Frequency of Diabetes in Hepatitis

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Abstract

Introduction: The presence of hepatitis and diabetes is a known factor. Insulin resistance in muscular, hepatic and adipose tissues as well as hyperinsulinemia, seem to be pathophysiologic bases for hepatogenous diabetes. World Health Organization (WHO) ranks Pakistan 7th on diabetes prevalence list.

Objective: The objective of this study was to determine the prevalence of type 2 diabetes in chronic liver disease.

Methods: The descriptive cross-sectional survey based study was carried out at public sector government hospitals of Karachi, Pakistan. Patients with positive diagnosis of hematologic parameters were included. ANOVA was conducted to observe the difference between the clinical parameters between hepatitis B and C. Data was normally distributed as evaluated by Shapiro-Wilk test ($p > 0.05$). The study protocol was approved by ethical review committee.

Results: The two groups of hepatitis B and C showed statistically significant difference when compared with diabetes mellitus on chi square test. This study showed diabetes associated with HCV is more as compared to HBV.

Study Limitation: Small sample size was the study limitation.

Conclusion: diabetes associated with HCV is more as compared to HBV.

Key words: Diabetes, HBV, HCV, Chronic liver disease

Introduction

The association between liver disease and Diabetes Mellitus (DM) is well established, the overall prevalence being significantly higher than that expected by chance and such an association increases the risk of morbidity and mortality significantly.[1] The most common liver diseases include infection with Hepatitis A Virus (HAV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), fatty liver disease, such as alcoholic and Non Alcoholic Fatty Liver Disease (NAFLD), hemochromatosis and advanced disease states such as Non Alcoholic Steatohepatitis (NASH), cirrhosis, liver failure and Hepatocellular Carcinoma (HCC). Autoimmune hepatitis and drug induced liver disease also have an important impact on liver.[2] Diabetes Mellitus is a chronic disease that has increased in prevalence and incidence around the world over the last few decades. According to WHO, 347 million people worldwide have diabetes and as an estimate, diabetes will be the 7th leading cause of death in 2030.[3,4]

Diabetes developed as a complication of cirrhosis is known as hepatogenous diabetes.[5] In physiological conditions, hepatocytes are the main site of hepatic glucose metabolism; nevertheless, a small, but significant, role in insulin metabolism is played by non-parenchymal liver cells, that is Kupffer cells, endothelial sinusoidal cells and hepatic stellate cells (HSC) that contribute to insulin degradation and are involved in the modulation of hepatocyte glucose metabolism during inflammatory processes via the release of cytokines. Insulin is a key mediator in glucose homeostasis and any change in its action results in the impairment of glucose metabolism.[6]

Insulin resistance in muscular, hepatic and adipose tissues as well as hyperinsulinemia, seem to be pathophysiologic bases for hepatogenous diabetes. An impaired response of the β-islet cells of the pancreas and the hepatic insulin resistance are also contributing factors. Diabetes develops when defective oxidative and nonoxidative muscle glucose metabolism develops. Non-alcoholic fatty liver disease (NAFLD), alcoholic cirrhosis, chronic hepatitis C, and hemochromatosis are more frequently associated with hepatogenous diabetes. Hepatogenous diabetes in early cirrhosis stages may be sub clinical. Only insulin resistance and glucose intolerance may be observed. As liver disease advances, diabetes becomes clinically manifest, therefore hepatogenous diabetes may be considered as a marker for liver function deterioration.[5] In CLD patients, the prevalence of impaired glucose tolerance (IGT) is estimated to be about 60–80% and that of overt diabetes is about 7–15%.[5]

According to surveys it was proved that more than 80% of diabetes deaths occur in low- and middle-income countries.[7] WHO ranks Pakistan 7th on diabetes prevalence list .In Pakistan; 6.9 million people are affected by diabetes with the International Diabetes Federation estimating that this number will grow to 11.5 million by 2025 unless measures are taken to control the disease.[8]

Hepatitis C is a global health problem. The World Health Organization has estimated that approximately 3.3 per cent of the world's populations (200 million people) have been infected with the hepatitis C virus. Hepatitis C is one of the commonest causes of chronic liver disease in Pakistan and is one of the leading indications for liver transplant. Several studies have looked at the prevalence of hepatitis C in chronic liver disease in Pakistan. The role of hepatitis C in the causation of liver cancer has been well documented.

According to WHO Pakistan is standing at second position in prevalence of hepatitis C in the whole world after Egypt. "The Shadow Epidemic," it's been labeled because In Pakistan more than 10 million people are living with Hepatitis C virus (HCV) with high morbidity and mortality. According to Pakistan medical research Council approximately 7% of total population of Pakistan is infected with Hepatitis C virus. The Silent Killer," health professionals call this virus that can slowly destroy the liver. Hepatitis C earned its label as the Silent Killer precisely because the virus leaves so few noticeable tracks of its presence. The Lancet termed Pakistan as a cirrhotic state in one of its articles. Hepatitis C is responsible for a significant proportion of liver disease in various regions of Pakistan. The high risk of chronicity of this blood-borne infection and association with cirrhosis and liver cancer underscores its public health importance. Hepatitis c like a ticking time bomb for health authorities[9] Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections have become endemic in our community.[10] This study was therefore conducted to determine the prevalence of type 2 diabetes mellitus in chronic liver disease in patients of Karachi, Pakistan.

Materials and Methods

Study design and study cases

Data Collection

This descriptive cross-sectional survey based study was carried out at public sector government hospitals of Karachi, Pakistan namely; Jinnah Post Graduate Medical Center (JPMC), Civil Hospital and Abbasi Shaheed Hospital during the period of 4 months from July – October 2013. A total of 165 known cases of chronic liver disease (CLD), both inpatient and outpatient and irrespective of their type, were included in the study based on purposive sampling. The subjects with confirmatory diagnosis from lab or biopsy results along with complete supportive lab data of clinical parameters like CBC (complete Blood Count), LFT (Liver Function Test), and serum Glucose level were considered as a part of the study. Diabetes mellitus was confirmed if the RBS (Random Blood Sugar Level) was above 200 mg/dl or they were already on medications for hypoglycaemic therapy. Undiagnosed symptomatic patients of CLD, diagnosed CLD patients with incomplete supportive lab data as per the study requirements were not included in the study.

Statistical Analysis

Categorical and continuous variables were presented as mean ± SD or percentages. All analysis was performed using statistical package for social sciences version 20 (SPSS, Inc., Chicago, IL, USA). Data was presented as mean ± standard deviation. Outliers were assessed by Shapiro-Wilk test and homogeneity of variances was assessed by Levene's test. Results were analyzed using one-way analysis of variance (ANOVA). Chi square was used to assess significant differences between the groups of hepatitis B and C with type 2 diabetes mellitus.

Results

A one-way ANOVA was conducted to determine if the clinical parameters of body mass index (BMI), systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), glucose levels (mg/dl), platelets10^3, hemoglobin g/dl, alanine aminotransferase (ALT U/L), aspartate amino transferase (AST, U/L), alkaline phosphatase (U/L), gamma glutamyl transferase (U/L), total proteins (g/dl), total albumin (g/dl), total proteins (g/dl) total albumin (g/dl), total bilirubin (gm/dl), direct bilirubin (mg/dl), indirect bilirubin (mg/dl), prothrombin time (sec), activitated partial thromboplastin time (sec), international normalized ratio (sec) were different for hepatitis B and C. There were no outliers and data was normally distributed for each group, as assessed by Shapiro-Wilk test ($p > 0.05$); and there was homogeneity of variances, as assessed by Levene's test ($p > 0.05$). Data is presented as mean ± standard deviation. The differences between the groups of hepatitis B and C was not statistically significant ($p > 0.05$). Chi square test showed statistically significantly difference between hepatitis B and C with type 2 diabetes mellitus ($p < 0.05$). All the subjects were briefed about the nature of the study and an informed consent was taken.

Study Limitation

Although the research has reached its aims, there was a limitation that needs to be mentioned. Due to time limit this research was conducted only on a small size of population who attended the department.

Ethical Considerations

The study protocol was approved by ethical review committee. Written informed consent was taken from the participants before their enrolment in this study. The participants' involvement in this study was voluntary and no financial incentives were provided to any study participant.

Discussion

There is a wide range in the prevalence of altered glucose metabolism in chronic liver disease patients in various studies.[11]. The total number of patients included in our study was 165 which were CLD positive. The frequency of type 2 diabetes mellitus was 27.9% among them 25.5% were HBV positive and 73.3% were HCV positive. This study found the prevalence of diabetes in CLD patients which was 38.2% during the 4^{th} and 5^{th} decades of life followed by 23.6% in $5^{th}$and 6^{th} decades of life which is similar to a result found in a study carried out in Peshawar.[11] Mason et al found that there is increase frequency of Diabetes associated with young age group who were HCV positive.[12] The result which we found showed there is second highest age related association in the 5^{th}-6^{th} decade of life i.e. 23.6% and >60 yrs i.e. 16.4%. Cacoub P et al showed that the advanced age is the most frequent risk factor for extra hepatic manifestation.[13]

Mehta SH and Knobler H have reported the prevalence of HBV in association with DM is up to 8-12% [14-15] and HCV in association with DM is up to 20-39%.[16-17] The result in our study showed that the prevalence of HBV in DM was 20.5% and HCV in DM was 86.4%. In a study carried out in JPMC there was equal occurrence of Diabetes in HBV and HCV. The reason for this distribution is thought to be due to equal exposure of HBV and HCV, while in developed countries HBV has been controlled by active HBV Vaccination programme which means HBV and its complication are very low.[18] The prevalence of HCV in association with diabetes is quite high as compared to HBV in our study that might be due to the fact that HBV vaccine is now included in that vaccine health program. Mason et al surveyed a large cohort of patients with viral chronic hepatitis showed a strong association between DM and HCV; they suggested HCV infection may serve as an additional risk factor for the development of DM.[12]

The pathophysiological mechanism for the development of DM in patients with HCV has not been clearly established, a generally accepted pathogenesis for DM includes impaired insulin secretion , peripheral insensitivity to insulin and dysregulation of hepatic glucose production.[19] Another important finding in our result is 1.9% cirrhotic patients were DM positive this is a valuable finding suggesting that as cirrhosis takes a longer time to develop therefore the associated pancreatic damage also takes longer, finally resulting in Diabetes (as pancreas is a extra hepatic site of viral replication leading to B cell damage). This theory is also confirmed b Caronia S et al. Progress of HBV is over a prolonged period of time therefore very few patients reach the cirrhotic process this is the reason DM is low in that population.[20] The frequency of chronic liver disease in patients with HBV infection was 32.1% while in HCV infection was 67.6%, this increased frequency in HCV infection may be corresponding to the fact that most of the patients with HCV remain asymptomatic with 85% of the patients progressing to chronic liver disease it is diagnosed only on routine biochemical study, there is mild elevation of serum aminotransferases which may be fluctuating. Whereas in HBV infection patients presents with fatigue, persistent or intermittent jaundice and serum aminotransferases are markedly raised.

Conclusion

Our results are suggestive of diabetes associated with HCV is more as compared to HBV, might be that is because of active HBV vaccination the other step which is needed to reduce HCV is health education and multidimentional public health programs should be addressed and by following the international guidelines in surgeries and blood transfusions as these two are major sources of transmition of HCV.

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Conflict of Interest: The authors declare that they have no competing interests.

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Table 1: Descriptive Statistics

Variables	**Frequency (%)**
Gender	
Male	53.3
Age (yrs)	
20-30	6.7
31-40	15.2
41-50	38.2
51-60	23.6
>60	16.4
Chronic Liver Disease	
HBV	32.1
HCV	67.9
Type 2 Diabetes Mellitus	27.9
Hepatitis B	25.5
Hepatitis C	73.3
Primary Biliary Cirrhosis	.6
Cirrhosis	1.9
Hepatocellular carcinoma	4.4
Metastatic hepatic carcinoma	.6

Table 2: Tests of Normality of Clinical parameters

Clinical Parameters	**CLD**	**Shapiro-Wilk**		
		Statistic	Df	Sig.
body mass index	HB	.912	10	.294
	HC	.972	13	.914
systolic blood pressure	HB	.949	10	.662
	HC	.959	13	.742
diastolic blood pressure	HB	.934	10	.487
	HC	.943	13	.490
Glucose random mg/dl	HB	.957	10	.752
	HC	.846	13	.260
platelets m/l	HB	.911	10	.289
	HC	.860	13	.038
hemoglobin g/dl	HB	.911	10	.290

	HC	.984	13	.994
alanine transaminase U/L	HB	.786	10	.108
	HC	.645	13	.124
aspartate transaminase U/L	HB	.838	10	.072
	HC	.776	13	.079
alkaline phosphatase U/L	HB	.748	10	.387
	HC	.839	13	.217
gamma glutamyl transferase U/L	HB	.863	10	.082
	HC	.765	13	.373
total proteins g/dl	HB	.844	10	.049
	HC	.892	13	.103
total albumin g/dl	HB	.857	10	.071
	HC	.882	13	.077
total bilirubin mg/dl	HB	.799	10	.049
	HC	.742	13	.089
direct bilirubin mg/dl	HB	.826	10	.094
	HC	.733	13	.075
indirect bilirubin mg/dl	HB	.762	10	.070
	HC	.682	13	.679
prothombin time seconds	HB	.765	10	.569
	HC	.921	13	.259
activated partial thromboplastin time seconds	HB	.737	10	.276
	HC	.947	13	.553
International normalization ratio seconds	HB	.664	10	.451
	HC	.925	13	.292

Table 3: Test of Homogeneity of Variances

Clinical Parameters	**Levene Statistic**	**Sig.**
body mass index	.106	.745
systolic blood pressure	2.042	.155
diastolic blood pressure	.406	.525
random glucose mg/dl	1.541	.216
platelets m/l	2.664	.105
hemoglobin g/dl	1.886	.171
alanine transaminase U/L	.716	.399
aspartate transaminase U/L	30.153	.543
alkaline phosphatase U/L	1.341	.249
gamma glutamyl transferase U/L	10.045	.834
total proteins g/dl	4.946	.089
total albumin g/dl	.119	.730
total bilirubin mg/dl	.019	.889
direct bilirubin mg/dl	.681	.411
indirect bilirubin mg/dl	.738	.392
prothombin time seconds	.971	.326

activated partial thromboplastin time (sec)	3.238	.074
International normalization ratio seconds	4.773	.175

Table 4: ANOVA

Clinical Parameters	**F value**	**Sig**
body mass index	1.24	.26
systolic blood pressure	.25	.61
diastolic blood pressure	.001	.97
random glucose mg/dl	1.14	0.28
platelets m/l	.72	.39
hemoglobin g/dl	.29	.58
alanine transaminase U/L	.23	.62
aspartate transaminase U/L	4.55	.037
alkaline phosphatase U/L	1.72	.19
gamma glutamyl transferase U/L	7.70	.007
total proteins g/dl	1.5	0.22
total albumin g/dl	.77	.38
total bilirubin mg/dl	.18	.66
direct bilirubin mg/dl	.06	.79
indirect bilirubin mg/dl	.58	.44
prothombin time seconds	1.14	.28
Activated partial thromboplastin time (sec)	.72	.39
International normalization ratio seconds	4.96	.028

Table 5: Chi square test for Hepatitis B & C versus Type 2 diabetes mellitus

	Diabetes mellitus		***p*-values**
Hepatitis B	Yes (%)	No (%)	
	20.5	27.8	.342
Hepatitis C	86.4	71.3	.048