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.

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[1-3]. 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
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 tomography (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.
Table 1 Frequency of DM2 in HCC patients and in controls

|                     | Number of subjects | DM2 absent (%) | DM2 present (%) | OR (95% CI) | P |
|---------------------|--------------------|----------------|-----------------|-------------|---|
| 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)       | 3.14 (2.14-4.63) | < 0.001 | 2.45 |
| Males               |                    |                |                 |             |        |     |
| HCC                 | 364                | 246 (67.6)     | 118 (32.4)      | 3.11 (1.38-7.4) | 0.002 | 2.55 |
| Controls            | 385                | 334 (86.7)     | 51 (13.3)       |             |        |     |
| Females             |                    |                |                 |             |        |     |
| 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

| Diabetes | Odds ratio (95% CI) | P |
|----------|---------------------|---|
| 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)  |     |

Table 3 Etiology in the 465 HCC patients and prevalence of DM2

| Etiology | Number of HCC (% | Age (yr) | Prevalence of DM2 (%) |
|----------|------------------|----------|-----------------------|
| HBV      | 20 (4.3)         | 63.3 ± 10.3 | 3 (15.0)             |
| HCV      | 177 (38.1)       | 71.5 ± 7.3  | 47 (26.6)            |
| Alcohol  | 141 (30.4)       | 66.7 ± 8.5  | 52 (26.9)            |
| HBV + HCV| 8 (1.7)          | 60.8 ± 12.8 | 2 (25.0)             |
| HBV + alcohol | 9 (1.9)    | 62.9 ± 9.3  | 2 (22.2)             |
| HCV + alcohol | 81 (17.4)   | 67.7 ± 9.3  | 27 (33.3)            |
| HBV + HCV + alcohol | 2 (0.4) | 68.4 ± 10.3 | 0                    |
| Cryptogenic | 27 (5.8)       | 68.6 ± 9.3  | 11 (40.7)            |

1HCV 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; 2HCV vs alcohol, P = 0.048.

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

| Etiology | Diet with or without metformin | 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) | 65 (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)  |        |

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, 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 significantly higher in male HCC cases than in control cases (8.2% ± 2.55 vs. 2.28%, P < 0.001). The prevalence of DM2 was similar (30.2% ± 13.8 years and 78.6% for male cases vs 6.9% ± 2.28% and 78.3% for female cases, 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 anti diabetic 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 somewhat 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 anti diabetic oral agents were more frequently treated with insulin (sulfonylureas, with or without metformin (insulin sensitizer), than with simple diet, with or without metformin (Table 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 3. 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
Recent studies have suggested that treatments with anti-diabetic drugs, prone to increase circulating insulin levels, might favor tumor development, as shown with sulfonylurea and insulin\cite{36,37}, while treatment with drugs that contrast hyperinsulinemia may in fact be protective, as in the case of metformin\cite{38}. Many reports have described an increased risk for HCC in patients with DM2, particularly males\cite{39}. 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\cite{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\cite{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\cite{40}, 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 hyperinsulinemia and more complications, including microalbuminuria and ischemic heart disease\cite{41,42}. 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 secretagogue drugs and of insulin treatment, giving preference to insulin-sensitizers such as metformin and glitazones.

**DISCUSSION**

The association of type 2 diabetes with solid tumours\cite{36,37} has been long suspected and several studies have reported increased mortality rates for neoplastic diseases in patients with DM2\cite{3,13,19,36}. Recent studies would suggest that treatments with anti-diabetic drugs, prone to increase circulating insulin levels, might favor tumor development, as shown with sulfonylurea and insulin\cite{42}, while treatment with drugs that contrast hyperinsulinemia may in fact be protective, as in the case of metformin\cite{43}. Many reports have described an increased risk for HCC in patients with DM2, particularly males\cite{39}. 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\cite{3,13,19}.

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**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 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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