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EFFECT OF TYPE 2 DIABETES MELLITUS ON PATIENTS WITH HEPATOCELLULAR CARCINOMA

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ABSTRACT

OBJECTIVE: *The management of hepatocellular carcinoma is influenced not only by the tumour status and underlying liver function but also by any comorbid illness in the patients and diabetes mellitus is one of them. The present study was undertaking to evaluate the effect of diabetes mellitus on hepatocellular carcinoma.*
STUDY DESIGN: *Observational descriptive study.*
PLACE AND DURATION: *This study was conducted in the department of Medicine Liaquat University Hospital and Isra University Hospital, Hyderabad from November 2005 to October 2008.*
MATERIAL AND METHODS: *Total of 200 patients of HCC were analyzed. They were divided into two groups with and without diabetes mellitus. Clinical status and laboratory findings were noted and patients were followed for one year to see the prognosis in both groups.*
RESULTS: *There were 200 patients in this study with mean age + SD of the patients were 53.70 + 12 years. Amongst all cases of HCC 165(85.57%) were males and 35(17.0%) were females, 46(23.0%) were diabetic and 154(77.0%) were non diabetic. Alfa fetoprotein level was compared between two groups and we found that alfafetoprotein level was 2737.84+4149.564 ng/L in diabetics group whereas it was 11827.31+29287.392 ng/L in non-diabetics group (P = 0.03) which is statistically significant. In diabetic group one year mortality was 68.42% whereas in non diabetic group one year mortality was 45.23%(P = 0.03).*
CONCLUSION: *The overall survival rate in diabetic group was significantly lower than those the in non-diabetic group. Alpha fetoprotein level was significantly low in diabetic than in non-diabetic group.*

KEYWORDS: Hepatocellular carcinoma, Diabetes Mellitus, Alfa fetoprotein

INTRODUCTION:
The incidence of hepatocellular carcinoma has increased significantly over the past decades in many parts of the world. An estimated 600,000 new cases are diagnosed annually of which 82% are from developing countries.[1] The incidence of hepatocellular carcinoma varies according to the prevalence of hepatitis B and C infection. Areas such as Asia and sub-Saharan Africa with high rates of infectious hepatitis have high incidence of hepatocellular carcinoma.[2]
The majority of patients with hepatocellular carcinoma have co-existing cirrhosis,[3] often complicated by diabetes mellitus.[4] Major causes of cirrhosis worldwide are attributed to hepatitis B infection[5] and hepatitis C infection.[6] Both hepatitis C virus infection and diabetes mellitus type 2 are chronic conditions with significant morbidity and mortality. Over 4 million Americans are seropositive for hepatitis C virus infection.[7] Diabetes mellitus type 2 is approaching epidemic proportion worldwide and by the year 2025, over 300 million people will have been diagnosed with diabetes mellitus.[8] Epidemiologically there is a relationship between Diabetes mellitus and chronic HCV infection.[9] Diabetes mellitus has been reported to increase the risk of hepatocellular carcinoma in cases of chronic hepatitis C[10] and is also thought to contribute to the excess mortality seen in patients with hepatocellular carcinoma.[11] In Pakistan about 10 million persons are affected by Hepatitis C.[12] hence predisposed to the development of hepatocellular carcinoma.
The management of hepatocellular carcinoma is influenced not only by the tumour status and the underlying liver function, but also by any comorbid illness in the patients and diabetes mellitus is one of them, hence the effect of diabetes mellitus on hepatocellular

carcinoma is of considerable relevance.

MATERIAL AND METHODS:

This observational study was conducted at two major institutions of Hyderabad i.e. Liaquat University Hospital and Isra University Hospital. Data was collected from November 2005 to October 2008.

Included in this study were 200 cases of Hepatocellular carcinoma. For the diagnosis of Hepatocellular carcinoma, Saudi Gastroenterology Association guideline for the diagnosis of Hepatocellular Carcinoma[13] were followed. On clinical suspicion ultrasound abdomen was the initial radiological investigations. Further CT scan abdomen was performed if an abnormality was found. The diagnosis of HCC was made if the liver was cirrhotic, the lesion was larger than 2 cm in diameter, and either the Alpha feto protein was higher than 400 ng/L and one imaging modality confirms early arterial enhancement, or the AFP is normal and two imaging modalities confirm early arterial enhancement. Histological diagnosis was done only if lesion was found in a non-cirrhotic liver and radiological investigations were not conclusive.

Diabetes mellitus was diagnosed on the presence of hyperglycemia (> 180mg/dl) in at least 2 post absorptive samples or active treatment with insulin, oral hypoglycemic agents, or both.

Patients were divided into two groups (Group A and Group B). Group A included patients of Hepatocellular carcinoma with Diabetes mellitus and Group B patients included patients of Hepatocellular carcinoma without diabetes mellitus.

Demographic profile like age of presentation, clinical features, etiology of HCC, tumors size at presentation was compared diabetic with non diabetic HCC patients.

Biochemical parameters were determined including serum level of aspartate amino transferase (AST), alanine amino transferase (ALT), total bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, prothrombin time, international normalized ratio (INR) and alpha fetoprotein level and was compared diabetic with non-diabetic HCC patients.

All cases were followed for at least 1 year and ultimate outcome was compared in diabetic and non-diabetic HCC patients.

STATISTICAL ANALYSIS:

The data were evaluated in statistical program SPSS version 16.0. Qualitative data included descriptive statistics (frequency and percentage of categorical parameters are presented as n(%) and Fisher's exact and Pearson's tests of chi-square were applied on 95% confidence interval. Continuous variables are expressed as Mean + Standard Deviation and Student's t test (2 tailed) was used to compare the means among the diabetic and non-diabetic groups. A P-value < 0.05 was considered as statistically significant for all comparisons.

Table No. I
Demographic characteristics of patients of Hepatocellular carcinoma (n = 200)

Variable		n(%) Mean + SD(Range)
Age:		
< 45	59(29.5%)	53.70 + 12.0(23 – 90 years)
> 45	141(70.5%)	
Sex:		
Male	165(82.5%)	
Female	35(17.5%)	
Etiology:		
HCV	145(72.5%)	
HBV	42(21.0%)	
HCV & HBV	9(4.5%)	
HBV HDV	3(1.5%)	
HBV HCV HDV	1(0.5%)	
Alcohol	1(0.5%)	
alcohol + HCV	21(10.5%)	
Others	12(6.0%)	
Clinical cirrhosis:		
Yes	168(84.0%)	
No	32(16.0%)	
Child's Class:		
A	41(20.5%)	
B	82(41.0%)	
C	64(32.0%)	
Tumor characteristics		
Single < 5cm	60(30.0%)	
Single > 5cm	39(19.5%)	
Multicentric all < 5cm	68(34.0%)	
Multicentric few > 5 cm	33(16.5%)	
Portal vein Thrombosis:		
Yes	36(18.0%)	
No	147(73.5%)	
Alpha-fetoprotein (ng/L)		
< 400	83(41.5%)	
> 400	117(58.5%)	10544.15 + 26689.09(0.7 - 205093.0)

RESULTS:

There were two hundred patients in this study. Demographic characteristics are shown in table 1. The mean age + SD of the patients were 53.70 + 12 years. Amongst all cases of HCC 165(85.57%) were males and 35(17.0%) were females. Cirrhosis was present in 168(84.0%) patients amongst which 41(20.5%) were in Child's A class, 82(41.0%) in Child's B and 64(32.0%) in Child's C class. Fifty five (27.5%) cases were infected with HBV and 176 (88.0%) were infected with HCV. 22 (11.0%) cases were alcoholics. 12(6.0%) cases were having un-known aetiology.

Of the 200 patients with HCC, 46(23.0%) were diabetics whereas the remaining 154(77.0%) were non-diabetic. Table No. 2 shows the clinical characteristics at the time of diagnosis of HCC for patients with and without diabetes mellitus. There were no difference between the two groups in relation to age, mean age + SD was 53.8 + 9.71 in diabetics and 53.6 + 12.63 in non-diabetics(P = 0.90). Similarly no significant difference was observed in gender (P = 0.19). Out of 46 diabetic patients 35(76.1%) were male and 11(23.9%) were female and out of 154 non-diabetic patients 130(84.4%) were male and 24(15.6%) were female.

With respect to clinical features, in diabetic group 38(82.6%) were clinically having

cirrhosis and 08(17.4%) were without cirrhosis and in non-diabetic group 130(84.4%) were suffering from cirrhosis and 24(15.67%) were not, (P = 0.81). We have also compared the two classes with respect to Child's class and we have not found any significant difference with respect to Child's class (P = 0.83)(table 2).

We have compared the difference between two groups with respect to laboratory data i.e. total bilirubin, albumin, platelet count and prothrombin time and no significant difference was observed between two groups (table 2).

Alfa fetoprotein level was compared between two groups and we found that alfa fetoprotein level was 2737.84+4149.564 ng/L in diabetics group whereas it was 11827.31+29287.392 ng/L in non-diabetics group (P =0.03) which is statistically significant.

Patients were regularly followed for 1 year from the date of diagnosis. Amongst 46 diabetic patients 27 lost follow up and 19 were followed regularly for 1 year from which 13(68.42%) patients expired whereas in 154 non diabetic patients 112 lost follow up and 42 were regularly followed for 1 years from which 19 patients (45.23%) expired, showing a significant difference in between two groups (P =0.03)

Table 2.
Characteristics of hepatocellular carcinoma in Diabetic and non-diabetic (n= 200)

Parameters	Diabetes n = 46	Non-diabetes n = 154	P value
Age (in years)	53.8 + 9.71	53.6 + 12.63	0.90
Gender:			
Male	35(76.1%)	130(84.4%)	0.19
Female	11(23.9%)	24(15.6%)	
Clinical cirrhosis:			
Yes	38(82.6%)	130(84.4%)	0.81
No	08(17.4%)	24(15.6%)	
Child's class:			
A	14(30.4%)	40(26.0%)	0.83
B	18(39.1%)	64(41.6%)	
C	14(30.4%)	50(32.5%)	
Alfa feto protein (ng/L)	2737.84 + 4149.564	11827.31 + 29287.392	0.03
Etiology:			
HCV	31(67.4%)	93(60.4%)	0.90
HBV	05(10.9%)	24(15.6%)	
Multiple viruses	02(4.3%)	11(7.1%)	
Alcohol + HCV	05(10.9%)	16(10.4%)	
Alcohol	0	01(0.6%)	
Others	03(6.5%)	09(5.8%)	
Size of the largest tumour	4.078 + 2.4606	4.798 + 2.6623	0.10
No. of tumour:			
Single	26(56.5%)	73(47.4%)	0.31
Multiple	20(43.5%)	81(52.6%)	
One year mortality:			
Expired	13/19(68.42%)	19/42(45.23%)	0.03

Table 3.
Comparison of laboratory data in patients of hepatocelluar carcinoma between diabetic and non-diabetic (n = 200)

Parameters	Diabetes n = 46	Non-diabetes n = 154	P value
Investigations:			
Bilirubin	1.43 + 0.09	1.36 + 0.23	0.07
Albumin	2.18 + 0.17	2.20 + 0.17	0.47
Platelets	92934.78 + 42577.720	101428.57 + 42301.880	0.23
APTT	53.37 + 6.00	54.58 + 6.77	0.27

DISCUSSION:

Hepatocellular carcinoma is one of the most common malignancies, and is particularly prevalent in South and Southeast Asia.[14] Epidemiological surveys have shown the hepatitis B and hepatitis C virus to be causative agents.[15] The majority of hepatocellular carcinoma develops in the presence of cirrhosis which occurs as a complication of HBV or HCV.[16] In Pakistan various researches have reported variable figures about prevalence of HCC in cirrhosis ranging from 3.7% to 16.7%.[17] The incidence of HCC has been shown to be higher in patients with chronic hepatitis C than in those with chronic Hepatitis B.[18] In Pakistan the annual incidence of hepatocellular carcinoma is 8/100,000 population.[19] Some studies have suggested an association between diabetes and HCV infection [20] and other have shown that the prevalence of diabetics mellitus is higher in patients with cirrhosis[21] and the risk of diabetes depends on the stage of the disease.[22] Alteration in carbohydrate metabolism are frequent in patients with cirrhosis and decreased liver function may contribute to the development of diabetes. Therefore diabetes mellitus is one of the most common complication observed in patients with cirrhosis. In addition, a higher risk of primary level carcinoma has been reported in patients with cirrhosis having diabetes mellitus.[23]

However, to our knowledge few data exist regarding the effects of diabetes mellitus on the clinical features, laboratory parameters and on the survival of patients with hepatocellular carcinoma. In the current study we evaluated the effect of diabetes mellitus on the clinical features, laboratory data and on the prognosis of patients with hepatocellular carcinoma.

Table 2 shows the clinical characteristics at the time of diagnosis of HCC for patients with and without diabetes mellitus. There were no difference between the two groups with respect to patients age, gender, alcohol intake and viral aetiology. No significant difference was observed between two group with respect to clinical features, Child's class of cirrhosis and size of the tumour. Also

no significant difference was observed with respect to laboratory parameters including Bilirubin, albumin, APTT and platelet count. The only significant difference observed was in serum Alfa feto protein level which was markedly reduced in patients with diabetes mellitus suggesting that it could not be used as diagnostic tools for HCC in patients of diabetes mellitus.

Amarapurkar et al investigated the clinical features and prognosis of Hepatocellular carcinoma in patients of diabetes and non-diabetic in Indian patients[24] and he found no significant difference with respect to age, sex, alcohol consumption and etiology but they found significant difference with respect to stage of HCC and found that patients with diabetes mellitus present with advanced disease which differs from our study. Amarapurkar et al also found that mortality with in one year was significantly more in patients with diabetes mellitus. He found one year mortality was 78.2% in diabetes which is significantly higher than in non-diabetics in which mortality was 49.1%; whereas in our study the one year morality was 68.42% and 45.23% respectively in diabetics and non-diabetics which also shows that mortality is higher in diabetics. Similarly Huo TI et al [25] conducted an study in China and they also found that Diabetes mellitus has prognostic impact on HCC undergoing surgical and non-surgical therapy and found that Diabetes mellitus may affect the long term survival through diabetes related complications or inducing liver failure depending on treatment strategy and under the influence of tumoral and cirrhosis factors. In the current study it is difficult to distinguish clearly whether the impaired prognosis in diabetics were due to HCC progression or from liver failure, we observed an adverse effect of diabetes mellitus on the prognosis of HCC. In the previous study conducted by Toyoda H et all [26] have found that diabetes mellitus may not affect the progression or recurrence of HCC, but it may worsen the prognosis of patients with HCC by decreasing liver function and causing rapid progression to liver failure. Further studies are necessary to see the effect of diabetes mellitus on progression of chronic liver disease and hepatic decompensation in patients with or without associated HCC. If diabetes mellitus have an enhancing effect on hepatic decompensation, it will be of great interest to elucidate the underlying mechanism so that an effective strategy to reduce the negative impact of diabetes mellitus can be identified.

CONCLUSION:

Diabetes mellitus is identified as risk factor for development of hepatocellular carcinoma. Diabetes may not affect the age of presentation, clinical features, etiology and some laboratory parameters of hepatocellular carcinoma. Alpha fetoprotein level is significantly decreased in cases of hepatocellular carcinoma with diabetes but further studies are required thus impairing its diagnostic reliability in diabetes. The data from current study indicates that diabetes mellitus worsens the long term prognosis in patients with hepatocellular carcinoma.

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