PREVALENCE OF DIABETES MELLITUS IN LIVER CIRRHOSIS

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ABSTRACT: Prevalence of diabetes mellitus in liver cirrhosis is considered to be the major cause of mortality due to difference in natural history and clinical outcome of hepatogenous diabetes. This study was conducted to found the glucose metabolism disturbance in liver cirrhosis patients. Twenty control subjects, twenty diabetic patients and sixty diabetic patients with liver cirrhosis were included in this study. Blood samples of diabetic patients and diabetic patients with liver cirrhosis were collected from Services Institute of Medical Sciences Lahore and blood samples of control subjects were collected from different areas of the Lahore. The blood glucose levels were estimated by commercially available kit. It was found that prevalence of diabetes in liver cirrhosis patients was 93.30% in the population of Lahore, Pakistan. These results suggested that special measures should be adopted to control blood glucose level in diabetic patients with liver cirrhosis to reduce the incidence of complications of liver cirrhosis which increase the mortality of diabetic cirrhotic patients.

Key Words: Hepatogenous Diabetes, Cirrhosis, ELISA, Hyperglycemia

INTRODUCTION

Hepatogenous diabetes is a chronic disease of metabolism causing of abnormal glucose homeostasis [1]. Insulin resistance in cirrhotic patients is a characteristic feature of a glucose-intolerant and diabetes. However the pathogenic factors responsible for glucose intolerance remain unclear [2]. More than 171 million people globally are effected by diabetes mellitus and the figure is expected to rise up to 366 million people by 2030 [3].

Insulin resistance is parallel to the fibrosis stage [4]. In the presence of hepatic disease the metabolic homeostasis of glucose is impaired sensitivity of β-cells in the pancreas [5]. The accumulation of ECM protein distorts the hepatic structure by forming a fibrous scar and the subsequent development of regenerating hepatocytes cirrhosis. Cirrhosis further produces dysfunction and increase intrahepatic resistance to blood flow result in hepatic insufficiency and portal hypertension respectively [6].

Glycogenolysis is considered the primary source of nerves stimulation dependent released glucose, accounted for almost 100% of the basal hepatic glucose output [7]. Direct stimulation of hepatic glucose release by sympathetic hepatic liver nerves appears to be able to blunt insulin, in which hormonal response is impaired. However, if the endocrine axis is intact, an activity of hypoglycemia dependent increase in circulating glucagon rather than hepatic sympathetic nerves action was the main stimulus to augment hepatic glucose production [8].

Liver encephalopathy is a reversible neuropsychiatric state that complicated liver disease. The encephalopathy of cirrhosis portal systemic shunting as a component but hepato-cellular dysfunction is also important [9]. Non-alcoholic fatty liver disease (NAFLD) denotes a spectrum of liver disorders associated with abnormal insulin action [10]. Primary types of NAFLD found among peoples have insulin resistance. The secondary type can be associated with the use of certain medication and a variety of miscellaneous disorders [11, 12]. One of the major risk factor for the accumulation of excess liver fat is obesity which leads to insulin resistance [13].

The objective of this study was to elucidate the prevalence of diabetes mellitus in liver cirrhotic patients and to characterize the clinical background of these patients. This information is important to launch the public awareness to control the prevalence of diabetes mellitus among liver cirrhosis patients.

MATERIALS AND METHODS

A case control study was performed to determine the association between diabetes mellitus and liver cirrhosis in the people of Punjab, Pakistan. Study was designed as a prospective based clinical trial. Clinical facility for the present investigation to diagnose the association between liver cirrhosis and diabetes mellitus was available at Services Institute of Medical Sciences (SIMS) Lahore. The study was based on 20 control/healthy subjects, 20 diabetic patients and 60 diabetic patients with liver cirrhosis belonging to different age groups. Diabetic patients with liver cirrhosis were already diagnosed by hepatologist on the basis of endoscopy, ultrasound and biopsy. Blood samples of diabetic patients with liver cirrhosis, diabetic patients and control subjects were drawn during fasting state by the venipuncture method. The blood was collected in sodium fluoride and potassium oxalate containing agent vaccutainers to preserve glucose in blood. The serum was separated into labelled tubes.

Commercially available Spectrum Diagnostics liquizyme glucose reagent kit, GmbH Germany, was used to determine glucose in human serum. According to WHO Rep 2009 [14] the normal range of glucose in fasting serum is < 100 mg/dl and the value of glucose in fasting between 100-120 mg/dl is considered to be pre-diabetic. Serum glucose was determined after enzymatic oxidation in the presence of glucose oxidase. The formed hydrogen peroxide reacted under catalysis of peroxidise (PAP) with phenol and 4-aminoantipyrine to formed a red violet quinoneimine dye as indicator. Before proceeding with the testing, all reagents, serum references and controls were brought at room temperature (25-30 ^{o}C). Then 1ml of glucose reagent was poured into each test tube with the help of pipette. Then 10µl of standard reagent was added into one test tube and patient serum added in other test tubes. Mixed and incubated at 37 ^{o}C for ten minutes. The absorbance of standard reagent and patient serum was read within 30 minutes at 546 nm.

Mean ± S.D of serum samples of control subjects, diabetic patients and diabetic patients with liver cirrhosis were calculated and data was represented in different tables. Statistical analysis of the data was carried out by employing Student 't' test.

RESULTS

Twenty control/healthy subjects, twenty diabetic patients and sixty diabetic patients with liver cirrhosis were involved in the study. The average age among the different groups were

55.75 ± 2.55; 48.9 ± 2.07 and 52.3 ± 1.17 years for control subjects, diabetic patients and diabetic patients with liver cirrhosis respectively. In diabetic patients with liver cirrhosis hyperglycemia were found in 56 (93.30%) patients as compared to control subject.

The mean serum glucose level of control subjects, diabetic patients and diabetic patients with liver cirrhosis were studied. Fasting serum glucose level in diabetic patients with liver cirrhosis was elevated as compared to control subjects. In control subjects these values were 94.5 ± 4.39 mg/dl while in diabetic patients with liver cirrhosis these values were 237.5 ± 16.80 mg/dl. The observed difference was highly significant (P<0.001) in diabetic patients with liver cirrhosis (Table I).

Table I: Mean Serum Glucose Levels in Control (healthy) Subjects and Diabetic Patients with Liver Cirrhosis.

Category	No.	Serum Glucose (mg/dl) (Mean ± SEM)	S.D
Control Subjects	20	94.45 ± 4.39	19.65
Diabetic Patients with Liver Cirrhosis	60	237.5 ± 16.80**	130.18

**P < 0.001

Fasting serum glucose level in diabetic patients with liver cirrhosis was elevated as compared to diabetic patients. In diabetic patients these values were 231.8 ± 26.05 mg/dl while in diabetic patients with liver cirrhosis these values were 237.5 ± 16.80 mg/dl. The observed difference was non significantly higher in diabetic patients with liver cirrhosis (Table II).

Table II: Mean Serum Glucose Level in Diabetic Patients and Diabetic Patients with Liver Cirrhosis.

Category	No.	Serum Glucose (mg/dl) (Mean ± SEM)	S.D
Diabetic Patients	20	231.8 ± 26.05	116.50
Diabetic Patients with Liver Cirrhosis	60	237.5 ± 16.80	130.18

P > 0.05

DISCUSSION

The present study was conducted to check the prevalence of diabetes mellitus in liver cirrhosis patients. This study included twenty control (healthy) subjects, twenty diabetic patients and sixty diabetic patients with liver cirrhosis. Our results showed that prevalence of diabetes mellitus in liver cirrhosis patients was 93.30% and level of glucose is significantly higher in diabetic patients with liver cirrhosis compare to control subjects. These results are comparable with some previous studies. The association between diabetes mellitus and liver cirrhosis was first time studied in 1947 [15]. Many researchers in their studies described an association between diabetes mellitus and liver cirrhosis, and high prevalence of diabetes in patients of liver cirrhosis such as 95% in Hyderabad population [16], 90.4% in China [17], 50-80% in Italy population [18], 64.5% in Brazil population, 47% in John Hopkin Hospital of America [19] and 40% in Europe [20].

Pathophysiology of diabetes with liver disease is complex and not precisely known. Peripheral tissues of the body show insulin resistance which plays a central role in glucose metabolism disturbance [21-28].

It seems that glucose intolerance result from two abnormalities i.e. insulin resistance and β-cells inadequate response. Furthermore impairment in insulin secretion and hepatic insulin resistance together leading to hyperglycaemia and diabetic glucose tolerant profile [26, 27]. In alcoholic liver disease, decrease in insulin secretion due to pancreatic damage could be the cause of impaired glucose metabolism. In viral liver disease this case may be different. In liver cirrhosis excess insulin secretion is observed after loading glucose [29].

As discussed earlier, hyperinsulinaemia state could eventually induced insulin resistance. Entrance of glucose also delayed in liver cirrhosis due to the high resistance of hepatocytes to insulin. Previous reports suggested that insulin resistance, characterized by both decreased glucose transport and decreased non-oxidative glucose metabolism in skeletal muscles, could be the cause of diabetes in liver cirrhosis [30].

Studies showed that severity of liver disease could increase by itself the risk of diabetes in chronic liver disease [31]. It has also been speculated that genetic and environmental factors and some etiologic agents of liver disease such as hepatitis C (HCV) and iron infiltration impair the insulin secretion [32].

The second reason for hyperglycaemia in diabetic patients with liver cirrhosis is persistence of diabetes mellitus which accelerates the liver fibrosis and cause of severe liver failure. Persistence of insulin resistance by hepatocytes increases the level of adipokines which activate the inflammatory pathway of liver [33]. In another study conducted in transgenic animal model it has been demonstrated that TNF-α over production seems to have been the primary mechanism. The cytokines phosphorylates the serine residues of insulin receptors (IRS-1 and IRS-2) and stimulates the overproduction of suppressor of cytokines (SOC-3). All these disorders related to intracellular signaling of insulin could block the transactivation of GLUT-4, which would result in block of glucose uptake at cellular level [34].

The decrease in insulin sensitivity with menopause and subsequent improvement with estrogen replacement suggest that estrogen may play an important role in insulin sensitivity in women. In male lack of estrogen cause of insulin resistance and glucose intolerance is considered to be third major cause of hyperglycemia [35, 36].

Major contribution of already present risk factors of diabetes such as positive family history and advancing age also plays an important role among HCV infected persons [37, 38]. This finding correlated with the study of Mexican population [39]. In normal individuals 80% of the glucose production occurs after one night fasting by the mechanism of glycogenolysis but in cirrhotic patients mechanism of glycogenolysis is also affected [40].

The present study demonstrated the high prevalence of diabetes in liver cirrhotic patients. It might be due to insulin resistance in patients of liver cirrhosis. There are several factors which might be the cause of insulin resistance and more hyperglycaemia in diabetic patients with liver cirrhosis. Diabetes mellitus increase mortality by increase the incidence of bacterial infections in cirrhotic patients [41, 42]. Therefore strict control of blood glucose level and improvement in insulin resistance should be directed in patients with diabetic liver cirrhosis to prevent further complications. Future research is also suggested to reduce the incidence of complications of liver cirrhosis as well as high prevalence of

diabetes in patients of liver cirrhosis which increases the mortality of diabetic cirrhotic patients.

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