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A risk factor in the development of hepatocellular carcinoma: Insulin analogues

Pinar Gokcen[a,*], Kamil Ozdil[b]

[a] *Bahcesehir University, Medical Park Goztepe Hospital, Department of Gastroenterology, Istanbul, Türkiye*
[b] *Health Sciences University, Umraniye Training and Research Hospital, Department of Gastroenterology, Istanbul, Türkiye*

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Abstract

Aim: The most important mechanisms in the pathogenesis of the relationship between diabetes mellitus and cancer; hyperglycemia, insulin resistance and the inflammation resulting from the activation of insulin receptors. Apart from insulin resistance, hyperinsulinemia may also occur with the use of exogenous insulin. We aimed to investigate the effect of diabetes mellitus and insulin use as a risk factor for hepatocellular carcinoma development in a large patient population with chronic hepatitis B cirrhosis.

Materials and Methods: 493 chronic hepatitis B-associated cirrhotic patients were included in the study. The patients were evaluated at 3–6-month intervals during follow-up for hepatocellular carcinoma screening. Demographic and laboratory variables, presence of diabetes mellitus, insulin usage, and hepatocellular carcinoma occurrence were recorded.

Results: The mean age of patients was 53.5±13.9 years, and 66.2% were male. 18.7% of the patients had a diagnosis of diabetes mellitus and 12% of the patients had insulin use. 68 patients (13.8%) were decompensated cirrhotic. The mean follow-up period was 50.6±33.6 months, during which 43 patients (8.7%) developed hepatocellular carcinoma. In the multivariable analysis, older age, male gender, presence of decompensation, use of exogenous insulin were associated with HCC occurrence (all $p<0.05$).

Conclusion: Diabetes mellitus and insulin resistance have been associated with many cancers due to insulins' mitogenic effects. We showed that insulin use is a risk factor for hepatocellular carcinoma development in our chronic hepatitis B-associated cirrhotic patients. Further studies including antidiabetic treatment subgroups are needed.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and ranks seventh in all cancer prevalence worldwide [1]. Chronic hepatitis B (CHB) and C (CHC), non-alcoholic fatty liver disease (NAFLD) are the most common etiologies of HCC. The best-known risk factors for the development of HCC are advanced age, male gender, cirrhosis, alcohol consumption, smoking and diabetes mellitus (DM).

The most important mechanisms in the pathogenesis of the relation between DM and cancer; hyperglycemia, insulin resistance and the inflammation resulting from the activation of insulin receptors (IR). It has been observed that especially Type A (IR-A) is overexpressed in many cancer cells. IR-A can be activated by both insulin and insulin-like growth factor 2 (IGF-2). However, when stimulated by IGF-2, mitogenic effects and cancer cell survival are greater than when activated with insulin [2]. IR-A hemireceptors also stimulate cell growth by forming hybrid receptors with insulin-like growth factor 1 (IGF-1) hemireceptors [3]. Apart from insulin resistance, hyperinsulinemia may also occur with the use of insulin secretagogues such as sulfonylureas or exogenous insulin. While the risk of cancer increases with these treatments, the risk of cancer decreases with insulin sensitizers such as metformin by reducing insulin resistance and insulin level [4-6]. In our study, we aimed to investigate the effect of DM and insulin use as a risk factor for HCC development in a large patient population with CHB cirrhosis.

Materials and Methods

Patient population and follow-up definitions

493 CHB-associated cirrhotic patients followed up in the hepatology outpatient clinic of Umraniye Training and Research Hospital were included in the study between January 2007 and August 2021. Inclusion criteria were 18 years of age and older, and being on antiviral ther-

*Corresponding author:
Email address: pinar-gokcen@hotmail.com (Pinar Gokcen)

apy. Exclusion criteria were defined as being 18 years of age or younger, being diagnosed with HCC at or before the follow-up period, having undergone liver transplantation, hepatitis C, hepatitis D and human immunodeficiency virus coinfection.

The patients were evaluated at 3-6month intervals during the follow-up. Patients with HbA1c level ≥ 6.5 in medical records, or a random glucose level ≥ 200 mg/dl twice or who had a health report for antidiabetic drug use were considered as diabetic [7]. Insulin use of diabetic patients was also recorded. As laboratory analysis, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, alpha-fetoprotein (AFP) levels, international normalized ratio (INR), complete blood count, and HBV-DNA were recorded during follow-up. Patients underwent HCC surveillance with abdominal USG, triphasic computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) at 6-12 month intervals. A diagnosis of HCC was made following the current guidelines [8]. Findings of fibrosis stage 5 or 6 according to the ISHAK staging system in patients who have undergone the biopsy, or those with radiological (nodular appearance of the liver surface, parenchymal thickening, caudate lobe enlargement, portal vein diameter >13 mm) and endoscopic (varices, portal gastropathy) cirrhosis were considered compensated cirrhotic. Decompensated cirrhosis was defined as the presence of ascites, variceal bleeding and hepatic encephalopathy.

Statistical analysis

Statistical data were analyzed using SPSS v.23.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation for continuous variables. Variables were tested for normality using the Kolmogorov-Smirnov test. Independent t-test was used to compare parametric variables and chi-squared, continuity correction, or the Fisher's exact test was used to compare categorical variables. The univariate and multivariate logistic regression analysis models were used to determine the effects of the variables on the risk of developing HCC. Tests were interpreted at a 95% confidence interval. A P value ≤0.05 was considered statistically significant.

The study was approved by the local ethics committees of Umraniye Training and Research Hospital (Date: 28.10.21, Number: 311).

Results

The mean age of CHB cirrhotic patients was 53.5±13.9 years, and 66.2% were male. 18.7% of the patients had a diagnosis of DM and 12% of the patients had insulin use. 68 patients (13.8%) were decompensated cirrhotic. The mean follow-up period was 50.6±33.6 months, during which 43 patients (8.7%) developed HCC. The death occurred in 52 patients (10.5%) in the entire cohort. The demographic characteristics of the database are given in Table 1.

The patients who developed HCC were older (65.3 ±10.2 vs. 52.4 ± 13.7) and the male sex ratio was higher (90.7% vs. 63.8%) when compared with the patients who did not develop HCC (both p<0.001). The presence of DM and insulin use were found to be significantly higher in patients with HCC, respectively (p=0.007, p=0.009). In patients with HCC, AST, GGT, total bilirubin and INR levels were statistically significantly higher but albumin and platelet count were low (all p<0.005). Although the AFP level was found to be higher in patients with HCC (10.0±15.6 vs. 5.6±12.3 ng/ml), the difference was not statistically significant (p=0.188) (Table 2).

Table 1. Demographic characteristics of HBV-associated cirrhotic patients.

Patients characteristics (n=493)	Value
Age, years ± SD	53.5 ± 13.9
Gender, male n (%)	326 (66.1)
Follow-up, months ± SD	50.6 ± 33.6
Diabetes mellitus, n (%)	92 (18.7)
Use of exogenous insulin, n (%)	59 (12.0)
HBeAg positivity, n (%)	88 (18.4)
Decompensation, n (%)	68 (13.8)
HCC cases during follow up, n (%)	43 (8.7)
Mortality, n (%)	52 (10.5)

HCC: Hepatocellular carcinoma; SD: Standard deviation.

Advanced age, male gender, presence of decompensated cirrhosis, presence of DM and insulin use were found to be associated with the development of HCC in univariate analyzes (all p<0.005). In the multivariable analysis, older age (OR: 1.1; 95% CI: 1.0-1.1), male gender (OR: 0.2; 95% CI: 0.1-0.5), presence of decompensation (OR: 0.18; 95% CI: 0.1-0.4), use of exogenous insulin (OR: 0.1; 95% CI: 0.0-0.9) were associated with HCC occurrence (all p<0.05) (Table 3).

The presence of DM (33.8% vs. 16.2%) (OR: 2.6; 95% CI: 1.5-4.6) and insulin use (91.3% vs. 55.1%) (OR: 8.6; 95% CI: 1.9-39.4) were found to be higher in decompensated cirrhosis when compared with compensated cirrhosis in univariate analysis, respectively (p<0.001, p=0.002). Mortality was significantly higher in DM patients (32.7% vs. 17.0%) when compared to non-diabetics (OR: 2.4; 95% CI: 1.3-4.5), (p=0.013). Although mortality was found to be higher in insulin users compared to non-insulin users (82.4% vs. 60.0%), the difference was not statistically significant (p=0.099).

Discussion

DM is one of the most common metabolic problems all over the world. Hyperinsulinemia is one of the clinical features of type 2 DM, and the excess of insulin seen in diabetic patients may be due to insulin resistance as well as to insulin replacement therapy. Insulin is an anabolic hormone with mitogenic effects and has an important role in cell metabolism that it is thought to cause cancer [9]. DM and insulin resistance have been associated with many cancers [10].

Numerous studies are showing that DM is a risk factor for liver cirrhosis, HCC and mortality. However, most of these studies were conducted in patients with CHC infection or NAFLD [11-14]. It has been shown that besides mal-

Table 2. Comparison of clinical and laboratory data of patients with and without HCC.

	Patients with HCC (n=43)	Patients without HCC (n=450)	p value
Age (years) mean ± SD	65.3 ±10.2	52.4 ± 13.7	<0.001
Male gender, n (%)	39 (90.7)	287 (63.8)	<0.001
Diabetes mellitus, n (%)	15 (34.9)	77 (17.1)	0.007
Use of exogenous insulin, n (%)	14 (93.3)	45 (58.4)	0.009
Laboratory (mean ± SD)			
HBeAg positivity, n (%)	4 (10.8)	84 (19.0)	0.273
ALT (IU/L)	57.0±52.8	46.1±54.9	0.363
AST (IU/L)	60.7±59.2	35.4±26.8	0.002
GGT (IU/L)	106.9±103.9	41.0±56.1	<0.001
Albumin (g/dl)	3.5±0.7	4.2±0.5	<0.001
Total bilirubin (mg/dl)	1.1±0.7	0.9±0.7	0.032
AFP (ng/ml)	10.0±15.6	5.6±12.3	0.188
INR	1.2±0.2	1.1±0.2	0.003
Platelet (10^3/ml)	129.2±49.0	203.3±68.0	<0.001
Ferritin (ml/ng)	263.7±173.1	109.4±156.1	0.059
HBV-DNA (log IU/ml)	4.7±2.0	5.2 ±2.1	0.497

ALT: Alanine transaminase; AST: Aspartate transaminase; AFP: Alpha-fetoprotein; GGT: Gamma-glutamyl transferase; HCC: Hepatocellular carcinoma; SD: Standard deviation.

Table 3. Clinical factors associated with HCC development.

	Univariate analysis OR (95% CI)	p value	Multivariate analysis OR (95% CI)	p value
Age (per year increase)	1.1 (1.0-1.1)	< 0.001	1.1 (1.0-1.1)	< 0.001
Gender (male vs. female)	5.5 (1.9-15.8)	< 0.001	0.2 (0.1-0.5)	0.002
HBeAg status (positive vs. negative)	0.5 (0.2-1.5)	0.273		
Diabetes mellitus (yes vs. no)	2.6 (1.3-5.0)	0.007	1.6 (0.7-3.3)	0.251
Use of exogenous insulin (yes vs. no)	10.0 (1.2-79.6)	0.009	0.1 (0.0-0.9)	0.039
Decompensation (yes vs. no)	9.2 (4.7-18.0)	< 0.001	0.18 (0.1-0.4)	< 0.001

CI: Confidence interval.

nutrition and a sedentary lifestyle; hepatic inflammation, steatosis and fibrosis are also responsible for the development of DM in these patients [15,16]. The relationship between CHB and DM is still controversial. Some studies have shown that HBsAg positivity is associated with DM and insulin use [17,18]. In a study conducted in 2019, DM was an independent risk factor in CHB patients with cirrhosis, but not in non-cirrhotic patients [19]. Although the relationship between DM and liver cirrhosis has not been clarified, it has been shown that high serum glucose and insulin levels stimulate the production of collagen and other fibrosis-related precursors in hepatic stellate cells [20]. Our study is important because it evaluated these parameters in a large group of patients with CHB cirrhosis. Since the entire patient population was cirrhotic in our study, DM has not examined an independent risk factor for cirrhosis. However, when the correlation between cirrhosis stage and DM was examined, it was observed that the presence of DM in decompensated cirrhotic patients was statistically significantly higher than in compensated cirrhotic patients ($p<0.001$). This result supports the fact that DM is a factor that increases mortality in patients with liver cirrhosis admitted to the hospital with variceal bleeding [21]. On the contrary, some other studies have shown that the presence of DM in cirrhotic CHB patients is not associated with increased mortality [22,23]. In our study, it was observed that mortality in diabetic patients increased approximately 2.5 times during an average follow-up period of five years. In addition to the end-organ damage directly caused by DM, this statement also can occur as a result of DM-cancer relevance. Hyperglycemia is thought to initiate the first stage of carcinogenesis by triggering oxidative stress [24]. With an increasing incidence, DM increases the risk of HCC approximately three times [25]. In a meta-analysis of approximately ten thousand cases with HCC, DM was shown to reduce overall survival and disease-free survival [26]. Current studies investigating the relationship between DM and HCC have begun to focus on genetics. In a study conducted in 2019, nine critical genes were shown to play a critical role in the pathogenesis of both DM and HCC [27]. In our study, it was observed that the presence of DM increased the risk of HCC development 2.7 times in univariate analyzes. However, this finding was not statistically significant in multivariate analyses. Similarly, in another study of cirrhotic CHB patients, DM was not seen as a risk factor for HCC [28]. Both our and this study have a lack of sufficient information about the age and duration of DM diagnosis which may have caused these results. However, there are also studies showing that the duration of DM is not associated with HCC [29,30].

In addition to regulating glucose metabolism, insulin also stimulates cell growth [31]. The effect of exogenous insulin use on growth and carcinogenesis has also been one of the research topics of recent years. Long-acting insulin analogues have been shown to stimulate cancer proliferation in vitro more than endogenous insulin [32]. Activation of the MAP-ERK pathway is the reason for this increased mitogenic activity [33]. In a meta-analysis including 27 cohort studies, it was shown that the risk of pancreatic, liver, kidney and lung cancers increased but the risk of prostate cancer decreased in patients using insulin. In the same study, it was observed that insulin glargine decreased the risk of colon cancer but increased the risk of breast cancer when compared to other insulins [34]. However, since the patient population is very heterogeneous, it seems difficult to reach a definite conclusion. In our study, it was observed that the use of insulin increased the risk of HCC development 10 times in univariate analyzes. This relationship was also found to be statistically significant in multivariate analyzes. Insulin and sulfonylurea use in patients with CHC infection with or without cirrhosis has been shown to increase the risk of developing HCC in both univariate and multivariate analyzes [9]. There are studies in the literature supporting the relationship between insulin treatment and HCC development [35,36].

However, given the patients with insulin use have worse controlled DM profiles, it is difficult to determine the development of HCC whether is associated with worse controlled DM or with exogenous insulin use. In our study, when cirrhosis stage and insulin use correlation was examined, it was observed that DM and insulin use was significantly higher in decompensated cirrhotic patients. It is thought that this may be related to hesitation from non-insulin treatments for patients as decompensation progresses. In our study, although mortality was higher in patients using insulin than in non-insulin users, the difference was not statistically significant (p=0.099). On the other hand, intensive insulin therapy has been shown to reduce mortality in surgical intensive care patients on mechanical ventilators [37]. In a meta-analysis consisting of 13567 patients and 26 studies, the mortality-increasing effect of hyperglycemia was emphasized and the effect of insulin use on mortality was investigated in intensive care patients. Accordingly, it has been shown that intensive insulin therapy increases the risk of hypoglycemia and does not have a positive benefit on mortality [38]. Considering that cirrhotic patients are more susceptible to hypoglycemia due to insufficient liver reserve, it would not be wrong to conclude that the use of insulin may increase mortality, but for this, blood glucose and insulin levels should be added to the database in patient follow-up.

Our study has some limitations. Since it is a retrospective study, patients' body mass index, DM duration, and antidiabetic drugs and insulin subgroups could not be included in the study.

Conclusion

DM and insulin resistance have been associated with many cancers due to insulins' mitogenic effects. We showed that insulin use is a risk factor for HCC development. in our cirrhotic CHB patients. Further studies including antidiabetic treatment subgroups are needed.

Acknowledgements

Authors' contributions

K.O. and P.G designed the Conceptualization and methodology. P.G. collected and analyzed data. K.O. performed experiments and contributed ideas and insights. P.G wrote the article with input from K.O.

STROBE guidelines statement

The authors have read the STROBE guidelines, and the manuscript was prepared and revised according to the STROBE guidelines.

Ethics approval

The study was approved by the local ethics committees of Umraniye Training and Research Hospital (Date: 28.10.21, Number: 311).

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