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CHRONIC VIRAL HEPATITIS;
SERUM INSULIN LEVEL

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ABSTRACT… Objectives: To examine the serum insulin level in viral hepatitis B and C patients at different stages of disease. **Study Design:** Observational study. **Period**: Twelve months. **Setting:** Biochemistry Department BMSI, JPMC Karachi. **Methods:** The diagnosed patients for hepatitis B and C virus infection with and without cirrhosis were included. Patients were selected after diagnosis of the disease by ELISA method. Subjects diagnosed as negative were enrolled as controls in the study. Serum insulin estimation was done by ELISA and blood glucose by Hexokinase method, prothrombin time by one stage (coagulation) method and liver enzymes were assayed was by enzymatic (Kinetic) method. For paired and correlation data analysis, SPSS 10.0 version for windows was used. For all comparisons, upto 0.05 P value was considered significant. **Results:** The insulin, fasting blood glucose and albumin mean values as compared to control were found significant statistically ($P<0.05$). However in all groups AST and ALT mean values found statistically highly significant ($P<0.01$), which indicates liver damage progression with consequent increase in serum insulin levels in these patients. **Conclusion:** Tests for early analysis of serum insulin levels should be performed in those cases that are diagnosed as hepatitis B or C positive, along with liver function tests, to reduce the increased rate of morbidity and mortality in co-morbid condition.

Key words: Insulin, Hexokinase, Viral Hepatitis, Liver Enzymes, Co-morbid.

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INTRODUCTION

Insulin is secreted by the pancreas. It is a polypeptide hormone.[1,2] Its action is regulated through a complex interplay between the liver, adipose tissue and the muscle.[3] The endogenous insulin activities are mainly concerned with yielding glycogen by the liver that is storage form of glucose excess. It also help muscles and adipose tissues for glucose intake which is utilized for energy yield.[2]

Viral hepatitis is a major global health problem.[4] It is recognized as a systemic disease and can affect lipid metabolism, oxidative stress and mitochondrial function.[5] It produces the necrosis and inflammation of hepatic tissue.[6] In susceptible individuals it also trigger autoimmune mechanism[7], which leads to the development of extrahepatic complications.[8] In humans, different viruses produce hepatitis.[9] Hepatitis B and C viruses cause persistent and chronic infection. If the disease is left untreated at initial stages of developing, it can produce hepatocellular carcinoma.[10] However in western countries HCV infection is a major cause of chronic liver disease with a heavy toll of morbidity and mortality.[11,12]

In chronic viral hepatitis patients increased serum insulin level is due to impaired glucose metabolism and insulin resistance.[13] In the general population, insulin sensitivity varies. In lifestyle-related diabetes mellitus, insulin levels are found lower as compared with diabetes as a result of chronic liver disease.[14] Unfavorable body fat distribution, obesity, lack of physical activity and genetic predisposition are the factors contribute to this variability.[15] In chronic viral hepatitis hyperinsulinemia can be due to damage to liver cells.[16] Hyperinsulinemia by stimulating stellate cells proliferation enhance the secretion of extracellular matrix.[17]

Moreover, the abnormal glucose metabolism occurs due to intracellular fat accumulation.[18,19] The fatty degeneration is induced by inhibition of secretion of very low density lipoprotein in the liver affected by virus core protein.[20] Due to decreased insulin catabolism higher serum insulin levels are observed without increase in the synthesis of insulin secretion by pancreas. Hyperinsulinemia primarily occurs due to insulin resistance.[13] Gradually, the insulin becomes functionally inactive, which ultimately affect the metabolism of glucose.[21] So, inspite of presence of insulin in body, the cells can not utilize blood glucose for energy production.[18] Consequently, this condition leads to high blood glucose levels along with a high level of insulin in the serum. Ultimately it can lead to development of diabetes, which may damage to eyes, kidneys and nerves.[2]

Keeping in view the fateful effects of condition, the present study designed to examine the serum insulin level in the patients of chronic viral hepatitis types B and C.

METHODS

This observational study completed in twelve months was conducted at the Biochemistry Department BMSI, JPMC Karachi. Patient selection was done in collaboration with liver clinic, medical wards and PMRC, Jinnah Postgraduate Medical Center (JPMC) Karachi. Eighty patients in total of both sexes included in the study after confirmation of their diagnosis as hepatitis B and C patients of both with and without cirrhosis [mean age of 39 years (range of 20-59 years)]. According to type and cause of the disease they were grouped as: group I and group III of hepatitis B patients with and without cirrhosis respectively; while group II and group IV of hepatitis C patients with and without cirrhosis respectively. The patients excluded from the study were those having history of any associated chronic illness. Also the patients having co-infection of both hepatitis B and C virus were excluded. Twenty subjects diagnosed as negative were enrolled as controls in the study for comparative analysis.

Insulin was estimated by ELISA method (Biosource, USA) by QM Lab (Germany) Analyzer. Hemaclot Human (Germany) Analyzer was used for prothrombin time estimation by coagulation (one stage) method, while Slectra Junior of Vital Scientific (Netherland) was used for fasting blood glucose estimation by Hexokinase method, AST and ALT by Kinetic (enzymatic) method and serum albumin by End Point (Monochromator) method.

Statistical Analysis

The data analysis was performed by using SPSS 10.0 version for windows for paired and correlation analysis. Paired 't' test (P value) was used for determination of significance of results. Probability value of 0.05 or less was considered for to indicate significance statistically.

RESULTS

As compared with control, insulin, fasting blood glucose and albumin mean values statistically found significant ($P<0.01$) in all groups. However in groups I and II AST and ALT mean values were significant statistically ($P<0.01$). While these values in groups III and IV were found statistically highly significant ($P<0.001$). Prothrombin time mean values difference was less significant ($P<0.05$) in groups III & IV, while it was non-significant as compared with controls in other groups (Table-I). The insulin in all groups showed statistically significant ($P<0.05$) good positive correlation with fasting blood glucose. It also showed positive correlation with prothrombin time, AST and ALT and it was statistically significant ($P<0.05$). However with albumin statistically non-significant correlation was present (Table-II). Figure-1 reflect the graphical presentation of the observations. Thus increased serum insulin level along with fasting blood glucose high values and also AST and ALT levels indicates more rapid progression of disease in patients with cirrhosis.

DISCUSSION

With a broad spectrum of viral hepatitis infection, it ranges from mild chronic hepatitis to cirrhosis and hepatocellular carcinoma. Chronic viral hepatitis infection is also associated with a wide spectrum of liver histological lesions.[22] Various mechanisms can explain the insulin resistance role in hepatic fibrosis development.[17]

Parameter	Control (n 20)	Group I (n 20)	Group II (n 20)	GroupIII (n 20)	Group IV (n 20)
Insulin (μU/ml)	3.8±0.45	13.9±1.12*	19.2±1.69*	25.60±3.87*	24.3±4.57*
Fasting Blood Glucose (mg/dl)	88±3.40	89±3.60	94±4.80	117±10.87*	134±15.85*
Prothrombin time (Control: 11 to 16 sec)	13.7±0.38	17.2±1.02	16.1±0.69	19.4±1.28*	19.6±0.95*
AST (U/L)	15.2±1.08	76.6±7.3**	72.9±5.95**	123.7±17.41***	128.2±15.6***
ALT (U/L)	27.4±1.25	81.6±7.94**	79.4±5.90**	95.6±10.42***	87.1±10.65***
Total protein (g/dl)	7.2±0.14	6.7±0.18	6.5±0.15	7.4±0.22 NS	7.6±0.15 NS
Albumin (g/dl)	4.66±0.14	3.86±0.11*	3.56±0.15*	2.87±0.08**	2.88±0.06**

Table-I. Biochemical parameters comparison among different groups

Parameter	Group I (n 20)	Group II (n 20)	Group III (n 20)	Group IV (n 20)
Fasting Blood Glucose (mg/dl)	0.85*	0.87*	0.94*	0.97*
Prothrombin time (Control: 11 to 16 sec)	0.83*	0.59*	0.86*	0.55*
AST (U/L)	0.88*	0.79*	0.92*	0.70*
ALT (U/L)	0.88*	0.77*	0.90*	0.59*
Total protein (g/dl)	-0.74*	-0.50*	0.77*	0.60*
Albumin (g/dl)	-0.86*	-0.10	0.57*	0.48*

Table-II. Insulin versus biochemical parameters correlation coefficient (r)

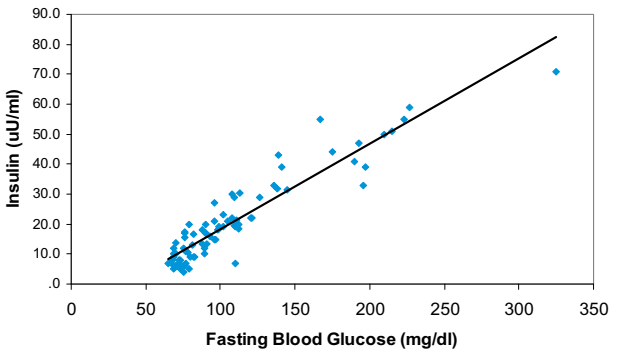

Figure 1. Correlation coefficient among insulin (μu/ml) and blood glucose (mg/dl)

It is of great clinical relevance to enlighten the relationship between viral hepatitis and insulin resistance.[23] In 1947, Bohan[24] first described association of liver cirrhosis with diabetes mellitus. While Megyesi et al., (1967)[25] named that correlation as hepatogenous diabetes. In their study 57% of patients showed increased serum insulin level.[16]

Keeping in view fateful outcome of the condition, various studies has been performed to find out reasons of increase in serum insulin level in patients of viral hepatitis. In susceptible individuals it results in rapid progression of disease which leads to development of co-morbid condition with serious complications like diabetes. Hassan et al[22], Rehman et al[26], Butt et al[27] studied the relation of liver enzymes at different stages of liver disease and observed increasing level of enzymes and the reversal of ratio with progression of disease to cirrhosis. They also observed increase in serum insulin level with increase of stage of disease irrespective of cause. In our study both AST and ALT showed same relationship with the stage of disease. Both showed statistically significant positive correlation with insulin, fasting blood glucose and prothrombin time and statistically non-significant correlation with albumin (Table-II).

In both hepatitis B and C virus infected cases higher serum insulin level was associated with higher blood glucose and ALT levels and lower albumin level. While comparing groups of without cirrhosis with cirrhosis, more rise in serum insulin level observed in cirrhotic patients of both hepatitis B and C infected patients, which indicates concomitant progression with stage of disease. Hepatic transaminases (enzymes AST and ALT) mean values showed statistically significant positive correlation with insulin, which is an indicator of ongoing liver damage besides development of hyperinsulinemia in these patients. Our these observations are found in accordance with the observations of Wilson[28], Alizadeh et al[13] and Takahashi et al.[2]

CONCLUSION

Increased serum insulin levels along with increased AST, ALT and fasting blood glucose in hepatitis B or C infected cases are the indicator of development of co-morbid condition. These findings of hepatic biochemical changes along with increased blood glucose level, associated with increased serum insulin levels, highlights the need of further studies at mass level.

RECOMMENDATION

Tests for early analysis of serum insulin levels should be performed in those cases that are diagnosed as hepatitis B or C positive, along with liver function tests, to reduce the increased rate of morbidity and mortality in co-morbid condition. For earlier diagnosis of disease, more studies are required especially focusing on genetic factors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Habibullah Shaikh	Study design, Data collection, Data analysis, Results	
2	Yasmin Shaikh	Introduction, Discussion.	
3	Anwar Ali Jamali	Data analysis.	