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Diabetes & its Complications

Type 2 Diabetes Mellitus as A Risk Factor for Development of Hepatocellular Carcinoma: Case-Control Hospital Based Study

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ABSTRACT

Aim: *To study the relationships between Type 2 diabetes mellitus (DM2) and the risk of hepatocellular carcinoma (HCC).*

Methods: *We studied the association between DM2 and HCC in a large case-control study that enrolled 255 Egyptian patients with HCC (71.4% males, mean age 62± 10.2 years) matched for age and sex and free from hepatocellular carcinoma 305 patients constituted the control group.*

Results: *Prevalence of DM2 was significantly higher in HCC patients (29.1.2% vs 10.2.7%; OR = 3.35 95% CI: 1.31-3.29.). The highest prevalence of diabetes was found in patients with hepatitis C was 30% followed by hepatitis B infection 20%.*

Conclusion: *DM2 in our patients is associated with a 3-fold increase risk of HCC so that we encourage prompt screening for HCC in diabetic patients with cirrhosis.*

Keywords

Type 2 diabetes, Hepatocellular carcinoma, Insulin resistance.

Introduction

Hepatocellular carcinoma (HCC) accounts for 70-85% of primary liver cancers, ranking among the most common malignancies worldwide and the third cause of cancer death. Many factors are contributed in the incidence of HCC, as hepatitis B infection in Asia, and exposure to aflatoxin in sub-Saharan Africa, and in Western countries, HCC often occurs as a complication of chronic viral hepatitis B and C, alcohol use and inherited disorders like haemochromatosis [1,2].

Multiple observational epidemiologic studies from Europe, Asia and North America, and subsequent meta-analyses are supporting the link between diabetes mellitus and insulin resistance is independent factors for HCC [3,4].

The development of HCC has been related to the proliferative effects of insulin and insulin - like growth factor 1, onchogenic effects of hyperglycaemia and inflammatory effects of obesity [5].

HCC is increasingly common in USA, with an age-adjusted incidence rising from 1.5 to 4.9 per 100.000 persons, between the year 1975 and 2005 epidemiological case-control study in USA of American populations that included 2061 patients with HCC compared with non-cancer controls 6183 persons, has shown a significant association between diabetes mellitus and the risk of HCC, with an odds ratio of 2.87 [6].

In Taiwan, the data also indicated an important interaction between obesity and diabetes on HCC risk, either alone or in those with chronic hepatitis B virus or hepatitis C virus infection [7,8], with infection with these viruses the relative risk surpasses 50 fold [8].

Type 2 diabetes mellitus is an independent risk factor for hepatitis C virus-related HCC, as well as for disease recurrence after resection of the tumor [9], and the onset of HCC among those

patients with a sustained response to antiviral drugs [10]. The role of insulin resistance and its path physiologic consequences as hyperinsulinaemia are not apparent from these epidemiological studies, however the link and association between metabolic syndrome with increased incidence of HCC has been reported in USA and Europe [11].

The chronic inflammatory condition associated with diabetes mellitus may promote the development of HCC through the action of cytokines produced in inflammatory condition [12]. Also it was observed in several studies that elevated levels of tumour necrosis alpha (TNF-) and interleukin-6 are contributing factors in obese patients with type 2 diabetes mellitus [13,14]. These cytokines regulate the apoptotic regulator Bcl-2 and Bax, suggesting their potential apoptotic and inflammatory markers for HCC [15,16].

Patients and Methods

This is a case - control study, 251 patients with hepatocellular carcinoma were included in the study and were interviewed face to face between Feb. 2018 to March 2019, in the department of radiotherapy and oncology in Tanta University Hospital Egypt. The diagnosis of HCC was histologically confirmed by needle biopsy or based on the findings of typical radiological features in at least two images examination including ultrasound scan (US), multislice computerized tomography (CT) and magnetic resonance imaging or by a single positive imaging technique associated with serum - Fetoprotein (AFP) level more than 400 ng/ml [17]. This group of patients with HCC are called HCC group. The control group was including patients with other diseases except HCC selected from internal medicine outpatient clinic in Tanta University Hospital and patients excluded if they have malignancies, virus related liver diseases and alcohol - related diseases (neuropathy, gastric ulcers), and patients with type 2 diabetes mellitus in the control group and the prevalence of diabetes mellitus in the control group was 16%.

That is similar for the prevalence of diabetes mellitus in populations in Egypt.

The patients in HCC group and control cases, the demographic, clinical and biochemical features were recorded, also age, gender and glycated haemoglobin (HbA1c). Ant hepatitis C was detected by using a third-generation micro particle enzyme immunoassay [18]. Anti-HBV surface antigen was detected by using commercial assays (Abbott diagnostic division - Germany. The diagnosis of diabetes mellitus was based on criteria of American Diabetes Association guidelines [19]. Alcohol intake was defined as a daily consumption of more than 30 grams in males and 20 grams in females, considering the average content of 5% for beer, 12% for wine and 40% for super alcoholics [20].

Aim of the work

To study the relationships between Type 2 diabetes mellitus (DM2) and the risk of hepatocellular carcinoma (HCC).

Statistical Analysis

The data of this study were collected and analyzed by SPSS version 25, descriptive results were expressed in mean ± SD, Chi-square was used to compare quantitative frequency data. Odds ratios (OR) and 95% confidence interval were calculated using simple logistic regression analysis. P value< 0.05 was statistically significant at 95% confidence interval.

Characteristics						
Age	**Sex**	**[No. (%)]**	**Child Pugh Class**	**[No. (%)]**	**Alpha Feto-protein**	**[No. (%)]**
Yrs, mean ± SD	Males	140 (55.8)	A	89 (35.5)	<20 ng/ml	65 (26.0)
	Females	111 (44.2)	B	77 (30.6)	21-200 ng/ml	50 (20.0)
			C	85 (33.8)	>200 ng/ml	136 (54.0)

Table 1: Demographic, clinical, and laboratory characteristics of patients with hepatocellular carcinoma.

HCC Type	[No. (%)]	Solitary HCC	[No. (%)]	Okuda Stage	[No. (%)]
Solitary	102 (40.6)	<3 cm	75 (30.0)	I	28 (11.2)
Paucifocal (two or three nodes)	52 (20.7)	3.15 cm	100 (40.0)	II	128 (51.0)
Multifocal (>3 nodes)	75 (30.0)	>5cm	76 (30.0)	III	95 (37.8)
Diffuse	22 (8.7)				

Table 2: Macroscopic Features and Stage of Cancer in the Patients with Hepatocellular Carcinoma (HCC).

		Number of Patients	DM2 Absent (%)	DM2 Present (%)	OR (95% CI)	P	RR
	HCC	251	178 (70.9)	73 (29.1)	3.35 (1.31-3.29)	<0.001	2.25
	Controls	305	274 (89.8)	31 (10.2)			
Males	HCC	196	140 (71.4)	56 (28.5)			
	Controls	230	195 (84.5)	35 (16.5)			
Females	HCC	55	40 (72.7)	15 (27.3)			
	Controls	75	67 (89.3)	8 (10.6)			

Table 3: Diabetic Patients among the HCC Patients and Control Patients. HCC: Hepalocellular carcinoma; DM2: Type 2 diabetes mellitus; OR: Odds ratio; Cl: Confidence interval; RR: Relative risk.

		Odds ratio (95% CI)	P Value
Diabetes	Absent		0.01
	Present	2.4 (1.1-3.5)	
HBV	Absent	1	≤ 0.001
	Present	94.1 (48.9-170.6)	
HCV	Absent	1	≤0.001
	Present	120.5 (42.2-188.6)	

Table 4: Multivariate Analysis of Variables Associated with HCC.

Etiology	N° HCC (%)	Age (Yr)	Prevalence of DM2 (%)
HBV	50.00 (19.9)	56.9 ± 10 a[1]	10 (20.0)
HCV	150 (59.8)	66.55 ± 7.3	45 (30.0)[2]
Alcohol	10 (3.9)	71.2.7 ± 8.5'	3 (.30)[2]
HBV + HCV	6 (2.3)	58.8 ± 11.6[1]	2 (30.0)
HBV + alcohol	8 (3.2)	61.8 ± 8.2[1]	2 (25.0.)
HCV + alcohol	20 (7.9)	65.7 ± 8.6'	6 (30.0)
HBV+ HCV +alcohol alcohol	2 (0.01)	67.5 ± 11.2	
unknown	7 (3.0)	68.6 ± 9,3	11 (40.7)

Table 5: Causes of HCC and Prevalence of NIDDM among the Study Group.
1HCV vs HBV + HCV, P < 0.001; HCV vs HBV, P < 0.001; HCV vs HBV + alcohol, P < 0,01, HCV vs HCV + alcohol; HCV vs alcohol P < 0.001; 2HCV vs alcohol P = 0.04.

		Number of subjects	Diet with or without metfominln N° cases (%)	Sulfonylureas with or without metforrnin N° cases (%)	*P*
Total	HCC	73	5 (6..8)	68 (93.2)	0.120
	Controls	31	2 (6.4)	33 (93.6)	
Males	HCC	56	2 (3.6.)	54 (96.4)	0.049
	Controls	35	2 (5.7)	33 (94.3)	
Females	HCC	55	3(5.4)	52 (94.6)	0.312
	Controls	75	3(4.0)	72 (96.0.)	

Table 6: Type of Therapy with Oral Antidiabetic Agents in HCC Patients and Controls with DM2.

Results

The study included 251 patients with hepatocellular carcinoma with the mean age 62 ± 10.2 years of age and males were the majority of cases (71.4%) and the control group included patients with age 63 ± 8.6 years of age and included 84.5% of the group were males. The study revealed that about the third of cases are in grade A,B and C Child-Pugh class (Table 1). Serum α-fetoprotein was at the highest level above 200 ng/ml in more than 50% of cases with hepatocellular carcinoma (Table 2).

The prevalence of type 2 diabetes mellitus was 29.1% in patients with hepatocellular carcinoma as their HbA1c was above 6.5% compared with 10.2% in the control group and there was significant statistical difference between both groups, Odds ratio was 3.35 and P value < 0.001 (Table 3).

Using Multivariate logistic regression analysis, it was revealed that patients infected with HBV, HCV infection and diabetes as independent variable and HCC as dependent variable, all these conditions are associated with increased risk of HCC. The prevalence of type 2 diabetes mellitus in the different etiological groups about 20% in HBV patients, 30% in patients with HCV and 0.3% in patients drinking alcohol in the study.

In HCC carcinoma patients, males were more than females in using sulfonyl urea (insulin secretagogues) than HCC patients, also the great majority female patients in control group were using sulfonyl urea than patients on diet therapy only.

Discussion

Hepatocellular carcinoma occurs usually secondary to either cirrhosis or viral infection with hepatitis B or hepatitis C [21]. The present study has showed the role of diabetes mellitus in HCC as a risk factor. This study has reported that diabetes mellitus was recorded in 29.1% of patients with HCC compared with 10.2% in control group.

This difference was statistically significant with and odds ratio 3.35 (CI 1.31 - 3.29). Multivariate logistic regression has showed that diabetes mellitus is an independent variable, and is associated with increased risk of HCC, so this result coincides with El-Serag et al.2006 [22] where they have reported that diabetes mellitus is associated with an increased risk of developing HCC (Approximately 2.5 fold).

This result coincides also with the result of veldt et al. 2008 [23], their reports showed the increased risk of development of HCC in diabetic patients compared with non-diabetic. Also, in another systematic review that reported that patients with diabetes mellitus have had 3.64 times (95% CI= 2.61-5.07) to develop HCC compared with non-diabetics [24]. Also this result coincides with the result of study done by Tanaka et al. 2014 [25], where they systematically reviewed epidemiological studies on diabetes mellitus and HCC among Japanese populations, 9 of 10 relative risk (RR) estimates in the case - control studies and 17 of the 24 RR estimates in cohort studies, indicating that the overall evidence in Japan strongly support increased risk of HCC in patient with diabetes mellitus.

Our results are not consistent with the study of LU et al. 1988 [26], and the study of Huo et al. 2004 [17], where their studies did not demonstrate any association between diabetes mellitus and HCC. This discrepancy can be explained that these studies were conducted in regions with high prevalence of HBV infection. Earlier onset in HBV-related HCC [27], which implies earlier mortality, may preclude the possibility of developing type 2 diabetes mellitus because the mean age of type 2 diabetes onset was 56.8 years (28,29).

The synergistic effect of diabetes with chronic hepatitis either with C or B viruses was observed in this study to cause development of HCC, as many epidemiological studies has shown that diabetes mellitus is associated with a 2-3 folds increase in risk of development of HCC in chronic HCV infection, regardless of whether the patient was treated by curative hepatectomy or by antiviral drugs [30-32]. There are several mechanisms that can demonstrate the effect of diabetes mellitus on the risk of HCC in patients with chronic hepatitis C, as insulin is a growth hormone and insulin resistance in diabetic patients associated with high level of insulin, so this may interfere with the action of interferon and other antiviral drugs, thereby decreasing both rapid and sustained

virological responses, also hyperglycemia in diabetes mellitus may impair the process of HCV eradication [33-35]. Also hepatic fibrosis progresses more rapidly to cirrhosis in patient with insulin resistance in type 2 diabetes mellitus [36].

Hepatitis B infection was observed in about 20% of total cases of HCC. It is well known that hepatitis B virus Hepatocarcinoma and 85% of reported HCC cases reported globally are found in china [37]. Our results coincide with Gao et al. 2013 [38], they reported that diabetes mellitus is an independent risk factor for cirrhosis progression to HCC patients with hepatitis B infection. Also Hsiang et al. 2015 [39], have found that type 2 diabetes was a predictor of liver complications and HCC patients with HBV cirrhosis.

Hepatitis C was observed in 150 patients, about 60% of total cases of HCC, this coincides with many epidemiological studies as the population -based study SEER-Medicare Linked Database has detected 2-3 fold increase in HCC in patients with chronic hepatitis C with diabetes mellitus [5]. Also the European study that involved 541 patients with chronic hepatitis Chas recorded the incidence of diabetes mellitus was 11.4% in patients with HCC and 5% of patient without diabetes mellitus in the control group.

On the other hand, our results did not coincide with that Gao et al. 2009 [40], they included a cohort 54,979 patients followed from year 1999 to 2002. It revealed that type 2 diabetes mellitus increased the risk only in HCV negative participants (Relative Risk 2.08; 95% CI 1.03-4.18). The reason for this results is not clear, but may be attributed to including patients with high rate of hepatitis infection, which was rare in the most of populations previously studied

Conclusion

The current study suggests that patients with type 2 diabetes mellitus have a high risk to develop hepatocellular carcinoma, co morbidities as hepatitis B and C significantly aggravate the risk of developing HCC. High rate of hepatitis C in study has done synergism with high incidence of diabetes mellitus in those patients so this gives us a new insight for prevention of HCC, and we need further studies with a large number of patients with HCC to study whether if antidiabetic drugs (insulin sensitizers) and metformin have the same similar effects on development of HCC among diabetic patients with liver comorbidities.

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