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THE RESPONSE OF DIABETICS TO A STANDARD TEST DOSE OF INSULIN

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That some diabetics improve on high carbohydrate diets is an established fact (1, 2). The selection of suitable patients for this type of diet has, until the present, been one of trial and error. Recently MacBryde (3) has made an attempt to select cases on the basis of insulin sensitivity. He studied the response of a small group of diabetics to a standard test dose of insulin and concluded that they fell into two groups, the relatively insulin-resistant and the relatively insulin-sensitive. The resistant group gained tolerance on high carbohydrate diets while the sensitive group did not. In addition, the patients showing insulin-resistance were usually older, frequently obese, often had vascular hypertension and showed little tendency to acidosis. The relatively sensitive group were usually younger, often thin, had as a rule low blood pressure and were more prone to develop acidosis and coma. Although the insulin requirement of the resistant group was larger, the sensitive group were looked upon as more serious, judged by their tendency to acidosis. On the basis of a somewhat different test, Himsworth (4) classified diabetics in a similar manner, but concluded from his experimental findings and clinical data that insulin-sensitive patients tolerated high carbohydrate diets better than did the insulin-insensitive.

Since these two investigators appear to have come to diametrically opposite conclusions in regard to the relationship between insulin sensitivity and response to high carbohydrate diets, it was felt worth while to study this problem further. The purpose of the present investigation has been to study a relatively large group of diabetics with respect to their blood sugar response to a standard test of insulin, and to correlate, if possible, insulin sensitivity with their clinical characteristics and responses to diets of variable carbohydrate content.

METHOD OF STUDY

Fifty of a total of 197 patients attending the adult Diabetic Clinic of the Strong Memorial Hospital were chosen for this study. Each had previously had a complete physical examination, blood count, urinalysis, and Wassermann reaction. They represented a fair cross-section of the total clinic population and were arbitrarily selected from amongst those who had attended the clinic for at least five months and who had been most co-operative and regular in their attendance. None was suffering from infection at the time of the studies. Cases in which the diagnosis of diabetes mellitus was at all questionable were subjected to a sugar tolerance test and were accepted only if they had typical diabetic responses (Cases 7, 25, 40, 45).

Each patient was subjected to an "insulin tolerance test" and classified as relatively insulin-sensitive or relatively insulin-resistant. His past record in our clinic and on any admission to the hospital was then studied and analyzed. These studies constitute the basis for this report. The patients had previously been followed from 5 to 123 months, an average of 42 months each, and had usually been seen at monthly intervals—the severe cases more, and the mild cases less frequently.

"Insulin-tolerance test." Following the technique of MacBryde (3), one unit of insulin per·ten pounds of body weight was administered subcutaneously in the fasting state. The test was performed in the clinic between 9:00 and 9:30 a.m., in a special room set aside for that purpose. The patients were required to sit quietly or lie down for the following three hours. Venous blood specimens for sugar determinations were drawn fasting, at one, one and one-half, two, and three hours. The fourth hour specimen was omitted for the convenience of the patients and staff. This appears to be a justifiable omission since twelve of MacBryde's fifteen patients showed their maximum responses by the end of the third hour, and of the remaining three, none would have fallen into another group had the fourth hour specimen been omitted. The one and one-half hour specimen was included after a preliminary study revealed that a fair number of patients had minimum blood sugars at that time (Cases 20, 25, 26, 37, 45).

Weight. The patients were weighed in their street clothes (minus hat and coat) at each visit to the clinic. Their height in stockinged feet was measured on admission and at approximately yearly intervals. Normal weight for height, age and sex[1] was recorded from time to time. Patients who were 10 per cent or more over normal were considered overweight, those 10 per cent or more under normal were considered underweight.

Diets were prescribed by the examining physician in grams of protein, fat, and carbohydrate. The diet was then calculated in terms of household measures of food by one of the dietitians permanently assigned to the Diabetic Clinic and was discussed with the patient. At each visit to the clinic, the patient was required to bring in a detailed report of his food for the preceding day. This was reduced to grams of protein, fat, and carbohydrate by the dietitian and recorded on the chart. With this frequent check on cooperation and understanding it was possible to correct errors and re-instruct the patients in the use of diets.

Although no standard diets were used, they contained, as a rule, little fat, moderate carbohydrate, and from 0.75 to 1.0 gram of protein per kilogram of normal body weight. These were modified at frequent intervals, however, to improve control, to suit the patients' tastes and purses, and to adjust weight. An effort was made to maintain the weight normal for height and age or, preferably 10 per cent below. In many cases, this was not possible because of a patient's unusual appetite or unwillingness to cooperate when on a low-caloric intake.

In order to compare diets in patients of different weights, it was found necessary to resort to a common denominator. The total glucose value per kilogram of body weight seemed the only logical one to choose, since the caloric values and protein-fat-carbohydrate ratios were not constant. The glucose value was calculated as 58 per cent of the protein, plus 10 per cent of the fat, plus 100 per cent of the carbohydrate, and expressed in grams per kilogram. The control diet described by MacBryde (3) contained protein 1.0 gram, fat 1.7 grams, and carbohydrate 2.0 grams, or a total glucose value of 2.7 grams per kilogram. His high carbohydrate diets (Tables IV and V (3)) contained 3.0 or more grams. For simplicity of expression and analysis, the diets herein described containing 3.0 or more grams of total glucose per kilogram are considered "high carbohydrate," all others "low carbohydrate" diets. The designation "low carbohydrate," therefore, obviously includes moderate carbohydrate diets as well. This classification appears sound since it is not the purpose of this study to report on the effects of high or low carbohydrate diets *per se*, but rather to compare the effects of diets of variable carbohydrate content on single individuals and on groups.

Insulin, when required, was self-administered 15 to 30 minutes before meal time. Of the patients requiring insulin, six took it once a day (before breakfast), eleven twice a day (before breakfast and supper), and two three times a day (before each meal). Patients recorded as having insulin reactions had at least one record of a reaction in their charts. Any attempt to estimate the number or degree of reactions would, of course, have been futile.

Glycosuria. On admission to the clinic, patients were taught to test their urines with Benedict's qualitative solution in the usual fashion (5). This was usually done at least once a day (before breakfast) and frequently as often as three times a day. The color of the reaction and the amount of precipitate was noted. The examining physician recorded this as 0 to 4+. In addition, at each visit an overnight specimen of urine, voided before breakfast, was brought in and tested qualitatively for sugar and diacetic acid as a check on the patient's record.

Blood sugars. In the clinic it was found impracticable to do fasting blood sugars because of the difficulties attending subsequent dietary management and insulin dosage. Therefore, all studies were done on blood taken one and one-half to three hours after breakfast. Venous blood was drawn and sugar determined by Benedict's (6) method at intervals of one to three months, depending on the severity of the disease. Blood sugars were averaged for each year and separately for the duration of each diet. In determining the average blood sugar level for a patient's total period of observation only the yearly averages were considered.

Control. For practical purposes, the control of diabetes is synonymous with the control of glycosuria. There are some who would question this view, but since the other aspects of diabetic regulation are considered elsewhere, the term "control" has been adopted here to designate the degree to which glycosuria was restrained. Patients were classified as "good" whose urines remained sugar-free at all times or showed an occasional trace of sugar. The first month, during which diet and insulin were being adjusted, was excluded from consideration. One case (Number 23) was considered "good" in spite of two attacks of acidosis of short duration, because of the absence of glycosuria at all other examinations over a long period. Control was considered "fair" where the patient usually showed mild glycosuria (0 to 1+) with occasional larger excretion of sugar (2 to 4+). "Poor" control was reserved for those patients who showed considerable glycosuria (2 to 4+) on most examinations. It should be noted that the degree of glycosuria recorded occurred in spite of adjustments of diet and insulin.

The patients were classified after a careful study of their records and before the insulin tolerance or other data had been computed, so that estimates of their condition might be unprejudiced.

Blood pressure was determined on admission and at irregular intervals thereafter with a Tycos aneroid sphygmomanometer. A systolic pressure of over 150 mm. Hg was considered hypertension. Several patients (Cases 32, 9, 3, 12, 13, 44, 28, 27) had normal pressures on admission, but subsequently developed hypertension. These have been classified as hypertensive.

Arteriosclerosis. Patients were said to have arteriosclerosis when the peripheral arteries were palpably

[1] Metropolitan Life Insurance Company Tables. Howe Scale Co., Rutland, Vt.

thickened or beaded and when the retinal vessels showed changes generally ascribed to arteriosclerosis.

RESULTS

The clinical and laboratory data of the fifty patients studied are presented in Tables I and II. The terms "sensitive" and "resistant" are hereafter used synonymously with "relatively insulin-sensitive" and "relatively insulin-resistant," respectively.

Subcutaneous insulin tolerance. The fasting blood sugars fell from 30 to 85 per cent during the three-hour test period (Table II). The average fall for the entire group was 60 per cent.

In general, the absolute fall was proportional to the height of the fasting blood sugar (Figure 1). From the distribution of the points in this figure, there did not appear to be any tendency for the patients to fall naturally into sensitive and resistant groups. For purposes of comparison they were, therefore, arbitrarily divided into two groups, as in MacBryde's (3) study, using the average percentage fall for the entire group as the dividing line. Those which fell more than 60 per cent were classified as sensitive, those which fell less than 60 per cent were classified as resistant.

Clinical characteristics. There did not appear to be any significant difference between the sensitive and resistant groups with respect to weight, insulin requirement, controlability of glycosuria, average blood sugar, or incidence of arteriosclerosis and hypertension (Table I). The average age of the insulin-sensitive group was lower than that of the insulin-resistant. This was related to the fact that all four cases below the age of 21 fell into the former group. As was to be expected, the sensitive group had a greater incidence of insulin reactions (Table I).

Acidosis occurred more frequently in the sensitive than in the resistant group. This appeared to be related to the fact that all the juvenile diabetics were in the sensitive group. Of the four patients in the entire series who were under 21 years of age, three developed acidosis on one or more occasions while of the remaining 46 cases, only two had acidosis (Tables I and II).

Relation of insulin tolerance to diet. The control on high and low carbohydrate diets was compared in the insulin-sensitive and insulin-resistant

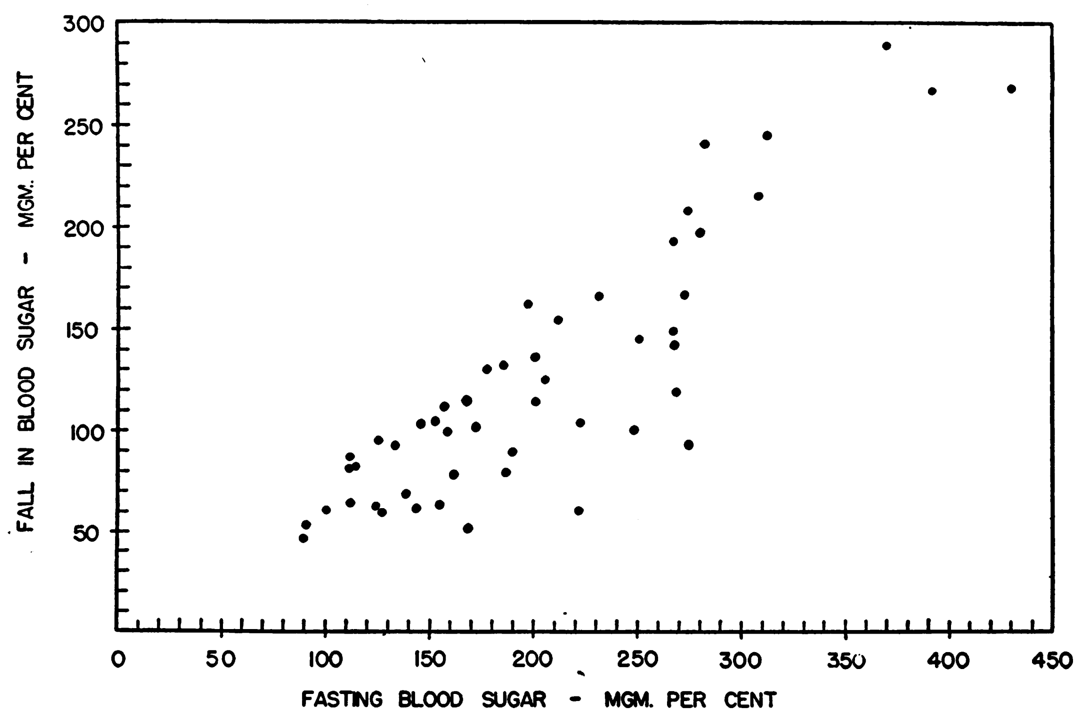

FIG. 1. INSULIN TOLERANCE TESTS

TABLE I

Summary of findings

	Insulin-sensitive	Insulin-resistant
Number of cases	28	22
Sex:		
Male	12	7
Female	16	15
Average age:		
Years	53.2	56.9
Under 21 years	4	0
Weight:		
Normal	11	8
Overweight	10	11
Underweight	7	3
Average duration of diabetes, *years*	6.4	7.2
Insulin tolerance:		
Average fasting blood sugar, *mgm. per cent*	217	185
Average test dose of insulin, *units*	14.6	15.9
Average fall, *per cent*	70.7	47.3
Insulin:		
Average 24-hour requirement, *units*	19.1	18.8
Cases requiring:		
0 units in 24 hours	9	9
1–30 units in 24 hours	13	8
31+ units in 24 hours	6	5
Reactions	12	8
Control:		
Good	13	11
Fair	13	6
Poor	2	5
Average blood sugar after meals, *mgm. per cent*	216.2	213.6
Complications:		
Acidosis	4	1
Hypertension	10	9
Arteriosclerosis	14	12

TABLE II

Clinical data

Case number	Insulin tolerance test: Blood sugar: Fasting	Insulin tolerance test: Blood sugar: Fall	Insulin tolerance test: Fall	Insulin tolerance test: Test dose	Age	Weight	Carbohydrate content of diet	Control	Hypertension	Arteriosclerosis	Acidosis
	mgm. per cent	*mgm. per cent*	*per cent*	*units*	*years*						
1	282	241	85	15	70	Normal	Low	Fair	+	+	−
2	197	162	82	20	68	Underweight	High	Good	+	+	−
3	370	289	78	16	36	Normal	Low	Fair	+	−	+
4	274	208	75	13	44	Normal	Low	Fair	−	−	−
5	211	154	73	11	68	Underweight	High	Fair	−	−	−
6	267	193	72	11	68	Underweight	High	Fair	−	+	−
7	114	82	72	13	66	Normal	High	Good	−	−	−
8	231	166	72	15	18	Overweight	Low	Fair	−	−	+
9	156	111	71	16	69	Overweight	High	Fair	+	+	−
10	308	215	70	14	20	Overweight	Low	Fair	−	−	−
11	280	197	70	13	68	Underweight	High	Good	−	+	−
12	205	125	61	15	62	Overweight	Low	Good	+	+	−
13	111	81	73	19	70	Overweight	Low	Good	+	+	−
14	185	132	71	12	56	Underweight	High	Good	+	+	−
15	177	130	73	12	62	Underweight	High	Good	−	+	−
16	312	245	79	12	55	Underweight	High	Fair	−	+	−
17	145	103	71	20	65	Overweight	Low	Good	−	−	−
18	272	167	61	14	59	Normal	Low	Fair	−	−	−
19	392	267	68	12	16	Normal	High	Poor	−	−	+
20	152	104	68	16	50	Normal	Low	Good	−	−	−
21	430	268	62	12	25	Normal	High	Poor	−	−	−
22	200	136	68	16	65	Overweight	Low	Fair	+	−	−
23	167	114	68	12	16	Normal	High	Good	−	−	+
24	111	77	69	12	55	Normal	High	Fair	−	−	−
25	100	60	60	16	59	Overweight	Low	Good	−	+	−
26	133	92	69	17	52	Overweight	High	Good	−	+	−
27	158	99	63	17	69	Normal	Low	Good	+	+	−
28	125	95	76	17	60	Overweight	Low	Fair	+	+	−
29	168	51	30	17	40	Overweight	Low	Fair	−	−	−
30	143	61	43	20	51	Overweight	Low	Good	−	+	−
31	268	119	44	14	63	Normal	Low	Poor	−	−	−
32	126	59	47	15	59	Normal	High	Poor	+	+	−
33	222	104	47	19	45	Overweight	Low	Poor	+	−	−
34	161	78	48	20	52	Overweight	Low	Fair	−	−	−
35	138	68	49	20	57	Overweight	Low	Good	+	−	+
36	124	62	50	16	36	Overweight	Low	Good	−	−	−
37	89	46	52	13	60	Underweight	High	Good	−	+	−
38	267	149	56	18	68	Overweight	Low	Good	+	+	−
39	250	145	58	14	75	Normal	High	Good	−	+	−
40	90	53	59	16	48	Normal	Low	Good	−	−	−
41	172	101	59	15	67	Normal	Low	Poor	−	+	−
42	274	93	34	16	54	Overweight	Low	Fair	+	+	−
43	189	89	47	12	46	Normal	Low	Good	−	+	−
44	267	142	53	16	62	Overweight	Low	Fair	+	+	−
45	111	64	58	14	76	Underweight	Low	Good	+	+	−
46	248	100	40	16	59	Normal	Low	Good	+	−	−
47	221	60	27	16	73	Overweight	Low	Poor	−	+	−
48	186	79	42	14	57	Normal	High	Fair	+	+	−
49	200	114	57	13	52	Underweight	Low	Fair	−	−	−
50	154	63	41	16	54	Overweight	Low	Good	−	−	−

TABLE III

The relationship between diet and diabetic control

Control	Insulin-sensitive group: High carbohydrate diets	Insulin-sensitive group: Low carbohydrate diets	Insulin-resistant group: High carbohydrate diets	Insulin-resistant group: Low carbohydrate diets
Good	7	6	2	9
Fair	5	8	1	5
Poor	2	0	1	4

groups. The last prescribed diet in each case was used as the basis for comparison since it was presumably the optimal one under the circumstances, having usually been adjusted several times. If the resistant group gains tolerance on a high carbohydrate intake, as suggested by MacBryde (3), those of the group on high carbohydrate diets should have been better controlled than those on low carbohydrate diets. Also, the resistant group should have been better controlled on high carbohydrate diets than the sensitive group on similar diets. No such relationship could be demonstrated (Table III).

There were fourteen cases in the series who at one time or another during their period of observation were changed from a low to a high carbohydrate diet, or *vice versa*. These were studied in detail with respect to changes in glycosuria, blood sugar and 24 hour insulin requirement (Table IV). If the resistant group gains tolerance on high carbohydrate intake, a change from low to high carbohydrate diet in a resistant patient should have resulted in improvement, whereas in a sensitive patient either no change or an aggravation of his condition should have occurred. No such correlation could be demonstrated. Some patients gained and others lost tolerance on high carbohydrate diets quite without relation to their insulin sensitivity (Table V).

TABLE IV

Effect of changing from low to high carbohydrate diet

Case number	Dietary total glucose per kgm.	On diet	Average 24-hour insulin requirement	Average p.c. blood sugar	Glycosuria
	grams	*months*	*units*	*mgm. per cent*	
INSULIN-SENSITIVE GROUP					
3	2.2 3.7	2 2	44 30	208 245	No change
6	2.5 3.1	4 12	5 10	150 140	Increased
7	2.9 3.3	3 5	35 10	109 96	No change
8	2.3 3.2	11 1	52 34	334 257	No change
9	2.3 3.3	61 3	6 28	197 110	Increased
10	1.7 3.4	9 7	37 43	194 243	Decreased
11	2.9 3.3	9 18	33 32	240 297	No change
15	2.5 3.1	0.5 59	13 23	338 217	Decreased
18	1.4 3.0	66 1	9 0	286 258	No change
21	2.3 4.0	22 1	30 38	156 229	No change
INSULIN-RESISTANT GROUP					
32	1.8 3.0	10 3	7 53	137 294	Increased
38	2.1 3.2	4 6	18 0		Decreased
39	2.1 3.8	12 46	21 21	196 245	No change
48	2.0 3.2	3 28	0 16	215 260	Increased

TABLE V

Effect of changing from low to high carbohydrate diet

	Insulin-sensitive group	Insulin-resistant group
Glycosuria:		
Increased	2	2
Decreased	2	1
Unchanged	6	1
Average p.c. blood sugar:		
Increased	4	3*
Decreased	6	0
Average 24-hour insulin requirement:		
Increased	5	2
Decreased	5	1
Unchanged	0	1

* No blood sugar values obtained in Case 38.

COMMENT

Fifty cases of diabetes mellitus were studied with respect to their response to a standard test dose of insulin. In general, the absolute fall in blood sugar was proportional to the height of the fasting level, a finding first noted by Radoslav (7). Although the percentage blood sugar fall varied widely, between 30 and 85 per cent, the distribution of cases was such that no natural cleavage between insulin-sensitive and insulin-resistant groups could be made out. The division of diabetics into two such groups on the basis of a standard test dose of insulin appeared, therefore, to be an arbitrary one. When the cases were divided in that manner, using the average percentage blood sugar fall for the entire series as the dividing line, no appreciable difference in clinical characteristics or response to high carbohydrate diets could be made out between the sensitive and resistant groups. The lower average age and the greater incidence of acidosis in the sensitive group were related to the fact that all four juvenile diabetics fell into that group. The greater tendency of juvenile diabetics to acidosis is a well known fact (8). Whether there was any significance in their all having fallen into the sensitive group cannot be determined from the available data. A much larger group of juveniles would have to be investigated before any definite conclusions could be drawn.

There has been a growing conviction among students in this field (4, 9, 10) that there are extra-pancreatic factors operating in certain diabetics. In some instances the operation of such factors, for example, liver disease (11, 12), thyrotoxicosis (13), and pituitary disease (14) can be clearly demonstrated. In others, in whom there is simply a resistance to test doses of insulin, extra-pancreatic factors have been assumed (4, 9, 10). In the present state of our knowledge such assumptions do not appear to be justified. Himsworth's (4) demonstration of the inability of "insensitive-diabetics" to transfer sugar from the blood to the tissues under the influence of insulin is highly suggestive of such a factor. On the other hand, the available data on the significance of the response to a standard test dose of insulin do not warrant any conclusions regarding the pathogenesis of diabetes. A study of the response to a standard test dose of insulin in normals and in diabetics with known extra-pancreatic influences at work might shed further light on the significance of the insulin tolerance test.

CONCLUSIONS

(1) In diabetics the response of the fasting blood sugar to a standard test dose of insulin varies greatly.

(2) The division of diabetics into relatively insulin-sensitive and relatively insulin-resistant groups is an artificial one.

(3) There does not appear to be any significant relationship between the insulin-sensitivity of diabetics and their clinical characteristics or their responses to high carbohydrate diets.

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