CARBOHYDRATE METABOLISM IN LIVER CIRRHOSIS

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ABSTRACT

Patients with cirrhosis of liver are more prone to have accompanying diabetes mellitus. The present study was conducted to investigate various biochemical parameters in patients with hepatic cirrhosis without diabetes. In these patients blood pyruvate, total bilirubin and globulin levels were elevated as compared to normal individuals. In contrast serum albumin level declined significantly whereas no significant change was observed in the concentrations of blood glucose, total proteins, total lipids, urea and serum cholesterol. These studies confirm the previous reports that carbohydrate metabolism is deranged in hepatic cirrhosis which may lead to diabetes mellitus (JPMA 41: 298,1991).

INTRODUCTION

Stimulation of glucose uptake by muscles and certain other tissues is generally recognized as one of the most characteristic and important actions of insulin. This acceleration is the principal course of the fall in blood glucose following administration of the hormone. The absence of this effect accounts in large part for the abnormal elevation of the blood glucose in certain types of diabetes. It therefore, seems clear that stimulation of glucose uptake is an appropriate phenomenon for investigation of the locus of insulin action[1]. Abnormalities of carbohydrate metabolism in hepatic disorders have been reported by various workers from Europe. Reports available from the Indian subcontinent reveal that the syndrome of chronic hepatic failure, the cirrhosis of liver, rather differs from that of the west[2]. A study of patients with compensated liver diseases revealed inappropriately high serum insulin levels in response to a glucose load administered either orally or intravenously and a diminished glucose response to injected insulin[3]. A constant finding in cirrhosis of liver is impaired glucose tolerance in association with hyper-insulinemia[4]. In the presence of insulin resistance, glucose uptake and glycogen synthesis by the liver will be impaired resulting in a decreased glycogen storage in the liver. This might explain the impaired glycemic response to intravenous glucagon administration[5]. The importance of the liver in the intermediary metabolism of protein, fat and carbohydrate is well known. It is quite possible that impaired intermediary metabolism may be of fundamental signifiicance in the appearance of acute hepatic failure[5]. The liver occupies a key position in carbohydrate metabolism and disturbances are encountered in almost all forms of hepatic dysfunction. Oral and intravenous glucose tolerance tests show impairment in patients with liver diseases, but the findings are neither constant nor specific enough to be of practical importance[6]. Laboratory findings revealed decreased glucose tolerance and elevated blood glucose. The essence of this kind of disease is different from that of diabetes mellitus and it is thus called hepatogenous diabetes[7]. Observation of glucose intolerance and hyperinsulinemia in patients with hepatic cirrhosis and the association of diabetes and cirrhosis have been discussed by various researchers[9]. The present study was carried out to assess carbohydrate metabolism in liver cirrhosis, to establish fasting blood insulin levels and hepatic function in cirrhosis and also to find some relationship between diabetes and cirrhosis.

MATERIAL AND METHODS

Sixty patients with liver cirrhosis were studied, They were selected from those attending as outpatients at the Pakistan Medical Research Council, Karachi and those admitted in medical wards of Jinnah Postgraduate Medical Centre Karachi. All of them were biopsy proved patients of liver cirrhosis. Twenty apparently normal and healthy subjects of the same age, sex and socioeconomic status were taken as a control group. They were selected from the staff and students of Basic Medical Sciences Institute, Karachi, Patients were divided according to Childs classification in three groups, mild, moderate and severe cirrhosis, on the basis of hepatic function reserve in decreasing order of prognosis with aid of five clinical indicators, i.e., serum bilirubin, serum albumin, neurological disorders, nutritional status and degree of ascites as shown in Table I.

TABLE I. Childs's classification[22].

	Mild Cirrhosis	Moderate Cirrhosis	Severe Cirrhosis
Laboratory Investigations			
Serum bilirubin μmol/l	<35	35-50	>50
Serum albumin g/l	>35	30-35	<30
Clinical observations			
Ascite	None	Easily controlled	Poorly controlled
Neurological disorders	None	Minimal	Advanced
Nutrition	Excellent	Good	Poor/Wasting
Score for each factor	(1)	(2)	(3)

A total score is reached, mild cirrhosis (5,6), moderate cirrho sis (7,8,9), severe cirrhosis (10-15).

Blood was drawn from both the patients and controls early in the morning after a 12 hour fast. It was then separated into three sub-fractions for the study of blood pyruvate, separation of serum and plasma, by centrifugation within two hours of the withdrawal. The samples were analysed for blood glucose[10], blood pyruvate[11], serum proteins[12], total lipids[13], total cholesterol[14], blood urea[15], serum insulin (RIA Kit obtained from Radiological Centre, Amersham, Buckinghamshire, England), serum bilirubin[16], alkaline phosphatase (Automated analysis Boehringer, Mannheim GmbH).

RESULTS

TABLE II. Comparison of fasting blood glucose, pyruvate, total lipids, cholesterol and urea between controls and different groups of cirrhotics.

Subject	Glucose mg/dl	Pyruvate mg/dl	Total Lipids mg/dl	Cholesterol mg/dl	Blood Urea mg/dl
Controls (20)	88.03 ± 2.24	0.97 ± 0.10	725.65 ± 44.06	161.15 ± 10.78	29.99 ± 1.53
Mild Cirrhotics (15)	83.96 ± 13.43	1.95*** ± 0.14	600.36 ± 53.00	197.75* ± 13.29	49.81** ± 6.14
Moderate Cirrhotics (23)	78.06 ± 5.90	2.24*** ± 0.18	544.13** ± 31.69	180.79 ± 10.93	35.73 ± 3.95
Severe Cirrhotics (22)	108.93** ± 7.73	1.67*** ± 0.11	579.06** ± 28.92	160.31 ± 13.04	29.49 ± 1.83
Total Cirrhotics (60)	90.85 ± 5.18	1.96*** ± 0.09	571.00*** ± 20.70	177.47 ± 7.31	36.96* ± 2.42

The values are expressed as mean ± s.e.m. Number of cases are given in parenthesis.
* P < 0.05 Significant.
** P < 0.01 Markedly Significant.
*** P < 0.001 Highly Significant.

TABLE III. Comparison of serum insulin, alkaline phosphatase, bilirubin and protein between controls and different groups of cirrhotics.

Subject	Insulin μU/ml	Alkaline Phosphatase I.U/l	Bilirubin μmols/l			Proteins g/dl			
			Total	Conjugated	Unconjugated	Total	Albumin	Globulin	A/G
Controls	12.16 ±1.40 (14)	56.13 ±7.55 (17)	12.61 ±0.99 (20)	3.22 ±0.27 (20)	9.38 ±0.83 (20)	7.44 ±0.15 (20)	4.68 ±0.12 (20)	2.86 ±0.15 (20)	1.75 ±0.08 (20)
Mild Cirrhotics	13.78 ±4.15 (15)	165.60*** 48.47 (16)	46.45*** ±3.77 (15)	38.20** ±3.51 (15)	8.33 ±0.63 (15)	7.51 ±0.30 (15)	4.00* ±0.28 (15)	3.51 ±0.35 (15)	1.38 ±0.21 (15)
Moderate Cirrhotics	10.45 ±0.77 (18)	70.25* ±9.78 (18)	20.26** ±2.38 (23)	20.26** ±2.18 (23)	13.27*** ±0.71 (23)	7.36 ±0.26 (23)	7.09 ±0.18 (23)	3.78*** ±0.19 (23)	3.27 1.40* ±0.16 (23)
Severe Cirrhotics	11.66 ±0.89 (22)	100.20*** ±9.30 (22)	35.28*** ±3.85 (22)	28.71*** ±3.62 (22)	6.59** ±0.45 (22)	7.33 ±0.22 (22)	3.57*** ±0.16 (22)	3.77** ±0.22 (22)	1.03*** ±0.08 (22)
Total Cirrhotics	11.97 ±1.14 (50)	110.04*** ±7.53 (51)	32.32*** ±2.33 (60)	25.16*** ±2.20 (60)	7.32* ±0.36 (60)	7.28 ±0.15 (60)	3.75*** ±0.11 (60)	3.52** ±0.16 (60)	1.26*** ±0.09 (60)

The values are expressed as mean ± s.e.m. Number of cases are given in parenthesis.
* P < 0.05 Significant.
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*** P < 0.001 Highly Significant.

Tables II and III show serum levels of blood glucose, pyruvate and insulin in all groups (based upon the severity of disease) of patients in comparison with controls. These tables also show the comparative levels of total lipids, cholesterol, urea, alkaline phosphatase, serum bilirubin and serum proteins. Blood glucose levels patients as compared to control group. Cholesterol and urea level was significantly higher only in mild cirrhotics, not in other groups. No significant change was observed in the insulin

levels. Serum alkaline phosphatase level was significantly higher in all the groups of patients as compared to controls. Serum bilirubin level was also raised and the level was significantly higher in all the groups of patients as compared to controls. Serum bilirubin level was also raised and the level was significantly higher in all the groups of patients in comparison with the controls. Serum albumin level was significantly decreased with increase in the level of globulins in all the groups of patients and with change in A/G ratio.

DISCUSSION

The relationship of chronic liver disease and abnormalities of carbohydrate metabolism associated with raised serum insulin level have long been discussed. Liver occupying a key position in the metabolic activities of the body may produce glucose intolerance when discussed[2]. Oral glucose tolerance tests tend to be impaired in patients with cirrhosis. This is not due to malabsorption of glucose. The fasting blood glucose is normal but the level rises higher after glucose administration[17]. In cases of cirrhosis of liver having normal and impaired glucose tolerance fasting blood glucose value were found to be lowered as compared to controls and in case of cirrhosis of liver with diabetic glucose tolerance test blood glucose level was higher than normal. These findings were statistically not significant[2]. Patients with liver cirrhosis were studied. Fasting hyperglycemia and glucose intolerance was found. In addition fasting hyperinsulinemia and abnormally high insulin response to intravenous glucose were observed[18]. Hypoglycemia is rare in cirrhosis liver. Even in terminal hepatocellular failure, patients maintained their blood glucose level above 50 mg/dl[19]. Hypoglycemia may also develop after alcohol ingestion in alcoholics, especially if they are cirrhotic[7]. In the metabolism of carbohydrate, pyruvic acid occupies a central position, under normal conditions pyruvic acid may contribute to the formation of carbohydrate and may ‘undergo reversible and irreversible transformation[6]. Hyperinsulin reaction and glucose intolerance were observed in liver diseases. Similar responses were observed in cirrhosis liver and chronic hepatitis except glucose intolerance and IRI maximum, which were remarkable in liver cirrhosis than chronic hepatitis[20]. Hyperinsulinemia and insulin resistance have been the most intriguing observation in the cirrhotic patients. The present study confirms the results reported previously by several groups of investigators[3]. Significantly high levels of fasting plasma insulin (IRI) were found in cirrhotic groups as compared to the controls[2]. In the present study blood glucose level was significantly higher in severe cirrhotics only. Pyruvate level was significantly higher in all the individual groups of patients. However, fasting serum insulin level was within normal range as compared to the controls. In the present study patients having hyperglycemia were having normal serum insulin although not clearly known but probably it seems to be related with alcohol consumption. High serum insulin levels were observed in those regions where alcohol consumption is frequent. In the present study alcoholics were almost negligible. The present study also included assay of total lipids, cholesterol and blood urea, in which no significant change was observed, although serum cholesterol and blood urea were significantly higher in mild cirrhotics. Serum bilirubin and alkaline phosphatase were markedly raised in all the groups of patients. Reverse change was observed in serum albumin and globulin, with alteration of albumin/globulin ratio. Various workers have observed that the impairment of glucose intolerance may eventually lead to clinical diabetes in chronic hepatic diseases[21]. Plasma insulin levels are initially normal but rise slowly to values greatly above those found in normal subjects[17]. The patients of hepatogenous diabetes may be particularly marked in the presence of a portocaval anastomosis. It seems possible that cirrhosis is diabetogenic or unmasks a genetically determined diabetogenic trait. These findings may account for the often quoted association of cirrhosis with diabetes mellitus[7]. Findings of the present study and those carried out by previous workers

indicate that in patients with liver cirrhosis carbohydrate metabolism is always deranged, although findings in different studies were variable. Inspite of the variability of the findings, it is well known and agreed by almost all the workers (present and previous) that, in chronic liver disease, carbohydrate metabolism is altered with associated changes in plasma insulin level. Different workers proposed their own reasons for these metabolic changes but the exact mechanism is not known and further studies are needed to be able to know the exact nature of the metabolic changes.

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