The insulin response to glucose in patients with pancreatic disease

M. T. MCKIDDIE*
M.B., M.R.C.P.
Registrar in Medicine

G. C. MCBAIN
M.B., F.R.C.S.
Registrar in Surgery

K. D. BUCHANAN
M.D., M.R.C.P.
Consultant Physician

G. BELL
M.B., F.R.C.S.
Senior Registrar in Surgery

Royal Infirmary, Glasgow

Summary

The insulin response to glucose was studied in twenty-five patients with pancreatic disease, of whom twelve had chronic pancreatitis, five developed glycosuria following an attack of acute pancreatitis and eight had a carcinoma of the pancreas.

A low insulin response was found in subjects with frank diabetes mellitus but in the majority of those with chronic pancreatitis the insulin response was prolonged and of normal degree. This suggests that glucose intolerance in these patients is not due to simple insulin deficiency but may be due to the release of an abnormal insulin or to insulin antagonists.

All eight patients with carcinoma of the pancreas had a low insulin response to glucose.

Introduction

Impaired glucose tolerance is common in patients with chronic pancreatitis (Chey *et al.*, 1967) and carcinoma of the pancreas (Salmon, 1966). Because of the anatomical relationship of the islets of Langerhans to the exocrine pancreas one might expect that abnormalities of glucose tolerance in these patients would be associated with insulin deficiency. Low plasma insulin levels in 'pancreatic diabetes' were found by Berson & Yalow (1962) and by Peters *et al.* (1966). However normal or high fasting insulin levels (Keller *et al.*, 1965) and a variable insulin response to oral glucose (Bank *et al.*, 1968) have also been reported.

Materials and methods

Patients studied

Subjects with pancreatic disease: (a) Twelve patients (aged 48-76 years) were studied in whom a

diagnosis of chronic pancreatitis had been made. Features on which the diagnosis was based were steatorrhoea with normal xylose absorption, pancreatic calcification on X-ray or diagnostic features at laparotomy.

A further five patients, referred to the diabetic clinic with glycosuria, had a well-documented history of acute pancreatitis. Four of these patients had frank symptomatic diabetes, the fifth had chemical diabetes only. One of these patients had required insulin therapy for 1 week only during his attack of acute pancreatitis. The others were untreated at time of study. All five are now well controlled on diet alone. (b) Eight patients were studied in whom a diagnosis of carcinoma of the pancreas was later confirmed at laparotomy or necropsy. All were jaundiced at the time of study.

Control subjects: Eight normal subjects aged 50-65 years and within 10% of ideal body weight were used as controls.

Standard 50 g oral glucose tolerance tests were performed after an overnight fast, venous blood being removed fasting and at 30, 60, 90 and 120 min for blood sugar and plasma insulin estimation.

Blood sugar was measured as total reducing substances on the Technicon AutoAnalyzer.

Plasma insulin was assayed by the immunoprecipitation technique of Hales & Randle (1963) using standards and antisera previously described (Buchanan & McKiddie, 1967a).

Results

(a) Patients with pancreatitis

Of the twelve patients with chronic pancreatitis, three had normal and nine mildly abnormal glucose tolerance (Table 1).

Two of the patients with a normal GTT had a

* Present address: Ward 6, Maryfield Hospital, Dundee, DD4 7TL.

TABLE 1. Insulin response to glucose in patients with pancreatitis

Subjects	Age (years)	Time after 50 g oral glucose									
		Blood sugar (mg/100 ml)					Plasma insulin (μ U/ml)				
		0 min	30 min	60 min	90 min	120 min	0 min	30 min	60 min	90 min	120 min
Normal GTT											
1	68	82	155	155	135	92	16	242	230	186	156
2	50	84	134	178	104	84	3	35	25	10	8
3	54	102	153	116	71	78	66	265	230	90	100
Abnormal GTT											
4	64	96	154	196	208	242	9	105	100	111	132
5	54	87	171	199	150	125	30	157	176	106	75
6	53	126	220	264	204	170	37	70	108	120	87
7	72	97	220	258	150	88	33	71	105	100	51
8	59	97	174	181	129	127	42	215	220	166	107
9	67	73	130	209	210	144	30	124	197	307	220
10	48	120	160	174	168	161	13	20	29	50	45
11	72	110	202	248	246	204	21	60	58	62	72
12	76	109	148	223	144	73	13	181	72	127	31
Diabetic											
13	68	290	345	420	483	474	40	45	44	38	41
14	54	119	190	260	284	253	20	30	42	57	55
15	56	177	195	237	372	345	30	40	32	32	37
16	28	134	278	292	243	202	19	29	38	33	27
17	70	88	164	156	154	136	15	74	60	79	65
Mean of patients (4-12)	63	102	175	218	179	138	25	111	118	128	91
Controls	55	93	145	141	104	80	18	102	129	85	34
P		NS	0.05	0.001	0.001	0.01	NS	NS	NS	NS	0.01

peak insulin response outwith the normal range for our laboratory (Buchanan & McKiddie (1967b); the third had a rather low response. In all three the peak insulin level occurred at 30 min.

Most of the nine patients with a mildly abnormal GTT had insulin responses in the upper range of 'normal'; one was very high and one rather low. In only one of these patients did the peak response occur at 30 min, in two it was delayed until 90 min and in two did not occur until 120 min. The mean insulin response of these nine patients was similar in degree to that of the eight normal subjects of similar age. However, the response was more prolonged in the pancreatic group so that the 120-min value was significantly higher than in the controls ($P < 0.01$). The blood sugar levels were significantly higher at all times following oral glucose.

The four patients with frank diabetes mellitus following acute pancreatitis all had a low insulin response to glucose. The one patient in this group with asymptomatic diabetes resembled the chronic pancreatic group in that she had a prolonged insulin response to glucose.

(b) Patients with carcinoma of the pancreas

These patients all had abnormal glucose tolerance. Six had a low insulin response to glucose; in the remaining two the response was normal in degree

but the peak did not occur until 120 min after glucose (Table 2).

TABLE 2. Plasma insulin response to oral glucose in patients with carcinoma of pancreas

	Time after oral glucose*				
	0 min	30 min	60 min	90 min	120 min
1	6	42	43	50	62
2	0	34	22	13	17
3	15	43	34	21	15
4	21	46	55	46	68
5	24	34	33	41	37
6	20	30	60	35	40
7	14	22	0	8	13
8	18	18	19	27	18

* Plasma insulin (μ U/ml).

Discussion

The finding of low insulin levels in the four patients with symptomatic diabetes in association with pancreatitis is in keeping with the results of Berson & Yalow (1962) and Peters *et al.* (1966). However, although the patients of Berson & Yalow (1962) had severely impaired glucose tolerance, those of Peters *et al.* (1966) were only mildly abnormal and clinically resembled more closely the ten patients presented here with clinical diabetes in whom there was a prolonged insulin response of normal degree.

This type of response was also shown in a single case of acute pancreatitis described by Yalow & Berson (1960). The insulin levels, however, may be low in relation to the associated elevated blood sugars, although similar levels were able to prevent similar hyperglycaemia in the normal subjects.

The prolonged insulin response with, in many cases, a progressive increase in insulin levels up to 120 min, suggests a continuing pancreatic response to a hyperglycaemic load. This type of response has been shown to occur in a number of patients with maturity-onset diabetes mellitus (Yalow & Berson, 1960; Buchanan & McKiddie, 1967c). In all three patients with normal glucose tolerance the peak insulin response occurred at 30 min which may be of significance since it has been suggested (Seltzer & Allen, 1963) that 'biochemical inertia' of the β cell is the primary abnormality in diabetes mellitus.

The results of the present study do not suggest that simple pancreatic deficiency is the cause of the diabetes mellitus which may develop in association with pancreatitis, although it is likely that these patients have impaired reserve (Joffe *et al.*, 1968). However, they are still capable of producing normal or greater than normal insulin levels in response to glucose, and it is interesting that patients with pancreatic disease should develop glucose intolerance in the face of normal plasma insulin levels. One would expect that in pancreatic disease a decrease in insulin levels would first occur, followed by glucose intolerance. The opposite event might suggest that the circulating insulin is in an inactive form, e.g. pro-insulin (Rubenstein, Cho & Steiner, 1968) or A and B chains (Varandani, 1968) or that the pancreatic disease has disturbed the release mechanism of insulin itself. Another possibility might be that the damaged pancreas releases excessive amounts of insulin antagonists (Ensink, Mahler & Vallance-Owen, 1965).

It is possible that these patients had essential diabetes mellitus unrelated to their pancreatic disease, though the proportion with abnormal glucose tolerance seems rather high. Certainly six of them were over 60 years of age and glucose tolerance is known to decline with age.

The finding of abnormal glucose tolerance in carcinoma of the pancreas is common, figures quoted varying from 12–32% (Salmon, 1966) to 86% (Dashiell & Palmer, 1948). All eight patients studied have had abnormal glucose tolerance but all had progressed to the stage of obstructive jaundice, and this alone may impair glucose tolerance (Berkowitz,

Blinkoff & Glassman, 1966). The low delayed insulin response is in keeping with destruction of the pancreatic islets.

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