Triamcinolone-augmented glucose tolerance in non-diabetic patients with chronic pancreatitis

B. I. JOFFE
M.B., M.R.C.P.

W. P. U. JACKSON
M.D., F.R.C.P.

S. BANK
M.B., F.R.C.P.

Department of Medicine, Witwatersrand University Medical School, Johannesburg, and the Gastrointestinal and Endocrine Research Units of Cape Town University Medical School, South Africa

Summary

Seven non-diabetic patients with chronic pancreatitis were shown to have a diminished acute insulin secretory response after intensive beta cell and intravenous tolbutamide stimulation. In an attempt to unmask their 'latent' diabetic state, triamcinolone-augmented glucose tolerance tests were performed some days after documenting normal standard 50 g oral glucose tolerance tests. A matched group of non-diabetic controls was similarly investigated. Although the steroid-augmented glucose tolerance tests showed marked impairment in the patients, becoming frankly diabetic in three cases, the normal control subjects reacted in a similar though less striking fashion. There was no significant difference between the mean glucose values in the two groups. The ability of patients with chronic pancreatitis to maintain normal glucose tolerance in the face of diminished insulin output is commented on. We conclude that, as an ancillary investigation for diagnosing chronic pancreatitis, the triamcinolone glucose tolerance test is unreliable.

Introduction

Although chronic pancreatitis is frequently complicated by diabetes, there are, nevertheless, a substantial number of patients who maintain normal glucose tolerance (Bank *et al.*, 1968; Anderson *et al.*, 1970). Recent studies (Joffe *et al.*, 1968; Deckert *et al.*, 1972) have indicated that even when glucose tolerance is apparently unaffected in chronic pancreatitis, insulin reserve has already been significantly decreased. Thus non-diabetic patients with chronic pancreatitis could be regarded as 'pre-diabetic' subjects (Rogers, Howard and Pairent, 1970). This being the case an investigation that may be expected to unmask this 'latent' diabetic state would be a steroid-augmented oral glucose tolerance

test (GTT). A study was therefore designed to assess the diagnostic value of an oral GTT augmented with triamcinolone (Navarette and Torres, 1965) in a group of non-diabetic patients with chronic pancreatitis, with reference to their insulin secretory capacity.

Patients and methods

Patients and controls

Seven non-obese patients with well-proven chronic pancreatic disease were studied. There were six men and one woman, ranging from 40 to 54 years of age. The diagnosis of pancreatitis was confirmed in each case on the basis of a gross abnormality in the secretin/pancreozymin pancreatic function test (Bank *et al.*, 1963). Furthermore, radiological evidence of pancreatic calcification was observed in five cases and chemical evidence of steatorrhoea in two cases. Alcohol was thought to be of aetiological importance in all except one instance (where the cause was unknown); despite this, clinical, biochemical and histological evidence of liver disease was uniformly absent. All the patients had recent documentation of a normal 50 g oral GTT. There was no known family history of diabetes, although one patient had a brother with calcific pancreatitis and impaired carbohydrate tolerance. A group of seven healthy non-obese subjects, matched with the patients as regards age and sex, acted as controls. None had a family history of diabetes or evidence of pancreatic disease. Their oral GTTs were normal.

Experimental design

The insulin secretory capacity of the patients and controls was first established using the techniques of: (a) intensive beta cell stimulation with a combination of 75 g oral glucose, followed 30 min later by the combined intravenous administration of $\frac{1}{2}$ g tolbutamide and 1 mg glucagon (Ryan, Nibbe and Schwartz, 1967); and (b) intravenous administration

Correspondence: Dr B. I. Joffe, Department of Medicine, Witwatersrand University Medical School, Johannesburg, South Africa.

of 1 g tolbutamide alone (undertaken some days later). In each test, serum samples for immuno-reactive insulin determinations were obtained fasting and after stimulation. Since the 5 min post-injection sample in each test generally represented the peak insulin response, this (together with the fasting sample) was used for subsequent analysis. Oral GTTs were then performed, at a later date, in both groups of subjects. For the standard GTT, 50 g of glucose was administered orally after an overnight fast and employing the usual precautions (Jackson, 1964). Triamcinolone-augmented GTTs were done at least 2 days later, using triamcinolone 8 mg 11 hr and 1 hr before the 50 g oral glucose load.

Methods

Glucose was determined half hourly for 2 hr on capillary whole blood using a Technicon Auto-Analyzer and the modified ferricyanide method of Hoffman (1937). In addition, hourly urine samples were tested for glycosuria with Testape. Serum insulin during the intensive beta cell stimulation and tolbutamide tests were measured by radio-immunoassay (Hales and Randle, 1963).

Criteria for analysis of GTTs

For both the standard GTT and the triamcinolone GTT the same criteria were used (Jackson *et al.*, 1972). Normal: all blood glucose levels below 120 mg/100 ml fasting, 185 maximum and 140 at 120 min. Borderline: one high value only. Diabetic: at least 2 high values.

Results

Table 1 indicates the acute insulin secretory capacity of the non-diabetic patients with chronic pancreatitis, together with that of the matched controls, as evidenced by their fasting and early insulin responses to intensive stimulation and tolbutamide alone. Fasting insulin levels were similar in the two groups, but the patients produced less than half the peak insulin output of the controls after intensive stimulation. A similar, although

statistically less impressive, response was noted after tolbutamide alone. (Mean 30 min % blood glucose falls after tolbutamide were similar in the two groups, at 35% in patients and 43% in controls).

The results of the standard and triamcinolone-augmented GTTs in the two groups are outlined in Table 2. Standard GTTs were normal in both groups, as anticipated; none of the differences between the mean values were statistically significant. Regarding triamcinolone GTTs, a statistically significant deterioration (compared to standard GTT) occurred in both groups ($P < 0.05$ at 60, 90 and 120 min). Although the mean glucose level was generally higher in the pancreatitis patients than in the controls during the triamcinolone test, at no time did it become significantly greater. Of interest was the observation that the mean triamcinolone GTT had, in fact, become 'diabetic' in the chronic pancreatitis patients, while still remaining 'normal' in the controls.

Glycosuria was uniformly absent during standard GTTs. It was detected in all seven chronic pancreatitis patients during the triamcinolone GTT, but also in four of the seven controls.

Table 3 summarizes the fate of individual triamcinolone GTTs in the two groups, analysed according to the criteria set out earlier. The test became diabetic in three patients and one control.

Discussion

The primary object of the present study was to ascertain whether a steroid-augmented glucose tolerance test would be a useful ancillary investigation in chronic pancreatitis, by unmasking the diabetes susceptibility of those patients who preserve normal glucose tolerance in the face of diminished insulin reserve. Although marked deterioration in the triamcinolone GTT was, indeed, noted and nearly half the tests became diabetic, much of the impact of these observations was lost in view of the fact that normal controls reacted in a similar, though less striking, manner. This lack of specificity of the triamcinolone GTT has recently been commented on

TABLE 1. Fasting and peak insulin responses (mean $\pm$ SEM) after intensive beta cell and intravenous tolbutamide stimulation in non-diabetic patients with chronic pancreatitis and normal controls

Group	No. of subjects	Serum insulin (μ u/ml) after stimulation		
		Fasting	5 min after intensive stimulation	5 min after tolbutamide
Chronic pancreatitis	6	28 $\pm$ 6	400 $\pm$ 148	66 $\pm$ 16
Normal controls	7	33 $\pm$ 7	867 $\pm$ 79	113 $\pm$ 23
Significance		n.s.	< 0.05	n.s.

n.s. = not significant.

TABLE 2. Effect of triamcinolone augmentation on glucose tolerance in non-diabetic patients with chronic pancreatitis and normal controls. All values are means $\pm$ SEM*

Time (min)	Blood glucose (mg/100 ml) after glucose administration			
	Chronic pancreatitis (7)		Normal controls (7)	
	Standard GTT	Triamcinolone GTT	Standard GTT	Triamcinolone GTT
Fasting	90 $\pm$ 4	95 $\pm$ 5	87 $\pm$ 3	96 $\pm$ 6
30	133 $\pm$ 13	163 $\pm$ 14	140 $\pm$ 10	157 $\pm$ 7
60	147 $\pm$ 16	206 $\pm$ 19	139 $\pm$ 10	177 $\pm$ 13
90	117 $\pm$ 7	184 $\pm$ 16	112 $\pm$ 9	150 $\pm$ 14
120	98 $\pm$ 11	156 $\pm$ 9	78 $\pm$ 8	124 $\pm$ 13

* There is no significant difference between the two groups, for either the standard or the triamcinolone GTT values.

TABLE 3. Fate of individual triamcinolone GTTs in non-diabetic patients with chronic pancreatitis and normal controls

Result of triamcinolone GTT	Chronic pancreatitis (7)	Normal controls (7)
Remained normal	1	2
Borderline	3	4
Diabetic	3	1

in relation to offspring of diabetic couples (Jackson *et al.*, 1972). It would thus appear that an abnormal triamcinolone GTT in a non-diabetic patient with suspected chronic pancreatitis is of uncertain diagnostic reliability.

The pathogenesis of steroid 'diabetes' is not very clear, but direct antagonism of insulin at a cellular level seems to be an important factor (Berger *et al.*, 1966). This results in compensatory hypersecretion of insulin, both from the acutely releasable and slowly responding functional insulin pools in the beta cell (Porte and Bagdade, 1970), and if this is inadequate, impaired carbohydrate tolerance will ensue. In chronic pancreatitis, the defect in insulin output appears to mainly involve its early secretion from the acutely releasable insulin pool (Porte and Bagdade, 1970), so that a steroid-augmented GTT may not be the most effective means of revealing this abnormality. Agents that more directly compromise the early release of insulin from the beta cell, such as epinephrine, diazoxide and mannoheptulose (Levine, 1970) might have greater diagnostic merit in this regard.

Finally, the ability of patients with chronic pancreatitis to maintain normal glucose tolerance in the face of considerably diminished insulin secretory capacity is of interest. It implies a state of insulin sensitivity in chronic pancreatitis, and this has indeed been demonstrated after exogenous insulin administration (Joffe, Bank and Marks, 1968). Reasons for this are speculative, although decreased secretion of anti-insulin factors, such as growth

hormone (Vinik *et al.*, 1970), and pancreatic glucagon (Persson *et al.*, 1971) may be partly responsible.

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