GLYCOSYLATED HAEMOGLOBIN
IN
BILHARZIAL LIVER FIBROSIS

THESIS

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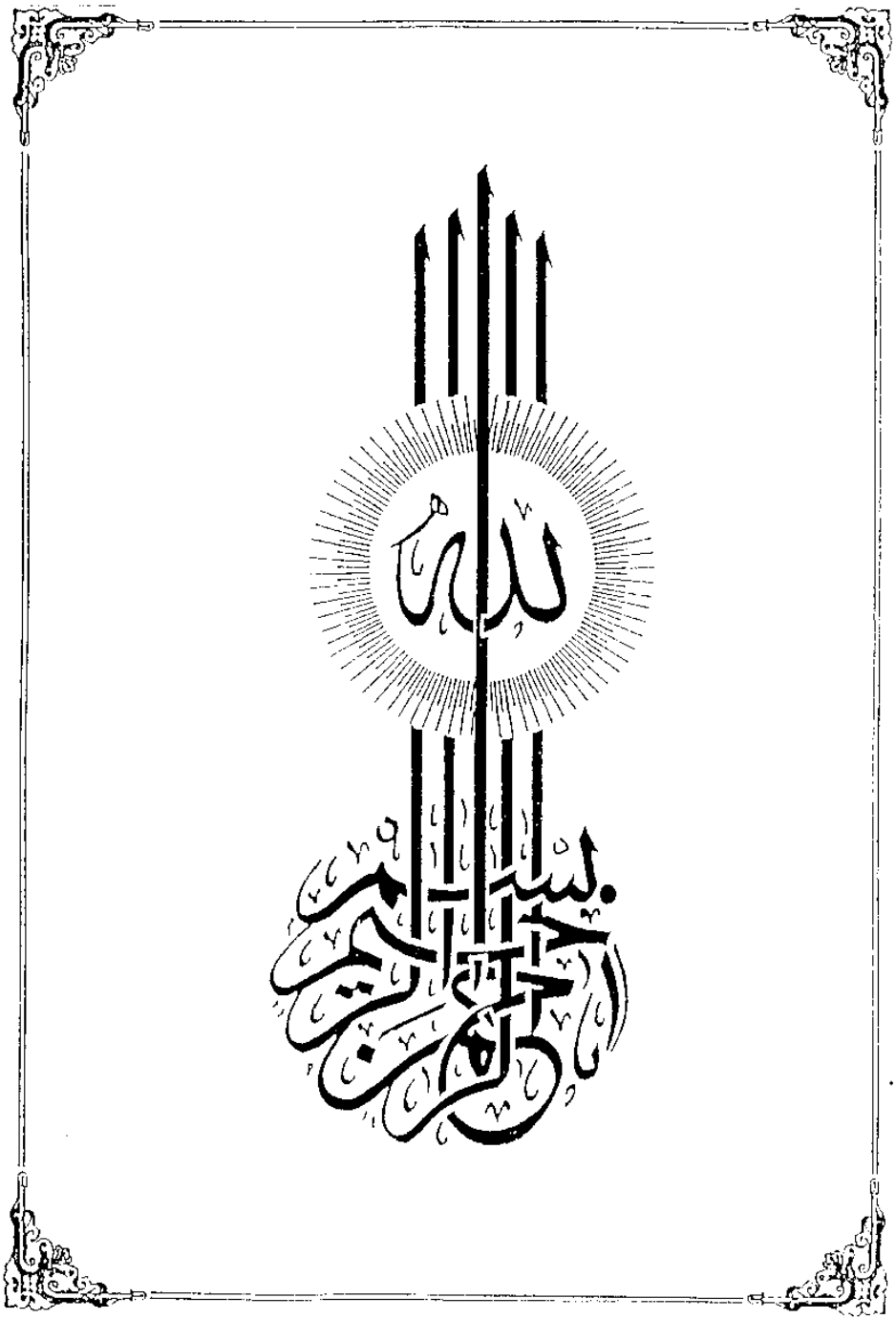

C O N T E N T S

INTRODUCTION

AND

AIM OF WORK

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The liver occupies a key position in the carbohydrate metabolism and disturbances are encountered in almost all forms of hepatic dysfunction . Glucose intolerance has been frequently reported in hepatic disorders including chronic liver diseases and cirrhosis (Meygesi et al., 1967; Sherlock, 1970; Ghanem et al., 1971 and Ghareeb , 1973) .

Although histopathological damage to liver cells is minimal in hepatic schistosomiasis , yet functional derangement of carbohydrate metabolism has been demonstrated causing "chemical" diabetic abnormalities. The degree of intolerance can be related to stage and severity of liver affection (Ghanem et al., 1971) .

Recent studies have demonstrated that haemoglobin and other several plasma proteins undergo postribosomal non enzymatic glycosylation both in vivo (Bunn et al., 1976 and Stevens et al., 1978) and in vitro (Day et al., 1979 and Shapiro et al., 1980) .

Since the interaction of glucose with protein is a condensation reaction in which the degree of glyco - sylation is proportional to the ambient glucose concentration (Day et al., 1979), this process is affected in cases of altered glucose tolerance .

The glycosylated haemoglobin (Hb A_1c) has now become a widely used tool for assessing the long term glycaemic state . The test aroused great interest as it is an indicator of the integrated plasma glucose level over prolonged periods of time because of the long survival time of haemoglobin , corresponding to the life span of erythrocytes . This recent test has an advantage over fasting or post-prandial plasma glucose determination which represents only one point in time .

In this work , we aimed to apply this recent investigation , glycosylated haemoglobin level, in cases of schistosomal liver fibrosis compared with control, as a trial to throw further light on the relation between such chronic liver disease and the blood sugar level .

REVIEW OF LITERATURE

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Carbohydrate Metabolism and Liver Disease

Since the liver is the main organ indulged in glycogen storage (glycogenesis), release (glycogenolysis) or formation of glucose from protein (gluconeogenesis) , disturbances of carbohydrate metabolism are encountered in almost all forms of hepatic dysfunction .

Carbohydrate Changes in Hepatic Cirrhosis :

Both hypo- and hyperglycaemia can be found in cases of liver cirrhosis, but the latter is much more common .

In a study over 165 patients with liver cirrhosis by Zimmerman et al., (1953), there was only two values of fasting blood sugar determination below 50 mg/100 ml. This hypoglycaemia could be related to the entry of pancreatic insulin into the systemic venous system without passing through the liver, which proved by immunoassay studies to be responsible for removing

20 - 50 % of the insulin in blood passing through it on a single passage (Samols and Ryder, 1961) . Decreased hepatic blood flow with reduced hepatic glucose output may also be an important factor in inducing hypoglycaemia as patients with portocaval anastomosis tend to have subnormal fasting blood glucose levels (Sherlock, 1970) . Hyperglycaemia is a more common finding in liver cirrhosis . In 1967, Meygesi et al., evaluated glucose tolerance in well investigated cases of liver cirrhosis, the results revealed that 32 % of the patients were diabetics with blood glucose level 190 mg / 100 ml or higher in the postprandial sample (2 hours after ingestion of 100 mg liquid glucose), 25 % had an impaired glucose tolerance with the 2 hours blood glucose level between 115 and 190 mg / 100 ml, and 43 % were normal as regarding blood glucose tolerance . The plasma insulin levels were initially normal but these rose slowly to values greatly above those found in normal subjects. With the intravenous tolbutamide tolerance test, blood sugar falls more in cirrhotics than in control and plasma insulin level rises higher . Such patients were labelled " hepatogenous diabetics " by Creutzfeldt, (1962) .

Berkowitz (1969), in a study of 25 cirrhotics, measured their glucose tolerance, free fatty acids (FFA) and immunoreactive insulin (IRI) after a 75 gram oral glucose load . 22 of the patients had impaired glucose tolerance which was associated with elevated FFA in 17 instances, 2 patients had increased FFA with normal glucose tolerance . Hyperinsulinaemia (IRI) was demonstrated in each patient with liver disease including the patients with normal glucose tolerance . Similar results were reported by El-Badry et al., (1973) on 23 patients with liver cirrhosis . 7 cases (32 %) had impaired glucose tolerance test while IRI was elevated in all cases denoting increased insulin resistance .

Glucose Intolerance in Hepatic Schistosomiasis :

Schistosomiasis induces a unique type of cirrhosis characterized by a periportal fibrosis with minimal parenchymal damage and absence of regeneration (Erfan et al., 1957 and Salah, 1962) . In spite of the minor pathological findings in the liver cells , functional derangement is often demonstrable .

Intravenous glucose tolerance, insulin sensitivity tests, intravenous glycodiazine tolerance (similar to tolbutamide test) and intravenous glucagon tests were carried out in patients with schistosomal hepatic cirrhosis by Ghanem et al., (1971) . The glucose disappearance rate was significantly slow in hepatic schistosomiasis especially in advanced cases with ascitis . Resistance to exogenous insulin was observed in 72 % of ascitic patients . Fifteen percent of non-ascitic patients and 61 percent of ascitic cases showed diabetic response to intravenous glycodiazine . Diminished glycogenolytic action of glucagon was markedly demonstrated in presence of ascitis . The concomitant fall in plasma free fatty acids (FFA) after glucagon was significantly correlated to the rise in blood glucose .

Ghareeb et al., (1972) studied 44 cases with hepatosplenic schistosomiasis : 14 cases were given 40 gm oral glucose alone; 10 patients I.V. glucose ; 14 were given 1 gm tolbutamide alone and 6 patients were given combined I.V. glucose and tolbutamide . Blood sugar, FFA and immunoreactive insulin were estimated at 15 minutes intervals. Glucose tolerance was impaired in 50 % of the cases while hyperinsulinaemia and increased FFA were present in almost all cases .

Blood sugar was significantly higher in hepato-splenic schistosomiasis than in the normal in a study done by Sadek et al., (1979), together with absence in early insulin release and delayed hyperinsulinaemia.

Carbohydrate Metabolism Disturbance in Liver Diseases other than Cirrhosis :

- Fulminant hepatitis and hepatic coma :

Hypoglycaemia may complicate fulminant virus hepatitis especially in children (Mellinkoff and Tumulty , 1952) . Enhanced insulin production plus failure of insulin degradation were suggested as possible factors concerned . In hepatic coma, the intermediary carbohydrate metabolism is grossly disturbed, oxoglutaric and pyruvic acids have a raised blood level (Summerskill et al., 1957) . Sherlock (1970) suggested that the rise of these acids is due to failure of tricarboxylic acid cycle to handle the products of glycolysis .

Hemochromatosis and other forms of iron overload :

The association of hemochromatosis with diabetes has led to the term " bronzed diabetes ". Simple insulin

lack due to pancreatic damage is one factor while insulin resistance as seen in other forms of cirrhosis is another factor . Very occasionally, patients with transfusion iron overload, refractory anaemia and hemosiderosis develop frank diabetes (Sherlock, 1968) .

- Primary disorders of carbohydrate metabolism :

Certain, apparently primary, disorders of carbohydrate metabolism are associated with development of cirrhosis . Type IV glycogenesis (Anderson's disease) is one of the rarest varieties and is due to decrease of the branching enzyme amylo-1,4,1,6 transglucosidase . The cirrhosis is apparently related to this abnormal glycogen (Sidbury et al., 1962) . Galactosemia is related to a lack of the specific enzyme galactose-1-phosphate uridyl transferase . The liver shows a cirrhosis with pseudoglandular and ductular structure, around canaliculi, which may contain bile (Fisher et al., 1964) ..

Toxic Liver Injury :

Hypoglycaemia is a prominent feature of the rare condition of fatty liver with encephalopathy that affects children between ages of 2 months and 10 years (Reye et al., 1963) .

Mechanism of Glucose Intolerance in Chronic Liver Disease :

Various hypotheses have been postulated to explain the mechanism of glucose intolerance in chronic liver disease.

Insulin resistance is the most important factor accepted by many authors (Meygesi et al., 1967; Ghanem et al., 1971; Ghareeb, 1973 and Sadek et al., 1979) .

Impairment of glycogen storage and release is another factor .

Although Peterson (1960) and Zumoff et al., (1967) found that cortisol production is not elevated in hepatic cirrhosis, yet decreased degradation has been reported by other investigators (Sodeman and Sodeman, 1967). This may partly contribute to glucose intolerance in cirrhosis .

In schistosomiasis, pancreatic involvement may be added as a contributing factor which was shown to be about 4.7 % of cases of the intestinal lesions . Two types of lesions were described by Arafa and Hashem (1954), a diffuse type and a focal type with variable degrees of destruction of islets of Langerhans. They also reported the occurrence of two types of glucose intolerance; a hyperglycaemic and a hypoglycaemic type which, as they said, may correspond to the pathological lesions .