Plasma Insulin Studies in Patients with Lag Curves

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Summary. The significance of the lag curve, i.e. one in which the blood sugar rises rapidly from a normal fasting value to more than 180 mg/100 ml but returns to the fasting value within 120 min, remains controversial. In order to study this further, plasma insulin levels were measured by immunoassay during oral and intravenous glucose tolerance tests in 3 groups of age/weight matched subjects: Group 1, 14 with unexplained lag curves; Group 2, 14 with lag curves following gastric surgery and Group 3, 14 normal subjects. The mean insulin levels were higher in Group 1 than in Group 3 but the hyperglycaemic stimulus was greater. The insulin response in Group 2 did not differ significantly from the controls. The mean blood sugar curves were similar in Groups 1 and 2, but despite this the insulin response was significantly prolonged in Group 1, suggesting a degree of insulin resistance or antagonism. In the intravenous test 2 patients from each of Groups 1 and 2 had a K value in the diabetic range. The mean K value was higher in Group 1 than in Group 2. Both groups showed a similar rather low insulin response.

Etude de l'insuline plasmatique chez des patients présentant un pic élevé dans leur courbe

Résumé. La signification de la courbe pointue ('lag-curve') c-à-d celle dans laquelle le sucre sanguin monte rapidement à partir de la valeur normale à jeun à plus de 180 mg/100 ml mais retourne à la valeur à jeun en 120 min, reste controversée. Pour étudier cela plus profondément, le taux de l'insuline plasmatique a été mesuré par dosage radio-immunologique, pendant des épreuves de tolérance au glucose orales et intraveineuses, chez trois groupes de sujets comparables en ce qui concerne l'âge et le poids. Groupe 1, 14 avec des courbes pointues inexpliquées [(lag-storage curves) caractéristique de l'absorption intestinale rapide]. Groupe 2, 14 avec des courbes pointues à la suite d'une intervention chirurgicale gastrique. Groupe 3, 14 sujets normaux. Le taux moyen d'insuline était plus élevé dans le groupe 1 que dans le groupe 3, mais le stimulus hyperglycémique était plus grand. La réponse insulinaire dans le groupe 2 n'a pas différé des témoins d'une façon

significative. La courbe moyenne du sucre sanguin était semblable dans les groupes 1 et 2, mais en dépit de ceci, la réponse insulinaire était significativement prolongée dans le groupe 1 suggérant un degré de résistance ou d'antagonisme insulinaire. Dans les épreuves intraveineuses, 2 malades de chacun des groupes 1 et 2 avaient une valeur K dans le domaine des valeurs diabétiques. La valeur moyenne de K était plus élevée dans le groupe 1 que dans le groupe 2. Les deux groupes montraient une réponse insulinaire semblable mais plutôt basse.

Plasma insulin-Untersuchungen bei Patienten mit spitzgipfligen Glucose-Toleranz-Kurven

Zusammenfassung. Die Bedeutung von spitzgipfligen Blutzuckerkurven, die von normalen Nüchternspiegeln auf mehr als 180 mg% ansteigen, um in 120 min auf die Ausgangswerte zurückzukehren, bleibt strittig. — Um diese Frage weiter zu klären, wurden immunologisch die Plasma-Insulinwerte bei 3 Gruppen von je 14 Probanden gemessen, die nach Alter und Gewicht übereinstimmten: Gruppe 1 bestand aus Probanden mit derartigen Kurven ohne ausreichende Erklärung, Gruppe 2 aus Patienten nach Magenoperationen und Gruppe 3 diente als Vergleichskollektiv. Im Teilkollektiv 1 fanden sich höhere Insulinwerte als in 3, doch bestand gleichzeitig eine stärkere Blutzuckererhöhung als Stimulans. Die Insulinausschüttung in der Gruppe 2 unterschied sich nicht signifikant vom Vergleichskollektiv. In den Gruppen 1 und 2 stimmten die Blutzuckerspiegel weitgehend überein, doch hielt die Erhöhung der Insulinkonzentration in Gruppe 1 signifikant länger an, was auf einen gewissen Grad von Insulin-Resistenz oder -Antagonismus schließen lässt. Bei der i.v. Belastung ergaben sich für je 2 Probanden der Gruppen 1 und 2 k -Werte im diabetischen Bereich. In Gruppe 1 lagen die mittleren k -Werte höher als in Gruppe 2. Beide Teilkollektive zeigten eine eher erniedrigte Insulin-Ausschüttung.

Key-words: Plasma insulin, glucose tolerance test, post-gastrectomy, carbohydrate metabolism, lag curves.

Introduction

Glucose tolerance tests have been used in the detection of diabetes mellitus for many years but their interpretation and the definition of normality are controversial (Butterfield, 1964; Keen, 1964; Sharp, 1964). Subjects with normal glucose tolerance and those with frank symptomatic diabetes form two extremes. Between lie a large number of people who have minor abnormalities of glucose tolerance. One such abnormality is the 'lag' curve in which the blood sugar rises

rapidly from a normal fasting value to a peak of more than 180 mg/100 ml but, unlike the diabetic curve, returns to the fasting value by 120 min. This is regarded by some workers as a prelude to frank diabetes (Lundbaek, 1962), although the mechanism is ill-understood. Even patients who have a lag curve following partial gastric resection, presumably due to more rapid absorption of glucose, may show an increased tendency to develop diabetes (Berkowitz and Glassman, 1966; Tobe *et al.*, 1967).

The introduction of a reliable immunoassay method for insulin (Yalow and Berson, 1960) has added another parameter to the investigation of glucose tolerance, and may throw some light on the mechanism and significance of the 'lag' curve.

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Materials and Methods

Patients studied. Group 1. Twenty-seven patients, referred to the diabetic clinic at Glasgow Royal Infirmary because of glycosuria detected at a routine medical examination, were discovered to have a lag curve. A number of these patients were overweight and in a few others the height had not been recorded so that percentage weight could not be calculated. Of the remainder, 14 were selected to form age/weight matched pairs with the patients in Group 2.

Group 2. Fourteen patients had lag curves following partial gastrectomy or vagotomy and drainage. A number of these had also been referred because of glycosuria, the remainder were being investigated for post-gastrectomy symptoms.

Group 3. Fourteen normal subjects, aged 31–65 years, mean 48 and of weights 84–113 per cent of ideal, mean 99, were studied as a control group.

tolerance tests (IVGTT) were performed according to the method of Lundbaek (1962), blood being taken fasting and at 10 min intervals for one hour following the intravenous injection of 25 g of glucose as a 50% solution. All subjects were instructed to eat a normal diet for at least 3 days prior to the tests.

Plasma insulin was assayed according to the immuno-precipitation technique of Hales and Randle (1963). Standards and antisera are as described elsewhere (Buchanan and McKiddie, 1967a). Blood sugars were estimated as total reducing substances using a Technicon autoanalyser.

*Results**Oral glucose tolerance tests*

The plasma insulin response to oral glucose in the 27 patients in Group 1 is shown in Table 1. Eight patients had at least one plasma insulin value outside

Table 1. *Insulin response to glucose in 27 subjects with lag curves, comparison of means of patients 14–27 with 14 age/weight matched controls*

Subject	Age yrs.	Weight %	Minutes after oral glucose Plasma insulin μ -units/ml				
			0	30	60	90	120
1	51	—	50	190	174	85	46
2	47	—	9	22	67	82	10
3	43	—	27	49	60	81	64
4	60	—	2	55	75	40	18
5	37	113	21	81	72	99	51
6	72	146	70	158	205	136	69
7	61	153	51	102	186	208	111
8	57	120	46	165	180	83	45
9	55	147	42	90	140	67	50
10	33	114	33	58	49	41	29
11	42	110	46	162	78	69	60
12	58	147	52	135	119	100	70
13	40	98	32	82	118	28	38
14	39	117	35	48	75	52	37
15	43	95	0	93	49	12	11
16	41	88	12	47	41	31	18
17	38	99	18	80	91	53	30
18	50	100	32	153	151	56	26
19	64	98	27	97	193	173	87
20	40	100	30	190	70	35	30
21	47	108	20	53	71	53	31
22	31	100	35	91	81	118	51
23	71	100	22	86	139	—	53
24	63	82	41	81	260	223	129
25	56	116	80	183	171	96	84
26	52	80	32	220	245	195	41
27	34	100	20	210	112	—	84
Mean (14–27)	48	98	29	117	125	91	51
Controls	48	99	18	86	99	53	26
			<i>P</i> NS	NS	NS	NS	0.05
			Blood sugar mg/100 ml				
Mean (Patients 14–27)			97	192	172	106	78
Controls			94	137	121	92	79
			<i>P</i> NS	0.001	0.01	NS	NS

Test procedure. Standard oral glucose tolerance tests (GTT) were performed, venous bloods being taken fasting and at 30, 60, 90 and 120 min after 50 g oral glucose. In a number of patients intravenous glucose

our normal range (Buchanan and McKiddie, 1967b), but 4 of these 8 were also obese. Fourteen of the patients, all within 20% of ideal weight (Nos. 14–27 in Table 1) were compared with the 14 normal subjects

of Group 3 who formed age/weight matched pairs. The mean plasma insulin levels were higher throughout in the lag curve group, and the response tended to be more prolonged. However, because of the wide scatter of results the difference was significant only at 120 min.

As might be expected the 30 and 60 min blood sugar values were significantly higher in the lag curve group. The fasting and 120 min levels were virtually identical.

The insulin response to oral glucose of the 14 patients whose lag curve followed gastric surgery is shown in Table 2. Three of these patients had one plasma insulin level outside our normal range. There was no significant difference between the mean plasma insulin levels of these patients and those of the normal controls. The mean peak insulin response in the ulcer patients appeared considerably higher than in the controls (136 ± 84 : 86 ± 50), but again because of the wide scatter statistical significance was not achieved ($p < 0.10$). The mean blood sugar values were again significantly higher at 30 and 60 min in the Group 2 patients than in the controls.

There are inherent difficulties in comparing plasma insulin responses in patients with widely different

Fig. 1. The mean blood sugar and plasma insulin responses to oral glucose of Group 1 (idiopathic lag curves) are compared with those of Group 2 (post-gastrectomy lag curves)

Table 2. Insulin response to glucose in patients with lag curves following gastric surgery. Comparison with means of 14 age/weight matched normal subjects

Subject	Age yrs.	Weight %	Minutes after oral glucose				
			Plasma insulin μ -units/ml				
			0	30	60	90	120
1	31	115	26	105	45	44	27
2	45	90	25	220	102	35	20
3	41	80	35	104	78	48	48
4	37	93	28	105	48	43	30
5	56	101	22	64	35	30	10
6	66	89	33	108	140	135	52
7	46	90	16	153	62	31	20
8	46	85	17	54	40	26	26
9	23	100	43	—	87	42	35
10	68	120	12	75	82	57	32
11	56	90	35	100	60	45	40
12	59	100	32	82	118	28	38
13	52	84	25	240	74	42	25
14	32	100	26	358	61	38	24
Mean	47	96	27	136	74	46	31
Controls	48	99	18	86	99	53	26
			Blood sugar mg/100 ml				
Patients Mean			97	212	160	98	75
Controls			94	137	121	92	79
			<i>P</i> NS	0.001	0.05	NS	NS

blood sugar values. However, when the mean blood sugar values of the two groups of patients with lag curves were compared they were closely similar. Therefore in this respect these two groups are directly comparable. The fasting plasma insulin level was similar in the two groups. The peak insulin response occurred in both groups at 30 min and was slightly, though not significantly, higher in the 'post-gastrectomy' group. Thereafter the insulin levels fell rapidly in the latter,

whereas they remained elevated for longer in the patients of Group 1, who therefore had significantly higher insulin levels at 60, 90 and 120 min.

Intravenous glucose tolerance tests

In order to overcome the problem of variable absorption of oral glucose intravenous glucose tolerance tests were performed in 9 patients from Group 1, 6 patients from Group 2 and 6 of the control group. Two

patients from each of Groups 1 and 2 had a glucose disappearance rate (K value) in the diabetic range (< 0.95). A further 2 patients in Group 2 had a borderline K value ($0.95-1.05$). The mean K value of the patients in Group 1 (1.53) was higher than that of patients in Group 2 (1.02) ($p < 0.05$).

The mean insulin response to intravenous glucose was similar in both lag curve groups (Table 3) and rather lower than in the normal subjects studied.

to insulin and this may well be an early manifestation of diabetes. From our data of normal oral glucose tolerance (Buchanan and McKiddie, 1967b) we have shown positive correlations between the sugar and insulin responses only at 90 and 120 min after oral glucose, so that higher insulin levels at this latter part of the oral GTT may be consistent with decreased effectiveness of circulating insulin. The factors governing the insulin response to oral and intravenous glucose

Table 3. Plasma insulin response to I.V. glucose means ± 1 standard deviation

	K	Minutes after 25 g glucose I.V. Plasma insulin μ -units/ml						
		0	10	20	30	40	50	60
Group 1. (9)	1.53	14 $\pm$ 9	42 $\pm$ 18 ^a	38 $\pm$ 15	40 $\pm$ 21	44 $\pm$ 17	42 $\pm$ 14	42 $\pm$ 16
Group 2. (7)	1.02	20 $\pm$ 5	35 $\pm$ 16 ^a	39 $\pm$ 9	39 $\pm$ 14	34 $\pm$ 14	44 $\pm$ 4	46 $\pm$ 10
Group 3. (6)	2.22	34 $\pm$ 12	80 $\pm$ 31 ^a	71 $\pm$ 37	49 $\pm$ 19	46 $\pm$ 18	37 $\pm$ 21	32 $\pm$ 20

^a Significance of difference between Groups 1 and 2 and normals $p < 0.02$.

Discussion

The mechanism of the lag curve is poorly understood. In post-gastrectomy patients the obvious explanation is the more rapid passage of glucose into the jejunum and thence into the blood stream, although Samols *et al.* (1966) have also implicated increased levels of plasma glucagon. Whether a similar mechanism is responsible in non-surgical cases, or whether it is the peripheral or hepatic disposal of glucose which is at fault is not known.

The finding of impaired tolerance to intravenous glucose is in favour of the latter being at least a factor. This delayed clearance of intravenous glucose has been shown previously both in surgical (Robertson, 1966) and non-surgical cases (Lundbaek, 1962), although not all workers are agreed (Schechter and Necheles, 1949). There is also doubt in the post-gastrectomy patients whether this abnormality follows or precedes surgery, an increased incidence of both lag curves and abnormal IVGTT having been reported in uncomplicated peptic ulcers (Platt *et al.*, 1949), although our data in this respect (Buchanan *et al.*, 1967) did not show evidence of either abnormal or IVGTT in subjects with duodenal ulcers.

It has been suggested (Berkowitz and Glassman, 1966) that a lag curve, at least in post-gastrectomy subjects, may be the cause rather than the result of a tendency to develop diabetes. The hyperglycaemia may cause excessive beta cell stimulation with secondary failure, just as perfusion of the pancreas with concentrated glucose solutions in animals has been shown to produce at least temporary diabetes (Dohan and Lukens, 1948; Barron and State, 1949). Support for this is given by the autopsy finding of vacuolization and decrease in beta cell granules in older post-gastrectomy patients (Tobe *et al.*, 1967).

The finding of a prolonged higher insulin response, in the idiopathic lag curve group, suggests that these patients have some form of antagonism or resistance

are different (McIntyre *et al.*, 1964). Various intestinal factors have been implicated in the increased insulin response seen after oral glucose as compared with intravenous glucose. These include secretin (Dupré *et al.*, 1966) pancreozymin (Meade *et al.*, 1967) glucagon (Samols *et al.*, 1966) and gastrin (Unger *et al.*, 1967). It might be that the lag curve is the result of an altered response of insulinogenic gut factors following a glucose load. The study of this possibility must await reliable assay methods for these hormones.

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