Brief Communications

Association of liver cirrhosis severity with type 2 diabetes mellitus in hepatocellular carcinoma

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Impact statement

We have explored the association of type 2 diabetes mellitus (T2DM) on liver cirrhosis severity along with response toward sorafenib in hepatocellular carcinoma (HCC). Most HCC patients exhibit prior history of liver cirrhosis that results following long span of chronic liver disease. T2DM constitutes as an important risk factor for HCC development which is known to elevate its incidence. Further, sorafenib is the FDA approved therapy for HCC whose therapeutic outcome is not investigated in HCC patients with T2DM till date. This observation-based study has unveiled a positive association between T2DM and severity of liver cirrhosis as well as sorafenib response in HCC as examined in a clinical setting.

Abstract

Type 2 diabetes mellitus (T2DM) is a major risk factor associated with hepatocellular carcinoma (HCC). However, the association of T2DM with liver cirrhosis and therapy response in HCC patients is not clear. Hence, in this study, we have evaluated the influence of T2DM on liver cirrhosis severity of HCC and sorafenib response. HCC patients were divided in two groups: T2DM ($n = 20$) and non-T2DM (nT2DM; $n = 50$). We found significantly higher number of patients in T2DM group had decompensated liver disease with Child–Turcotte–Pugh score ≥ 7. Additionally, 71.4% patients were observed to be sorafenib sensitive in T2DM group which was significantly higher as compared to 30% in nT2DM group. This study has highlighted the predisposition of HCC patients with T2DM toward more severe liver disease who were found to be better respondents of sorafenib.

Keywords: Type 2 diabetes mellitus, hepatocellular carcinoma, cirrhosis, sorafenib

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Introduction

Hepatocellular carcinoma (HCC) most often develops in patients with liver cirrhosis. Liver cirrhosis exhibits major impact on hepatic reserve and is frequently an essential cause of the morbidity and mortality related to HCC. Thus, the presence and assessment of cirrhosis severity is fundamental for HCC patients in order to assess disease prognosis and make treatment recommendations accordingly.[1,2] Further, HCC has been allied to a number of comorbidities including hypertension, arrhythmias, chronic bronchitis, and diabetes mellitus (DM). DM is the chronic metabolic disorder which is usually characterized by hyperglycemia. Type 2 diabetes mellitus (T2DM) has been demonstrated to be one of the predominant risk factors for HCC development which is known to elevate its incidence by two to four fold.[3] Additionally, DM is also very frequent in patients with liver cirrhosis.[4] However, association of liver cirrhosis severity, T2DM, and HCC is relatively unknown.

Patients with T2DM in many non-HCC cancers have been linked to inferior response towards systemic therapy.[5] Sorafenib is the only approved drug for the management of advanced HCC. It is a multikinase inhibitor which is known to inhibit the mitogen-activated protein kinase and vascular endothelial growth factor pathway genes thereby impeding proliferation as well as angiogenesis.[6]

Therapeutic effect of sorafenib may be influenced by various underlying factors like tumor status, liver functionality, and co-morbid illness.[3] T2DM is known to influence therapeutic efficacy of sorafenib in patients with metastatic renal cell carcinoma (RCC).[7] Although sorafenib has been proved to be safe for patients with advanced HCC and RCC having T2DM,[8] the data relating HCC, T2DM, liver cirrhosis severity, and sorafenib response is lacking till date. In this study, we investigated the status of liver cirrhosis and sorafenib response in HCC patients with T2DM.

Materials and methods

A retrospective study approved by Institute's Ethics Committee (NK/1228/PhD/20418, date: 8/11/2013) was performed examining medical record of confirmed HCC patients recruited between November 2013 to April 2015 in PGIMER, Chandigarh, India. Informed consent was collected from all participants. Total HCC patients (n = 70) were classified either under T2DM (n = 20) or non-T2DM (nT2DM; n = 50) group based on their medical history, before the commencement of sorafenib therapy. Estimation of blood sugar was performed in the clinical laboratories of PGIMER, Chandigarh. Patients with fasting plasma glucose over 126 mg/dL were designated as hyperglycemic.

The drug response was calculated for viable target lesions following modified response evaluation criteria in solid tumors.[9] Responses to treatment were characterized as complete response, partial response, stable disease, and progressive disease (PD). Patients having PD despite sorafenib treatment were considered as sorafenib resistant and rest as sorafenib sensitive.

Statistical data analysis was performed using GraphPad Prism 6.01 (GraphPad Software, Inc., La Jolla, CA, USA) software for Windows. Chi square and Fisher's exact tests were used to statistically compare different clinical parameters of the two study populations. A p value < 0.05 was considered as significant. However, student's t-test was used to compare the alpha fetoprotein (AFP) levels between the two groups. Similarly, variation in random blood glucose concentration in T2DM patients after three months of treatment with or without sorafenib was statistically examined using t-test.

Results

The clinical parameters of all patients are presented in Table 1. The median age was 58 years for the T2DM group (range 41–73 years) and 60 years for the nT2DM group (range 30–84 years). The T2DM group consisted of 88.2% males and 11.8% females, while the nT2DM group consisted of 86.8% males and 13.2% females. Majority of HCC patients with T2DM (70.5%) had diabetic background running for 10+ years time period. The treatment details of HCC patients with T2DM are oral hypoglycemic agents including glimepiride (21%), metformin (55%), and exogenous insulin (24%). Along with these antidiabetic drugs, diabetic diet was also recommended in 13% of the total T2DM patients. Hepatitis C virus (HCV) infection and non-alcoholic steatohepatitis etiology (NASH) were significantly more common in T2DM patients.

Table 1. Clinical characteristics of T2DM versus nT2DM HCC patients.

	T2DM	nT2DM	p-value
Number	20	50	–
Age (median)(range, yrs)	58 (41–73)	60 (30–84)	–
Gender (M:F)	15:2	46:7	–
Mean duration of diabetes (years)	11.7± 5.2	–	–
Etiology, n (%)			
HBV	6 (30%)	15 (30%)	1.0000
HCV	12 (60%)	15 (30%)	0.0198
Alcohol	9 (45%)	30 (60%)	0.2537
NASH related	4 (20%)	0	0.0053
Metastasis, n (%)			
Yes	7 (35%)	15 (30%)	0.6839
No	13 (65%)	35 (70%)	0.6839
CTP score, n (%)			
< 7	9 (45%)	36 (72%)	0.0332
≥ 7	11 (55%)	14 (28%)	0.0332
Child Pugh class, n (%)			
A	5 (25%)	28 (56%)	0.0373
(B+C)	15 (75%)	22 (44%)	0.0373
Sorafenib administration, n (%)			
Received	7 (35%)	23 (46%)	0.4008
Sorafenib sensitive	5 (71.4%)	7 (30%)	0.0396
Sorafenib resistant	0	10 (44%)	0.0396
Not received	13 (65%)	27 (54%)	0.4008

AFP: alpha fetoprotein; CTP: Child–Turcotte–Pugh; F: female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; M: male; NASH: non-alcoholic steatohepatitis; nT2DM: non-Type 2 diabetes mellitus; T2DM: Type 2 diabetes mellitus; yrs: years.
Chi square and Fisher's exact test were used to statistically compare different clinical parameters of the two study populations ($p < 0.05$ was considered significant).

There was negligible difference in the number of patients with metastasis in T2DM as compared to nT2DM group. However, 55% (n = 11/20) of the T2DM patients had decompensated liver disease as compared to 28% (n = 14/50) nT2DM patients (Child–Turcotte–Pugh (CTP) score ≥ 7 T2DM 55% versus nT2DM 28%; p = 0.0332). Likewise, significantly increased number of patients belonged to Child Pugh B + C class in T2DM group (n = 15/20; 75%) than in nT2DM group (n = 22/50; 44%). Further, mean AFP levels were found to be elevated in T2DM patients (307 ng/mL) as compared to nT2DM patients (102 ng/mL) (Figure 1).

Out of 20 T2DM patients, seven (35%) received sorafenib, whereas 23/50 patients (46%) received sorafenib in nT2DM group. Five out of seven patients (71.4%) were observed to be sorafenib sensitive in the former group and seven out of 23 patients (30%) in the latter group. Sixty percent sorafenib-sensitive patients (n = 3/5) in T2DM group were on insulin therapy while the remaining (40%) were on OHAs out of which 16% were on metformin. Interestingly, all sorafenib-sensitive patients of T2DM group were found to be hyperglycemic from the onset of treatment. However, a significant reduction in blood glucose level was observed in all the sorafenib-treated patients (n = 5) as compared to the patients (n = 15) who were not treated with sorafenib in T2DM group after three months (Figure 2). Surprisingly, one of them also experienced hypoglycemia.

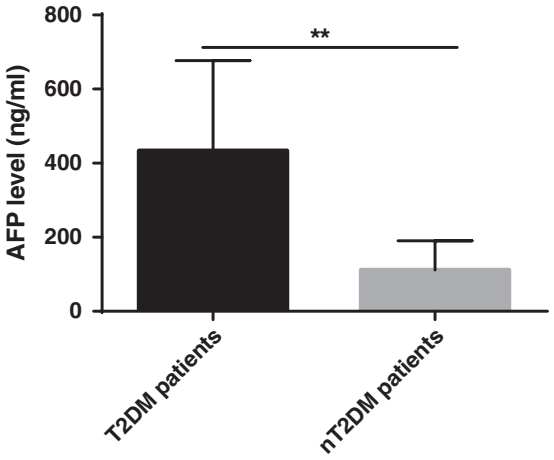

Figure 1. AFP level difference in T2DM versus nT2DM HCC patients (** $p < 0.01$). AFP: alpha fetoprotein; nT2DM: non-Type 2 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

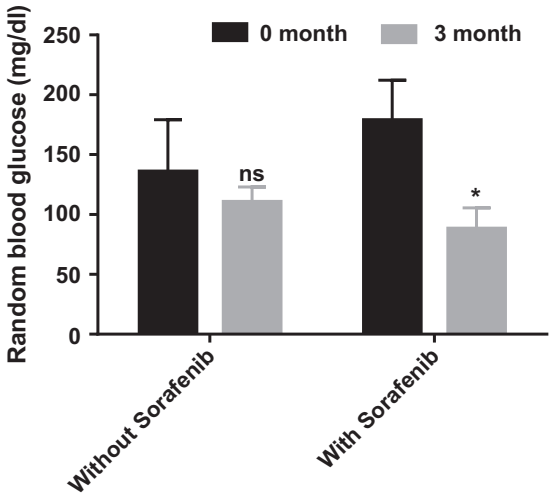

Figure 2. Variation in random blood glucose concentration in T2DM patients after three months of treatment (with and without sorafenib) (*$p < 0.05$).

Further, no T2DM patient was found to be sorafenib resistant while 40% ($n = 10/23$) patients who received sorafenib were assessed to be sorafenib resistant in nT2DM group. Response evaluation could not be performed for two patients in T2DM group and six patients in nT2DM group administered with sorafenib due to the lack of follow-up.

Discussion

The overall prevalence of T2DM in our study population was 28.6%. This study has demonstrated that significantly higher percentage of patients in T2DM group had decompensated liver disease indicating increased severity of liver cirrhosis as assessed by their CTP score and child pugh classification. This suggests higher prevalence of decompensated liver disease in HCC patients with T2DM in the present study. Etiological factor might play a vital role in association of liver cirrhosis severity and T2DM in HCC patients. HCV infection is known to result in an increased oxidative stress leading to severe liver damage resulting in enhanced cirrhosis.[10] In our study, we found that HCV infection was significantly more common in T2DM group which might be the reason behind extended cirrhosis. In previous studies, patients with decompensated cirrhosis have been shown to have decreased survival rate in HCC.[11] Besides, a study has shown an inverse proportionality relationship between AFP and survival across all BCLC stages of HCC.[12] In our study, we found a significant increase of AFP level by 3.5-folds in T2DM patients as compared to nT2DM patients. A previous study has associated DM with lower survival rate of HCC patients belonging to BCLC stage A and B.[13] Seventy percent of HCC patients with T2DM group belonged to BCLC A and B stages in our study population. This suggests that the increased level of cirrhosis along with enhanced serum AFP level in HCC patients with T2DM may result in poor survival rate.

Further, estimation of response toward sorafenib in HCC patients having T2DM has not been well defined till now. However, sorafenib was demonstrated to be safe and effective in both diabetic as well as in non-diabetic HCC patients.[8] In our study, it was observed that percentage wise sorafenib-sensitive patients were higher in T2DM as compared to nT2DM group. All these patients were hyperglycemic at the onset of the treatment indicating poor glucose utilization which might be linked to down-regulated glycolysis.[14] Although after three months of sorafenib treatment, their blood glucose level decreased significantly demonstrating enhanced glucose utilization. This decrease in blood glucose level might be due to the enhancement of glycolysis by sorafenib.[15] Hence, there is a need for vigilant blood glucose monitoring during the administration of sorafenib in HCC patients with T2DM.

Further, a study by Casadei Gardini *et al*.[16] has demonstrated that diabetic patients treated with insulin were found to be less resistant to sorafenib than those treated with metformin. Similarly, in our study, we also observed that higher percentage of sorafenib-sensitive patients (60%) in T2DM group received insulin for controlling diabetes. Additionally, insulin is known to exert mitogenic as well as antiapoptotic effects. Besides, it can also escalate the bioavailability of insulin-like growth factor-1 thereby assisting in cancer growth.[17] However, this observation may infer that insulin might have increased cell membrane permeability leading to enhanced sorafenib uptake by tumor cells thus increasing its anticancer efficacy.[18] However, the mechanisms underlying the combinatorial effects of insulin and sorafenib are required to be investigated.

In conclusion, although tumor progression in terms of metastasis was found to be alike in both T2DM as well as nT2DM group, severe liver cirrhosis was observed in HCC patients with T2DM. This implies that T2DM might not effect HCC progression but may result in extended liver damage in terms of severe cirrhosis. On the other hand, sorafenib was found to be more effective in T2DM patients since higher percentage of sensitive patients were observed in this group. Thus, this study has shed more light on the association of T2DM on severity of liver cirrhosis and

sorafenib response in HCC. However, some limitations of the current study need to be taken under consideration. First, it is an observational study conducted in a retrospective manner with small sample size that needs to be confirmed in the larger cohorts. Second, multiple confounding factors may be associated with sorafenib response, all of which could not be considered in this study. Thus, stratified prospective studies on this important issue are needed in order to consolidate the findings of this observational study.

AUTHORS' CONTRIBUTIONS: AM and SK participated in study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. RKD participated in study concept and design, study supervision, data interpretation, and critical review of the manuscript for important intellectual content. NK and YKC participated in interpretation of data and review of manuscript. AC participated in study concept and design, analysis and interpretation of data, study supervision, drafting of the manuscript, and critical review of the manuscript for important intellectual content.

DECLARATION OF CONFLICTING INTERESTS

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REFERENCES

1. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;**127**:S35–50
2. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open* 2016;**1**:e000042
3. Amarapurkar DN, Patel ND, Kamani PM. Impact of diabetes mellitus on outcome of HCC. *Ann Hepatol* 2008;**7**:148–51
4. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. *WJG* 2009;**15**:280–8
5. Richardson LC, Pollack LA. Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Prac Oncol* 2005;**2**:48–53
6. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378–90
7. Procopio G, Bellmunt J, Dutcher J, Bracarda S, Knox J, Brueckner A, Molnar I, Escudier B, Hutson TE. Sorafenib tolerability in elderly patients with advanced renal cell carcinoma: results from a large pooled analysis. *Br J Cancer* 2013;**108**:311–8
8. Imarisio I, Paglino C, Ganini C, Magnani L, Caccialanza R, Porta C. The effect of sorafenib treatment on the diabetic status of patients with renal cell or hepatocellular carcinoma. *Future Oncol* 2012;**8**:1051–7
9. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010;**30**:52–60
10. Hiotis SP, Rahbari NN, Villanueva GA, Klegar E, Luan W, Wang Q, Yee HT. Hepatitis B vs. hepatitis C infection on viral hepatitis-associated hepatocellular carcinoma. *BMC Gastroenterol* 2012;**12**:64
11. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;**44**:217–31
12. Gomaa AI, Hashim MS, Waked I. Comparing staging systems for predicting prognosis and survival in patients with hepatocellular carcinoma in Egypt. *PLoS One* 2014;**9**:e90929
13. Su YW, Liu PH, Hsu CY, Lee YH, Hsia CY, Ho SY, Hou MC, Chen HS, Huo TI. Prognostic impact of diabetes mellitus on hepatocellular carcinoma: Special emphasis from the BCLC perspective. *PLoS One* 2017;**12**:e0174333
14. Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Patel N, Madan A, Amarapurkar A. Hafeezunnisa. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *J Gastroenterol Hepatol* 2004;**19**:854–8
15. Tesori V, Piscaglia AC, Samengo D, Barba M, Bernardini C, Scatena R, Pontoglio A, Castellini L, Spelbrink JN, Maulucci G, Puglisi MA, Pani G, Gasbarrini A. The multikinase inhibitor Sorafenib enhances glycolysis and synergizes with glycolysis blockade for cancer cell killing. *Sci Rep* 2015;**5**:9149
16. Casadei Gardini A, Marisi G, Scarpi E, Scartozzi M, Faloppi L, Silvestris N, Masi G, Vivaldi C, Brunetti O, Tamberi S, Foschi FG, Tamburini E, Tenti E, Ricca Rosellini S, Ulivi P, Cascinu S, Nanni O, Frassineti GL. Effects of metformin on clinical outcome in diabetic patients with advanced HCC receiving sorafenib. *Expert Opin Pharmacother* 2015;**16**:2719–25
17. Key TJ. Diet, insulin-like growth factor-1 and cancer risk. *Proc Nutr Soc* 2011;**3**:1–4.
18. Damyanov C, Gerasimova D, Maslev I, Gavrilov V. Low-dose chemotherapy with insulin (insulin potentiation therapy) in combination with hormone therapy for treatment of castration-resistant prostate cancer. *ISRN Urol* 2012;**2012**:140182

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