

DIABETES MELLITUS, OBESITY AND UNDERLYING NON ALCOHOLIC FATTY LIVER DISEASE - INDEPENDENT RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

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Abstract


Background and Aims. Hepatocellular carcinoma (HCC) is one of the most common malignancies. Obesity, together with the underlying liver steatosis, has received increased attention as a risk factor for HCC. Diabetes Mellitus (DM) is also reported to be associated with HCC. We aimed to estimate the risk of HCC in obese and diabetic patients. **Material and method.** We prospectively analyzed 414 obese and diabetic patients, over a period of 5 years. We evaluated all patients using screening methods such as abdominal ultrasound and serum alpha-fetoprotein every 6 months, in order to detect HCC occurrence. Kaplan-Meier analysis estimated the cumulative incidence of HCC. Univariate and multivariate Cox regression analysis assessed the association between HCC and obesity. **Results.** Median follow-up was 4.3 years. 11 from 77 cirrhotic obese patients, and 18 from 150 non-cirrhotic obese patients developed HCC ($p=ns$). 7 from 51 patients with DM and cirrhosis, and 14 from 136 non-cirrhotic patients with DM developed HCC ($p=ns$). The cumulative incidence of HCC was 2.8%, respectively 2.6%, in cirrhotic patients with obesity or DM, compared with 2.2%, respectively 2.0%, in non-cirrhotic patients with obesity or DM ($p=ns$). **Conclusion.** Obesity and DM, along with nonalcoholic fatty liver disease (NAFLD), seems to be independent risk factors for HCC occurrence.

key words: obesity, hepatocellular carcinoma, NAFLD.

Background and Aims

Hepatocellular carcinoma (HCC) is one of the most common malignancies, with an increasing incidence in developed countries. Researchers have shown that liver cirrhosis is no longer a preliminary and necessary condition for HCC occurrence.

Obesity has recently received increased attention as a risk factor for HCC [1-4]. Together with the underlying liver steatosis, obesity has been shown to be involved in the progression of liver fibrosis; whether obesity is an independent risk factor for HCC is a hypothesis to be demonstrated. In addition, obesity may impact disease progression. Thus,

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a large prospective trial revealed an association between increased weight and overall cancer mortality. A body mass index (BMI) > 35 kg/m² negatively impact mortality from HCC, with a relative risk (RR) of 1.68 in women and 4.52 in men [5].

Obesity and non-alcoholic steatohepatitis (NASH) lead to increased levels of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and leptin, as well as decreased adiponectin [6]. Increased levels of TNF- α leads to activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and allows for hepatic carcinogenesis [7]. In the setting of obesity, IL-6 levels are elevated, and weight loss reduces both IL-6 and TNF- α levels [8,9]. High levels of TNF- α and IL-6 promotes inflammation and fibrosis, and contributes to hepatic carcinogenesis. Decreased adiponectin, seen in obese patients, has been consistently demonstrated in the setting of NASH, and has also been shown to play a role in hepatic fibrosis [9]. Hypoadiponectinemia accelerates hepatic tumor formation in mice [10]. Adiponectin is also important in anti-angiogenesis and apoptosis, revealing the role of low adiponectin in tumor formation [11]. Conversely, the 167-amino acid protein leptin is elevated in the setting of obesity [12]. Leptin is a mediator of hepatic fibrosis, as well as a contributor to elevated TNF- α level [13,14].

Diabetes Mellitus (DM) has been previously reported to be associated with HCC, but insufficient data is available regarding this association. El Serag et al., in a large meta-analysis including 13 case-control studies, showed that DM was significantly associated with HCC in 7 of these studies

[15]. In the majority of these studies, the significant association between DM and HCC was independent of alcohol use or viral hepatitis.

DM is characterized by insulin resistance and secondary hyperinsulinemia. Hyperinsulinemia up-regulates the production of IGF-1 (insulin-like growth factor), and IRS-1 (insulin receptor substrate-1). IGF-1 is a peptide hormone that stimulates growth, via cellular proliferation and inhibition of hepatic apoptosis [16]. IGF-1 significantly activates MAPK (mitogen-activate protein kinase), as well as over expression of *c-fos* and *c-jun* proto-oncogenes in vitro, which is thought to contribute to hepatic carcinogenesis [17,18].

All the above data indicate that insulin-mediated factors are involved in hepatocarcinogenesis in both cirrhotic and non-cirrhotic NASH patients.

Challenged by the question whether DM and obesity could be independent risk factors for HCC, we aimed to estimate the risk of HCC in 414 obese or diabetic patients from South-Eastern Romania.

Material and Method

We prospectively analyzed 414 obese or diabetic patients, diagnosed and followed-up in the Gastroenterology, Oncology, and Nutrition Departments of “St. Apostle Andrew” Constanta Clinical Emergency Hospital over a period of 5 years (between December 2007 and December 2012). According to the underlying disease, our patients were split-up in 187 patients diagnosed with diabetes mellitus and 227 non-diabetic patients with obesity. We excluded all patients with both pathologies.

Patients with regular/daily alcohol consumption or diagnosed with liver viral infections were also excluded.

The diagnosis criteria for obesity were the patient body mass index (BMI) over 30kg/m^2 and for diabetes mellitus the diagnostic criteria of the American Diabetes Association (ADA) [19]: a fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, or a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), or a random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

We evaluated all patients by abdominal ultrasound (US) and serum alpha-fetoprotein (AFP) every 6 months, in order to detect HCC occurrence.

Patients were also explored biologically, regarding lipid and glucose profiles: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, serum glucose, and HbA1c were tested in every patient, and correlations with HCC occurrence were done.

The diagnostic cut-off value of AFP was 200ng/ml , but smaller values in association with focal lesion diagnosed by US, were also considered diagnostic criteria for HCC.

The diagnosis of HCC was supposed by US and AFP, and confirmed by contrast CT scan or contrast MRI with highly specific liver enhancement (eg. acidum gadoxeticum) according to the 2011 diagnostic criteria of the American Association for the Study of Liver Diseases. Few cases with uncertain HCC diagnosis after high resolution imagistic techniques were referred to liver biopsy and confirmed by the anatomo-pathological exam. Abdominal US was made using Logiq700 and ALOKA PROSOUND equipment.

Non-alcoholic fatty liver disease (NAFLD) classification was done using the FIBROSCAN, a device used to determine the value of liver stiffness (EchoSens, Paris, France); liver stiffness was used to stage the degree of liver fibrosis. According to the value obtained after FIBROSCAN examination, we made the correspondence with the liver fibrosis using the system devised by the Pathology Committee of the NASH Clinical Research Network, as follows:

F1– perisinusoidal or periportal fibrosis

F2 – both perisinusoidal and portal/periportal fibrosis

F3 – bridging fibrosis;

F4 – cirrhosis.

Our study results were compared with those obtained from a control group of 50 patients diagnosed, treated and followed-up for HCC, all of them without any evidence of obesity or diabetes mellitus.

Statistical analysis: Kaplan-Meier analysis estimated the cumulative incidence of HCC. Univariate and multivariate Cox regression analysis were used to assess associations between HCC and obesity.

Results

The median follow-up was 4.3 years. The mean age of HCC diagnosed patients was 69 ± 7.28 years. By comparing our study group with a control group of patients matched by age and sex, admitted in the hospital for HCC, but without obesity or DM, we observed that the mean age at diagnosis was significantly higher in the control group, than in our study group ($p=0.04$; 95%CI, 25.55-69.91).

Multivariate regression analysis showed that older age ($p=0.04$) was an independent variable associated with the development of HCC in the study group.

According with the presence of cirrhosis, abdominal US divided our patients in 2 subgroups: 128 patients with cirrhosis, respectively 286 patients without liver cirrhosis.

The diagnosis of NAFLD, and mainly of NASH, requires liver biopsy [20], an invasive procedure that may be associated with potential risks or complications [21,22]. In

order to avoid this, we used FIBROSCAN to stage liver fibrosis. According to the measured value (kPa), our patients were classified as follows (Figure 1): 128 patients with F4, 177 patients with F3, 109 patients with F2, and no patients with F1.

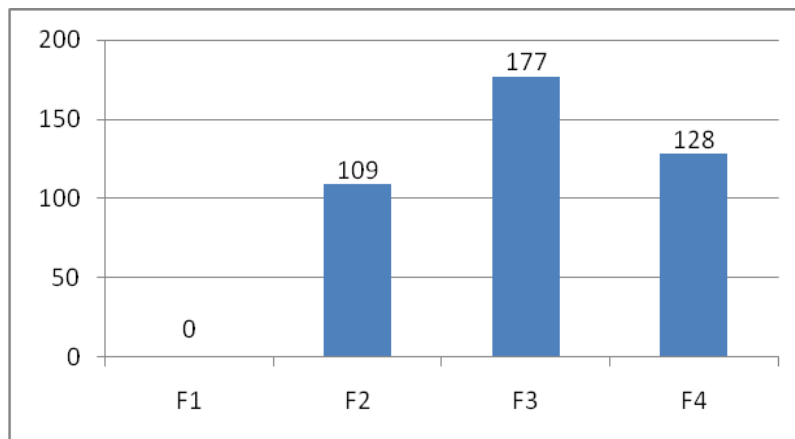


Figure 1. Classification of patients according to the stage of fibrosis using FIBROSCAN.

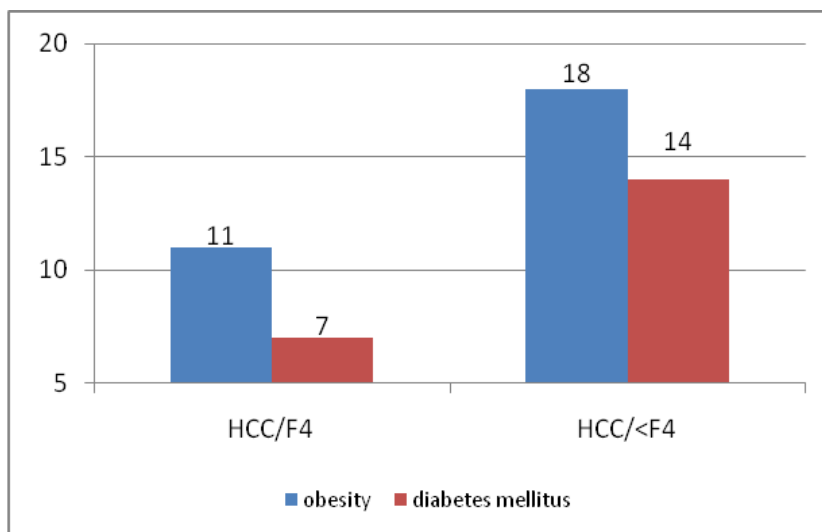


Figure 2. Distribution of patients with HCC according to the presence of underlying cirrhosis.

The distribution of obese, respectively diabetic, patients according to the stage of fibrosis obtained by FIBROSCAN examination is shown in Table 1.

During the 5 years study period, 11 from 77 cirrhotic obese patients (14.28%), and 18 from 150 non-cirrhotic obese patients (12%), developed HCC ($p=ns$) (figure 2). Regarding DM patients, 7 from 51 patients with DM and

cirrhosis (13.72%), and 14 from 136 non-cirrhotic patients with DM (10.29%), developed HCC ($p=ns$) (Figure 2).

Table 1. Distribution of patients with DM mellitus or obesity, according to the stage of fibrosis.

FIBROSCAN	DM	Obesity
F1	-	-
F2	48	61
F3	88	89
F4 (liver cirrhosis)	51	77

The Kaplan Meyer analysis showed that the cumulative incidence of HCC was 2.8% in cirrhotic patients with obesity, respectively 2.6% in cirrhotic patients with DM, compared to 2.2% and 2.0%, in non-cirrhotic patients with obesity, respectively DM ($p=0.08$, ns; respectively, $p=0.07$, ns).

Discussions

Obesity and DM, with the underlying NAFLD, have become a universal public health problem with increasing prevalence in both adults and children, especially in developed countries, but even in developing ones. Epidemiological studies revealed a strong link between these pathologies and the development and progression of various types of cancers. Their association with HCC is particularly strong, especially in liver diseases

such as NAFLD and the more severe NASH. NASH is characterized by fatty liver inflammation and it is believed to cause fibrosis and cirrhosis. The latter is a known liver cancer risk factor. In fact, due to its much higher prevalence, obesity may be a more substantial contributor to overall HCC burden than infection with hepatitis viruses [23].

Our study results came to confirm literature data, regarding the involvement of obesity and DM (with accompanying NAFLD in different stages) in HCC occurrence, without the compulsoriness of cirrhosis presence. The cumulative incidence of HCC was 2.8% in cirrhotic patients with obesity, respectively 2.6% in cirrhotic patients with DM, compared to 2.2% and 2.0%, in non-cirrhotic patients with obesity, respectively DM ($p=ns$).

Conclusions

Obesity and DM, along with the secondary liver disturbances such as NAFLD or NASH, seems to be independent risk factors for HCC occurrence, regardless the presence of advanced liver fibrosis/cirrhosis.

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