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Original Article

Effect of diabetes mellitus on prognosis and development of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis

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Abstract

Aim: Hepatitis C virus (HCV) infection and diabetes mellitus (DM) negatively affect each other. HCV patients diagnosed with DM have more complications than patients with HCV infection alone. In this study, we aimed to investigate the effect of DM on complication rate, hepatocellular cancer (HCC) development and mortality in HCV RNA (+) cirrhosis patients.
Material and Methods: Patients admitted with Hepatitis C-related cirrhosis and followed up for at İzmir Katip Çelebi University Atatürk Training and Research Hospital Gastroenterology and Internal Medicine Clinic for at least six months between 2005and 2014 were retrospectively evaluated.
Results: A total of 146 patients with HCV-related cirrhosis were included in the study. Of these patients, 53 (36.3%) had diagnosis of DM. In 108 patients who did not develop hepatocellular carcinoma (HCC), the mean CHILD score at final admission (p=0.024), difference between mean CHILD scores at final and initial admission (p=0.011), and annual rate of increase in CHILD score (p=0.047) was significantly higher in the DM group. There was no significant difference between the DM and non-DM groups according to both overall survival (p=0.115) and time of HCC development (p=0.567).
Conclusion: While HCC development and overall survival were similar in both groups, in the subgroup of patients who did not develop HCC, the annual increase in CHILD score and final CHILD score were significantly higher in DM patients.

Keywords: Diabetes mellitus; HCV; cirrhosis; survival; hepatocellular carcinoma.

INTRODUCTION

Hepatitis C virus (HCV) infection, chronic liver disease, and cirrhosis are the top causes of hepatocellular carcinoma (HCC) (1). Chronic HCV infection is defined as HCV viremia lasting more than 6 months (2). Studies on the natural course of patients infected with chronic HCV report causes of mortality as chronic liver disease in 55-85%, cirrhosis in 15-30%, and decompensated cirrhosis and HCC in 1-15% of patients (3).

Population-based studies have found a strong relationship between HCV infection and diabetes mellitus (DM) (4). According to data from animal models and human studies, HCV infection induces hepatic steatosis and increased production of tumor necrosis factor α. Both of these conditions result in insulin resistance and subsequent development of type 2 DM. Presence of both diabetes and hepatic steatosis together has been suggested to increase fibrosis, chance of HCC, and atherosclerosis (5).

Type 2 DM is a risk factor for development and progression of hepatic fibrosis. There is a strong relationship between insulin resistance and stage of hepatic fibrosis (6). Studies on patients with type 2 DM have found a 2-2.5 times increased risk of cirrhosis development and chronic liver disease-related mortality (7-9). Inflammation plays an important role in the development of hepatic fibrosis (10). Type 2 DM is known as an autoinflammatory disease and the relationship between DM and inflammation is well-defined (11). Other findings on the pathophysiology of the other complications of diabetes have shown that insulin resistance and diabetes-related systemic inflammation may contribute to the progression of hepatic fibrosis. Insulin resistance and diabetes cause hepatic fibrosis progression in Hepatitis C patients (12-13).

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The relationship between type 2 DM and cancer is well known. Hyperglycemia and hyperinsulinemia may affect the growth pathways, epigenetic modifications, and changes in mitochondria, causing tumor formation and development (14). Type 2 DM has been shown to increase HCC risk in chronic Hepatitis C patients (15), however, data on its effects on cirrhosis complications in the Hepatitis C subgroup is limited. Therefore, in our study we aimed to investigate the effect of DM on cirrhosis complications, HCC development, and mortality in patients with Hepatitis C-related liver cirrhosis.

MATERIAL and METHODS

Patients admitted with Hepatitis C-related cirrhosis and followed up for at least six months at the İzmir Katip Çelebi University Atatürk Training and Research Hospital Gastroenterology and Internal Medicine Clinic between the years of 2005-2014 were retrospectively evaluated. Patients with additional Hepatitis B virus, alcohol use, HCC detected at admission, and those with follow-up of less than six months were excluded from the study. Hepatic cirrhosis diagnosis was made with patient anamnesis, and clinical, imaging, and laboratory findings. Patients were scored according to encephalopathy, ascites presence, serum albumin, bilirubin ,and prothrombin time. Patients with score of 5-6 were classified CHILD A, 7-9 CHILD B, and 10-12 CHILD C. Patients with and without diagnosis of DM were compared according to CHILD score, HCC development, and mortality. The study was conducted in accordance with the Helsinki Declaration.

Statistical Analysis

Statistical analysis was performed using the SPSS 17 software program. Normal distribution of the variables was assessed using analytical methods. Kaplan Meier Survey analysis and Log Rank test was used to analyze survival between the groups. For parametric data with normal distribution, Student's t-test was used for independent sampling, and Mann-Whitney U test was used to assess data with non-normal distribution. Results were expressed as frequency and percentage for categorical variables, and for continuous variables, mean ± standard deviation for variables with normal distribution, and median (min-max) for variables without normal distribution. P value of <0.05 was considered statistically significant.

RESULTS

A total of 146 patients diagnosed with HCV-related cirrhosis were included in the study. Of these patients, 53 (36.3%) had DM diagnosis. Comparison of gender, age at HCV diagnosis, age at cirrhosis diagnosis, and log HCV-RNA between the patients with and without DM diagnosis and incidence of macrovascular and microvascular complications in diabetic patients is presented in Table 1.

Patients with and without DM diagnosis were compared in terms of CHILD stage, CHILD score, rate of CHILD score increase, HCC development, and mortality. Patients with DM diagnosis had longer follow-up period compared to those without DM (p=0.014). There was no statically significant difference between the groups according to CHILD stage, CHILD score, annual CHILD increase, HCC development age, and mortality. The results of these comparisons are presented in Table 2.

Of the 146 patients included in the study, 38 developed HCC during the follow-up period; prognostic characteristics of patients who did not develop HCC were examined separately. Of the patients without HCC development, 38 had DM diagnosis and 70 did not. These patients were compared according to CHILD score and annual increase in CHILD score. Mean CHILD score at last admission (p=0.024), difference between mean CHILD scores at last and initial admission (p=0.011), and annual increase in CHILD score (p=0.047) were significantly higher in patients diagnosed with DM. The results are presented in Table 3.

There was no statistically significant difference between patients with and without DM diagnosis according to both HCC development time (p=0.567) and survival (p=0.115) following HCV-related cirrhosis diagnosis. These findings are presented in Figure 1 and Figure 2, respectively.

Table 1. General characteristics of patients

		DM diagnosis n:53	No DM diagnosis n:93	p
Gender				
	Male	28 (52.8)	50 (53.8)	
	Female	25 (47.2)	43 (46.2)	
HCV diagnosis age		63.8±9.8	63.6±11.1	0.920
Cirrhosis diagnosis age		65.3±9.1	64.6±11	0.654
Log HCV-RNA		6±0.7	5.6±0.8	0.053
Macrovascular complications		11 (20.8)		
Microvascular complications		32 (60.4)		

Data is appropriately presented as n (%) or mean (±SD)

Table 2. Comparison of cirrhosis complications, HCC development, and mortality between patient groups

	DM Diagnosis	No DM Diagnosis	P value
Follow-up period (months)	42.6±28.3	30.1±25.5	0.014*
Mortality age (years)	69.8±8.6	67.7±10.7	0.220
HCC onset age	69.2±7.5	67.4±8.6	0.260
CHILD stage (admission) A/B/C	44/8/1	64/19/5	0.400
CHILD initial	5.75±1.2	6.1±1.5	0.137
CHILD final	8.1±2.5	7.4±2.1	0.084
CHILD increase/year	0.5±0.9	0.3±0.7	0.280

*P<0.05

Table 3. CHILD score and increase in patients who did not develop HCC

	DM Diagnosis n:38	No DM Diagnosis n:70	P value
Gender			
Male	17 (44.7)	30 (42.9)	0.99
Female	21 (55.3)	40 (57.1)	
CHILD initial	5.9±1.3	6.1±1.5	0.284
CHILD final	8.2±2.7	7.2±2.1	0.024*
CHILD increase/year	2.4±2.2	1.4±1.7	0.011*
CHILD initial	0.7±1	0.3±0.7	0.047*

*p<0.05
Data is appropriately presented as n (%) or mean (±SD)

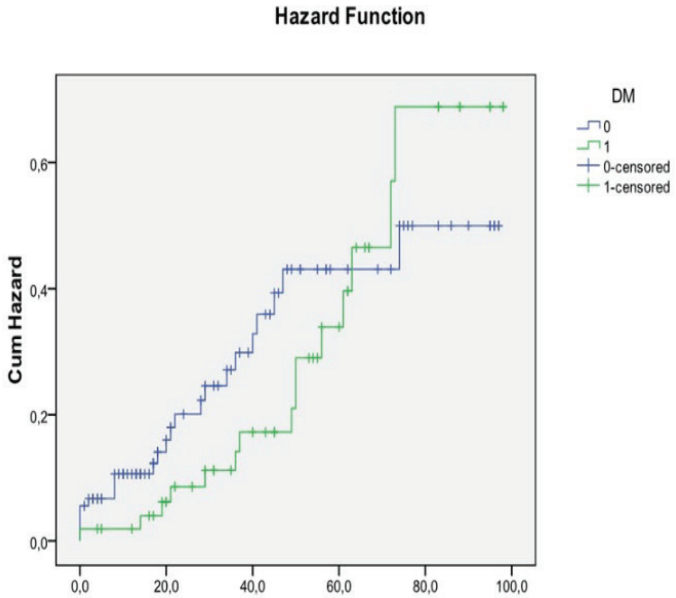

Figure 1. HCC development time following HCV-related cirrhosis diagnosis in patients with and without DM

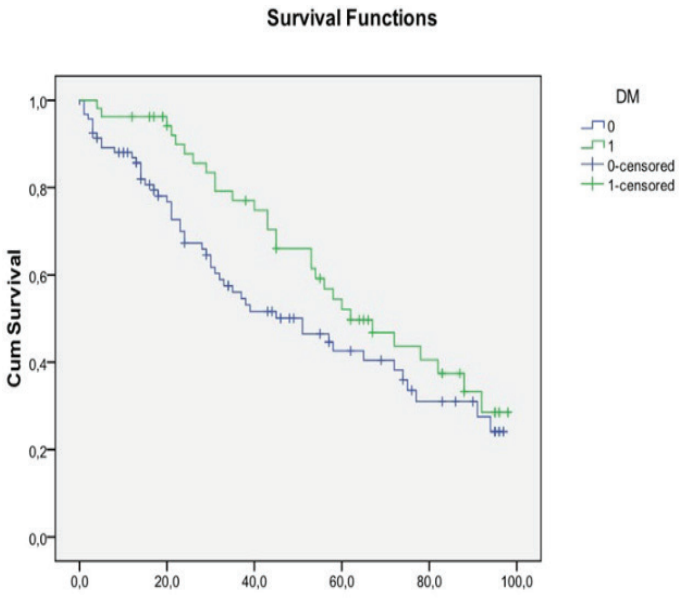

Figure 2. Exitus time following HCV-related cirrhosis diagnosis in patients with and without DM

DISCUSSION

Chronic hepatitis C infection increases risk of DM. At the same time, a relationship between DM and serious fibrosis, HCC frequency, increase in other complications, and decreased survival has been found in chronic hepatitis C patients (16). In our study, annual increase in CHILD score, and final CHILD score was significantly higher in the DM non-HCC subgroup, while HCC development and survival were found to be similar among all patient groups.

Epidemiological studies have demonstrated that in patients with DM and chronic HCV infection, there was a 2-3 times increased risk of HCC independent of whether or not patients underwent curative hepatectomy or antiviral treatment (15,17,18,20). According to a population-based study that used data from the SEER Medicare database, DM patients with chronic hepatitis C had 2-3 times increased risk of HCC (21). One European study that followed-up 541 chronic hepatitis C patients for 5 years reported that HCC occurred in 11.4% of DM patients and 5.0% of non-DM patients (22). A Japanese study found 9.5% risk of HCC development in patients diagnosed with DM, and 2% without DM diagnosis, in a 5-year follow-up period of 279 hepatitis C patients without cirrhosis development. Patients with ISHAK fibrosis score of 4.5 and 6 were included in the aforementioned study (23). However, in a study comprised of 54,979 patients, Type 2 DM only increased HCC risk in HCV-negative patients (RR, 2.08; %95 CI, 1.03–4.18) (24). In our study, HCC development time following HCV diagnosis was similar in both patient groups with and without DM diagnosis (p=0.363). While a majority of studies found that DM increased HCC risk, our study found similar HCC risk in both DM and non-DM groups. In addition to the fact that HCC development requires a long period of time, our study differed from other studies in that cirrhosis patients were included and that cirrhosis-related complications decreasing survival may have prevented this difference from emerging.

Cirrhosis due to any reason has been shown to increase DM complications and decrease survival (25, 26). DM may aggravate hepatic inflammation and cause serious liver damage by inducing fibrosis (27).One population study on 7000 people showed that type 2 DM caused 2.52 times increased 5-year mortality (28). Quintana Jo et al. conducted a study on 110 compensated cirrhosis patients and found that CHILD score, complications, and mortality were significantly higher in DM patients. Multivariate analysis had been unable to show effect of DM alone on mortality (29). In our study, however, only HCV-related cirrhosis patients were included. In our study, while there was no significant difference between DM and non-DM groups according to mortality, annual CHILD score progression (p=0.047) and CHILD score at final admission (p=0.024) was significantly higher in the DM group without HCC diagnosis. At the same time, follow-up period was significantly longer in the DM group (p=0.014). However, this difference may be attributed to DM patients having been followed-up for a longer period of time. In addition, DM not having effect on mortality in this study may be due to inclusion of both compensated and decompensated cirrhosis patients and the fact that cirrhosis and decompensated cirrhosis are directly associated with decreased survival may have surpassed its effect on DM.

Limitations of our study included oral glucose tolerance test (OGTT) not performed on the non-DM group, in which patients with impaired glucose tolerance may have been included in the study. Other limitations were that DM patients had longer follow-up period, and that the study was of retrospective design. In addition, since the number of diabetic patients was small, subgroup analysis could not be performed according to the treatment (metformin, sulfonylurea, insulin, etc.). Strengths of our study were that all patients were HCV-RNA positive cirrhotic patients, and that patients had not received HCV treatment. This provided the opportunity to study the effects of a multisystemic and immunosuppressive disease such as DM on untreated individuals only infected with HCV.

CONCLUSION

In conclusion, while annual increase in CHILD score and final CHILD score was found to be higher in the DM non-HCC subgroup, HCC development and overall survival was similar in all patient groups. There is need for further prospective studies on larger numbers of patients in order to examine the effects of DM on cirrhosis complications, HCC, and mortality, especially in patients with HCV-related cirrhosis.

Competing interests: The authors declare that they have no competing interest.
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REFERENCES

1. Davis GL, Albright JE, Cook SF. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl 2003;9:3318.
2. Global surveillance and control of hepatitis C. Report of a WHO consultation organized in collaboration with the viral hepatitis prevention board, antwerp, belgium. J Viral Hepat 1999;6:3547.
3. WHO. Hepatitis C: Fact sheet N°164.
4. Serfaty L. Metabolic Manifestations of hepatitis c virus: diabetes mellitus, dyslipidemia. Clin Liver Dis 2017;21:475-86.
5. Noto H, Raskin P. Hepatitis C infection and diabetes. J Diabetes Complications 2006;20:113-20.
6. Elkrief L, Rautou PE, Sarin S. Diabetes mellitus in patients with cirrhosis: clinical implications and management. Liver Int 2016;36:936-48.
7. de Marco R, Locatelli F, Zoppini G. Cause-specific

mortality in type 2 diabetes. The Verona diabetes study. Diabetes Care 1999;22:756–61.
8. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460–8.
9. Zoppini G, Fedeli U, Gennaro N. Mortality from chronic liver diseases in diabetes. Am J Gastroenterol 2014;109:1020–5.
10. Seki E, Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. Hepatology 2015;61:1066–79.
11. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 2011;11:98–107.
12. Petta S, Camma C, Marco VD, et al. Insulin resistance and diabetes increase fibrosis in the liver of patients with genotype 1 HCV infection. Am J Gastroenterol 2008;103:1136–44.
13. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. Gastroenterology 2003;124:97–104.
14. Stanley S. Schwartz, Struan FA. et al. Intersections and clinical translations of diabetes mellitus with cancer promotion, progression and prognosis, Postgraduate Medicine. Accepted article: August 15, 2019. Published online: Sep 5,2019.
15. Dyal HK, Aguilar M, Bartos G, et al. Diabetes mellitus increases risk of hepatocellular carcinoma in chronic hepatitis C virus patients: a systematic review. Dig Dis Sci 2016;61:636-45.
16. Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review. 2017;23:1697-711.
17. Perz JF, Armstrong GL, Farrington LA. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529–38.
18. Wang YG, Wang P, Wang B. Diabetes mellitus and poorer prognosis in hepatocellular carcinoma: a systematic review and metaanalysis. PloS ONE 2014;15;9:95485.
19. Huang, Lin TS, Shyu CL, Chiu YC, et al. Diabetes, hepatocellular carcinoma, and mortality in hepatitis C-infected patients: A population-based cohort study. J Gastroenterol Hepatol 2016;32:1355–62.
20. Li X, Xu H, Gao Y, et al. Diabetes mellitus increases the risk of hepatocellular carcinoma in treatment-naive chronic hepatitis C patients in China. Medicine 2017;96:6508.
21. Davila JA, Morgan RO, Shaib Y. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut. 2005;54:533–9.
22. Veldt BJ, Chen W, Heathcote EJ, et al. Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. Hepatology 2008;47:1856–62.
23. Tazawa J, Maeda M, Nakagawa M, et al. Diabetes mellitus may be associated with hepatocarcinogenesis in patients with chronic hepatitis C. Dig Dis Sci 2002;47:710-5.
24. Lai MS, Hsieh MS, Chiu YH. Type 2 diabetes and hepatocellular carcinoma: A cohort study in high prevalence area of hepatitis virus infection. Hepatology 2006;43:1295–302.
25. Petrides AS, Stanley T, Matthews DE, et al. Insulin resistance in cirrhosis: prolonged reduction of hyperinsulinemia normalizes insulin sensitivity. Hepatology 1998;28:141-9.
26. Holstein A, Hinze S, Thiessen E. Clinical implications of hepatogenous diabetes in liver cirrhosis. J Gastroenterol Hepatol 2002;17:677-81.
27. Roden M. Mechanisms of Disease: hepatic steatosis in type 2 diabetes pathogenesis and clinical relevance. Nat Clin Pract Endocrinol Metab 2006;2:335-48.
28. Trombetta M, Spiazzi G, Zoppini G. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. Aliment Pharmacol Ther 2005;2:24-7.
29. Quintana JO, García-Compean D, González JA, et al. The impact of diabetes mellitus in mortality of patients with compensated liver cirrhosis a prospective study. Ann Hepatol 2011;10:56-62.