Diabetes mellitus is a predictive factor for longer overall survival in patients with Hepatitis-C Virus-induced hepatocellular carcinoma with or without curative therapy.

Juliane Heeren*, Thomas Gamstaetter*, Sandra Koch, Jens Uwe Marquardt, Marc Nguyen-Tat, Ina Maria Niederle, Marcus Schuchmann, Peter Robert Galle, Arndt Weinmann, Marcus-Alexander Woerns

Department of Internal Medicine I, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

* Authors contributed equally to this work.

Introduction

Chronic hepatitis-C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC) in the western world. Increasing evidence has linked HCV infection with the development of insulin resistance and diabetes mellitus. HCV patients with impaired glucose metabolism show more rapid progression to cirrhosis and HCC. However, the clinical relevance and the impact on survival of diabetes in HCC-patients with chronic HCV infection are insufficiently defined.

Methods

We retrospectively analyzed data of 241 patients with HCV-associated hepatocellular carcinoma with and without diabetes treated at our center since 2003.

Demographics	All patients	HCV Diabetes	HCV no Diabetes	p (fisher exact)
Total number	241	57	184	
Median age at diagnosis (range)	63.6 (36.1-86.1)	63.3 (36.1-86.1)	63.6 (43.2-84.9)	0.52
Overweight (%)	45 (18.7)	18 (31.6)	27 (14.7)	0.02
Median BMI (range)	26.6 (0-48.4)	29.6 (20.9-48.4)	26.2 (0-38.1)	0.02
Male	171 (71)	38 (66.7)	133 (72.3)	0.58
Female	68 (28.2)	17 (29.8)	51 (27.7)	
HCV Therapy (%)	39 (16.2)	14 (24.6)	25 (13.6)	0.79
OLT (%)	54 (22.4)	13 (22.8)	41 (22.3)	0.29
Resection (%)	28 (11.6)	2 (3.5)	26 (14.1)	0.89

Fig. 1: Demographics, rates of LTX and resection

Comorbidities (%)	All patients	HCV Diabetes	HCV no Diabetes	p (fisher exact)
Renal failure	20 (8.3)	5 (8.8)	15 (8.2)	0.51
Myocardial infarction	7 (2.9)	4 (7)	3 (1.6)	0.70
Stroke	0 (0)	0 (0)	0 (0)	0.70
CAD	12 (5)	5 (8.8)	7 (3.8)	0.89
Depression	5 (2.1)	3 (5.3)	2 (1.1)	0.79
Drugs (%)				
Insulin	46 (19.1)	38 (66.7)	8 (4.3)	< 0.001
Statins	13 (5.4)	6 (10.5)	7 (3.8)	0.70
Metformin	6 (2.5)	6 (10.5)	0 (0)	0.52
ACE-inhibitors	28 (11.6)	12 (21.1)	16 (8.7)	1.00

Fig. 2: Comorbities and comedication

Results

Of 241 HCV-HCC patients analyzed, 57 (23.7%) showed concomitant diabetes mellitus according to WHO standards. Median OS for diabetic vs non-diabetic HCV-HCC patients in total was 28.1 vs 15.5 months (0.95 CI 20.4-48.3 vs 12.5-21.9). Median OS for HCV-HCC patients not eligible for liver transplantation (LTX) was 23.7 vs 11.6 months (0.95 CI 17.68-32.0 vs 9.17-14.2), respectively. Median age at initial diagnosis of HCC, severity of liver disease, male:female ratio and BCLC tumor stage showed no significant differences between the groups. Overweight was more abundant in diabetic patients (29.6% vs 13.3%) with a median BMI of 28.7 vs 25.5 (p=0,0091). Diabetics were more likely to receive antiviral HCV therapy (19.7% vs 10.4%). Both groups had overtly low rates of cardiovascular comorbidities and appropriate comedication.

Liver Characteristics	All patients	HCV Diabetes	HCV no Diabetes	p (fisher exact)
Portal vein thrombosis (%)	45 (18.7)	8 (14)	37 (20.1)	1.00
Ascites (%)	76 (31.5)	13 (22.8)	63 (34.2)	0.53
Cirrhosis (%)	220 (91.3)	54 (94.7)	166 (90.2)	0.53
No LCI/Child A	128 (53.1)	34 (59.6)	94 (51.1)	0.65
Child B	83 (34.4)	19 (33.3)	64 (34.8)	
Child C	30 (12.4)	4 (7)	26 (14.1)	
Platelets (range)	109 (25-469)	113 (48-469)	106.5 (25-454)	0.94
HCV RNA (range)	3x10^5 (15-9.7x10^6)	8.35x10^5 (15-5.1x10^6)	1.95x10^5 (15-9.7x10^6)	0.29
AST (range)	100 (23-5200)	97.5 (24-377)	100 (23-5200)	0.12
ALT (range)	73 (12-5390)	80.5 (12-421)	68 (18-5390)	0.18
Bilirubin (range)	1.5 (0.3-24.2)	1.2 (0.3-12)	1.5 (0.3-24.2)	0.77
Albumin (range)	33 (17-55.6)	32.4 (23-45)	33 (17-55.6)	0.41
gGT (range)	129.5 (17-1594)	164.5 (30-1594)	122 (17-1445)	0.05
AFP (range)	68.7 (1.9-5.16x10^5)	114.3 (4.5-2.35x10^5)	54.5 (1.9-5.16x10^5)	0.90

Fig. 3: Laboratory values and liver function parameters

Tumor Characteristics	All patients	HCV Diabetes	HCV no Diabetes	p (fisher exact)
Metastatic spread (%)	24 (10)	4 (7)	20 (10.9)	0.69
BCLC A	55 (22.8)	14 (24.6)	41 (22.3)	0.75
BCLC B	38 (15.8)	12 (21.1)	26 (14.1)	
BCLC C	112 (46.5)	25 (43.9)	87 (47.3)	
BCLC D	32 (13.3)	4 (7)	28 (15.2)	0,69
Median tumorsize (range)	3.6 (0-18)	3.6 (1.5-14)	3.6 (0-18)	0.88

Fig. 4: Tumor size and BCLC classification

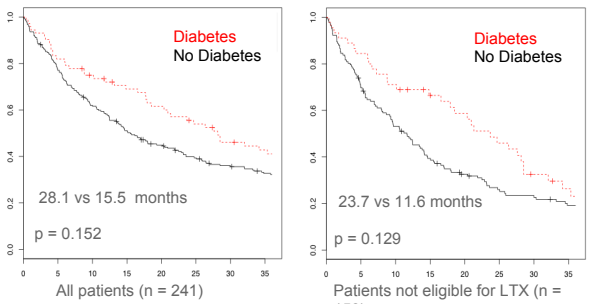

Fig. 5: Survival for patients with HCV-related HCC with or without diabetes.

Conclusion

Although insulin resistance and diabetes mellitus are regarded as predictive factors of poorer disease outcome for patients with chronic HCV infection, diabetes is independently associated with improved overall survival in patients with HCV-associated HCC. Moreover, diabetes mellitus related to HCV infection in HCC patients is accompanied with low rates of cardiovascular morbidity. This data should be confirmed in prospective studies and should stir translational efforts to further investigate the relationship of HCV-HCC, impaired glucose metabolism and patient outcome.