Insulin and Glucagon Response in Patients with Chronic Pancreatitis

AKIRA OHNEDA, YUKIHIRO KAI, SHOJI ISHII, KIYOSHI MATSUDA, KEN HORIGOME, YOSHIKUKE MARUHAMA, TAKAAKI TAKEBE and SHOICHI YAMAGATA

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OHNEDA, A., KAI, Y., ISHII, S., MATSUDA, K., HORIGOME, K., MARUHAMA, Y., TAKEBE, T. and YAMAGATA, S. Insulin and Glucagon Response in Patients with Chronic Pancreatitis. Tohoku J. exp. Med., 1976, 120 (3), 287-298 — The oral glucose tolerance test and arginine infusion test were carried out on 22 patients with chronic pancreatitis and 11 normal control subjects. According to the glucose tolerance curve, the patients were divided into three groups; group I (normal or slightly impaired), group II (mildly diabetic) and group III (moderately diabetic). Markedly impaired insulin responses to oral glucose as well as to arginine infusion were observed in groups II and III. In group I, the mean plasma insulin levels during glucose tolerance test were the same as those in the controls, but the insulin response to arginine was reduced except in two cases. On the other hand, the glucagon levels during arginine infusion test were within the normal range in group I and slightly reduced in the other groups with diabetic glucose tolerance. The ratio of increment area of insulin to that of glucagon during arginine infusion in the patients was slightly decreased in comparison with the controls. Neither insulin nor glucagon response after arginine infusion showed a significant correlation with pancreatic exocrine function. It is concluded that in chronic pancreatitis insulin response to glucose as well as to arginine is markedly decreased, and that glucagon rise after arginine infusion is lowered compared with the controls. ——— insulin; glucagon; chronic pancreatitis

Most patients with chronic pancreatitis reveal glucose intolerance, which is classified as pancreatic diabetes. Since the development of radioimmunoassay for insulin, there have been various reports referring to insulin response to different stimuli in chronic pancreatitis. These patients showed a reduced insulin response to oral glucose (Peters et al. 1966; Bank et al. 1968), intravenous tolbutamide (Deckert et al. 1972; Joffe et al. 1969), combination of oral glucose with intravenous tolbutamide and glucagon (Joffe et al. 1968), and also to secretin or cholecystokinin-pancreozymin (Rapits et al. 1971; Kalk et al. 1974a).

On the other hand, there are only a few reports concerning the glucagon response in chronic pancreatitis. Aguilar-Parada et al. (1969) showed a decreased glucagon response to arginine infusion in patients with severe calcified pancreatitis. A reduced response of glucagon to hypoglycemia induced by insulin injection in

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chronic pancreatitis was demonstrated by Persson et al. (1971). Recently Kalk et al. (1974b) demonstrated normal or reduced glucagon response to arginine in these patients. To the contrary, recent studies on the glucagon response in primary diabetics have revealed a fasting hyperglucagonemia, relative or absolute (Unger et al. 1970; Heding and Rasmussen 1972), and increased response to arginine (Unger et al. 1970; Ohneda et al. 1975). Furthermore, Unger and Orci (1975) suggested that the abnormality in glucagon secretion is a primary factor in the etiology of diabetes mellitus.

In the present study, therefore, the response of plasma insulin and glucagon in patients with chronic pancreatitis were investigated and compared with those in primary diabetes.

**SUBJECTS AND METHODS**

*Subjects*

Twenty-two patients with chronic pancreatitis (19 males and 3 females) were studied. Clinical data of these subjects are shown in Table 1. Body weight indices were below 110% in all the patients except for two in whom the index was 111 and 117%. A hereditary relationship of diabetes mellitus was found in only two patients, cases 3 and 10. Diagnosis of chronic pancreatitis was made by clinical history of typical episode of pancreatitis, calcified pancreas on X-ray examination and the results obtained by the pancreozymin-secretin test using three parameters: volume of pancreatic juice, maximum concentration of HCO₃ and amylase output. Pancreatic calcification was proved in 17 of 22 patients, and the diagnosis of chronic pancreatitis was confirmed at operation in cases 1, 3, 5, 7, 10, 14 and 20. Alcohol seemed to be a main etiological factor in all the patients except in cases 5, 6 and 15. These three cases were near relatives and familial chronic pancreatitis was diagnosed. Namely, case 15 was the mother of case 6 and an aunt of case 5; and moreover, the mother of case 5, a sister of case 15, was also suffering from chronic pancreatitis. All subjects had been on their usual diet and none of them was ketotic. All studies were done at the time when they were free from abdominal pain.

As normal controls, 11 healthy young male volunteers were studied. None of them was obese and they did not reveal any endocrine or gastrointestinal disturbance.

*Oral glucose tolerance test and arginine infusion test*

After an overnight fast, the 50 g oral glucose tolerance test (GTT) was performed. Blood smaples for measurement of blood glucose and plasma insulin were obtained from the ear lobe and the antecubital vein, respectively, at fasting and at 30-min intervals for 2 hr.

The arginine infusion test was done within a week before or after GTT. Each subject was at rest after an overnight fast and a butterfly needle was placed in the antecubital vein for blood sampling. 300 ml of 10% solution of L-arginine monohydrochloride was infused through the antecubital vein on the other side for 30 min. Blood was drawn into heparinized syringes for measurement of immunoreactive insulin (IRI) and glucagon (IRG) at -10, 0, every 10 min in the first 1 hr, then at 75, 90 and 120 min. At the same time, capillary blood was obtained from the ear lobe for measurement of blood glucose. Blood samples for measurement of hormones were poured into test tubes containing 2000 KIU of Trasylol®, a protease inhibitor (Bayer Co.).

*Analyses*

Blood glucose was determined by the glucose oxidase method (Teller 1956). Blood samples for hormone assay were centrifuged at 4°C immediately after the completion of
TABLE 1. Clinical data of 22 patients with chronic pancreatitis

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* In all patients except for cases 1 and 3, the pancreozymin-secretin test was carried out. The lower levels of the controls in secretion volume, maximum HCO₃ concentration and amylase output in the test are 1.2 ml/kg, 101 mEq/liter and 1650 U/kg, respectively. The cases 1 and 3 received the standard secretin test, in which the lower levels of the controls in secretion volume, maximum HCO₃ concentration and amylase output are 1.6 ml/kg, 79 mEq/liter and 775 U/kg, respectively. Results are presented as the percent of these values. † No: normal GTT, Sl: slightly impaired GTT, Mi: mildly diabetic GTT, Mo: moderately diabetic GTT.

experiments, and plasma was kept at -20°C until the assay. Plasma IRI was measured by a modification (Ohneda et al. 1970) of the Morgan and Lazarow method (1963) in all patients except two, cases 18 and 22, who had been treated with insulin. Plasma IRG was measured by the method previously described (Ohneda et al. 1972). The antiserum, G-21, used for plasma IRG assay was produced in our laboratory and is highly specific for pancreatic glucagon (Ohneda et al. 1975).

The mean values and the standard errors of the mean were calculated and statistical analyses were performed by Student's t-test.

RESULTS

Glucose tolerance test

The changes in blood glucose and plasma IRI during GTT are shown in Fig. 1, in which the values for normal controls are presented as a shadowed area. In the normal controls, blood glucose rose from the fasting level of 88.9±2.2 mg/100 ml to a peak of 131.9±7.2 mg/100 ml at 30 min and fell thereafter. The plasma IRI in the normal controls rose from the fasting level of 20.0±5.9 μU/ml to a peak
Mean blood glucose and plasma insulin during 50 g glucose load in normal controls and patients with chronic pancreatitis. These patients were divided into three groups according to the glucose tolerance curve, I (○—○), II (Δ—Δ) and III (■—■). See text for the criteria. The mark at each point represents a significant difference as compared with controls: * p<0.05, † p<0.02, ‡ p<0.01.

The subjects with chronic pancreatitis were divided into three groups according to the results of GTT: group I, 8 patients, showed normal or slightly impaired glucose tolerance; group II, 8 patients, mildly diabetic glucose tolerance with a fasting blood glucose level below 120 mg/100 ml; and group III, 6 patients, moderately diabetic glucose tolerance with a fasting blood glucose level over 120 mg/100 ml. In this study, diabetic glucose tolerance means that the blood glucose levels at the peak and 120 min after oral glucose loading are higher than 180 and 140 mg/100 ml, respectively.

All groups of the patients showed very low plasma IRI levels at fasting, and after glucose loading reduced responses of plasma IRI were revealed in proportion to the degree of glucose intolerance. In group I, plasma IRI rose from the fasting level of 4.6±1.1 μU/ml to a peak of 52.4±14.4 μU/ml at 60 min, falling to 29.4±8.7 μU/ml at 120 min. In group II, the fasting level of plasma IRI was 6.0±1.6 μU/ml, which slightly rose to a peak of 15.4±1.4 μU/ml at 90 min. In group III, the fasting plasma IRI level was 3.5±1.0 μU/ml and there was no response to glucose ingestion. Although the mean IRI response in group I was the same as that of the normal controls, some cases of this group showed minimal IRI
response; namely the maximum levels of plasma IRI were lower than 20 μU/ml in cases 2, 4 and 5.

Arginine infusion test

The changes in blood glucose, plasma IRI and IRG during the arginine infusion test are shown in Fig. 2. The shadowed areas show the values for the controls. In the controls, blood glucose increased from the initial level of 90.4±1.2 mg/100 ml to a peak of 110.3±2.4 mg/100 ml at 20 min. The changes in blood glucose in groups I and II were similar to those in the controls for the first 30 min, but they still remained at elevated levels after the completion of the arginine infusion. In group III, only a small change of blood glucose level was seen during the arginine infusion test.

Plasma IRI in the controls rose from the baseline level of 14.5±3.1 μU/ml to a peak of 82.3±12.3 μU/ml at 30 min, returning to the initial level at 60 min. In group I, the baseline level of plasma IRI was 3.9±0.8 μU/ml and plasma IRI rose to a peak of 43.4±14.4 μU/ml at 30 min, but the IRI levels in the first 30 min were significantly reduced compared with the controls. In groups II and III, the IRI responses were reduced after arginine infusion. The initial level of plasma IRI was 7.0±2.0 μU/ml and the peak level was 17.8±5.1 μU/ml at 40 min in the former,

![Graphs showing changes in blood glucose, plasma insulin, and plasma glucagon during arginine infusion test.](image)

Fig. 2. Changes in blood glucose, plasma insulin and plasma glucagon during arginine infusion test in normal controls and patients with chronic pancreatitis. Abbreviations are the same as in Fig. 1.
while the initial level was 3.5±1.0 µU/ml and the peak level was 17.5±8.9 µU/ml at 30 min in the latter. Among the three groups of the patients, group I showed higher levels of plasma IRI after arginine infusion, but this was due to the normal or excessive IRI response to arginine in cases 6 and 7. The peak level of plasma IRI in case 6 was 77 µU/ml at 40 min and that in case 7 was 140 µU/ml, while the maximum response in the other cases of group I were reduced as those of the other two groups. These results showed reduced IRI response to arginine in chronic pancreatitis in the face of normal or slightly impaired glucose tolerance.

On the other hand, the responses of plasma IRG in chronic pancreatitis during arginine infusion test were slightly reduced in comparison with the normal controls. In the controls, the plasma IRG rose from the initial level of 77±8 pg/ml to a peak of 229±19 pg/ml at 30 min, and then fell to 54±8 pg/ml at 75 min. The plasma level of IRG in group I rose from the initial level of 33±4 pg/ml to 255±19 pg/ml at 30 min, and the levels at 0 and 40 min were significantly different from those in the controls (p<0.01 and p<0.05, respectively). In group II, the initial level of plasma IRG was 80±16 pg/ml and the peak level was 159±30 pg/ml at 20 min, and a significant difference was observed at 10 and 20 min (p<0.02 and p<0.05, respectively). In group III, the initial level was 56±23 pg/ml and the peak level was 169±43 pg/ml at 30 min, and the level at 20 min was significantly reduced as compared with the controls (p<0.05). There was no significant difference between the levels of plasma IRG in each group at anytime.

Increment areas of IRI and IRG

The increment areas of IRI (ΣIRI) and of IRG (ΣIRG) during the first 60 min in the arginine infusion test were calculated and the results are shown in Fig. 3. ΣIRI in chronic pancreatitis was remarkably reduced except in cases 6 and 7. The means of ΣIRI in the controls, and groups I, II and III were 2.11±0.39, 2.45±1.28, 0.46±0.13 and 0.30±0.10 mU·min/ml, respectively. The values of groups II and III were significantly decreased compared with the controls (p<0.01 and p<0.05, respectively).

The means of ΣIRG were 5.94±0.98, 7.21±0.08, 3.62±0.61 and 3.92±0.79 ng·min/ml in the controls, and groups I, II and III, respectively. These values in groups II and III seemed reduced compared with the value of the controls, although significant difference was observed only between the controls and group II (p<0.05), while the values of groups II and III were significantly reduced compared with that of group I (p<0.01 and p<0.05, respectively).

The correlation between ΣIRI and ΣIRG was studied, but no significant correlation was observed.

Molar ratios of insulin to glucagon

The molar ratio of the fasting level of IRI to IRG (IRI/IRG) and the molar ratio of ΣIRI to ΣIRG (ΣIRI/ΣIRG) were calculated and the mean value of each group is shown in Fig. 4. The mean values of IRI/IRG were
Fig. 3. Insulin increment area ($\Sigma dIRI$) (A) and glucagon increment area ($\Sigma dIRG$) (B) during arginine infusion test in normal controls and patients with chronic pancreatitis. Abbreviations are the same as in Fig. 1.

Fig. 4. Molar ratio of fasting level of insulin to glucagon (A) and molar ratio of increment area of plasma insulin to plasma glucagon during arginine infusion test in controls and patients with chronic pancreatitis. Abbreviations are the same as in Fig. 1.
4.39±1.11, 3.37±0.91, 2.42±0.63 and 3.23±0.49 in the controls, and groups I, II and III, respectively (Fig. 4 A). No significant difference was observed between them. While the mean values of ΣA IRI/ΣA IRG in the controls was 8.60±1.86, and those in groups I, II and III were 7.87±4.08, 3.42±1.05 and 3.07±0.91, respectively (Fig. 4 B). The values of ΣA IRI/ΣA IRG in groups II and III seemed decreased compared with that of the controls, although the difference was statistically significant for only group II (p<0.05). On the other hand, the mean of ΣA IRI/ΣA IRG in group I was the same as the normal controls, but this was caused by its exceptionally high values in cases 6 and 7.

The correlation between the fasting blood glucose level and the IRI/IRG and between total glucose area during the first 60 min and the ΣA IRI/ΣA IRG was studied, but no significant correlation was observed.

Correlation between exocrine and endocrine function of the pancreas

In order to investigate if the impairment in endocrine function relates to exocrine function of the pancreas, correlation coefficients between each of the three parameters of exocrine function in the pancreozymin-secretin test and ΣA IRI or ΣA IRG were calculated. But no significant correlation was demonstrated in these studies.

DISCUSSION

In the present study, all except for one case showed impaired glucose tolerance and 14 patients (64%) were regarded as diabetic in GTT. In order to investigate the relationship between glucose intolerance and endocrine function of the pancreas, the patients were divided into three groups according to the degree of glucose intolerance. Among these three groups, however, no difference was found in age, body weight index, possible duration of pancreatitis or exocrine function of the pancreas.

In the subjects with chronic pancreatitis, the mean levels of plasma insulin following oral glucose were normal or reduced in proportion to the degree of glucose intolerance. Moreover, those during the arginine infusion were also reduced not only in groups II and III but also in group I. Many authors documented a reduced insulin response in chronic pancreatitis to various stimuli, and this was demonstrated much more prominently by the intensive stimulation proposed by Ryan et al. (1966) in which glucagon and tolbutamide were administered 30 min after oral glucose loading (Joffe et al. 1968). Therefore, it is evident that the beta cell function of the pancreas is impaired in patients with chronic pancreatitis and that it causes the glucose intolerance in these patients.

However, it is not pertinent to explain the abnormality in glucose metabolism in chronic pancreatitis by only reduced insulin response. For example, some cases of chronic pancreatitis showed normal or slightly impaired glucose tolerance in spite of reduced insulin response during glucose tolerance test, while the insulin responses in groups II and III were much more reduced for their
changes in blood glucose levels after glucose loading. In addition to these findings in glucose tolerance test, the insulin response to arginine in the patients with chronic pancreatitis was markedly reduced except in two cases as shown in Figs. 2 and 3. Moreover these values are lower than those in primary diabetics as previously reported (Ohneda et al. 1975). As a result, it is reasonable to state that glucose intolerance in chronic pancreatitis seems to be slight for its impairment in insulin response. Bank et al. (1968) and Joffe et al. (1968) obtained similar results to ours. Is a small amount of insulin enough to elicit its effect on glucose metabolism in chronic pancreatitis? In this context, Joffe et al. (1970) reported lower levels of serum lipids in diabetics secondary to chronic pancreatitis, and Vinik et al. (1970) observed decreased growth hormone response in these patients. In an early observation from our laboratory (Matsuda 1974), however, it was shown that the fall of blood glucose level after administration of exogenous insulin was slightly decreased and delayed in chronic pancreatitis compared with the controls. This investigation suggests that the action of insulin on the peripheral tissue is not enhanced in chronic pancreatitis.

Recent studies on glucagon secretion revealed a hyperglucagonemic state at fasting (Unger et al. 1970; Heding and Rasmussen 1972) or after arginine infusion (Unger et al. 1970; Ohneda et al. 1975) in primary diabetes mellitus. To the contrary, in the subjects with chronic pancreatitis, the glucagon levels at fasting were normal or rather decreased. After arginine infusion, the glucagon response was within the normal range in group I, while they were at the lower limit of the controls or reduced in the groups with diabetic glucose tolerance. These results suggest that the function of alpha cells as well as beta cells is also impaired in patients with chronic pancreatitis, especially in those with diabetic glucose tolerance. The ratios of insulin to glucagon, which are regarded as an important factor in glucose metabolism (Unger and Lefebvre 1972), were studied in patients with chronic pancreatitis. The ratios of insulin to glucagon at fasting were not so different from those of the controls, but the ratios of increment area of insulin to that of glucagon after arginine infusion were decreased in the groups with diabetic glucose tolerance. Although the latter findings appear similar to those of primary diabetics, it should be emphasized that the decrease in this ratio is caused by reduced insulin response and increased glucagon response in primary diabetics. To the contrary, it is due to markedly reduced insulin response in spite of rather reduced glucagon response in chronic pancreatitis. Moreover, the decrease in this ratio in chronic pancreatitis is still slight in comparison with that in primary diabetics as reported previously (Ohneda et al. 1975). Consequently, the impairment in the alpha cell function of the pancreas in patients with chronic pancreatitis seems to have a favorable effect on glucose tolerance and contribute to the slight glucose intolerance, in spite of markedly decreased levels of plasma insulin in these patients.

From the results in arginine infusion test, it is suggested that the insulin response is much more impaired than the glucagon response in patients with
chronic pancreatitis. The reason of this finding is unknown. Kalk et al. (1974b) suggested that the reduced insulin levels might cause relatively higher levels of glucagon after arginine infusion in chronic pancreatitis. In our study, however, the glucagon response to arginine was not increased but rather reduced in the patients with decreased insulin response, although significant correlation was not found between increment area of insulin and glucagon. From the histological observation, Sors and Lemaigre (1965) and Wacjner (1965) showed a predominance of alpha cells over beta cells in the process of regeneration of pancreatic endocrine tissue after damage from chronic pancreatitis. These reports are attractive to explain the different degree of impairment in insulin and glucagon response in chronic pancreatitis, although there has been no evidence supporting the real endocrine function of these cells appearing in the process of regeneration. Another possibility is extra-pancreatic secretion of glucagon or glucagon-like immunoreactive substance. The presence of the substance which reacts with a specific antibody for pancreatic glucagon in pancreatectomized dogs was reported by Matsuyama and Foa (1974), Vranic et al. (1974) and Mashiter et al. (1975). Moreover, Sasaki et al. (1975) demonstrated the presence of gut glucagon in crude extract of porcine duodenum, which showed the same characters as pancreatic glucagon in its immunological and several chemical properties. Therefore, it is likely that glucagon or glucagon-like material is secreted from extra-pancreatic origin under the condition of severely damaged pancreas as in chronic pancreatitis. Lastly, the specificity of the antiserum used for glucagon assay must be considered. The antiserum, G-21, used in this study had little cross-reactivity with the Peak I or Peak II (Valverde et al. 1968) of gut glucagon-like immunoreactivity, which was extracted from canine intestinal mucosa by the method of Kenny (1955) and purified through gel filtration and affinity chromatography (Ohneda et al. 1976). Moreover, this antiserum did not cross-react with secretin, 25% pure cholecystokinin-pancreozymin, gastric inhibitory polypeptide or vasoactive intestinal peptide at all (Ohneda et al. 1975). Therefore, this antiserum is highly specific for pancreatic glucagon, and so it is unlikely that the cross-reactivity of this antiserum is a cause of the relatively slight impairment in glucagon response in chronic pancreatitis.

Another interesting problem in chronic pancreatitis is whether the impairment in exocrine function relates to that in endocrine function. Slight correlation between insulin response and exocrine function of the pancreas in chronic pancreatitis was reported by Ohlsén (1968) and Deckert et al. (1972), while Peters et al. (1966) did not find any direct relationship between the insulin response during oral glucose ingestion and pancreatic exocrine function in their subjects. On the other hand, there is no report referring to the correlation between glucagon response and pancreatic exocrine function in patients with chronic pancreatitis. In the present study, the insulin response to oral glucose did not seem to be related to the results of pancreozymin-secretin test, and neither the increment areas of insulin nor those of glucagon after arginine infusion showed a correlation with the parameters of pancreatic exocrine function. The difference in the location of the pancreatitie
lesion may cause these results. However, precise relationship between the exocrine and endocrine function of the pancreas is still to be examined on a larger number of patients with chronic pancreatitis.

References


