Diabetologia 20, 87–93 (1981)

Diabetologia

Review Articles

Diabetes in Identical Twins

A Study of 200 Pairs

A. H. Barnett, C. Eff, R. D. G. Leslie, and D. A. Pyke

Diabetic Department, King's College Hospital, London, England

Key words: Identical twins, concordance, discordance, insulin dependent diabetes, non-insulin dependent diabetes, genetics, aetiology

The object of this work is to try to elucidate the role of genetic and environmental factors in the aetiology of diabetes by studying a series of identical twins.

Concordance in identical (monozygotic) twins does not necessarily mean that a disease is genetic in origin. Twins usually live together in early life and thus share the same environment. Concordance could therefore be the result of genetic or environmental similarity. However, in later life most twins live apart and then concordance does suggest a genetic disease. *Discordance,* on the other hand, must indicate that a disease is due, at least in part, to non-genetic factors. We are therefore particularly interested in discordance in younger and concordance in older twins.

Previous Twin Studies

There have been five large studies of diabetic twins [1–5] but all have defects; none has categorised the twins as insulin dependent diabetics (IDDs) or non-insulin dependent diabetics (NIDDs) and in only two were the unaffected twins examined by glucose tolerance.

Then Berg [1] reported 47 identical twin pairs of whom 35 were over 43 years old. All of these were concordant for diabetes on history or glucose tolerance testing, but of the 12 younger twin pairs only 6 were concordant. White [2] found 16 of 33 pairs to be concordant but did not categorise them by age or type of diabetes. Gottlieb and Root [3] who, like White, worked at the Joslin Clinic but, we assume, were reporting on different patients, found seven out of 10 pairs in whom diabetes was diagnosed over the age of 40 were concordant, compared to only two out of 20 younger twins. Harvald and Hauge [4] ascertained twins from the Danish twin register. Of 47 "maturity-onset" pairs 26 were concordant, of 36 younger onset pairs only 12 were concordant but unaffected twins were not tested. Pollin et al [5] studied 53 identical twin pairs among US ex-service men aged 43 to 53 and found only three pairs were concordant but again unaffected twins were not tested.

All but one of these studies have also reported concordance rates in *non-identical* twins. Then Berg [1] found nine out of 50 pairs of non-identical twins to be concordant, White [2] two out of 63, Gottlieb and Root [3] two out of 70 and Harvald and Hauge [4] 22 out of 158. The overall figure for concordance in nonidentical twin pairs in these four studies is 35 out of 341 (10%).

In spite of the limitations of these studies three broad conclusions can be drawn.

1) Identical twins always show a higher concordance rate than non-identical twins irrespective of their age at diagnosis.

2) Younger onset pairs of identical twins are often discordant for diabetes.

3) Older onset pairs, on the other hand, are usually concordant for diabetes.

Our own previous results [6] confirm these general conclusions. Of 96 pairs of identical twins 59 index twins became diabetic before the age of 40, 31 were concordant and 28 discordant; of the 37 pairs in which the index twin was diagnosed after the age of 40 all but three were concordant. Similar proportions were found as the study has continued [7, 8]. In this study glucose tolerance tests were done on all non-diabetic twins.

0012-186X/81/0020/0087/$01.40

Table 1. Concordance and discordance for diabetes in 200 pairs of identical twins

Type of diabetes	Number of pairs		
	Concordant	Discordant	Total
Insulin dependent (IDD)	80	67	147
Non-insulin dependent (NIDD)	48	5	53
	128	72	200

Table 2. Sources of ascertainment of diabetic twin pairs

	Total	IDD	NIDD	Ratio $\frac{IDD}{NIDD}$
King's College Hospital	28	12	16	0.75 : 1
Other physicians	112	88	24	3.7 : 1
British Diabetic Association	36	30	6	5 : 1
Radio/TV	24	17	7	2.4 : 1
	200	147	53	2.8 : 1

Present Study

We have now enlarged our series to a total of 200 pairs of identical twins in whom one or both is diabetic. As insulin dependent diabetes (IDD) and non-insulin dependent diabetes (NIDD) are aetiologically distinct diseases [8] we have divided the twins into these two categories (Table 1) rather than into young and old as in our previous papers [6, 7].

Ascertainment of Twins

There is no twin register in Britain so a systematic survey of all twins is not possible. The twins in our series were found because they were diabetic, not because they were twins. The large, dense and relatively immobile population of Britain makes it a particularly suitable country for studies of this kind. Furthermore, there is no financial impediment to doctors collaborating as nearly all the patients are under the care of the National Health Service. Finally, there is an active Medical and Scientific Section within the British Diabetic Association many of whose members have referred twins to us. The twins come from four sources (Table 2) – our own clinic, physicians at other hospitals, the British Diabetic Association and self-referral after programmes on radio or television.

We do not believe that we have ascertained all the diabetic twins in Britain as (1) we estimate that there should be about 2,000 pairs of diabetic twins in the whole country assuming a frequency of identical twins in the population of 1:250 and of diabetes of 1:100, (2) there are many densely populated areas from which no twins have been referred to us and (3) only a quarter of our twins have non-insulin dependent diabetes whereas this type of diabetes is much commoner than insulin dependent diabetes.

The method of ascertainment has almost certainly led to a bias towards discovery of concordant as against discordant twin pairs as they have a double chance of recognition.

The proportion of IDD and NIDD pairs is very different in the four groups. In our own clinic there are more NIDD pairs than IDD but in the rest of the series IDD pairs heavily outnumber NIDDs. This suggests that not only is the selection of the whole series biased but that different degrees of bias operate in each category, in particular that there is a strong tendency towards selection of IDD pairs by those who have notified twins to us, including those twins who have notified themselves.

Proof of Identity

It is essential to establish whether the twins are in fact monozygous. We therefore confirmed monozygosity in 120 pairs by typing for blood groups ABO, CDE, MN, S, P, Lu^a, K, Le^a and Fy^a which establishes identity with probably no more than a 3% chance of error [9].

Blood grouping has never disproved identity which we have deduced clinically so in practice it is not important. The twins in whom blood grouping was not done gave such a typical clinical story of similarity, of parents, close friends and school teachers mistaking one for the other, and looked so much alike that we can be reasonably sure that they are identical. Any errors as regards monozygosity in these 200 pairs must, we think, be very small.

Diagnosis and Treatment

The diagnosis of diabetes in the index twins was unequivocal; in all pairs one at least was already under treatment.

Of 80 concordant IDD pairs only two differed in treatment – one twin being treated with oral therapy and the other with insulin. In one pair both twins were diagnosed in 1976; in the other the twin on insulin was diagnosed in 1974 and his co-twin in

Table 3. Age at diagnosis of diabetic twins

Age at diagnosis (of index twin) years	IDD				NIDD			
	Concordant		Discordant		Concordant		Discordant	
	M n	F n	M n	F n	M n	F n	M n	F n
0–9	10	13	7	9	0	0	0	0
10–19	13	11	8	10	0	0	0	0
20–29	4	11	7	7	0	1	1	0
30–39	3	2	6	4	0	2	0	1
40–49	2	3	0	4	6	3	1	1
50–59	3	0	1	0	3	14	0	0
60–69	1	1	0	0	2	6	1	0
70 +	0	1	0	1	5	4	0	0
Not known	1	1	1	2	2			
Mean (± SD) years	21 (±17)		20 (±14)		55 (±12)		46 (±16)	
Total	37	43	30	37	18	30	3	2

Table 4. Sex of twin pairs

	Female	Male
IDD Concordant	43	37
IDD Discordant	37	30
	80	67 = 147
NIDD Concordant	30	18
NIDD Discordant	2	3
	32	21 = 53

There is an excess of female NIDD pairs, which is to be expected, and a smaller excess in IDD pairs which is not, presumably due to selection bias

Table 5. Period of discordance in IDD twins

Years[a]	Number of pairs	
	Concordant	Discordant
0–5	56	28
6–10	14	10
11–15	3	13
16–20	3	4
20 +	2	10
Not known	2	2
	80	67

[a] Between diagnosis of diabetes in first and second twin in concordant pairs, or between diagnosis of diabetes in affected twin and the most recent test of unaffected twin in discordant pairs

1976. In each case the twin on insulin seems to be genuinely insulin dependent.

Of the 48 concordant NIDD pairs both twins are on the same treatment in 30 (diet alone in seven, diet and oral agents in 23). In 14 of the remaining 18 one twin is on oral therapy and the other on diet alone. In the four other pairs one is on insulin and the other on oral therapy. These four twins, however, were put on insulin at least 2 years after the diagnosis of diabetes and because of generally poor control not because of ketosis.

Of the 48 concordant NIDD pairs 16 were referred to us as discordant but glucose tolerance testing showed the second twin to be diabetic. Indeed in 25 of the 48 concordant pairs the second twin was asymptomatic and was tested only because they were twins of diabetics. The diagnosis of diabetes in the second twin was unequivocal in all but two cases: in pair 67 the second twin had a peak glucose value of 10.3 mmol/l and a 2 h figure of 7.4 mmol/l after 50 g glucose; in pair 167 the figures were 10.0 mmol/l and 8.5 mmol/l respectively.

Age and Sex

These twins are younger than the general diabetic population, two-thirds having been diagnosed under the age of 40 (Table 3). There was a slight excess of women among both the IDDs and NIDDs (Table 4).

Concordant and Discordant Pairs

There was a striking difference in concordance rates between IDDs and NIDDs. Of the 147 IDD pairs nearly half were discordant, but of the 53 NIDD pairs all but five were concordant.

Insulin Dependent Diabetic Twins

The observation that IDD twins can be discordant for diabetes, if true, shows that this type of diabetes cannot be entirely due to genetic causes.

It might be argued that discordance is a temporary feature and that eventually the IDD twin pairs will all become concordant. Our observations suggest this is unlikely. The interval between diagnosis in concordant twins tends to be only a few years while many of the discordant twins have remained discordant for a long time (Table 5). Of the 80 concordant pairs the second twin became diabetic within five years of the first in 56 (70%). In 14 pairs the interval was between 5 and 10 years and in only 8 did it exceed 10 years. The discordant pairs are quite different. Of 67 pairs 37 (55%) have been discordant

Table 6. Concordant (C) and discordant (D) twin pairs living together (T) and apart (A) at time of diagnosis of diabetes

		IDDs		NIDDs	
		T	A	T	A
0–19	C	44	3	0	0
	D	33	1	0	0
20–39	C	9	10	0	3
	D	3	23	1	1
40 +	C	1	11	3	36
	D	0	6	1	3
(Not known		3		5)	

At age 20–39 there is a preponderance of discordant IDDs living apart as compared to concordant but no difference earlier, when most pairs were living together, or later, when all but one were living apart

for more than 5 years, 27 for more than 10 years, 10 for more than 20 years. Furthermore, in the 15 years since this study began only three unaffected IDD twins have become diabetic, all within about one year of their co-twins. These three pairs (numbers 124, 148 and 160) developed IDD at the ages of 12, 8 and 4. Their co-twins were then normal (i.e. had normal glucose tolerance tests, random blood glucose or urine tests), but developed diabetes 8, 13 and 10 months later. In the remaining discordant pairs there has been no tendency for glucose tolerance in the unaffected twins to deteriorate on repeated testing over the years of the study.

HLA Typing

IDD is characterised by an increased frequency of certain HLA types, especially B8, B15, B18, DRw3 and DRw4 [10]. We have studied HLA B frequencies in the IDD twins [11]. The discordant as well as the concordant pairs show the expected increase of B15; figures for the other alleles are less definite. This must mean that even the discordant pairs have an HLA-linked susceptibility to diabetes. Whether it is the same as in the concordant pairs we do not yet know. Analysis of the HLA D frequencies, which are more closely related to IDD than HLA B types [10], may clarify this point.

Environmental Factors in Discordant Twins

We have been unable to identify any environmental factor which might have led to diabetes in the affected twin of the discordant pairs. There is no difference between twins with respect to birth weight, present weight, parity or history of infectious disease. Nor did we find any evidence of virus infection in the diabetic twins which might account for the difference although it is possible that we tested for such infections too long after the diagnosis [12]. There is, however, a difference in the number of twins living together and apart in the concordant and discordant pairs (Table 6). In early life most of the co-twins were living together and in late life apart but in middle life (age 20–39) most of the discordant pairs but only half the concordant pairs were living apart. This finding is consistent with the possibility that an environmental factor might be responsible for the diabetes in the affected twin of the discordant pairs. However, the concordant/discordant ratio was about the same in the young-onset pairs, who were nearly all living together, as in the old-onset pairs, who were all living apart.

Islet Cell Antibodies

Three of the non-diabetic twins of IDD pairs (numbers 94, 102, 115) showed islet cell cytoplasmic antibodies (ICAs) when examined 11 years after, 2 years after and at the same time as the diagnosis of diabetes in their co-twins, at titres of 1:8, 1:16 and not known. In two of these ICAs persist. In the other they disappeared after four years. All three twins remain unaffected, six, six and five years after ICAs were first detected. As all these pairs have remained discordant for over five years we think that the unaffected twins are now unlikely to develop diabetes. We conclude therefore that ICAs do not necessarily act as a marker for IDD [13].

Necrobiosis Lipoidica Diabeticorum

Five twins, all insulin-dependent, have necrobiosis. Four of the five twins are from two concordant pairs. In both pairs the co-twin developed necrobiosis within two years of the index twin. The only diabetic who has necrobiosis and whose co-twin has not developed the condition less than 16 months ago. These observations raise the question of whether inherited factors are involved in the aetiology of necrobiosis.

Non-insulin Dependent Diabetes

Of 53 identical twin pairs 48 are concordant for NIDD and only five are discordant (Table 1). As with the IDD pairs, the interval between diagnosis in concordant NIDD co-twins is usually short. In 35 of

Table 7. Period of discordance in NIDD twins

Years[a]	Number of pairs	
	Concordant	Discordant
0–5	35	5
6–10	11	–
11–15	2	–

[a] Between diagnosis of diabetes in first and second twin in concordant pairs, or between diagnosis of diabetes in affected twin and most recent test of unaffected twin in discordant pairs

Table 8. Number of twins with first degree family history of diabetes

		FH+	FH–	Unknown
IDD	Concordant	16	57	7
	Discordant	8	56	3
NIDD	Concordant	21	27	0
	Discordant	1	4	0

FH = Family history

the 48 pairs (73%) the second twin became diabetic within five years of the first (Table 7). Of the remaining 13 pairs 11 became concordant between six and ten years and the remaining two became concordant 11 and 12 years after the diagnosis in the first twin. As few of the co-twins had been tested at the time of diagnosis of diabetes in the index twin it is probable that the real period of discordance is even less than these figures suggest. In all the five discordant pairs the affected twin has been diagnosed only within the last three years. We suspect that the unaffected twins in these pairs will before long become diabetic, indeed all show early metabolic changes already, especially a reduced insulin response to glucose [14]. We have not yet seen a pair of twins in which NIDD was diagnosed in one and the other has remained normal on glucose tolerance testing after more than seven years.

This concordance rate in NIDD pairs is high despite the fact that they are middle aged or elderly and almost all were living apart at the time of diagnosis of diabetes. If any non-genetic factor were operating in this type of diabetes it must presumably have been either one to which the twins were exposed in their youth, when they were living together, or an extremely common factor to which all, or nearly all, the twins were exposed despite their living apart.

It might be argued that the high concordance rate is due to bias in ascertainment. We think this is unlikely. If we had not done glucose tolerance tests but had accepted the previous assessment of discordance the apparent concordance rate amont the NIDD pairs would have been 31 out of 53–61% which is similar to the concordance rate in IDD pairs.

Nine NIDD pairs were referred to us as monozygotic who turned out on clinical assessment and blood grouping to be dizygotic. All these pairs were discordant. This makes it even more unlikely that bias in ascertainment could account for the high concordance in the monozygotic NIDD pairs.

Family History of Diabetes

The importance of genetic factors in causing NIDD is emphasised by the strong family history in NIDD twins, twenty two of the 53 pairs gave a first degree family history of diabetes a much higher figure than in IDD twins (Table 8).

Concordance of NIDDs under Observation

We have observed two discordant NIDD twin pairs become concordant. The index twin of the first pair (No. 140) developed diabetes in 1971 at the age of 50. She was treated with diet and then oral hypoglycaemic agents. Her co-twin had normal glucose tolerance in 1977 (peak value 8.5 mmol/l, at two hours 5.5 mmol/l) and no glycosuria on regular testing; in 1978 she became frankly diabetic and was treated with diet and oral agents. The index twin of the second pair (No. 167) developed diabetes in 1978 at the age of 73. She was treated with diet and glibenclamide from the start. Her co-twin had normal glucose tolerance in 1978 (peak value 7 mmol/l at 2 h 4.5 mmol/l) and no glycosuria. In January 1980 on routine glucose tolerance test she was found to have a peak glucose value of 10 mmol/l and a 2 h figure of 8.5 mmol/l. Haemoglobin A_1 was 9.8%, (normal range 6–8.9%) and we have classified her as diabetic. Metabolic studies of the remaining 5 pairs of discordant twins suggest that the concordance rate may indeed be higher than that observed using conventional glucose testing. Despite normal glucose tolerance tests they all show metabolic abnormalities highly suggestive of early diabetes [14].

Body Weight

Obesity is widely assumed to be implicated in the aetiology of non-insulin dependent diabetes [15]. Diabetes is commoner in fat people than lean and NIDDs are on average overweight [16]. Weight

Table 9. Difference in body weight between co-twins in concordant NIDD pairs

Weight difference kg	No.	Weight difference Percentage of average body weight	No.
0–4	5	0–9	6
5–9	8	10–19	5
10–14	1	20–29	6
15–19	5	30+	1
20+	2		
	21		18[a]

In three pairs (numbers 13, 68, 113) one twin was overweight (i.e. exceeded average weight by at least 10%) and the other was not. Their weights, expressed as % ideal body weight, were respectively: 114 and 96, 108 and 80, 140 and 87. In all the pairs the lighter twin developed diabetes first

[a] In three pairs information on height was inadequate so expected body weight could not be calculated

The mean weight of the first diagnosed twin (in the 18 concordant pairs) was 108% of ideal; of the second 113%. Thus the NIDD pairs were on average overweight but it was more often the lighter than the heavier cotwin who developed diabetes first

reduction is almost universally advocated as treatment for NIDD. If obesity is important in the aetiology of NIDD how can we explain the high concordance rates in identical twins with this type of diabetes? Are they concordant for obesity and is this the reason for their concordance for diabetes?

We have reliable figures for the weight at time of diagnosis of diabetes in only 21 of our NIDD pairs. In the others information is lacking or incomplete, usually because one or both of the twins of a pair could not recall his weight at the relevant time or because one of the twins was not available for questioning.

It is striking that in these 21 pairs body weight in the two twins was often different (Table 9). In 16 the co-twins differed from each other by at least 5 kg at the time of diagnosis of diabetes in the first, in 8 by 10 kg, in 7 by 15 kg and in two pairs one twin was more than 20 kg heavier than his co-twin, yet in all these pairs both had diabetes.

Expressing the results in percentage terms co-twins differ from each other by at least 10% of average body weight in 12 of 18 and by at least 20% in seven, (in three of the 21 pairs we do not have adequate figures for height). In three of the pairs one twin was obese (over 110% of average body weight calculated from the figures of Metropolitan Life Assurance Company 1959) and the other was not. In 12 of the pairs the lighter twin was the first to develop diabetes.

In six of 18 pairs both twins exceeded the 110% of average body weight, in five one twin exceeded the 110% and the other did not, in seven pairs neither twin was overweight.

Thus these twin pairs are concordant for diabetes even when their weight differs considerably and when neither twin is overweight. This unexpected finding suggests that the genetic component which is so powerful in NIDD acts independently of obesity.

Of the five still discordant pairs the diabetic twin was heavier in two and lighter in three.

In contrast to the differences in weight the height of the co-twins was very similar. In all 18 pairs in which the height of both twins at the time of diagnosis was known it differed by no more than 2.5 cm.

Diet and Parity

Other possible aetiological factors in diabetes are diet and parity. It is difficult to make any satisfactory dietary assessment; we were not able to demonstrate any difference between the concordant and discordant twins in this respect.

Information concerning parity was likewise scarce. In only two discordant IDD pairs had both twins given birth before the onset of diabetes; in two other pairs only the non-diabetic twin had had a baby. We can therefore draw no conclusions concerning a possible role of parity in the aetiology of IDD. Nor can we say anything about parity and NIDD since almost all our pairs of NIDD twins are concordant.

Conclusions

The fact that about half the IDD pairs are discordant and seem likely to remain so suggests that this type of diabetes does not have an entirely genetic basis. Some further support for an environmental cause comes from the greater number of discordant than concordant pairs aged 20–39 who were living apart at the time of diagnosis of diabetes. On the other hand in later life when almost all pairs were living apart concordant pairs outnumbered discordant, as they did in early life when all pairs were living together.

It might be thought that some idea of the relative importance of the genetic and environmental factors in the aetiology of IDD could be gained by determining the concordance rates of twins. About 55% of our IDD twins are concordant but this is unlikely to be the true concordance rate as ascertainment is biased in favour of concordant pairs and, furthermore, concordance does not necessarily denote genetic effect. For these reasons we do not believe that

concordance rates for an inherited disease indicate the strength or penetrance of the gene nor that, in this case, they support the theory that IDD is due to a single, autosomal recessive gene.

The nature of the environmental factors responsible for IDD has not been elucidated in this study. We have no evidence to support the virus theory of its aetiology, but we cannot suggest a better one.

That the discordant IDD pairs show the characteristic HLA pattern of insulin dependent diabetes demonstrates that their diabetes cannot be entirely due to environmental factors, there must be some genetic susceptibility as well. We do not know whether concordant and discordant IDD pairs are genetically identical or whether there is genetic heterogeneity within insulin dependent diabetes. We hope to settle his question when we have been able to do HLA D typing on the IDD pairs.

In non-insulin dependent diabetes the situation is different. There is no association with the HLA system and there is nearly complete concordance in the twin pairs (and the "unaffected" twins already show metabolic abnormalities) – this despite the fact that most twins were living apart when diabetes was diagnosed and they were frequently different in body weight. It has long been accepted that obesity is important in the pathogenesis of NIDD but on these results it is difficult to assess its significance.

We conclude that genetic factors are predominant in the aetiology of non-insulin dependent diabetes.

Acknowledgements. This work has been supported by the Medical Research Council and the Nuffield Foundation.

We are grateful to Drs. R. B. Tattersall, P. G. Nelson and C. G. Theophanides who have worked on the twin project in the past.

We are also grateful to colleagues in the British Diabetic Association for referring twins to use and to the twins themselves for their unstinting co-operation.

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Dr. D. A. Pyke
Diabetic Clinic
Kings's College Hospital
London SE5 9RS
England