

Glucose Tolerance and Serum Insulin in Identical Twins of Diabetics

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Summary: Glucose tolerance with serum insulin assay has been carried out in 24 apparently unaffected identical twins of diabetics. Glucose values were significantly higher and insulin values significantly lower than in control subjects, but there was considerable individual variation and in half the cases glucose tolerance was normal. There was no case of increased insulin response. In these twins glucose tolerance and insulin response were not correlated with weight, family history of diabetes, age at diagnosis of diabetes in the affected twin, time since that diagnosis, nor with age at testing the unaffected twin. On retesting 12 of the twins after two years no significant differences were found from the first testing.

We conclude that not all these twins are likely to develop diabetes, that the assumption that identical twins of diabetics are necessarily "prediabetic" is probably erroneous, and that factors other than genetic ones are important in the aetiology of diabetes.

Introduction

The study of diabetes in twins might be expected to throw light on the inheritance of the condition and possibly on its early development. In this paper we report investigations on 24 pairs of apparently unaffected identical twins of known diabetics. We have already reported our findings in nine of these 24 cases (Pyke and Taylor, 1967).

There have been several case reports of individual pairs of monozygotic twins, one or both of whom have diabetes, but only three large series have been published (Joslin *et al.*, 1959; Harvald and Hauge, 1963; Gottlieb and Root, 1968; Gottlieb *et al.*, 1969). Harvald (1967) found that 58 out of 97 pairs were concordant and predicted that all would eventually become so, but no series has been published in which all pairs were in fact concordant. A study similar to ours is that of Cerasi and Luft (1967), who measured carbohydrate tolerance and insulin response in five unaffected identical twins of diabetics.

Clinical Data

Some of the twins attended King's College Hospital, but most were referred to us by colleagues in other centres or through the British Diabetic Association. The diagnosis of diabetes in the affected twins was unequivocal, having been made on clinical grounds, usually several years before we tested the unaffected twins. Of the 24, 20 were taking insulin, one was taking a sulphonylurea, and three were on diet alone. That the twins were in fact monozygous was established on clinical grounds and confirmed in 20 pairs by detailed blood grouping (kindly done for us by the Lister Institute Blood Group Reference Laboratory, London) for the following groups: ABO, CDE, MN, S, P, Lu^a, Le^a, Le^b, Fy^a. If twins are the same with respect to these blood groups the probability that they are identical is about 98% (Maynard Smith and Penrose, 1955).

The main clinical features of the 24 pairs of twins are

shown in Table I. Of the unaffected twins, four were more than 10% above expected weight; a family history of diabetes was known in 15 (first degree relative in four). The time intervals between the diagnosis of diabetes in the affected twin and our testing the apparently unaffected twin was less than 1 year in 4, 1-5 years in 7, 6-10 years in 6, 11-15 years in 4, 16-20 years in 0, and 21-26 years in 3. The range was 0-26 years and the mean interval 7.9 years.

Test Procedure

The tests on the unaffected twins were done at King's College Hospital or, more often, in the patients' homes. The subjects were taking a free diet; after an overnight fast they had a 50-g. oral glucose tolerance test, samples of venous blood being taken before glucose administration and 30, 60, and 120 minutes after. Glucose was determined by a glucose oxidase method and serum insulin by a double antibody radioimmunoassay as in our previous paper (Pyke and Taylor, 1967). Results were compared with those obtained from 50 normal controls of similar age and weight studied in our laboratory.

Results

Blood glucose and serum levels for each of the 24 unaffected twins and mean values are shown in Table II. Mean glucose values were significantly higher in the twins than in the normal controls. Nevertheless, not all the twins had impaired glucose tolerance; in 12 the glucose tolerance tests were normal—that is, all blood glucose values lay within two standard deviations of the mean values for the normal controls. Mean insulin values for the whole group were significantly lower than those of normal controls, but there was considerable individual variation. In no case were serum insulin values, fasting or after glucose, abnormally high.

We have analysed the results according to the age of the twins at the time of testing (Table III). There are no significant differences in glucose or insulin values in 10 twins aged 30 or less and the 14 aged over 30. The results when the twins are divided by age at diagnosis of diabetes in the affected twin into those aged less than 20 (8) and those aged 20 or more (16) are shown in Table IV. Glucose values at 30 and 60 minutes are slightly higher in the twins of the later-onset diabetics (who were 27 years older at the time of testing), but neither these nor any of the other results are significantly different in the two groups.

Since mean glucose tolerance in these unaffected twins of diabetics was impaired it might be concluded that this was due to a general decline in islet cell function which would culminate in clinical diabetes. To test this hypothesis we have examined our results in relation to the time interval since diabetes was diagnosed in the affected twin. If the apparently unaffected twins were undergoing a progressive deterioration in glucose tolerance then twins of diabetics of long-standing should show a greater impairment of glucose tolerance than twins of more recently diagnosed diabetics. We have therefore divided our results (Table V) into cases where the unaffected twin was tested within 10 years of the diagnosis of diabetes in the affected twin (15) and those in whom the interval was longer (9). The only significant difference

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TABLE I.—Twenty-four Pairs of Identical Twins Discordant for Diabetes: Clinical Features

Pair No.	Sex	Family History of Diabetes	Diabetic Twin		Unaffected Twin				Age at 1st Test	Age at 2nd Test
			Age at Diagnosis	Treatment	Height		Weight			
					in.	cm.	lb.	kg.		
1	F.	Grandfather, 2 great-aunts, uncle	13	Insulin	64	162.6	99	44.9	23	26
2	M.	Maternal aunt, paternal aunt	52	Diet					55	
3	M.	Father	50	Tablets	72	182.8	258	117.0	55	58
4	F.	O	28	Insulin, now diet only	63	160.0	112	50.8	31	34
5	M.	O	28	Insulin	70	177.8	151	68.5	30	32
6	F.	Maternal uncle	43	Insulin	65	165.1	124	56.2	43	46
7	F.	Mother	44	Insulin (has since died)	63	160.0	120	54.4	44	47
8	F.	Sister	44	Insulin	66	167.6	140	63.5	56	58
9	F.	Maternal great-uncle	5	Insulin	62	157.5	98	44.5	14	17
10	F.	O	21	Insulin	61	154.9	137	62.1	45	
11	F.	Grandmother, maternal great-aunt	29	Insulin	63	160.0	147	66.7	36	
12	F.	O	17	Insulin	65	165.1	172	78.0	18	20
13	M.	First cousin once removed	12	Insulin	51	129.5	85	38.6	13	15
14	M.	O	26	Insulin	66	167.6	133	60.3	41	43
15	M.	Maternal aunt	35	Insulin	68	172.7	144	65.3	46	
16	F.	O	21	Insulin	63	160.0	126	57.2	28	
17	F.	Paternal great-grandfather	15	Insulin	67	170.2	126	57.2	22	
18	F.	O	43	Insulin	63	160.0	143	64.9	45	
19	M.	O	36	Insulin	68	172.7	168	76.2	48	
20	M.	First cousin	5	Insulin	55	139.7	79	35.8	12	60
21	F.	First cousin	37	Insulin	65	165.1	105	47.6	58	
22	F.	Sister	56	Diet	64	162.6	168	76.2	56	
23	F.	O	4	Insulin	64	162.6	126	57.2	30	
24	F.	Great-grandmother, great-great-grandmother	8	Insulin	52	132.0	70	31.8	8	

TABLE II.—Glucose Tolerance and Serum Insulins in the Apparently Unaffected Identical Twins of Diabetics and in 50 Normal Subjects

Twin No.	Blood Glucose (mg./100 ml.)				Serum Insulin (µu./ml.)			
	Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
1	77	163	137	118	24	65	63	53
2	80	162	183	125	9	22	29	22
3	95	145	162	125	27	26	50	50
4	67	71	65	55	10	11	16	13
5	78	114	59	63	29	100	45	11
6	94	147	154	71	13	41	43	18
7	76	145	185	123	—	16	32	2
8	86	129	136	38	11	14	10	11
9	92	122	163	110	18	25	26	6
10	83	152	146	85	24	79	38	27
11	87	103	109	86	8	16	27	18
12	84	87	105	93	25	37	58	69
13	81	—	96	93	22	—	67	47
14	124	114	82	70	9	57	35	13
15	81	115	114	56	15	70	77	15
16	81	107	73	72	13	52	37	13
17	76	78	118	107	6	15	11	19
18	69	138	94	109	18	41	30	53
19	71	129	108	68	18	37	55	18
20	79	—	96	78	13	—	31	21
21	81	87	98	80	15	19	25	22
22	113	214	188	92	24	43	73	27
23	68	87	71	62	13	32	16	13
24	76	112	73	81	8	48	45	48
Mean (±S.E. of M)	83±9	124±7	117±8	86±5	16±1	39±5	39±4	25±4
Normal subjects	73±2	104±3	82±3	68±2	14±1	62±4	53±4	22±3
P	<0.01	<0.01	<0.001	<0.001	N.S.	<0.001	<0.025	N.S.

TABLE VI.—Repeat Glucose Tolerance and Serum Insulins After Two Years in Twelve Identical Twins of Diabetics

	Blood Glucose ± S.E. of Mean (mg./100 ml.)				Serum Insulin ± S.E. of Mean (µu./ml.)			
	Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
First test	86±4	120±9	120±12	87±8	19±1	37±8	39±5	26±6
Second test	80±4	116±9	104±13	80±12	16±1	41±6	46±8	27±8

TABLE III.—Glucose Tolerance and Serum Insulins in the Identical Twins of Diabetics in Relation to Age at Time of Testing

Age at Testing	No.	Mean Age at Time of Testing	Blood Glucose ± S.E. of Mean (mg./100 ml.)				Serum Insulin ± S.E. of Mean (µu./ml.)			
			Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
30 or less	10	20	79±2	109±10	99±10	88±6	18±2	46±8	42±5	30±6
Over 30	14	46	86±4	132±9	130±11	85±7	16±2	35±6	39±5	21±3

between the two groups is in the glucose values at 120 minutes, when the figure is actually lower in the twins of diabetics diagnosed more than 10 years previously.

Finally, we have retested 12 of the twins after two years, the results being shown in Table VI. There is no significant difference in glucose or insulin values between the first and second tests.

Discussion

These results show, as do those of Cerasi and Luft (1967), that the mean glucose tolerance of identical twins of diabetics is impaired as compared with control subjects, but, nevertheless, in about half the cases the glucose tolerance test is normal. We cannot relate any clinical features, such as age, weight, or family history, to the moderate impairment of glucose tolerance in some of these twins.

Serum insulin values in the twins show an impaired response despite higher glucose levels, in contrast to the findings of Gottlieb *et al.* (1969). Thus the suggestion that diabetes may be induced by a resistance to the action of insulin (Vallance-Owen, 1969) is not supported by our results nor by those of Cerasi and Luft (1967). Whatever the significance of the mild impairment of glucose tolerance and insulin release in our twins there is no evidence from this study that it is a progressive process. It might be argued that all or most of these twins were destined to develop diabetes and that, as time passes, glucose tolerance will deteriorate. There is no evidence of this in the 12 cases in which we have repeated glucose tolerance testing after two years; indeed, there is a remarkable similarity in the results in the two tests. Furthermore, if these apparently unaffected twins were destined to develop diabetes one would expect to find that those whose twin had only recently become diabetic would show less impairment of glucose tolerance than those whose twin had been diabetic for a long time; but we do not find this. In nine of the 24 pairs diabetes had been discovered in the

TABLE IV.—*Glucose Tolerance and Serum Insulins in Identical Twins of Diabetics According to Age at Diagnosis of Affected Twins*

Age at Diagnosis of Diabetes in Affected Twin	No.	Mean Age at Time of Test	Blood Glucose \pm S.E. of Mean (mg./100 ml.)				Serum Insulin \pm S.E. of Mean (μ u./ml.)			
			Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
Less than 20	8	18	79 \pm 3	108 \pm 13	107 \pm 11	92 \pm 7	16 \pm 3	37 \pm 7	40 \pm 8	35 \pm 8
20+	16	45	85 \pm 4	130 \pm 8	122 \pm 11	82 \pm 6	16 \pm 2	40 \pm 7	39 \pm 5	21 \pm 3

TABLE V.—*Glucose Tolerance and Serum Insulins in Identical Twins of Diabetics Tested within 10 Years of, or More than 10 Years after, the Diagnosis of Diabetes in the Affected Twin*

Years Since Diabetes Diagnosed in Affected Twin	No.	Mean Age at Time of Test	Blood Glucose \pm S.E. of Mean (mg./100 ml.)				Serum Insulin \pm S.E. of Mean (μ u./ml.)			
			Fasting	30 min.	60 min.	120 min.	Fasting	30 min.	60 min.	120 min.
< 10 (mean = 4.5)	15	34	83 \pm 4	117 \pm 11	112 \pm 13	92 \pm 9	17 \pm 3	37 \pm 4	42 \pm 7	29 \pm 7
10+ (mean = 17.1)	9	41	79 \pm 3	123 \pm 8	103 \pm 9	62 \pm 4	17 \pm 1	53 \pm 8	47 \pm 7	18 \pm 2
P			N.S.	N.S.	N.S.	< 0.05	N.S.	N.S.	N.S.	N.S.

affected twin more than 10 years before we tested the other, yet the glucose and insulin values for these nine show no significant difference from the rest (except at 120 minutes, when it was actually better).

In one pair—No. 23 in Table I, which has been reported separately (Malins *et al.*, 1970)—a twin showed normal glucose tolerance, even in late pregnancy, 26 years after her sister had developed diabetes and 20 years after she herself had shown a highly abnormal glucose tolerance test immediately after an appendicectomy.

All these results cast doubt on the idea of a progressive deterioration of glucose tolerance in identical twins of diabetics leading eventually to 100% concordance (Harvald, 1967). It is often assumed that all identical twins of diabetics are "prediabetic"—that is, certain to become diabetic. If this were so it would follow that diabetes was exclusively a genetic disease. Our results are consistent with the view that the aetiology of diabetes depends on several factors and that an

inherited element is only one of the components in its causation, perhaps not such an important one as is often supposed (Pyke, 1970).

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Single-dose Therapy with Streptomycin and Sulfametopyrazine for Bacteriuria during Pregnancy

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Summary: One hundred and sixty-three patients with bacteriuria in pregnancy were treated with a single dose of antibiotic. Four regimens were used: sulfadoxine (sulphormethoxine) 2 g., sulfametopyrazine 2 g., streptomycin 1 g., and a combination of sulfametopyrazine 2 g. and streptomycin 1 g. The highest cure rate of 77% was achieved with streptomycin and sulfametopyrazine. The long-acting sulphonamides alone gave a cure rate of 55% while streptomycin alone eradicated 43% of the infections. Despite the high cure rate with combined therapy bacterial resistance developed in some cases.

Introduction

In selecting chemotherapy for treatment of bacteriuria during pregnancy the clinical and social conditions of the patients must be considered in addition to the infecting organisms. To avoid side effects and toxicity to the fetus the amount of

chemotherapy should be the smallest necessary to eradicate the infection, and short courses are as effective as is prolonged therapy (Williams *et al.*, 1965, 1968). The reluctance of patients to complete a course of treatment has recently been re-emphasized (Sprunt, 1970), particularly among the poor. Pregnant women of high parity tend not to take their iron tablets.

In our antenatal clinic, where 70% of patients belong to socioeconomic groups 9, 10, or greater, and 15% cannot understand English, there has been additional urgency to find an effective form of treatment which can be given in the clinic in one dose. The recent introduction of ultra-long-acting sulphonamides which maintain therapeutic levels of sulphonamide in the urine and serum for one week led us to try two of these compounds, sulfadoxine‡ and sulfametopyrazine, for this purpose. We have also treated a few patients with streptomycin alone, and finally a group with a combination of sulfametopyrazine and streptomycin. In all cases only one dose of the drug was given.

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‡ The name sulfadoxine replaced sulphormethoxine as the approved title from January 1969.