CONSTITUTION AND INSULIN SENSITIVITY IN DIABETES MELLITUS

BY

JOHN LISTER, M.B., B.Chir., M.R.C.P.*Senior Medical Registrar, Royal Free Hospital***JOHN NASH, M.Sc., M.D., M.R.C.P.***Senior Medical Registrar, Royal Free Hospital*

AND

UNA LEDINGHAM, M.D., F.R.C.P.*Physician, Royal Free Hospital*

It has long been recognized that there are several clinical types of diabetes mellitus. In particular, Falta and Boller (1931), Falta (1936), Himsworth and Kerr (1939), and Himsworth (1949), and others have described two broad groups of diabetics—the young, thin, non-arteriosclerotic group with normal blood pressure and usually an acute onset to the disease, and the older, obese, arteriosclerotic group with hypertension and usually a gradual onset.

Clinically, the patients in the first group are rapidly responsive to insulin and are subject to both hypoglycaemia and ketosis, whereas the patients of the second group are clinically less responsive to insulin and are much less liable to either of these complications. This difference was more clearly defined when Himsworth (1936) devised his insulin sensitivity test and found that in general the first group of patients showed a sensitive response to that test, whereas those in the second group tended to be insensitive, although exceptions were encountered in both groups. Furthermore, he found that the patients tended to be either clearly sensitive or clearly insensitive in their response.

He considered that this difference could be explained by differing aetiologies of the diabetic state, the first group being due solely to insulin deficiency, whereas in the second group there is rather an insensitivity to the action of insulin.

From clinical observations of the response of patients to insulin therapy and from the results of insulin sensitivity tests it is clear that patients differ widely in their reaction to insulin, but it is our impression that the most important determining factor in insulin sensitivity is neither age nor weight, but rather the constitutional make-up of the patient, and that in particular there is a group of patients of characteristic physique who are almost uniformly insensitive in their response to insulin. The clinical features of these patients have been noted for many years by one of us (U. L.) and are described below.

Clinical Features

The skull tends to be small and the bones are generally slender with tapering extremities. The features are also small and characteristically neat and centrally placed. Thus the palpebral fissure appears too small for the eyeball, the nose is small and straight, there is a short upper lip, and the mouth is often of the "Cupid's bow" formation. These features together tend to give the patient a doll-like appearance.

The jaw-line is ill defined, partly owing to the small, slender mandible and partly to the tendency to plumpness in this situation. The teeth are large, white, even,

and often widely spaced, and when patients have lost their teeth inquiry supports these facts. The skin is fine and soft and unusually resistant to normal wear and tear, so that even working-class women preserve this characteristic. The nails are well shaped, long, and of good texture, usually displaying well-marked moons. Naturally these features are better displayed in young patients. The hair is fine and silky, with a hair line usually placed low and dipping over the temples, and patients report that it is easy to keep in place.

Obesity is a frequent finding, and is of girdle distribution. In the upper girdle the fat is deposited over the back of the shoulders, on the upper arms, and about the breasts. In the lower girdle it is deposited around the abdomen, the buttocks, and the thighs. The waistline is preserved as a boundary between the two girdles, the extremities are spared, and the furrow over the vertebral column is usually apparent. On inquiry it is clear that weight is gained to an unusual degree during or after pregnancy, and a sudden increase in weight occasionally coincides with adolescence or marriage, suggesting an apparent correlation between weight gain and times of unusual hormonal activity. It is important, however, to stress that frank obesity is not necessary for the recognition of this constitutional variation.

The menstrual pattern is often unusual. Two chief types of variation are met with. Either catamenia is early, with a tendency to heavy periods and at least normal fertility, or, as often, it is delayed, the periods are infrequent and scanty, and the women are subfertile. Finally, on detailed inquiry it is found in nearly every case that a patient with these features strongly resembles one or other parent or near relation, and that this person is reported to be obese, or diabetic, or both.

In addition to these basic characteristics, many of the patients have one or more of the findings usually associated with Cushing's syndrome, so that plethora, hirsuties, striae, and acne are not uncommon additional features. We have examined closely all patients attending the clinic to see whether those whose appearance falls outside this category have any features in common. We failed to find any such features, and we have accordingly divided our cases into those with an unremarkable constitution and those showing the characteristics described above. These types we have provisionally designated type I and type II, respectively.

Present Investigation

Having in mind the work of Himsworth (1936) on insulin sensitivity, we decided to apply his test to an unselected group of patients in our clinic so as to observe whether any correlation exists between the patients clinically and their sensitivity to insulin.

We have investigated 100 patients attending the Royal Free Hospital Diabetic Clinic with a distribution of age of onset as shown in Table I: 49 as in-patients; 47 as out-patients; and four who were investigated twice—once as in-patients and once as out-patients.

TABLE I.—Cases Investigated

Age at Onset	Male	Female	Total
1-30	2	16	18
31-40	4	14	18
41-50	6	19	25
51-60	4	25	29
Over 60	4	6	10
	20	80	100

These cases represent a random sample of the patients attending the clinic, the only factor in their selection being their willingness to co-operate. The high proportion of women must be attributed to the fact that until recently the Royal Free Hospital has been a women's training school, thus attracting a preponderance of women patients. In all other respects the numbers investigated in the various age groups correspond closely with the normal distribution of diabetics, the maximum incidence of onset being in the decade 51 to 60.

A subsidiary object of the investigation has been to see whether or not the test would have a place as a routine investigation in diabetics. We have accordingly applied the test with the minimum of inconvenience to the patient and with as little interference with stabilization as possible, and in two respects we have had to differ from Himsworth in the preparation of the patient. First, we have not omitted the protamine-zinc insulin on the day before the test, but we have examined our results and find no evidence that the protamine-zinc insulin given approximately 26 hours previously has affected our figures. Secondly, about half our cases have been investigated as out-patients. Conditions as near to basal as possible have been obtained by resting the patient in the laboratory for half an hour before the test, and, since estimations of basal metabolism are carried out under similar conditions without significant variation, we feel that this does not invalidate our results.

The method of blood-sugar estimation which we have used is that described by Lauber and Mattice (1944), which gives a true value for the level of glucose in the blood (average mean deviation is 3 mg. per 100 ml.).

Distribution of Insulin Sensitivity

In considering our findings we have first examined the insulin sensitivity of the patients throughout the whole group. Fig. 1 shows the frequency distribution

FIG. 1.—Distribution of insulin sensitivity.

in ranges of insulin sensitivity of 0.1. It is seen that in our series the sensitivity ranges from zero to just over 2, the main peak being situated between 0.6 and 0.8 and the mean insulin sensitivity for the whole group being 0.65. Of the cases 23% have a sensitivity of over 1 and 14% have a sensitivity of less than 0.25. Furthermore, it is noteworthy that at a point near where Himsworth found a gap in his series (between 0.7 and 0.9) our distribution falls below the expected normal (at 0.9), although there is no absolute gap such as he found.

Age of Onset and Insulin Sensitivity

Next we considered the possible effect of age of onset on insulin sensitivity. In general there is a tendency for insulin sensitivity to fall with age of onset, though exceptions are to be found in most age groups. Thus some cases in which the disease has started at an early age have given an insensitive response, whereas a number of cases of later onset have a sensitivity well above the average for the group. Nevertheless the average sensitivity below the age of 40 is above the mean for the group (0.65), whereas after this age it is a little below the mean. Fig. 2 shows the average insulin sensitivity

FIG. 2.—Average insulin sensitivity per decade.

per decade of age of onset. Any conclusions from these observations, however, must be modified by our examination of the relationship of insulin sensitivity to weight, and it must be remembered that there is often a tendency for weight to increase with advancing age.

Weight and Insulin Sensitivity

In our investigation of the relationship of insulin sensitivity to weight we have taken as our index of obesity the ratio of the weight in pounds to the height

FIG. 3.—Weight/height ratio in normal women over 25 years.

in inches. Fig. 3 shows the relationship of weight to height in normal women over 25 years of age. It was plotted from figures given by the Metropolitan Life Insurance Company, quoted by Stieglitz (1949), relating

to people of normal longevity, and it can be seen that the relationship of weight to height is an almost constant one, the weight/height ratio at any point on the curve being approximately 2.1. This authority claims that in normal people of over 25 the ratio has been found to be independent of age.

Fig. 4 illustrates the relationship of insulin sensitivity

FIG. 4.—Relationship of insulin sensitivity to weight/height ratio.

to weight/height ratio in the group as a whole. From this it is clear that a large proportion of the patients have a weight/height ratio over the normal figure of 2.1. Furthermore, it shows an apparent inverse relationship of insulin sensitivity to weight/height ratio. This is even more striking when the average insulin sensitivity for short ranges of weight/height ratio is plotted against the weight/height ratio (Fig. 5).

FIG. 5.—Average insulin sensitivity to weight/height ratio.

Owing to the wide scatter in Fig. 4 it may be unjustifiable to average the sensitivity in this way, and the absence of the normal scatter of a linear correlation could be due to the presence of two populations behaving differently in regard to insulin sensitivity. It appeared, therefore, that the patients studied could be divided into two groups.

In order to ascertain whether there is any correlation between insulin sensitivity and clinical characteristics we divided our patients at this stage into the two constitutional types already described. It was found that 38 of the patients were type I, 37 were type II, 20 we were unable to classify, and 5 could not be used owing to incomplete data. Many of the twenty unclassified cases had some of the features of type II but not in sufficiently marked degree to place them definitely in the group. Two of us typed the patients independently, arriving at almost identical conclusions.

TABLE II.—Type I (Unremarkable Constitution)

Case No.	Sex	Age	Age at Onset	Height in In.	Weight in lb.	W/H Ratio	Insulin Sensitivity
6	M	56	47	65	147	2.36	1.07
17	F	22	19	61	110	1.80	1.10
60	F	21	9	70	140	2.00	0.80
80	F	28	26	63	120	1.91	1.08
16	F	26	25	66	125	1.89	1.10
65	F	40	29	63	103	1.62	0.16
26	M	29	28	67	140	2.09	1.74
75	F	24	22	62	126	2.03	1.02
95	F	18	15	62	100	2.10	0.51
94	F	34	36	60	108	1.80	0.52
30	M	37	36	70	117	1.67	0.42
68	F	57	33	63	151	2.40	1.40
47	F	48	38	62	123	1.69	0.92
15	F	41	36	68	115	1.69	0.55
22	F	54	36	63	115	2.18	1.60
90	F	49	39	61	146	2.40	0.79
44	F	40	39	66	133	2.02	1.02
57	M	50	34	72	192	2.67	0.90
85	F	46	45	66	140	2.12	0.60
12	F	52	44	62	134	2.16	0.70
71	F	66	50	62	121	1.95	0.23
39	F	64	50	61	140	2.30	0.20
27	M	46	46	67	114	1.70	0.92
100	F	54	51	56	115	2.05	0.61
48	F	53	52	66	166	2.52	1.28
38	F	60	58	72	162	2.25	0.38
23	F	68	60	62	126	2.03	0.30
70	F	60	58	58	131	2.26	0.95
53	F	63	59	61	142	2.33	0.74
20	F	70	54	62	124	2.00	0.19
64	M	58	56	69	124	1.80	0.60
74	F	68	60	61	135	2.21	0.95
108	F	54	53	60	90	1.50	0.50
56	F	65	35	62	109	1.76	0.13
110	F	73	73	61	125	2.05	0.78
27	M	62	53	67	126	1.88	1.88
24	F	66	65	67	143	2.13	0.41
19	F	42	39	60	106	1.77	0.63

TABLE III.—Type II (Characteristic Constitution)

Case No.	Sex	Age	Age at Onset	Height in In.	Weight in lb.	W/H Ratio	Insulin Sensitivity
69	F	61	30	57	131	2.30	0.21
45	F	25	14	60	112	1.81	0.60
92	F	34	26	61	128	2.10	0.70
1	F	18	15	65	151	2.30	0.32
97	F	19	16	59	145	2.46	0.50
83	M	41	34	64	196	3.07	0.61
107	F	49	40	62	143	2.31	0.60
50	F	35	33	63	181	2.88	0.57
29	F	46	44	63	137	2.18	0.24
87	F	51	49	64	160	2.50	0.65
62	F	52	46	56	172	3.07	0.00
61	F	46	45	61	168	2.75	0.00
84	F	64	42	66	203	3.08	0.23
58	F	64	48	59	149	2.52	0.39
77	F	49	44	65	164	2.52	0.37
8	M	53	50	68	174	2.55	0.27
82	F	50	50	59	163	2.77	0.72
113	M	49	37	66	197	2.98	1.13
31	M	52	46	65	154	2.76	0.60
81	F	59	56	61	170	2.78	0.70
42	F	59	57	60	142	2.36	1.13
101	F	68	57	66	250	3.79	0.30
3	F	61	59	65	177	2.72	0.70
5	F	64	55	62	145	2.33	0.90
78	M	51	51	62	176	2.63	1.20
112	F	70	56	65	159	2.44	0.35
54	F	62	60	66	161	2.44	0.08
96	F	67	51	60	159	2.64	0.50
25	F	72	60	63	156	2.48	0.68
111	F	62	59	64	173	2.70	0.35
40	F	53	53	60	168	2.80	0.00
28	F	74	65	56	135	2.41	0.23
34	F	62	62	60	155	2.58	0.08
102	M	31	30	71	231	3.26	0.38
79	F	43	38	70	224	3.20	0.72
109	F	60	43	64	224	3.50	0.49
88	F	42	42	61	201	3.30	0.00

In Tables II and III are shown the details of the cases in the two groups. In type I the age of onset varies from 9 to 73, and on the whole the patients do not exceed their expected weight. The insulin sensitivity tends to be above the average for the whole series (0.65), the mean being 0.78. In type II the age of onset varies from 14 to 65, the patients are nearly all above their expected weight, and the mean insulin sensitivity is well below that for our whole series, being 0.48.

Statistical Analysis

The figures for type I and type II were analysed statistically, and Table IV shows the mean for each type of the weight/height ratio, the age of the patient, and the insulin sensitivity, together with the range and standard deviation of the last statistic.

TABLE IV

		Type I	Type II
Weight/height ratio..	Mean	2.07	2.79
Age of patient ..	"	50	52
Insulin sensitivity ..	"	0.78	0.48
	Range	0.13-1.88	0.00-1.20
	Standard deviation	0.44	0.31

The difference in insulin sensitivity in the two groups is highly significant—that is, the chances are less than 1 in 100 of a difference of this order arising purely by chance. But one must remember that 20 intermediate type cases have been discarded from this analysis.

Now although it was pointed out earlier that the presence of frank obesity was not necessary for the recognition of the constitution of the type II patient, many of our patients of this type were overweight (see Table III). Partial correlation coefficients were therefore calculated between insulin sensitivity and the weight/height ratio of the patients to see whether obesity could be eliminated as the possible cause of the insulin insensitivity of the group.

These partial correlation coefficients are as follows:

Insulin sensitivity-obesity: type I, + 0.24; type II, - 0.20.

Although the difference between these coefficients is significant, the variation of each of them from zero is not significant, and it is not considered justifiable to draw conclusions from them at this stage.

Discussion

In a study of 95 diabetic patients, 38 were found to have an unremarkable constitution and 37 conformed to a definite constitutional type which could be recognized clinically. The latter group tended to be overweight, using a weight (lb.)/height (in.) ratio of 2.1 as the standard of normality.

Although our statistical study does not enable us to define the influence of overweightness on the insulin sensitivity, our clinical impression is that the relative insensitivity of the type II patient is probably a fundamental constitutional characteristic and not directly related to the weight. The factor of overweightness does, however, require further investigation, and it is of interest to note in Tables II and III that, though the insensitive type II patients are generally overweight, nevertheless those patients of unremarkable constitution who are relatively insensitive are, in most cases, also relatively underweight.

Since the preparation of this paper was completed, and during the planning of further anthropometric studies in order to define the constitution of the type II diabetic more clearly, our attention has been drawn to the work of Draper, Dupertuis, and Caughey (1944).

Dupertuis, who is not a clinician, analysed anthropometric measurements and somatotypings from a series of 225 diabetics and observed that two clearly different morphological types could be recognized. He divided these patients into types I and II, and described those in type I as being more linear in form than those in type II, who were heavier and whose form was more rounded. He subdivided his type I cases into subdivisions IA and IB—the former showing good muscular development and the latter being more feminine in their features and occupying an intermediate position between types IA and II. He thought that because of their youth they were not yet obese, but that their form indicated a potentiality for that state later on.

It will be seen that such a classification of diabetics by constitutional type is almost identical with the one suggested by us—except that we would classify patients from type IB as type II patients, remembering our earlier statement that frank obesity is not a necessary feature for the recognition of this constitutional variation.

Furthermore, when Dupertuis asked his clinical colleague Caughey to correlate his constitutional variants with the clinical features of the cases they found more than an 80% correlation between morphology and clinical expression. Thus the type I patients were generally severe diabetics but insulin-sensitive, becoming ketosed with poor control, and the type II patients were generally less severe but insulin-resistant and having little tendency to ketosis or hypoglycaemia.

Thus although no insulin-sensitivity tests were carried out by these workers, and although we have so far done no somatotyping, there is a remarkable degree of accord between their observations and the observations recorded in this present paper—namely, that there are two constitutional types of diabetic who differ in their reaction to insulin and in whom we consider that the aetiology of the diabetic state is probably different.

Summary

There are two clinical types of diabetic, which can be identified by their appearance.

The first type are of an unremarkable constitution—that is, we could find no characteristic features common to the group. The second type present certain unmistakable features, although all the stigmata need not be present in each case.

One-fifth of the patients examined were intermediate in type and could not be classified.

The mean insulin sensitivity of the patients in our series falling into type I was 0.78 and in type II it was 0.48.

Partial correlation coefficients for insulin sensitivity and obesity in the two types do not enable us to define precisely the effect of weight on insulin sensitivity, but our clinical impression is that in most cases the actual sensitivity of a patient is a fundamental constitutional characteristic.

The similarity between these observations and those of other workers has been stressed and further anthropometric studies are being planned.

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