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Insulin Resistance and Liver Cirrhosis

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Abstract

This work was performed on 15 patients with liver cirrhosis or fibrosis and 15 healthy control subjects to study glucose utilization and insulin level using the intravenous glucose tolerance test (IVGTT). The results of glucose and insulin were illustrated on a curve, then glucose area and insulin area under the curve were calculated. In addition insulin area/glucose area ratio (insulinogenic index) and insulin stimulating activity (ISA) were estimated to evaluate B-cell response to hyperglycemia. Also the Kg-value was estimated to assess the rate of glucose assimilation per minute. The results obtained showed that the rate of glucose utilization in cirrhosis (Kg-value) was significantly decreased compared to controls. At the same time the B-cell function was not affected in cirrhosis, as concluded from the insignificant change in insulinogenic index and ISA compared to healthy controls. Also, there was fasting hyperinsulinemia associated, with fasting euglycemia indicating insulin resistance. It has been concluded that the cause of hyperinsulinemia, glucose intolerance and consequently insulin resistance in cirrhosis is defective peripheral tissue response to insulin, whether the defect is in the receptor binding or post-receptor defect, this remains to be investigated.

Introduction

MANY studies have reported hyperinsulinemia with normal or impaired glucose tolerance in liver cirrhosis [1,2]. Some investigators have claimed defective hepatic insulin metabolism [3]. Others suggested portosystemic shunting as a responsible factor for this hyperinsulinemia [4]. On the other hand, many workers have found elevated C-peptide levels in the fasting and postprandial state of patients with liver cirrhosis [5]. The high C-peptide levels and the presence of hyperinsulinemia with normal or impaired glucose tolerance have led to the assumption that an insulin resistant state is playing an important role in the aetiology of hyperinsulinemia of liver cirrhosis.

This work is planned to study glucose assimilation and the associated insulin levels in patients with liver cirrhosis during intravenous glucose tolerance test.

Subjects and Methods

The study was performed in 30 subjects. 15 male patients with liver cirrhosis or fibrosis. The age of the patients ranged from 25 to 65 years. The patients were not

suffering from diabetes mellitus (or family history of diabetes), cardiovascular (including hypertension), pulmonary or renal disorders. Those taking corticosteroids or giving history of alcohol intake were excluded.

The control group were 15 apparently healthy males, their age ranged from 27 to 60 years. Obese subjects were excluded. They were clinically free and had no history suggesting schistosomiasis, hepatitis, diabetes mellitus or hypertension.

In addition to history taking and careful clinical examination, both the control subjects and the patients were subjected to routine investigations including X-ray chest, ECG, upper GIT endoscopy, sigmoidoscopy, abdominal ultra sonography and liver biopsy.

In addition, routine laboratory tests were performed as stool and urine analysis, complete blood picture, erythrocyte sedimentation rate and blood urea.

Liver function tests like total serum proteins [6], serum albumin [7], serum bilirubin [8], serum transaminases [9] (AIT, AST) alkaline phosphatase [10] and prothrombin time and concentration [11], were performed. Also, hepatitis B-surface antigen [12] was done, (all subjects were HBsAg-ve).

Then intravenous glucose tolerance test was performed to all subjects of the study, where serum glucose was estimated by enzymatic calorimetric method according to Trinder [13]. All kits used were manufactured by Boehringer Mannheim GmbH, Diagnostic, France, AS., except serum insulin that was estimated by RIA kits provided by Diagnostic product corporation Los Angeles. CA. U.S.A. [14].

After an overnight fast, venous blood samples were taken and each subject was given intravenous glucose solution (25%) in a dose of 0.3 gm/kg body weight. The injection was completed within three minutes. Blood samples were taken after 5, 30 and 60 minutes of the end of glucose injection. Serum was separated and glucose level was estimated immediately by glucose oxidase method and the rest of the sample was stored at -20°C till the time of insulin assay.

Serum glucose levels after IVGTT of each subject were plotted on a semi-log paper. The rate of glucose assimilation in percent/minute (Kg-value) was calculated from the equation:

$$Kg = \frac{69.9}{T\ 1/2}\ \text{mg\% per minute [15].}$$

Methods of interpretation of the results:

1- Glucose utilization by the Kg value.

2- Response of B-cells to the glucose load. This was assessed by various methods:

a- Insulin area:

The insulin curve was plotted on a plain graph paper. The insulin area is the area over the basal level. It was determined by planimetry [16]. The mean insulin area for each group was calculated and the student "*t*" test used for statistical comparison.

b- Insulin stimulating activity [17]:

The insulin area above the base-line for thirty minutes after the end of glucose infusion was measured and divided by thirty. The mean value for each group was then determined and the student "*t*" test applied for comparison.

c-Insulinogenic index [18]:

This measures the insulin area divided by the glucose area. It shows the insulinogenic action of glucose i.e. the relation between the hyperglycemia and the response of the B-cells to it.

Results

There was insignificant difference between the mean values of fasting serum glucose ($p < 0.05$) and 5 minutes after I.V. glucose infusion ($p > 0.05$) between the control and the cirrhotic group. After 30 and 60 minutes of I.V. glucose the mean±SEM serum glucose in cirrhotic patients (136±7.64 and 101±4.81 respectively) were significantly higher than those of the control group (113±4.70 and 85±3.91 after 30 and 60 minutes respectively) ($P < 0.01$) (Table 1 and Fig. 1).

The mean±SEM of fasting serum insulin level in the cirrhotic group (17.80 ±2.65) was significantly higher than that of the control group (9.5±6.45), ($P < 0.005$). After 5, 30 and 60 minutes of I.V. glucose, serum insulin levels in cirrhotic group (94.3±12.45, 49.13±6.79 and 24±2.10 respectively) were all insignificantly higher than those of the control group (76.9±2.10, 36.3±1.18 and 23.2±1.65 after 5, 30 and 60 minutes respectively) $p < 0.05$ (Table 1, Fig. 2).

Out of the methods used for interpretation of the results the kg value (demonstrating glucose utilization), that was significantly reduced in the cirrhotic group (1.19 mg%/min±0.04) than that of the control group (1.89 mg%/min ±0.06), $p < 0.001$ (Table 1).

Each of the glucose area and insulin area were insignificantly higher in the cirrhotic group (31.4 units ±2.18, 45.1 units ±5.24 respectively) than that of the control group (30.8 units ±2.3 and 37.9 units ±1.76 respectively) $p > 0.05$ (Table 1).

The insulin/glucose ratio (insulinogenic index) was also demonstrated in Table (1). There was insignificant difference ($P > 0.05$) between the cirrhotic patients (1.63 ± 0.22) and the control group (1.3±0.107).

The mean insulin stimulating activity (ISA), in the cirrhotic group (1.04 units ±0.117) was insignificantly higher than that of the control group (0.89 units ±0.03), ($p > 0.05$).

Discussion

In this study we tried to localize the defect in glucose homeostasis in liver cirrhosis and to find out the inter-relation between plasma insulin and glucose concentration. Both serum glucose and insulin were estimated during IVGTT. IVGTT aims at stimulating insulin secretion with a physiological stimulus, viz abrupt rise of blood glucose level without interference of the gastrointestinal modulatory effects. Exclusion of GIT role is particularly important on studying glucose tolerance in liver cirrhosis as well as in other GIT disorders. Evaluation of glucose tolerance is suggested by Fajans and Conns [15] by calculating the rate of glucose utilization or the so-called kg-value. The higher the value, the better is the tolerance. The mean Kg-value of our cirrhotics was significantly lesser than that of the healthy controls. Hence, impaired glucose tolerance is suggested in cirrhotics. This is in agreement with El-Badry et al. [19] and Marchesini et al. [2]. On the other hand Tawfik [21] found that the Kg-value was not significantly altered in the cirrhotic group of patients compared to the control.

Table (1): Statistical Comparison between Cirrhotic Group and Control Group.

Group	Para-meter	G. area units	Insulin area units	I. area/ G. area	ISA units	Kg-value mg %/min	Glucose mg/dL				Insulin µU/ml			
							0 min.	5 min.	30 min.	60 min.	0 min.	5 min.	30 min.	60 min.
Control	Mean	30.30	37.90	1.300	0.890	1.89	80.00	197.00	113.00	85.00	9.50	76.90	36.30	23.20
n = 15	± S.D.	8.91	6.83	0.415	0.117	0.26	9.72	27.19	18.20	15.17	1.77	8.17	7.02	6.40
	±S.E.	2.30	1.76	0.107	0.030	0.06	2.51	7.02	4.70	3.91	0.45	2.10	1.81	1.65
Cirrhosis	Mean	31.40	45.10	1.63	1.040	1.190	33.00	194.00	136.00	101.00	17.80	94.30	49.13	24.00
n = 15	± S.D.	8.45	20.30	0.85	0.450	0.158	15.00	36.90	29.60	16.12	10.28	48.23	26.32	8.14
	±S.E.	2.18	5.24	0.22	0.117	0.040	3.87	9.52	7.64	4.18	2.65	12.45	6.79	2.10
	p	>0.05	>0.05	> 0.05	> 0.05	< 0.001	> 0.05	> 0.05	< 0.01	< 0.01	< 0.005	> 0.05	> 0.05	> 0.05

I = Insulin.
G = Glucose.

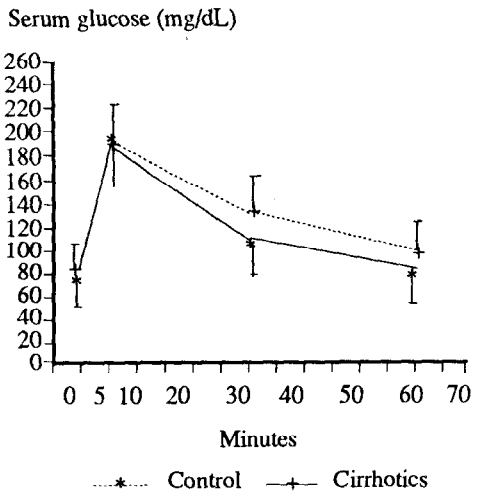

Fig. (1): Mean (± S.E) serum glucose in the cirrhotics and healthy control groups during IVGTT.

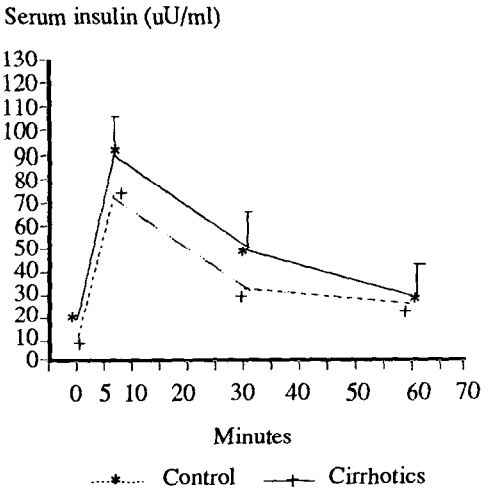

Fig. (2): Mean (± S.E) serum insulin in the cirrhotics and healthy control groups during IVGTT

The reduced glucose tolerance in our patients was not associated with rise of fasting or 5-minute mean serum glucose levels compared to the healthy subjects. This result is similar to those of Kenneth et al. [22] who stated that the fasting blood glucose values are normal in the vast majority of subjects with chronic hepatic disease and the abnormal glucose metabolism in these patients is usually slight and therefore, does not indicate the presence of the clinical syndrome of diabetes. They suggested that the numerous hormonal abnormalities that occur in chronic liver disease may have a role in the pathophysiologic alterations that lead to the slight glucose intolerance.

On the other hand, the mean fasting serum insulin in cirrhotic patients was significantly higher than that of the controls. This finding is consistent with the results of many workers as Taylor et al. [23], Marcheseni et al. [20] and Halawa et al. [24].

The presence of hyperinsulinemia in our patients associated with normal fasting glucose level means that higher serum insulin levels are required to attain the euglycemic state during fasting i.e. an insulin resistant state is existing in patients with liver cirrhosis.

After 30 and 60 minutes of glucose bolus, serum glucose of cirrhotic patients presented significantly higher levels than the healthy group, but associated serum insulin levels showed insignificant alteration among both healthy and cirrhotic groups. This finding suggests that insulin response to serum glucose is inadequate to metabolize glucose, either because of inefficient pancreatic islet B-cell function or lack of peripheral cells to respond to circulating insulin.

Insulin stimulating activity (ISA) has been calculated and its value was insignificantly changed in cirrhotics versus the controls. This suggests similar response of B-

cells of the pancreas in both controls and cirrhotics. In addition measuring the insulin area under-curve was also insignificantly changed. Therefore, the potency of the B-cells of the pancreatic islets appears not to be affected by the pathological changes in liver cirrhosis. These results are different from that of Marchesini et al. [25] who suggested diminished B-cell responsiveness in liver cirrhosis. Other investigators as Greco et al. [2] and Bosch et al. [26], showed statistically increased insulin levels after glucose administration. They attributed higher insulin values to defective degradation rather than to an increase in B-cell secretion.

The ratio of insulin area under the curve/glucose area under the curve (insulinogenic index) was also insignificantly altered in our cirrhotic patients compared to the healthy control group. This suggests also that the B-cell responsiveness is not altered in liver cirrhosis and it is in agreement with that of Leatherdole et al. [27].

The rate of glucose assimilation is decreased in our patients with cirrhosis (as indicated by the kg value), inspite of good serum insulin levels. This is probably because of lack of efficient hypoglycemic effect of insulin. One may suggest an interfering factor that affects insulin binding to target cells, increased internalization of insulin receptors and/or defective post-receptor effect inside the cells.

Plasma steroid hormones are antiinsulin hormones and their rise may account for diminished glucose utilization in cirrhosis. However, Riggio et al. [28] found that serum cortisol level is normal in cirrhotics. Growth hormone was reported to be elevated in cirrhotics both fasting and after glucose loading, compared to normal controls [21]. So, it may contribute to diminished glucose assimilation in cirrhosis. One may find auto-antibodies in cases of cirrhosis particularly the post-hepatitis type. Among these autoantibodies might be insulin receptor antibodies that interfere with insulin binding to its target cells.

To summarize, our results showed normal B-cell responsiveness to IV glucose load but diminished rate of glucose utilization in patients with liver cirrhosis.

Further work at cellular and subcellular or molecular level is required to clarify the inadequate glucose utilization in cirrhosis.

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