Is diabetes mellitus a risk factor for hepatocellular carcinoma in Egyptian patients?

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Abstract: Hepatocellular carcinoma (HCC) is a malignancy of the hepatocyte. The primary risk factors for HCC are viral hepatitis and chronic alcohol abuse. Diabetes Mellitus (DM) has been previously reported to be associated with HCC, insufficient data is available regarding the association between DM and HCC in Egypt. This work evaluated DM as a risk factor for HCC in Egyptian population. **Design:** Cross sectional study. **Methods and material:** This study was conducted on 300 patients divided into 3 groups. Group I: 100 consecutive patients with HCC, Group II: 100 consecutive patients with chronic liver disease (cirrhosis), Group III: 100 patients admitted with acute illness matched to group I and II regarding age and gender. All patients were subjected to a comprehensive clinical assessment, laboratory investigations including: fasting and 2 hours post prandial blood sugar, serum alpha fetoprotein, hepatitis B and C viral markers, glycated hemoglobin, abdominal ultrasound, triphasic abdominal spiral computed tomography and liver biopsy if needed. **Statistical analysis used:** The following statistical tests were used: independent t-test, Mann Whiteny test, Chi square x2 test and spearman correlations rho test. **Results**: The frequency of DM was higher in the HCC (38%) and the cirrhotic patients (38%) compared with the controls (22%) (p=0.014). There was a significant positive correlation between duration of DM and number and size of hepatic focal lesions (p=0.042, p=0.031 respectively).
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Key words: HCC, DM, hepatic focal lesion, risk factor. .

1. Introduction

Hepatocellular carcinoma (HCC) is a primary malignancy of the hepatocyte, generally leading to death within 6-20 months. It is the fifth most common cancer worldwide and the third most common cause of cancer mortality[1]. Hepatocellular carcinoma is rarely detected early and is usually fatal within months after diagnosis[2].

Although the main risk factors for HCC are hepatitis C virus (HCV), hepatitis B

virus (HBV) and chronic alcohol abuse, at least 25% of HCC cases have no known etiology, suggesting that further risk factors could be responsible for the increasing incidence of HCC[3]. Other risk factors that have been associated with HCC development in the United States include diabetes mellitus, alcohol consumption, and cigarette smoking[4].

Conflicting results have been reported on the association between diabetes mellitus (DM) and solid tumors, in particular HCC[5].

Wang et al.[6] conducted a meta-analysis to examine the association between diabetes and risk of HCC. They reported a statistically significant increased risk of HCC prevalence among diabetic individuals (RR = 2.31, 95% CI: 1.87-2.84).

In Egypt, The number of newly diagnosed patients with HCC has been shown to increase annually[7]. However, there is insufficient data on the association between diabetes mellitus and hepatocellular carcinoma in an Egyptian populations.

Aim

We sought to determine whether diabetes mellitus is a risk factor for hepatocellular carcinoma in an Egyptian population.

Design

This study was conducted on 300 patients recruited from internal medicine department and hepatology outpatient clinic in Ain Shams University Hospitals, with patients being divided into 3 groups:

Group I (HCC group): 100 consecutive patients with hepatocellular carcinoma diagnosed according to American Association of the Study of Liver Disease (AASLD) practice guideline on management of hepatocellular carcinoma[8].

Group II (liver cirrhosis group): 100 consecutive patients with chronic liver disease (cirrhosis) after exclusion of HCC (based on alpha fetoprotein, abdominal ultrasound and triphasic spiral computed tomography), identified according to clinical stigmata, laboratory manifestations and radiological data of liver cirrhosis.

Group III (control group): 100 patients admitted with acute illness matched to group I and II based on age and sex. Patients were excluded if admitted for malignancies, alcohol-related disease and diabetes mellitus, although co morbidity of these conditions was not considered as an exclusion criterion.

Methods:

The following demographic, clinical and laboratory data was obtained for all patients: Medical history including history of DM (onset and duration of DM and anti-hyperglycemic medications), fasting blood glucose, 2 hours post prandial, serum alpha feto protein (AFP), viral markers (HBs Ag, HBc IgG, HCV Ab) and glycated hemoglobin (HbA1c), abdominal ultrasound and triphasic abdominal spiral computed tomography (CT). Liver biopsy was obtained percutaneously in select patients (those with focal lesion <2 cm in diameter) using a modified Vim-Silverman needle with an internal diameter of 2 mm, fixed in 10% formalin, and stained with hematoxylin–eosin.

Type 2 DM was diagnosed by fasting glucose level of ≥126 mg/dL and/or postprandial glucose level ≥200 mg/dL[9].

Informed consent was obtained from all participants before enrollment in the study. The study was approved by the local ethical committee.

Statistical methods:

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 17.0. Descriptive statistics were done as mean±SD (standard deviation), median, 1st and 3rd inter-quartile range (IQR), and as number and percentage. The following tests were used: independent t-test, Mann Whiteny test, Chi square x2 test and spearman correlations rho test. The probability of error (P value) < 0.05 was considered significant, while <0.01 was considered highly significant.

Results

This study included:

Group I 100 patients with confirmed HCC. 98 patients diagnosed by the presence of hepatic focal lesions in abdominal ultrasound and triphasic CT scan with the characteristic pattern (hypervascular lesion during the hepatic arterial phase and hypodense appearance during the delayed phase, due to the early wash-out of contrast) with or without elevated AFP≥400 ng/ml. In 2 patients with lesions <2 cm in diameter, histological confirmation was required; one of them revealed high grade undifferentiated HCC and the other revealed grade II HCC. This group included 85 males (85%) and 15 females (15%). Their mean age was 55.3± 8.3 years. 64% of them were smokers. The radiological characteristics of the tumor are shown in table (1). 32% of group I had portal vein thrombosis.

Group II 100 patients with CLD (cirrhosis) after exclusion of HCC based on imaging and normal AFP levels. There were 73 males (73%) and 27 females (27%). Their mean age was 54.7± 8.9 years. 38% were smokers.

Group III 100 control patients with acute medical conditions matched based on age and sex. They were 79 males (79%) and 21 females (21%). Their mean age was 54.4±14.3 years. 39% were smokers. The admission diagnosis of the selected 100 control patients was heart failure (17%), cerebrovascular stroke (18%), anemia (15%), peptic ulcer disease (11%), chronic renal failure (10%), rheumatic heart disease (6%), atrial fibrillation (5%), deep venous thrombosis (5%), systemic lupus erythematosus (5%), pneumonia (3%), intracranial hemorrhage (3%) and pneumothorax (2%).

There was no significant difference in either sex or gender between the 3 groups (Table 2). Patients in group I were more likely to be smokers and had a higher AFP compared to groups II and III (Table 3). 38% of patients with HCC had an AFP >400 ng/ml. Among patients with HCC, 94% had HCV and 5% HBV. Only 1% had negative viral markers. In patients with liver cirrhosis, 92% had HCV, 8% had negative viral markers and only 4% of the controls had HCV.

The frequency of diabetes mellitus was 38% in group I, 38% in group II and 22% in the controls. This showed that DM was prevalent in the HCC and the cirrhotic patients. There was no statistically significant difference between HCC patients and those with CLD regarding the frequency of DM.

There was no statistically significant difference between the studied groups regarding the duration of DM or type of treatment (Table 4). We found a positive correlation between duration of DM and number and size of hepatic focal lesion as shown in table (5) & figure (1).

Table (1): HCC characteristics of group I

	Median (IQR)	Range
Size (cm)	4.0 (3.0-5.0)	1.0-13.0
	N	**%**
Number		
• **1**	57	57.0
• **2**	17	17.0
• **≥ 3**	26	26.0
Management		
• No intervention	57	57.0
• RF	20	20.0
• TACE	16	16.0
• RF& TACE	6	6.0
• Surgery & TACE	1	1.0

IQR: Inter-quartile range, RF: radiofrequency, TACE: Transarterial chemoembolization

Table (2): Comparison between the studied groups regarding patients age, gender and smoking

	Group I	Group II	Group III	I/II	I/III	II/III
Age (yrs)	55.3±8.3	54.7±8.9	54.4±14.3	t=0.490 p=0.625	t=0.577 P=0.564	t=0.213 P=0.832
Gender • Male • Female	 85 (85.0%) 15 (15.0%)	 73 (73.0%) 27 (27.0%)	 79 (79.0%) 21 (21.0%)	x2=4.34 **p=0.037***	x^2=1.220 P=0.269	x^2=0.987 P=0.321
Smoking	64 (64.0%)	38 (38.0%)	39 (39.0%)	x2=13.5 **P<0.001***	x^2=12.5 **P<0.001***	x^2=0.021 p=0.884

χ^2=Chi square test, t=Independent t-test, *Significant

Table (3): Comparison between the three studied groups as regards laboratory investigations

	Group I	Group II	Group III	I/II	I/III	II/III
FBS (mg/dl)	112.0±54.2	116.3±48.4	113.9±75.4	t=0.593 p=0.554	t=0.204 p=0.839	t=0.270 p=0.787
PPBS (mg/dl)	155.5±69.6	177.7±82.4	162.0±101.7	t=2.067 p=0.040	t=0.531 p=0.596	t=1.203 p=0.231
HbA1c	6.6±1.4	6.5±1.8	6.1±2.0	t=0.463 p=0.644	t=1.334 p=0.193	t=1.105 p=0.272
αFP (ng/dl)	107.5 (7.0-1170.0)	4.7 (1.8-10.0)	2.0 (1.1-2.0)	z=8.015 **p<0.001***	z=4.846 **p<0.001***	z=2.592 **p=0.010***

FBS=fasting blood sugar, PPBS=post prandial blood sugar,
t=Independent t-test, z=Mann Whitney test *Significant

Table (4): Comparison between different groups as regards DM characteristics.

	Group I	Group II	Group III	I/II	I/III	II/III
Frequency	38 (38.0%)	38 (38.0%)	22 (22.0%)	x2=0.000 p=1.000	x2=6.095 **p=0.014***	x2=6.095 **p=0.014***
Treatment • **Diet** • **Oral** • **Insulin**	 1 (2.6%) 12 (31.6%) 25 (65.8%)	 0 (0.0%) 9 (23.7%) 29 (76.3%)	 1 (4.5%) 10 (45.5%) 11 (50.0%)	x2=0.000 p=1.000	x2=1.464 p=0.481	x2=5.260 p=0.072
Duration (yrs)	5.0 (2.0-10.0)	5.5 (4.0-10.0)	8.5 (2.0-12.0)	z=0.805 p=0.421	z=1.136 p=0.256	z=0.773 p=0.440

χ^2=Chi square test, z=Mann Whitney test *Significant

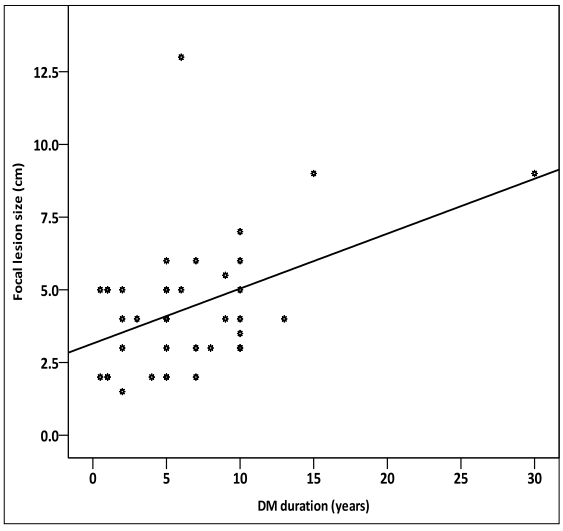

Fig. (1): Correlation between duration of DM and focal lesion size of group I.

Table (5): Correlation between duration of DM and HCC characteristics of group I.

	r^	P
FL number	0.331	**0.042***
FL size	0.350	**0.031***

^Spearman correlation test, *Significant

Discussion:

Hepatocellular carcinoma (HCC) is a worldwide malignancy, with the incidence increasing significantly over the past two decades[10]. The reason for this increase in HCC is incompletely understood but may be attributed to the increased incidence in hepatitis C virus and alcoholic liver disease. Diabetes mellitus (DM) has been shown to be a potential risk

factor for HCC in some studies; however, no consensus has been reached about the significance of DM and glycemic control in HCC[11].

The male predominance found in our study is in accordance with that reported by ***Lai et al.***[12].

Sex and age seems to modulate the natural history of chronic liver disease, in that chronic HCV infection progresses more rapidly in men than women, and that cirrhosis is predominately a disease of men and postmenopausal women[13]. ***Shimizu and Ito***[14] suggested that estrogens protect against oxidative stress in liver injury and hepatic fibrosis.

This study reported that smoking was found in 64% of patients with HCC compared to 38% in patients with liver cirrhosis and 39% in controls. ***Niu et al***.[15] conducted a case-control study in China, in which 345 HCC patients and 961 healthy control subjects were personally interviewed for several HCC risk factors. They reported that regular cigarette smoking was associated with HCC in men and found that passive cigarette smoking exposure was associated with HCC in women. Also, ***Ha et al***.[16] reported that heavy prolonged cigarette smoking was a significant independent predictor for HCC in patients with underlying liver disease.

Our study revealed that there was no statistical significant difference in prevalence of DM in HCC and liver cirrhosis patients. Our results are in agreement with ***Tung et al***.[17] who reported that diabetes was not shown to be significantly associated with HCC in Taiwan. The prevalence of diabetes was 9.7 % among patients with HCC compared with 9.6 % among controls.

The high prevalence of DM in liver cirrhosis and HCC is in agreement with ***Hickman and Macdonald***[18] who reported that up to 96% of patients with cirrhosis may be glucose intolerant and 30% may be clinically diabetic. This can be explained by the fact that the liver has an important role in carbohydrate metabolism and it is responsible for the balance of blood glucose levels by means of gluconeogenesis and glycogenolysis. In the presence of hepatic disease, the metabolic homeostasis of glucose is impaired as a result of disorders such as insulin resistance, glucose intolerance and diabetes[19]. Insulin resistance combined with hyperinsulinemia seem to be important pathophysiologic bases of diabetes in liver disease[18].

In a prospective study of diabetes and liver cancers in *Japan,* ***Fujino et al***.[20] found that diabetes increased the risk of liver cancers in patients with hepatitis and/ or cirrhosis. ***El-Serag et al.***[21] reported that DM was shown to increase the risk of primary liver cancers only in the presence of other risk factors such as hepatitis C or B, or alcoholic. ***Donadon et al.***[22] in a large case-control study of 465 consecutive Caucasian patients with HCC compared with an age and sex matched control group of 490 patients reported that DM is associated with a 3-fold increase risk of HCC.

El-Serag et al.[23] conducted a MEDLINE searches for published studies between January 1966 and February 2005 and identified a total of 26 studies which provided risk estimates and met criteria requiring the definition of their exposure and outcomes. Among the 13 case-control studies, 9 showed that DM was associated significantly with HCC. Among the 13 control studies, 7 showed that DM was associated significantly with HCC. Even though all of these studies were included in the analysis, the significant association between DM and HCC was independent of alcohol use or viral hepatitis in only 10 studies. This means that less than 40% of the reported studies provide the conclusion that diabetes may be an independent risk factor for HCC.

Wang et al.[6] conducted a meta-analysis to examine the association between diabetes and risk of HCC. A total of 17 case-control studies and 32 cohort studies were included in this meta-analysis. The combined risk estimate of all studies showed a statistically significant increased risk of HCC prevalence among diabetic individuals. The pooled risk estimate of 17 case-control studies was slightly higher than that from 25 cohort studies. Also, long duration of diabetes possibly increase HCC risk.

Our study found that DM was identified in 38% of patients with HCC and CLD and that increasing the duration of DM leads to increase the size and number of the existing HCC lesions.

Yang et al.[24] conducted a meta-analysis which suggest that DM may be both associated with elevated risks of both HCC incidence and mortality. Also, HCC patients with pre-existing diabetes have a poorer prognosis relative to their non-diabetic counterparts.

Type 2 diabetes is characterized by insulin resistance and secondary hyperinsulinemia. Hyperinsulinemia and hyperglycemia have been reported to promote tumor cell proliferation and metastases in type 2diabetes[25]. Hyperinsulinemia promotes increased phosphorylation and activation of the downstream serine/threonine kinase and extracellular signal-regulated kinase pathways and play an important role in tumorigenesis by decreasing apoptosis and increasing mitogenesis[26]. Insulin may stimulate cell proliferation through activation of the insulin receptor or insulin like growth factor (IGFI) receptor, or via inhibition of IGF binding proteins[27]. This triggers the initiation of multiple downstream signaling pathways, which result in cellular proliferation, transformation, and inhibition of apoptosis. Recent studies have shown altered IGF signaling in 90% of HCCs[28]. Moreover, hyperinsulinemia leads to up-regulation of proinflammatory cytokines[29], cellular proliferation,

and inhibition of apoptosis resulting in increase in size and number of the HCC lesions.

Conclusion:

DM is found in 38% of patients with HCC in consecutive Egyptian patients seeking health care. DM may play a role in progression of HCC. Further large number and multicentre studies are needed to document our results.

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