but very few in the group of the normal GT pattern showed retinopathy.

5) We give 1 point to each of the following factors and evaluate the fate of the borderline cases with points gained from these factors.

- (1) Fasting blood sugar value over 100 mg/dl
- (2) 120 min value in 50 g OGTT over 110 mg/dl

(3) Diabetic retinopathy

(4) Δ IRI/ Δ BS 30 min less than 0.4

Patients with a change to normal GT pattern have 1 point, those with a change to diabetic pattern have more than 3 points and those remaining at the borderline have 2 points. From these results it is predicted that borderline cases with a gain of more than 3 points will develop diabetic pattern.

(2) Assay of Blood Insulin during 100 g Glucose Tolerance Test as a Means for the Diagnosis of Diabetes Mellitus

Kinori KOSAKA, M D, Takehiko IDE, M D, Yasuo AKANUMA, M D
and Hiroshi KAJINUMA, M D

The Third Department of Internal Medicine, University of Tokyo, Faculty of Medicine

Takeshi KUZUYA, M D

Department of Medicine, Jichi Medical School, Tochigi

Ryoko HAGURA, M D

Institute for Adult Diseases, Asahi Life Foundation, Tokyo

Diabetes mellitus is a disease characterized by metabolic abnormality due to insufficient action of insulin. It possesses various features such as hereditary background, the characteristic natural history, and the tendency to develop microangiopathy. Although glucose intolerance is an important feature of diabetes, the mere abnormality of glucose tolerance is inadequate for the accurate diagnosis, since there are so many pathological conditions which impair glucose tolerance. The importance of differentiating true diabetes mellitus from other diseases with glucose intolerance should be emphasized. For this purpose, it is necessary to utilize findings, other than blood or urine sugar relevant to more inherent abnormality of diabetes mellitus.

Insulin secretory response to glucose load

is decreased in diabetes. In this report, we present evidences and propose to use insulin response during glucose tolerance test as an aid to reach a more specific diagnosis of primary diabetes.

Subjects for investigation

The 100 g oral glucose tolerance test (GTT) was used exclusively. Blood sugar and immunoreactive insulin were assayed before and 30, 60, 90, 120 and 180 minutes after glucose load. As many as 4800 tests were performed in about 1500 patients attending the diabetic clinic, about 400 patients with various diseases, 57 cases with both parents diabetic, and in about 120 healthy controls. The types of glucose tolerance curves were classified into normal, borderline and diabetic types, according to the

criteria of the Committee of the Japan Diabetic Society.

Insulin responses in definitely diabetic patients

We fedined those patients as definitely diabetic, whose fasting blood sugars (FBS, capillary blood, true sugar) exceeded 140mg/dl or who have clear diabetic retinopathy. In these definitely or unequivocally diabetic patients, the insulin responses during GTT were invariably smaller than normal. Insulin response remained subnormal even when glucose tolerance of the patient was improved to borderline or normal types after successful treatment of diabetes. As the insulin response of diabetes was more markedly depressed in its initial phase, the ratio of the increment of blood insulin (in $\mu\text{U/ml}$) to that of blood sugar (in mg/dl) 30 minutes after glucose load ($\Delta\text{IRI}/\Delta\text{BS}$) was characteristically decreased in diabetes, and provided a useful index for subsequent analysis. $\Delta\text{IRI}/\Delta\text{BS}$ was usually lower than 0.5 in diabetics, while it was higher than 0.5 in normal subjects.

Fig. 1. Relationship between ΣBS (mg/100 ml) and ΣIRI ($\mu\text{U/ml}$) during 100g GTT in various pathological conditions (non-obese subjects). $\blacktriangle$ Hyperthyroidism (36), $\blacktriangledown$ Gastrectomy (33), $\bigcirc$ Normal control (73), $\bullet$ Diabetes mellitus (511), $\times$ Diabetes Mellitus (7) (numbers in parenthesis)

Insulin responses in other pathological states which may cause glucose intolerance

Various pathological states such as gastrectomy, corticosteroid treatment, simple obesity, hyperthyroidism, acute hepatitis, liver cirrhosis, myocardial infarction and cerebral apoplexy, can cause glucose intolerance. In these conditions, unlike true diabetes, insulin responses during GTT were progressively enhanced when glucose tolerance was impaired to borderline and diabetic types. $\Delta\text{IRI}/\Delta\text{BS}$ usually exceeded 0.5 irrespectively of glucose tolerance, in various states other than true diabetes. When comparisons were made between patients with similar types of glucose tolerance, insulin response in definite diabetes was much smaller than those in other pathological states. These relationships are clearly visualized when the sums of six insulin values during GTT (ΣIRI) are plotted against the sums of blood sugar values (ΣBS) (Fig. 1). In hyperthyroidism and gastrectomy, ΣIRI became greater when ΣBS was increased (i.e. glucose tolerance was more impaired). Similar relationships were also observed in liver cirrhosis, acute hepatitis, steroid treatment and simple obesity. In contrast, ΣIRI remained low throughout the wide range of ΣBS in definitely diabetic patients.

Insulin responses before the development of definite diabetes

We have discussed so far on insulin responses of already established diabetes. What are the insulin responses of patients who had normal FBS and no retinopathy but later became definitely diabetic? In 20 such cases, their FBS became elevated and eventually exceeded 140 mg/dl during follow-up period. For example, the case 1 in Table 1 was first seen at her age of 53, when she had borderline type glucose tolerance and $\Delta\text{IRI}/\Delta\text{BS}$ of 0.19. Her FBS became elevated to 160 mg/dl after 7 years and 8 months. It is noteworthy, that the initial $\Delta\text{IRI}/\Delta\text{BS}$ ratios in these cases were all less than 0.5 whether their types of glucose tolerance were normal, borderline or diabetic.

Table 1. Types of 100 g GTT and Δ IRI/ Δ BS in patients who had normal FBS and no retinopathy initially but later developed definite diabetes with FBS higher than 140 mg/dl.

Age, sex	Family history of diabetes	Types of GTT and Δ IRI/ Δ BS	Time to develop definite diabetes	FBS(mg/dl) after development of diabetes	Types of GTT and Δ IRI/ Δ BS during observation period
53 F	mother, aunt	B 0.19	7y 8m	160	B 0.28, B 0.11, D 0.21
32 F	father, mother, sister, brother	D 0.22	6y 8m	173	D 0.16, D 0.34
43 M	(—)	D 0.33	6y 3m	150	D 0.13, D 0.13
21 F	mother, aunt, uncle	D 0.46	6y	195	B 0.42, D 0.38, D 0.06
49 M	(—)	D 0.04	6y	149	D 0.03, D 0.01
26 F	(—)	D 0.16	5y 3m	149	D 0.20, N 0.26, D 0.09
53 F	daughter	B 0.36	4y 8m	154	D 0.56, D 0.32, D 0.16
49 M	(—)	D 0.30	3y 11m	142	D 0.32, D 0.09, D 0.03
65 M	father	B 0.14	3y 10m	160	B 0.40, D 0.32, B 0.38, D 0.16
62 M	father	B 0.22	3y 10m	242	B 0.22, D 0.22
37 M	(—)	D 0.01	3y 9m	213	D 0.32, D 0.09, D 0.03
39 M	(—)	B 0.21	2y 11m	180	D 0.04, D 0.05, B 0.18, D 0.05
66 F	(—)	B 0.36	1y 10m	152	D 0.32, D 0.24
24 F	sister	N 0.11	1y 8m	170	B 0.37, B 0.30, B 0.21, D 0.06, D 0.02
50 F	(—)	D 0.35	1y 3m	145	D 0.12, D 0.22, B 0.54, N 0.36, D 0.39
35 M	mother, brother	D 0.07	1y 3m	157	D 0.17, D 0.12
65 M	(—)	B 0.16	1y 2m	160	D 0.05, D 0.24
17 F	father, mother, sister	B 0.16	0y 6m	212	D 0.42, D 0.01
42 M	mother, sister	D 0.42	0y 5m	199	D 0.21, D 0.08
65 F	(—)	D 0.11	0y 3m	160	D 0.23

With only few exceptions, Δ IRI/ Δ BS ratio remained low during follow-up period, regardless of types of glucose tolerance. The initial Δ IRI/ Δ BS ratios were also lower than 0.5 in 19 cases who were not definitely diabetic but later developed retinopathy. These results indicate that this characteristic low insulin response during GTT is not a consequence of moderate or severe derangement of carbohydrate metabolism as represented by elevated FBS or of diabetic microangiopathy, but rather a more specific feature of diabetes preceding the development of overt diabetes.

Insulin responses in "prediabetes"

Subjects whose both parents are diabetic have high chance of getting diabetes in the future. In 57 such cases, 23 had normal, 15 had borderline and 19 had diabetic type glucose tolerance. The number of cases with Δ IRI/ Δ BS less than 0.5 were 9, 10 and 17 cases in each group respectively. The overall prevalence of low insulin responders was about 60%, and it was fairly constant in different age groups. When these results

Fig. 2. Relationship between Σ BS and Σ IRI during 100 g GTT in outpatients of diabetes clinic (non-obese subjects).

—"definite" diabetes are excluded—

Δ IRI/ Δ BS (30)	deviated from both Σ BS: Σ IRI areas
• <0.5 290 cases	18 cases 6.2%
○ 0.5 ≤ 89 cases	9 cases 10.1%

are expressed by $\Sigma BS - \Sigma IRI$ plot, cases with $\Delta IRI/\Delta BS$ below 0.5 were distributed in the zone of definite diabetes, and those with $\Delta IRI/\Delta BS$ above 0.5 fell in the zone of various diseases other than diabetes.

Insulin responses of patients with equivocal diabetes

The data of patients who visited the diabetic clinic but were not definitely diabetic (i. e. FBS was below 140 mg/dl and without retinopathy), were analyzed. In non-obese 290 cases with $\Delta IRI/\Delta BS$ below 0.5, 272 (93.8%) were distributed in the zone of definite diabetes in $\Sigma BS - \Sigma IRI$ plot, and 80 among 89 cases (89.9%) with $\Delta IRI/\Delta BS$ above 0.5 were distributed in the zone of various diseases other than diabetes (Fig. 2). Similar results were obtained also in obese subjects. This is interpreted that patients visiting the diabetic clinic for some reasons consist of two groups, one of which resembles true diabetes and the other resembles non-diabetic states as far as their insulin responses are concerned. As discussed previously, definite diabetes developed exclusively from the group with lower insulin response.

Reproducibility of insulin responses during GTT

Among 1250 GTTs repeatedly performed in 446 definitely diabetic patients, only 15 tests (1.2%) have $\Delta IRI/\Delta BS$ values higher than 0.5 in 13 patients, (2.9%). In patients other than definite diabetes, 934 GTTs were repeated in 330 cases, and their $\Delta IRI/\Delta BS$ were analyzed. $\Delta IRI/\Delta BS$ ratios were subdivided into two ranges; higher and lower than 0.5. In 302 cases (91.6%), $\Delta IRI/\Delta BS$ belonged to the same range on repeated tests. The reproducibility of $\Delta IRI/\Delta BS$ during GTT seems adequate to be used as an aid for the diagnosis.

Conclusion

These results strongly suggest that (1) the decrease in early insulin response during GTT is a specific feature of true diabetes, (2) this characteristic low insulin response exists throughout all phases of diabetes, from the prediabetic stage to complete remission of glucose tolerance in established diabetes, and (3) therefore, it is probably a more inherent feature of diabetes mellitus than the derangement of glucose tolerance. Insulin response is reproducible and it provides an useful means for the early diagnosis of primary diabetes and for its differential diagnosis from other diseases.

(3-i) A Study on the Carbohydrate Intolerance in Association with Endocrine Disorders

Makio OKUYAMA, M D

Department of Medicine, Gifu University School of Medicine

Keigo YASUDA, M D

Department of Medicine, Tohoku University School of Medicine

Patients with endocrinopathies frequently have disordered carbohydrate tolerance and abnormalities of insulin secretion. Conceptively, it may be clearly distinguishable from idiopathic diabetes mellitus which

develops on the base of inheritance and has some relatively peculiar characteristics. But practically, there are considerable difficulties in differentiating these two conditions. The purpose of this study is to