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RAPID COMMUNICATION

Association between hepatocellular carcinoma and type 2 diabetes mellitus in Italy: Potential role of insulin

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Abstract

AIM: To investigate 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 465 consecutive Caucasian patients with HCC (78.3% males, mean age 68.5 ± 8.9 years) compared with an age and sex matched control group of 490 subjects.

RESULTS: Prevalence of DM2 was significantly higher in HCC patients (31.2% *vs* 12.7%; OR = 3.12, 95% CI: 2.22-4.43) and in HCC cases with alcohol abuse. DM2 has been diagnosed before the appearance of HCC in 84.1% of diabetic HCC subjects with mean duration of 141.5 mo, higher in cases treated with insulin than in those with oral antidiabetic agents (171.5 *vs* 118.7 mo). Compared to controls, males DM2 with HCC were more frequently treated with insulin (38.1% *vs* 17.6%, $P = 0.009$) and with sulfonylurea with or without metformin than with diet with or without metformin (84% *vs* 68.3%, $P = 0.049$).

CONCLUSION: DM2 in our patients is associated with a 3-fold increase risk of HCC. In most of our cases DM2 pre-existed to HCC. Patients with DM2 and chronic liver disease, particularly insulin treated males, should be considered for HCC close surveillance programs.

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Key words: Hepatocellular carcinoma; Type 2 diabetes mellitus; Hepatitis virus B and C; Insulin; Antidiabetic therapy

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INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) has increased significantly over the past decades in many parts of the Western world, including Italy. The reasons for this increase are only partially understood. The hepatitis C virus (HCV) epidemics certainly play a role due to the cohort effect of individuals infected in pre-serological age[1,2]. However, approximately 15%-50% of HCC cases are not associated with HCV or hepatitis B virus (HBV), suggesting that other risk factors are responsible for this increase[3]. Diabetes has been suggested to be a risk factor for HCC. During the past two decades the prevalence of Type 2 diabetes mellitus (DM2) has dramatically increased in most developed countries and several epidemiologic studies indicate that it is nowadays epidemic, mostly because of the exponential explosion of obesity[4]. A recent study reported that the prevalence of known diabetes mellitus has increased in Italy from 3.6% to 4.3% during the past 10 years[5]. DM2 is a compensatory high insulin state caused by insulin resistance in fat, muscle tissue and liver[6], associated with an insulin-secretory defect that varies in severity and may lead to a relative insulin deficiency during the patients' lifetime. Therefore, DM2 is initially treated with diet and antidiabetic oral agents; after years, to control glucose metabolism, many patients

are required exogenous insulin treatment. Several studies have shown a relationship between diabetes mellitus and liver diseases[7]. Indeed, diabetes has been recognized as a risk factor for non-alcoholic fatty liver disease (NAFLD), while chronic hepatitis C has been associated with an increased risk of diabetes[8-12]. Several studies have investigated the association of diabetes mellitus and solid malignancies[13-15], and particularly with HCC[3,16-20]. While early studies reported no association[21,22], more recent data have clearly identified DM2 as a risk factor for HCC[20,23]. On this line, a high concentration of insulin could stimulate the IGF pathway in DM2 and molecular studies have shown that insulin and insulin-like growth factor 1 (IGF-1) may have carcinogenetic effects on liver and other tissues[24-28]. Moreover, chronic hyperglycaemia may cause oxidative stress and cellular damage[29]. Although DM2 has been associated in the development of HCC, only few studies have considered the confounding role of HBV and of HCV, two of the major risk factors for HCC. Moreover, diabetes may be secondary to HCC and to the underlying cirrhosis. To our knowledge, there are no studies that have investigated the temporal relationship between the onset of diabetes and the development of HCC. The purpose of the present study was to explore the association between HCC and diabetes in a large cohort of Italian patients with HCC and to describe the temporal relationship between onset of diabetes and development of HCC, and the clinical and metabolic characteristics of patients with DM2 and HCC.

PATIENTS AND METHODS

HCC group

We conducted a population based case-control study recruiting a consecutive cohort of 465 Caucasian patients with HCC seen at the Liver Unit of the Division of Internal Medicine of the Pordenone General Hospital (Pordenone, Italy) between January, 1994 and June, 2006. For the diagnosis of HCC, histological or cytological confirmation was available from the majority (85.6%) of HCC cases. In the remaining HCC cases, the diagnosis was established by coincidental finding of two dynamic imaging techniques [computer tomograghy (CT) scan, magnetic resonance imaging (MRI) and Contrast Enhanced Ultrasound examination in the last 3 years] showing a nodule with arterial hypervascularization followed by portal wash-out, or with a single positive imaging technique associated with alpha-fetoprotein > 400 ng/mL. Patients were divided in two groups: the first group included 305 cases derived from a surveillance program of HCC in cirrhotic patients, consisting of periodical (every 3-6 mo) ultrasound and AFP monitoring (follow-up group, FU); the second group consisted of 160 cases presenting with clinically overt and advanced HCC (clinically overt group, CO).

Control group

A control group of 490 cases was chosen by matching age, sex and time of admission among 28 740 patients seen in our Division in the same period of enrollment of patients with HCC. Patients were excluded if admitted for malignancies, alcohol-related diseases (neuropathy, gastric ulcer), virus-related liver diseases, and diabetes mellitus. However, co-morbidity with these conditions was not considered exclusion criteria. The admission diagnosis of the selected 490 control cases was heart failure (34.9%), hypertension (21.4%), chronic obstructive broncho-pneumopathies or pneumonia (16.5%), atrial fibrillation (7.8%), deep venous thrombosis (6.5%), fever of unknown origin (5.3%), benign tumours (4.1%), and gastritis (3.5%). In order to ensure that the selected control group was indeed well representative of the general population of our region, we considered two main parameters: prevalence of chronic HCV infection, the main risk factor for HCC, and that of DM2. The prevalence of HCV infection in the control group was 5.3%, similar to that reported in our region for individuals aged more than 65 years[30,31]. The prevalence of DM2 by age groups was compared to that reported in Italy[32]. Thus, for the purposes of the present study, our control group could be indeed considered representative of the general population in our region.

Methods

For all HCC patients and control cases the following demographic, clinical and biochemical features were registered in a computerized database: age, gender, race, glycated hemoglobin (HbA1c). Biochemical parameters were determined in the Central Laboratory of our Hospital by standard and validated methods. Anti-HBV surface antigen (anti-HBs), anti-HBV core antigen (anti-HBc), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) were determined using commercial assays (Abbott Diagnostic Division, Wiesbaden; Germany). Sera were also screened for antibodies against HCV (anti-HCV) using a third-generation microparticle enzyme immunoassay (AxSYM HCV version 3.0, Abbott Diagnostic Division)[33]. Positive samples were tested for anti-HCV using a third generation line immunoassay (Innogenetics, Gent, Belgium) and for serum HCV RNA using the Roche Amplicor version 2.0 (Roche Molecular System, Pleasenton, CA). The diagnosis of DM2 was based on the American Diabetes Association guidelines[6,34]. Alcohol abuse was defined as a daily consumption of more than 30 g in males and of more than 20 g in females, considering an average alcohol content of 5% for beer, 12% for wine and 40% for superalcoholics[35].

Statistical analysis

Descriptive results were expressed as mean ± SD or number (percentage) of patients with a condition. The *t*-test or non parametric Mann-Whitney test was used to compare quantitative data and the chi-square test was applied for comparison of frequency data. $P < 0.05$ was considered significant. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated using simple logistic-regression analysis.

Table 1 Frequency of DM2 in HCC patients and in controls

	Number of subjects	DM2 absent (%)	DM2 present (%)	OR (95% CI)	*P*	*RR*
HCC	465	320 (68.8)	145 (31.2)	3.12 (2.22-4.43)	< 0.001	2.46
Controls	490	428 (87.3)	62 (12.7)			
Males				3.14 (2.14-4.63)	< 0.001	2.45
HCC	364	246 (67.6)	118 (32.4)			
Controls	385	334 (86.7)	51 (13.3)			
Females				3.11 (1.38-7.4)	0.002	2.55
HCC	101	74 (73.3)	27 (26.7)			
Controls	105	94 (89.5)	11 (10.5)			

HCC: Hepatocellular carcinoma; DM2: Type 2 diabetes mellitus; OR: Odds ratio; CI: Confidence interval; RR: Relative risk.

Table 2 Multivariate analysis of variables associated with HCC

	Odds ratio (95% CI)	*P*
Diabetes		
Absent	1	0.01
Present	2.2 (1.2-4)	
HBV		
Absent	1	⩽ 0.001
Present	252.1 (53.7-1183.9)	
HCV		
Absent	1	⩽ 0.001
Present	106.5 (58.2-194.9)	
Alcohol		
Absent	1	⩽ 0.001
Present	121.2 (61.9-233.7)	

Multivariate logistic regression analysis was used to assess the independent role of different variables.

RESULTS

Among the 465 patients with HCC, mean age was 68.5 ± 8.9 years and 364 (78.3%) were males. The corresponding figures for the control group were 69.4 ± 13.8 years and a male prevalence of 78.6%.

Prevalence of DM2

With regard to the type and frequency of diabetes mellitus in our patients[6,34], we found that every HCC patient of our population with abnormal glucose tolerance has the clinical and metabolic characteristics of DM2 and, therefore, nobody of our HCC patients was found affected by insulin dependent DM1. Overall, 145 (31.2%) HCC patients and 62 (12.7%) of control cases had DM2 (Table 1). This difference was statistically significant with an odd ratio of 3.12 (CI: 2.22-4.43). This odd ratio was higher for male than for female patients (3.14 *vs* 3.11, *P* = 0.632). Among DM2 patients, glycated haemoglobin was significantly higher in male HCC cases than in control males (7.8% *vs* 6.9%, *P* = 0.02). Multivariate analysis (Table 2) identified HBV infection, HCV infection, alcohol abuse and also DM2 as independent variables, all associated with an increased risk of HCC. In regards to the duration of DM2 in HCC patients, diabetes had been diagnosed at least 6 mo before the appearance of HCC in 122 of the 145 cases (84.1%). In 89 of these 122 cases, the time interval between diagnosis of DM2 and HCC could be precisely calculated and the mean time interval was 141.5 ± 9.4 mo. Moreover, in the subgroup of patients with pre-existing DM2, mean duration of diabetes was higher in patients treated with insulin than in those treated with oral antidiabetic agents (171.5 ± 87.6 mo *vs* 118.7 ± 95.2 mo, *P* = 0.05). The prevalence of DM2 in the different etiologic groups of HCC is described in Table 3. Patients classified as having cryptogenic cirrhosis had a somehow higher prevalence of DM2 compared to the other groups, but the difference did not reach statistical significance. On the other hand, alcohol related HCC had a significantly higher prevalence of DM2 compared to the HCV-related group of HCC (36.9% *vs* 26.6%, *P* = 0.048). Males HCC patients with DM2 were more frequently treated with insulin than control cases (38.1% *vs* 17.6%, *P* = 0.009). Among HCC cases, those using antidiabetic oral agents were more frequently treated with insulin secretagogues (sulfonylureas), with or without metformin (insulin sensitizer), than with simple diet, with or without metformin (Table 4).

Table 3 Etiology in the 465 HCC patients and prevalence of DM2 [mean ± SD, *n* (%)]

Etiology	N° HCC (%)	Age (yr)	Prevalence of DM2 (%)
HBV	20 (4.3)	63.3 ± 10.3[1]	3 (15.0)
HCV	177 (38.1)	71.5 ± 7.3[1]	47 (26.6)[2]
Alcohol	141 (30.4)	66.7 ± 8.5[1]	52 (36.9) [2]
HBV + HCV	8 (1.7)	60.8 ± 12.8[1]	2 (25.0)
HBV + alcohol	9 (1.9)	62.9 ± 9.3[1]	2 (22.2)
HCV + alcohol	81 (17.4)	67.7 ± 9.3[1]	27 (33.3)
HBV + HCV + alcohol	2 (0.4)	68.4 ± 10.3	0
Cryptogenetic	27 (5.8)	68.6 ± 9.3	11 (40.7)

[1]HCV *vs* HBV + HCV, *P* < 0.001; HCV *vs* HBV, *P* < 0.001; HCV *vs* HBV + alcohol, *P* < 0.001; HCV *vs* HCV + alcohol; HCV *vs* alcohol, *P* < 0.001; [2]HCV *vs* alcohol, *P* = 0.048.

Table 4 Type of therapy with oral antidiabetic agents in HCC patients and controls with DM2

	Number of subjects	Diet with or without metformin N° cases (%)	Sulfonylureas with or without metformin N° cases (%)	*P*
Total				
HCC	88	14 (15.9)	74 (84.1)	0.04
Controls	48	15 (31.2)	33 (68.8)	
Males				
HCC	75	12 (16.0)	63 (84.0)	0.049
Controls	41	13 (31.7)	28 (68.3)	
Females				
HCC	13	2 (15.4)	11 (84.6)	0.5
Controls	7	2 (28.6)	5 (71.4)	

Features of DM2 in FU and CO groups with HCC

The clinical features of DM2 in HCC cases of the FU and CO groups are compared in Table 5. The prevalence of diabetes was similar (30.2% *vs* 33.1%, *P* = 0.51). Mean HbA1c was somehow higher in FU group, but the difference was not statistically significant (8.2% ± 2.78% *vs* 7.1% ± 2.12%, *P* = 0.1). The mean duration of

Table 5 Clinical features of DM2 in HCC patients of the FU and CO groups (%)

	FU group	CO group	*P*
Prevalence of DM2	92 (30.2)	53 (33.1)	0.51
HbA1c (mean% ± SD)	8.2 ± 2.78	7.1 ± 2.12	0.1
Insulin therapy	45 (48.9)	15 (28.3)	0.01
Antidiabetic oral agents	47 (51.1)	38 (71.7)	0.01
Diet with/without metformin	7 (14.9)	4 (10.5)	0.55
Sulfonylureas with/ without metformin	40 (85.1)	34 (89.5)	0.55
Duration of DM2 (mean ± SD, mo)	127.8 ± 80.1	167.1 ± 114.3	0.03
Duration of insulin therapy (mean ± SD, mo)	50.0 ± 50.5	77.8 ± 86.4	0.12

FU: Follow-up group; CO: Clinically overt group; HbA1c: Glycated haemoglobin.

DM2 was higher in CO cases (167.1 ± 114.3 mo *vs* 127.8 ± 80.1 mo, $P = 0.03$). FU cases with DM2 were more frequently treated with insulin compared to CO cases with DM2 (48.9% *vs* 28.3%, $P = 0.01$).

DISCUSSION

The association of type 2 diabetes with solid tumours[36,37] has been long suspected and several studies have reported increased mortality rates for neoplastic diseases in patients with DM2[13,38-41]. Recent studies would suggest that treatments with anti-diabetic drugs, prone to increase circulating insulin levels, might favour tumour development, as shown with sulfonylurea and insulin[42], while treatment with drugs that contrast hyperinsulinemia may in fact be protective, as in the case of metformin[43]. Many reports have described an increased risk for HCC in patients with DM2, particularly males[13]. However, most of these studies did not assess the individual role of DM2 in relation to confounding cofactors such as HBV and HCV infection, particularly in patients with chronic liver disease. In this clinical setting, DM2 may be the consequence rather than the cause of HCC developing in a cirrhotic liver. Thus, precise definition in our study of the temporal relationship between onset of DM2 and of HCC is of major importance, and this information has been lacking in most previous surveys[3,13,19].

Our results confirm that patients with DM2 have a significantly increased risk of HCC, independently of cofactors such as HBV and HCV infection and alcohol intake, and demonstrate that DM2 pre-exists to the development of HCC in most cases, suggesting that DM2 is more likely a concourse rather than merely a consequence of the liver tumour. This conclusion is also supported by the finding of a similar frequency and severity of DM2 in patients with small HCC detected during follow-up of cirrhosis and in those with more advanced and diffuse cancers detected outside of a surveillance program.

Because diabetes may be due to HCC or to the underlying cirrhosis and the liver cirrhosis may be caused by diabetes[7,10], our data cannot fully explain the reciprocal connections between them. Therefore, further studies, including cirrhotic patients, must be planned in the future to evaluate whether the diabetes itself has a direct carcinogenetic effect.

The observation that patients with DM2, particularly males, treated with insulin had an increased frequency of HCC is intriguing and clinically relevant. These patients are those often showing the highest insulin blood levels[44], and this might have contributed to facilitate the development of HCC. It is well known that patients with DM2 treated with insulin are those with more severe hyperinsulinaemia and more complications, including microalbuminuria and ischemic heart disease[45,46]. Our results indicate the need for close surveillance for HCC in patients with chronic liver disease and DM2, particularly when males and treated with insulin. They also suggest that in these patients strategies to improve the metabolic control should be directed primarily against hyperinsulinaemia by avoiding, as much as possible, the use of oral secretogogue drugs and of insulin treatment, giving preference to insulin-sensitizers such as metformin and glitazones.

COMMENTS

Background

The association of type 2 diabetes mellitus (DM2) with solid tumours, and particularly with hepatocellular carcinoma (HCC), has been long suspected and several studies have reported increased mortality rates for neoplastic diseases in patients with DM2. However, the temporal relationship between onset of diabetes and development of HCC, and the clinical and metabolic characteristics of patients with DM2 and HCC are not been well examined.

Research frontiers

Whether the diabetes itself has a direct carcinogenetic effect remains unknown.

Innovations and breakthroughs

This study shown that DM2 is associated with a 3-fold increase risk of HCC. In most of patients DM2 pre-existed to HCC. Patients with DM2 and chronic liver disease, particularly insulin treated males, should be considered for HCC close surveillance programs.

Applications

Further studies, including cirrhotic patients, must be planned to evaluate the complex relationships between DM2, liver cirrhosis and HCC.

Terminology

DM2 is a compensatory high insulin state caused by impaired insulin action in fat, muscle tissue and liver. HCC is the most frequent cancer of the liver that occurs mainly in patients with chronic liver disease.

Peer review

This is a good paper that is well organized. The data shows the association between diabetes and HCC.

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