a	0
Not entirely of European descent	2	5
Diabetic diagnosed before age thirty in family	—	3
Number of probands in study	118	108

^a Four consanguinious marriages were between maternal grandparents and one was between maternal great-grandparents. The difference in the incidence of consanguinity was statistically significant ($p < 0.05$).

adult-onset diabetes in the relatives of either juvenile diabetics or nondiabetics. Therefore, probands who were not entirely of European descent were excluded from the study.

Families with a history of consanguinity were also excluded from the study because, theoretically, the incidence of diabetes among such families could be increased.

The selection of 118 juvenile diabetic and 108 nondiabetic probands who fulfilled the criteria for inclusion in the study is summarized in Table 1.

In the present study, the incidence of adult-onset diabetes among the grandparents of diabetic children was compared to that among the grandparents of nondiabetic children. The grandparents were chosen because it was thought that they would be the oldest relatives of the probands about whom a reliable medical history could be obtained; but who had lived long enough so that a significant percentage would have developed adult-onset diabetes by the time of this

Results

1. Incidence of Diabetes among Grandparents of the Probands

The incidence of diabetes diagnosed after age forty-five among the grandparents of the juvenile diabetics (0.078) was not significantly different from that among the grandparents of the nondiabetic children (0.071). Similar results were noted by comparing the total groups, regardless of age at onset. Although there tended to be more grandparents of juvenile diabetics than grandparents of nondiabetic children diagnosed as diabetic before age forty-five, this difference was not statistically significant. The differences between the incidence of diabetic grandmothers and grandfathers and the incidence of diabetic grandparents on the maternal and paternal sides of the families were also not statistically significant. However, among the grandparents of the juvenile diabetics, the incidence of diabetic grandmothers was greater than twice that of grandfathers, whereas the incidence was equal among the grandmothers and grandfathers of the nondiabetic children (Table 2).

The grandparents of the diabetic and nondiabetic children proved to be well matched in regard to mean age at onset, mean ultimate age, mean age at death and average number of years at risk for developing diabetes after age forty-five.¹ This indicates that the essentially equal incidence of diabetes among the grandparents in the two groups was not due to such factors as one group being under a greater risk for diabetes because their average life span was longer, or their average age greater at the time of the study. The fact that the mean age at death was the same for each group indicates that there was not a higher incidence of early deaths in one group due to a disease (such as diabetes) which went undetected in a large percentage of individuals in that group.

¹ See footnote Table 2 for an explanation of these terms.

The incidence of functional microangiopathy, the types of therapy for diabetes, and the frequencies of death from cardiovascular disease and cancer were also similar for the two groups of grandparents (Appendix 1).

Table 2. *Comparison of the grandparents of the diabetic and of the nondiabetic children*

Grandparents	Of diabetic probands	Of nondiabetic probands
Number diabetic, onset age 45 or after	33/423 (0.078)	28/395 (0.071)
Number diabetic, onset at any age	39/472 (0.082)	33/432 (0.076)
Onset of diabetes		
Before 35	3	0
35 to 45	3	5
45 to 60	16	16
After 60	17	12
Number of families with diabetic grandparents	32/118 (0.27)	28/108 (0.26)
Diabetic grandmothers, onset age 45 or after	23/216 (0.106)	15/193 (0.078)
Diabetic grandfathers, onset age 45 or after	10/207 (0.049)	13/202 (0.064)
Diabetic grandmothers, onset at any age	27/236 (0.114)	17/216 (0.079)
Diabetic grandfathers, onset at any age	12/236 (0.051)	16/216 (0.074)
Diabetic grandparents:		
On maternal side	21/236 (0.089)	18/216 (0.084)
On paternal side	18/236 (0.077)	15/216 (0.070)
Mean age at onset $\pm$ S.D. of diabetes	55.5 $\pm$ 11.6	56.7 $\pm$ 12.1
Mean ultimate age ^a of diabetic and nondiabetic grandparents $\pm$ S.D.	62.2 $\pm$ 11.5	60.0 $\pm$ 11.2
Mean age at death of deceased diabetic and nondiabetic grandparents $\pm$ S.D.	58.7 $\pm$ 14.4	58.5 $\pm$ 14.3
Average number of years at risk for diabetes after age 45 for diabetic and nondiabetic grandparents $\pm$ S.D. ^b	19.2 $\pm$ 9.2	17.8 $\pm$ 8.8
Grandparents questionably diabetic ^c	5	2

The number in parentheses is the incidence.

^a Ultimate age refers to the individual's age at death or at the time of this study.

^b To determine whether the risk of developing diabetes after age 45 was similar for the two groups of grandparents, the number of years each grandparent lived past 45 until he or she died, developed diabetes, or until the time of this study was averaged. Those grandparents who developed diabetes or died before age 45 were not included in this analysis.

^c Four grandparents of the diabetic children and one grandparent of a nondiabetic child were thought to have elevated blood glucose levels immediately after a myocardial infarction — a time when 65% of those examined have an elevated blood glucose (24).

2. Comparison of the Immediate Families of the Probands

There were no significant differences between the families of the juvenile diabetic probands and those of the nondiabetic probands in the incidence of infants who were large or small for gestational age, prematurely born infants, abortuses of the mothers of the probands, or in the percentages of deceased parents (Appendix 2).

Eighty-eight percent of the parents of the juvenile diabetics and ninety-two percent of the parents of the nondiabetic children said they were partially or entirely of English, French, German, Irish, Italian, Polish or Scottish descent (data not shown).

3. Factors Indicating Awareness of Diabetes

The percentage of families of diabetic children who knew that at least one non-relative was an adult-onset diabetic (onset after age forty-five) was twice that of families of nondiabetic children ($p < 0.01$). The families of the diabetic children also knew of twice the number of non-relative adult-onset diabetics as did families of nondiabetic children. The percentage of parents of diabetic probands who had been checked for diabetes was twice that of the parents of nondiabetic probands (Table 3). Also a greater number of families of nondiabetic probands (17 of 135) compared to families of diabetic probands (2 of 131) refused to participate in the study ($p < 0.01$, Table 1). These data indicate that families of juvenile diabetics are more aware of diabetes and are more willing to cooperate in a study on diabetes than are families of nondiabetic children.

Discussion

The finding of an equal incidence of adult-onset diabetes among the ancestors of juvenile diabetics and nondiabetics contrasts with the findings of earlier investigators who found a higher incidence of adult-onset diabetes among the ancestors of juvenile diabetics [15–19]. A reason for this could be that as a result of the increasing knowledge about diabetes among the general population, the incidence of diabetes reported by relatives of nondiabetics might be higher now than when previous studies were performed. The fact that some investigators studied the parents of juvenile diabetics [16, 18, 19] and in this survey the grandparents were studied, cannot explain the different results. Although the incidence of adult-onset diabetes should be lower among the grandparents than the parents of juvenile diabetics, the incidence of adult-onset diabetes among the grandparents should still be greater than that among the general population, if diabetes is a single disease and even if it is a multifactorially inherited disease [20, 21].

The markedly different clinical characteristics and the difference in age of onset between juvenile and adult-onset diabetes, as well as the increasing evidence

that diabetes is a heterogeneous group of disorders [4], suggest that juvenile and adult-onset diabetes might be under different genetic control and that, therefore, the incidence of adult-onset diabetes among the ancestors of juvenile diabetics should be equal to that among the ancestors of nondiabetics. However, only a

and interviewed a group of nondiabetic probands by themselves concurrently with their survey of the families of the diabetic children.

Simpson has conducted three surveys during the last decade on the incidence of diabetes among the families of over 6000 diabetics in Canada. In her first

Table 3. *Indices of awareness of diabetes*

	Relatives of diabetic probands	(Incidence)	Relatives of nondiabetic probands	(Incidence)
Families aware of diabetes among non-relatives	67/104	64%	35/98	36%
Number of nonrelatives with diabetes known	138	—	72	—
Parents checked for diabetes by urine test	163/212	77%	70/198	34%
Parents checked for diabetes by blood test	83/208	40%	35/180	19%

few investigators have found an equal incidence of adult-onset diabetes in the two groups [6, 22]. This raises the question of whether the incidence of adult-onset diabetes, found by some investigators, really was higher among the ancestors of juvenile diabetics, or whether it was due to methods used in selecting and interviewing probands. Some investigators who found a higher incidence of adult-onset diabetes among the ancestors of juvenile diabetics may not have interviewed all individuals in a uniform manner [16], or used data published by others as control data [15, 17—19]. In some cases in which published data was used, the control populations had resided in towns several miles away from, and had been interviewed several years earlier than the diabetic probands [15, 18, 19]. Since the control populations had been surveyed for different reasons than the diabetics and their relatives, it is likely they were interviewed, at least in regard to diabetes, less intensely than the families of the juvenile diabetics. Thus, the incidence of diabetes in the control populations could have been underestimated.

The studies of Joslin, Dublin and Marks [15], Simpson [18, 19, 22] and Lestrade [6] are comparable to the present study in that the incidence of diabetes among the ancestors of juvenile diabetics was compared to that among the ancestors of nondiabetics. Joslin, Dublin and Marks reported in 1937 that the incidence of diabetes among the parents and grandparents of 841 diabetic children seen between 1920 and 1934 was twice the incidence of diabetes in the general population. However, their data on the incidence of diabetes in the general population was derived from 1910 and 1930 mortality statistics [15]. It is possible that they might have found an incidence of diabetes in the general population greater than that which they derived from mortality statistics, if they had selected

survey, reported in 1962, in which the group of control probands was made up largely of clinic patients who were selected similarly to diabetic probands, she found that the incidence of diabetes among the parents of 233 diabetic children was equal to that among the parents of nondiabetic controls. She concluded from these results that the genetic control of juvenile diabetes may be different from that of adult-onset diabetes [22]. In her second survey, reported in 1964, she used data published in 1951 and 1953 by Kenny and Chute on the incidence of diabetes in three small Ontario towns [18] and in her third survey, reported in 1968, she used data from the 1964 vital statistics of Prince Edward Island [19] as control data. She compared the incidence of diabetes in these groups to that among the relatives of diabetics from all of Canada and found that the frequency of early plus late-onset diabetes among the parents of juvenile diabetics was about twice that of the control populations. As a result, she hypothesized that diabetes is a multifactorially inherited disease, but because she found that the risk for diabetes among relatives of diabetics who were younger than twenty at onset was much greater than that for relatives of diabetics who were older than twenty at onset, she concluded again that the genetic control of juvenile diabetes may be different than that for adult-onset diabetes [18, 19].

In 1972 Lestrade *et al.* published the results of a survey of diabetes among the relatives of 300 nondiabetic children who were selected identically to a group of 926 diabetic children. Their data show that the incidence of non-insulin-dependent diabetes among the parents and grandparents of insulin-dependent diabetics was equal to that among the parents and grandparents of nondiabetics, but that the incidence of insulin-dependent diabetes was significantly higher

among families of insulin-dependent diabetics than among the families of nondiabetics [6]. They concluded from these data that the inheritance of juvenile diabetes is completely independent from the inheritance of adult-onset diabetes. Their study and the present study demonstrate that if the probands and their relatives are suitably classified, it can be shown that there is no difference between the incidence of adult-onset diabetes among the ancestors of juvenile diabetics and nondiabetics.

It is possible that families of juvenile diabetics are unusually aware of diabetes and are, therefore, able to report a higher incidence of diabetes in their families than are families of nondiabetic children. This study shows that families of juvenile diabetics are both more willing to cooperate with the investigator and more aware of the existence of diabetes than families of nondiabetics. In general agreement with the present results, Keen and Track found that fifty-two percent of the relatives of control probands, but only twenty-nine percent of the relatives of diabetic probands, declined to participate in a study of diabetes in which it was required that participants have their blood drawn [23]. Since there is no good way of eliminating the problem of an increased awareness of diabetes among the relatives of juvenile diabetics, or adjusting data to compensate for a difference in awareness of diabetes, perhaps the only way to reduce this source of bias is to select homogeneous groups of probands and to survey the families of control probands as identically as is possible to those of the diabetic probands. If families of diabetic probands are already more knowledgeable of diabetes, it is doubtful that such techniques as using a mailed questionnaire, which does not allow questions from the participants or clarification of points by the investigator, can constitute a survey of control probands which is identical to that of diabetic probands. Therefore, information must be obtained by personal interview as was done in the present study.

If juvenile and adult-onset diabetes are controlled by the same gene(s), one would expect that regardless of the mode of inheritance, the incidence of adult-onset diabetes should be greater among the ancestors of juvenile diabetics than among the ancestors of nondiabetics. The fact that the incidence was found to be equal in the two groups in the present study indicates that juvenile and adult-onset diabetes are under different genetic control. This does not mean that juvenile and adult-onset diabetes are discrete genetic forms of diabetes, because this too is unlikely. Based on their studies of twins, Tattersall and Pyke have suggested that there are two types of juvenile diabetes — an inherited and a non-inherited type [25]. Genetic heterogeneity has also been found within adult-onset diabetes [26]. The fact that the incidence of overt diabetes among offspring of conjugal diabetics is only five to ten percent [27, 28] suggests that the cause of diabetes in one parent was not the same as that in the other parent in most of the diabetic couples in these

studies. These facts suggest that either diabetes is quite heterogeneous genetically or that the effect of environment on the causation of diabetes has been underestimated. For example, viral agents have been implicated as an etiologic factor in diabetes [29]. It is possible that the effect of an environmental agent, such as a virus, on an individual who is genetically susceptible to this agent, may be the cause of some types of diabetes.

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Appendix 1. *Therapy, complications, and causes of death of the grandparents of the diabetic and nondiabetic children*

Grandparents	Of diabetic probands			Of nondiabetic probands		
	Yes	No	Unknown	Yes	No	Unknown
Diabetics						
Overweight	15	5	19	20	11	2
Functional micro-angiopathy	9	17	13	11	17	5
Current therapy						
Insulin			15			15
Hypoglycemic agent			18			13
Diet alone			3			3
Unknown			3			2
Number of deceased diabetic grandparents			15/39			16/33
Before 40			0			0
40 through 59			3			3
After 60			12			13
Causes of death of diabetic grandparents						
Cardiovascular			4			8
Cancer			1			3
Other			4			1
Unknown			6			4
Number of deceased non-diabetic grandparents			175/433			142/399
Before 40			23			17
40 through 59			66			60
After 60			86			65
Causes of death of nondiabetic grandparents						
Cardiovascular			63			65
Cancer			36			37
Other			53			30
Unknown			26			23
Total ^a			178			155

^a In some cases death was attributed to more than one cause.

Appendix 2. *Comparison of families of diabetic and nondiabetic probands*

	Diabetic	Nondiabetic
Probands		
Number	118	108
Mean age at time of survey $\pm$ S.D.	11.7 ± 3.9	9.0 ± 3.2
Mean birth wt. $\pm$ S.D.	3.13 ± 0.65 kg.	3.36 ± 0.61 kg.
Birth wt. ≤ 2.50 kg.	12	5
Birth wt. ≥ 4.50 kg.	0	1
Gestational age ≤ 36 wks.	9	4
Gestational age ≥ 42 wks.	1	3
Mean age of mother at birth of proband $\pm$ S.D.	27.5 ± 6.0	27.6 ± 5.6
Siblings of probands		
Number	290	267
Mean age at time of survey $\pm$ S.D.	12.2 ± 6.4	11.1 ± 6.7
Mean birth wt. $\pm$ S.D.	3.23 ± 0.55 kg.	3.08 ± 0.55 kg.
Birth wt. ≤ 2.50 kg.	10	8
Birth wt. ≥ 4.50 kg.	2	1
Gestational age ≤ 36 wks.	8	10
Gestational age ≥ 42 wks.	1	5
Number diabetic	11 ^a	—
Number of probands with at least one diabetic sibling	10	—
Mothers of probands		
Number	118	108
Mean age at time of survey $\pm$ S.D.	38.8 ± 7.2	36.3 ± 6.6
Number diabetic	1	0
Number deceased	2	2
Fetal deaths		
Before three months gestation		
Number of fetuses	24	41
Number of mothers	13	25
Three to nine months gestation		
Number of fetuses	13	16
Number of mothers	8	9
Fathers		
Number	118	108
Mean age at time of survey $\pm$ S.D.	42.0 ± 7.9	40.6 ± 8.0
Number diabetic	3	1
Number deceased	6	0

^a Includes one identical twin of diabetic proband.