The Incidence of Diabetes Mellitus in the Offspring of Diabetic Couples Investigation Based on the Oral Glucose Tolerance Test

J. K. Radder and J. Terpstra

Diabetes Unit of the Department of Diseases of Metabolism and Endocrinology, University Hospital, Leiden, The Netherlands

Received: September 23, 1974, and in revised form: December 23, 1974

Summary. 88 of 137 offspring of 22 adult onset diabetic couples were subjected to an oral glucose tolerance test (G.T.T.); 35 were found to have a diabetic G.T.T. As 8 were already known as diabetics, 43 of 96 offspring (45%) were found to have diabetes mellitus. Neither the data pertaining to the parents, such as family history, treatment of diabetes or obstetric history, nor the data pertaining to the offspring, such as sex, age, parity or course of pregnancy, could be related to the incidence of diabetes in the offspring. It was

noted however, that overweight female, but not male, offspring are more likely to develop diabetes than those who are not overweight ($p < 0.05$).

Key words: Incidence of diabetes, offspring of adult onset diabetic couples, glucose intolerance, oral glucose tolerance test, heredity, inheritance, sex, age, body weight, family history of diabetes, treatment of diabetes, obstetrical history.

The mode of inheritance of diabetes mellitus is unknown, although the hereditary nature of the disease is generally accepted. If the genetic transmission is autosomal recessive, as has been assumed [1], the incidence of diabetes mellitus in the offspring of consubial diabetics would be 100%, except in the case of incomplete penetrance. However, according to a recent review of the literature by Rimoin [2], a maximum of about 50% has been reported so far. No conclusions can be drawn from Rimoin's data concerning the pattern of inheritance of diabetes mellitus.

In this paper we present our findings in the offspring of diabetic couples. In contrast to others [3, 4, 5] we tried to investigate all the offspring of diabetic couples. As far as we know this has only been done by Kahn [6]. We also made an attempt to relate some data pertaining to the parents to the incidence of diabetes in the offspring.

Materials and Methods

The offspring of 22 couples with proven adult onset [7] diabetes mellitus were examined.

Of the total of 137 offspring, 15 had died and 26 (14 men and 12 women) did not participate in the study for various reasons, such as inability or unwillingness. None of these 41 persons was known to have or have had diabetes. 8 of the remaining 96 individuals (4 men and 4 women) had already been diagnosed as diabetic. They were all receiving dietary therapy and one also took an oral hypoglycaemic agent. There were no indications of other major diseases.

The remaining 88 subjects (40 men and 48 women, ranging in age from 15 to 58 years) underwent an oral glucose tolerance test (G.T.T.) with a 100 g glucose load following the normal precautions [8, 9]. Blood samples were taken every half hour from the finger tip and the blood sugar was determined by the method of Nelson and Somogyi [10, 11, 12].

We set the following upper limits for a normal G.T.T.: fasting value 100 mg/100 ml, maximum value 180 mg/100 ml and 2 hr value 140 mg/100 ml. These criteria are based on those of Fajans and Conn [13] and on our own findings in normals. The diagnosis of diabetes mellitus was made when two or more values of the oral G.T.T. exceeded our criteria of normality. Our classification of diabetes mellitus is in accordance with that of the British Diabetic Association [14].

We performed no test, other than questioning, to confirm that the subjects were indeed the offspring of the diabetic parents.

Of the 44 parents, 24 were under control in our out-patient department, the rest elsewhere. The mean age at the time of diagnosis of diabetes in the parents was 61 years with a range of 38–75. 20 parents had a family history of diabetes, 23 did not; for one female parent no data were available. 18 parents were treated with a diet, 20 with a diet and an oral hypoglycaemic agent and 6 with a diet and insulin. Of the female parents, 13 were delivered of one or more heavy-for-date babies¹; 3 of them had also had one or more stillbirths; for 1 female parent the course of pregnancies was unknown.

¹ A baby weighing 4 kg or more at birth.

The offspring were divided into two age groups: younger than 40 years and 40 years or older.

Overweight was defined as 120% of ideal body weight or more. The percentage of ideal body weight was calculated according to the Metropolitan Life Insurance Company tables [15].

Of the 48 female offspring, 8 were nulliparous; for the 40 other females the mean parity was 3 with a range of 1–13; however, a parity of 2 was the most common (16 times). 6 female offspring had had one or more abortions; 8 gave birth to a heavy-for-date baby; 2 had had a stillbirth and 1 an immature delivery; 2 showed a combination of abortions and heavy-for-date babies and 1 a combination of an abortion, a heavy-for-date baby and a stillbirth.

Statistical analysis of the data was performed according to various conventional methods [16, 17, 18]. In analysing the data we had to take into account that in our out-patient department significantly more parents were treated with a diet alone or with diet and insulin than with diet and oral hypoglycaemic agents ($p < 0.025$), while in parents under control elsewhere the reverse occurred.

Results²

Glucose Tolerance Test

35 of the 88 G.T.T.'s (40%) were diabetic.

The remaining 53 G.T.T.'s (60%) were not diabetic according to our criteria. 26 persons (30%) had a completely normal G.T.T. For the other 30% one of the G.T.T. values was abnormal.

Parents

No significant relationship could be found between either the family history or the treatment of diabetes in the parents or the course of pregnancies in the female parents on the one hand and the incidence of diabetes in the offspring on the other.

Offspring

No significant difference in the frequency of diabetes in the offspring could be found between the different families.

We were not able to find a statistically significant relationship between the various combinations of sex, age and body weight on the one hand and the incidence of diabetes on the other (Table 1). This might be due to the fact that there were relatively few subjects in comparison to the number of possible combinations.

However, young overweight females seem to be more likely to develop diabetes than old overweight females (67% and 50%, respectively); on the other hand young overweight men seem to be less likely to develop diabetes than old overweight men (22% and 42%, respectively). For men and women who are not overweight, the incidence of diabetes with regard to age was approximately the same.

Table 1. *Distribution of sex, age, body weight and diabetes in the offspring^a*

		male		female	
		young	old	young	old
not overweight	non-diabetic	8	5	12	4
	diabetic	4	2	5	2
overweight	non-diabetic	7	7	5	5
	diabetic	2	5	10	5

^a see Materials and methods for definition of age, body weight and diabetes.

A statistically significant difference was only found when the incidence of diabetes was related to sex and body weight: more diabetes was detected in women who were overweight than in those who were not ($p < 0.05$). Such a difference could not be demonstrated in men. The use of oral contraceptive agents by 12 young women did not influence this result.

For the female offspring no statistically significant relationship could be found between either parity or an abnormal course of pregnancy on the one hand and the incidence of diabetes on the other. This result was not altered when we also took age and body weight into account.

Discussion

35 of the 88 from a total of 137 offspring of 22 adult onset diabetic couples were found to have a diabetic G.T.T. As 8 were already known as diabetics, 43 of 96 offspring, i.e. 45%, were found to have diabetes mellitus. This is in accordance with Rimoin's data [2].

There were no typical juvenile onset diabetics in the offspring. Thus with respect to the type of diabetes our material is homogeneous: the parents as well as the offspring had the adult onset type of diabetes.

As far as we know, only the report of Kahn *et al.* [6] is comparable with this study insofar as they also tried to investigate all the offspring of diabetic couples. The only fact which they mention with regard to the

² Additional detailed informations are available on request from J. K. Radder.

parents is that the diabetes was not of a secondary type. In 155 of the 274 offspring of 80 diabetic couples they performed 280 oral G.T.T.'s. This means that the G.T.T. must have been repeated at least once in many subjects. 33% of the 280 G.T.T.'s were found to be abnormal. They mentioned that when the oral G.T.T. was performed three times in 23 subjects, 26, 22 and 30% had abnormal G.T.T.'s. Because of the good reproducibility of the oral G.T.T. within a group [19], this finding is to be expected. However, the poor reproducibility of the oral G.T.T. per individual [19] means that the method used by these authors to calculate the frequency of diabetes is not justifiable. They detected 6 cases of diabetes with the initial G.T.T., 3 additional cases with the second test and 4 more on completion of the third test. In this way they found 13 cases of diabetes in 23 subjects, in their words an "overall frequency" of diabetes of 57%.

Other reports in the literature are not comparable. One study [3] does not state how many families and how many offspring of these families were investigated. In other investigations, the offspring of diabetic couples were selected via a known, typical, juvenile onset diabetic sibling [4] or they were studied together with the non-diabetic counterparts of identical diabetic twins [5].

In this study we tried to find a relationship between several parameters of the parents as well as of the offspring on the one hand and the incidence of diabetes mellitus in the offspring on the other. This could only be demonstrated for overweight and diabetes in the female offspring. In the male offspring a similar relationship could not be established. For many years diabetes mellitus has been associated with obesity [20]. It is possible, however, that the discrepancy we found between the sexes is caused by the fact that overweight, as defined in this report, is not synonymous with obesity [21], particularly in young males.

In contrast to others [22, 23, 24, 25, 26] we did not find a relationship between the incidence of diabetes in the offspring and their age, parity or course of pregnancy. However, our test subjects may still be too young or our group too small.

From our study it is not possible to draw any conclusions with respect to the mode of inheritance of diabetes mellitus. The 45% incidence of diabetes found for the offspring of diabetic couples provides no clue as to the pattern of inheritance of diabetes mellitus. Even autosomal recessive transmission of diabetes mellitus characterized by oral glucose intolerance cannot be excluded, because the incidence of diabetes in the offspring may increase with age, eventually up to the expected 100%. Testing glucose tolerance in some way other than orally seems to make no dif-

ference as far as the detection of diabetes mellitus is concerned [2, 6].

It is also possible that glucose tolerance tests are not sensitive enough to detect diabetes mellitus in all cases. It is then necessary to look for a more sensitive and perhaps more basic marker of diabetes mellitus. In this respect some have stressed the importance of a decreased insulin secretion [27, 28, 29, 30] and an increased growth hormone release [31, 32]; others refer to capillary basal membrane thickening [33]. However, these findings have not been confirmed [34, 35, 36, 37] and the interpretations have also been criticized [38, 39].

Further investigation of the offspring of diabetic couples in the future may possibly give some indication for the mode of inheritance of diabetes mellitus.

Acknowledgements. We owe thanks to Dr. F. M. Gerritzen, Dr. J. D. Mulder and Dr. R. Vink for helping us select our patient material, Drs. E. A. v.d. Velde for statistical analysis, Mrs. A. Cornelius — von Franquemont for technical assistance, Miss M. G. A. T. Paal for secretarial help and Mrs. G. P. Bieger — Smith for correcting the English text. The Organization for Health Research T.N.O. lent financial support.

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J. K. Radder, M.D.
 Diabetes Department
 University Hospital
 Rijnsburgerweg 10
 Leiden 2405
 The Netherlands