

## Impact of Metformin on the Prognosis of Cirrhosis Induced by Viral Hepatitis C in Diabetic Patients

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**Context:** Insulin resistance plays a role in hepatocarcinogenesis and is decreased by metformin treatment.

**Objective:** The aim of the study was to assess the influence of metformin treatment on the prognosis of compensated hepatitis C virus (HCV) cirrhosis in patients with type 2 diabetes.

**Design and Setting:** We studied an observational prospective cohort (1988–2007) at a university hospital referral center.

**Patients:** A total of 100 consecutive diabetic patients (53 men, age  $61 \pm 11$  yr) with ongoing HCV cirrhosis and no contraindication for metformin were included in a screening program for hepatocellular carcinoma (HCC).

**Main Outcomes:** The patients were prospectively followed up for HCC incidence, liver-related death, or hepatic transplantation.

**Results:** The level of platelet count was significantly lower in patients treated with metformin ( $n = 26$ ) compared with those not treated with metformin ( $n = 74$ ) [117 (interquartile range, 83–166) vs. 149 (105–192) Giga/liter,  $P = 0.045$ ]. During a median follow-up of 5.7 (3.8–9.5) yr, one patient was lost to follow-up, 39 developed a HCC, and 33 died from liver causes or were transplanted. The 5-yr incidence of HCC was 9.5 and 31.2% ( $P = 0.001$ ) and of liver-related death/transplantation, 5.9 and 17.4% ( $P = 0.013$ ), in patients who received metformin treatment and in those who did not, respectively. In multivariate analysis, metformin treatment was independently associated with a decrease in HCC occurrence [hazard ratio, 0.19 (95% confidence interval, 0.04–0.79);  $P = 0.023$ ] and liver-related death or transplantation [hazard ratio, 0.22 (95% confidence interval, 0.05–0.99);  $P = 0.049$ ].

**Conclusions:** In patients with type 2 diabetes and HCV cirrhosis, use of metformin is independently associated with reduced incidence of HCC and liver-related death/transplantation. (*J Clin Endocrinol Metab* 96: 2601–2608, 2011)

Type 2 diabetes mellitus (T2D) and hyperinsulinemia are common in patients with hepatitis C virus (HCV) cirrhosis and are associated with a higher incidence in hepatocellular carcinoma (HCC) (1, 2). HCC occurring in noncirrhotic livers (3) and many epithelial malignancies are also more frequent in patients with T2D than in nondiabetic individuals (4). Increasing data suggest that insulin resistance plays a role in hepatocarcinogenesis through the activation of insulin/IGF-I signaling axis (5) and/or through increased fatty accumulation in the liver (6). Therefore, improving insulin resistance and correcting hyperinsulinemia may be an attractive approach to improve the prognosis of HCV cirrhosis.

In addition to lowering glucose, metformin reduces insulin resistance, especially by decreasing gluconeogenesis (7, 8) and for some fatty liver accumulation (9). In experimental models, metformin was shown to prevent cancer development and to have antioxidant, antiinflammatory, growth inhibitory, and antiangiogenic effects (10, 11). In large observational studies including patients with T2D, the use of metformin was associated with a decreased incidence in various cancers and related mortality (12–16). Furthermore, women with T2D receiving neoadjuvant chemotherapy for breast cancer were reported to have a higher complete response rate if they were using metformin as compared with women not using metformin (17).

In a case-control study, Donadon *et al.* (18, 19) recently reported an inverse association between metformin treatment and HCC in diabetic patients with cirrhosis. Although these data suggested a beneficial effect of metformin on HCC incidence in patients with cirrhosis, no adjustment was made according to clinical and biological confounders that could influence metformin prescription and HCC incidence (18, 19). Therefore, the aim of this longitudinal study was to assess the impact of metformin therapy on outcomes in patients with T2D and compensated HCV cirrhosis who were prospectively screened for HCC detection.

## Patients and Methods

### Patients

Patients were recruited from a prospective cohort of patients who were included in a screening program for HCC detection between January 1988 and January 2007 and presented the following criteria: 1) a compensated, histologically proven cirrhosis (METAVIR F4) and the absence of suspicion of HCC; 2) the presence of anti-HCV antibodies; 3) the presence of serum HCV RNA detected by RT-PCR; 4) the absence of hepatitis B virus, HIV infection, hemochromatosis, biliary cirrhosis, Wilson's disease,  $\alpha$ 1 antitrypsin deficiency; and 5) no severe life-threatening disease including cardiac and renal failures. Patients

who achieved a sustained virological response during the follow-up period were excluded. The objective of the cohort was to evaluate the complications of HCV cirrhosis and their determinants, including age, body mass index (BMI), gender, and liver function (20).

We selected patients with T2D, defined at inclusion as a fasting plasma glucose of at least 7 mmol/liter (126 mg/dl) or by a previous antidiabetic treatment (21). No patient had type 1 diabetes. In our institution, patients with HCV cirrhosis are informed about the potential complications of their disease and are proposed to participate in an observational cohort study to evaluate clinical and biological factors that can impact their prognosis. For that purpose, they sign an informed consent. According to French regulatory law concerning clinical studies, no ethics committee was required for this study because clinical, biological, or biopsy specimens are those performed for the routine management of patients.

### Methods

At inclusion, serum samples were taken after an overnight (12-h) fasting period for routine analyses, including alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyl transferase (GGT), albumin,  $\alpha$ -fetoprotein (AFP), prothrombin activity, platelet count, glycated hemoglobin (HbA1c) (Dimension Technology; Siemens Healthcare Diagnosis Inc., Newark, DE). Glucose value was measured on venous plasma by the glucose oxidase method (colorimetry, Thermolab System; Kone Optima Corp., Paris La Défense, France). Creatinine clearance was calculated according to the Cockcroft formula. All subjects had antibodies against HCV (Monolisa anti-HCV; Sanofi Diagnostics Pasteur, Marnes-la-Coquette, France) and detectable HCV RNA by PCR (Amplicor HCV; Roche Diagnostics, Branchburg, NJ). HCV genotype was measured by reverse hybridization (InnooliPA HCV; Innogenetics NV, Gent, Belgium).

Macrovascular steatosis was evaluated on liver specimens obtained for the diagnosis of cirrhosis and fixed in formalin, embedded in paraffin, and stained with hematoxylin-eosin and Masson's trichrome. Macrovascular steatosis was graded as the percentage of hepatocytes containing macrovascular fat droplets in three classes: less than 10%, 10–30%, and at least 30% of hepatocytes affected. Only biopsies more than 10 mm in length were taken into account ( $n = 91$ ).

### Follow-up

After inclusion, patients were followed at least every 6 months and were screened for HCC by abdominal ultrasonography and serum AFP measurements every 3 to 6 months. Diagnosis of HCC (the primary endpoint) was based on histology or on noninvasive criteria as defined by the European Association for the Study of Liver recommendations (22). The secondary endpoint was a composite of death of liver cause and liver transplantation.

### Statistical analyses

Clinical data of all the patients were prospectively collected in a computerized database. Baseline continuous variables were expressed as means  $\pm$  SD or median (interquartile range). Categorical variables were expressed as frequencies (percentages). Comparisons between groups were performed using the Student  $t$  test or the Mann Whitney test for continuous variables, and the  $\chi^2$  test or the Fisher-exact tests for categorical variables. The

cumulative incidence of HCC and liver-related death or transplantation were compared according to metformin treatment at inclusion using the log-rank test or the Gray test when taking competing risks into account. In addition, univariate Cox regression models were used to identify predictive factors of primary and secondary endpoints. For each endpoint, variables with a *P* value less than 0.10 in the univariate analysis predicting outcomes were entered into stepwise Cox regression multivariate models. For sensitivity analyses, the incidence of HCC was also adjusted on usual risk factors (20) or on Propensity scores (23). The same models considering competing risks were tested using the Fine and Gray test. All tests were two-sided and used a significance level of *P* values 0.05. Analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC) and R 2.8 software (www.r-project.org).

## Results

### Baseline characteristics

Among 112 patients with T2D and HCV cirrhosis and no prospectively screened HCC, we excluded 12 patients who achieved a sustained virological response after one or more treatment courses (Fig. 1). Therefore, 100 patients were included in the current study. Baseline clinical and biological characteristics at the time of inclusion are shown in Table 1. No patient had ascites, lower limb edema, or any condition that could have prevented the use of metformin, such as respiratory, renal, or heart failure.

Diabetes was treated by a practitioner independent of the hepatologist with diet alone (*n* = 29) or with metformin monotherapy (*n* = 23), metformin plus insulin

(*n* = 3), insulin secretagogues (*n* = 17), or insulin therapy (*n* = 28) (Fig. 1). During the follow-up, the patients were addressed to the diabetologist only in cases of very poor glycemic control. Finally, the patients treated with metformin at inclusion stayed under metformin during follow-up, even when another treatment was added. Metformin was not started if it was not used at inclusion. When compared with metformin-treated patients, the group of patients who did not receive metformin had a lower platelet count, were slightly but nonsignificantly older, and more frequently tended to have a history of alcohol abuse (Table 1). Neither HbA1c nor diabetes duration was different in the patients treated with metformin and those who were not.

### HCC development

One patient treated with insulin was lost to follow-up and was excluded at the date of the last visit. During a median follow-up of 5.0 (range, 2.3–8.3) yr, 39 patients developed a HCC. HCC diagnosis was based on histology (*n* = 20) or noninvasive criteria (*n* = 19). Estimated HCC incidence according to metformin treatment is reported in Fig. 2A. The 5-yr occurrence of HCC was 9.5% [95% confidence interval (CI), 0.0–21.4] in metformin-treated patients and 31.2% (95% CI, 18.7–41.8) in those not treated with metformin (*P* = 0.001).

Multivariate Cox regression analysis identified male gender, metformin treatment [hazard ratio (HR), 0.19 (95% CI, 0.04–0.79); *P* = 0.023], and serum GGT and

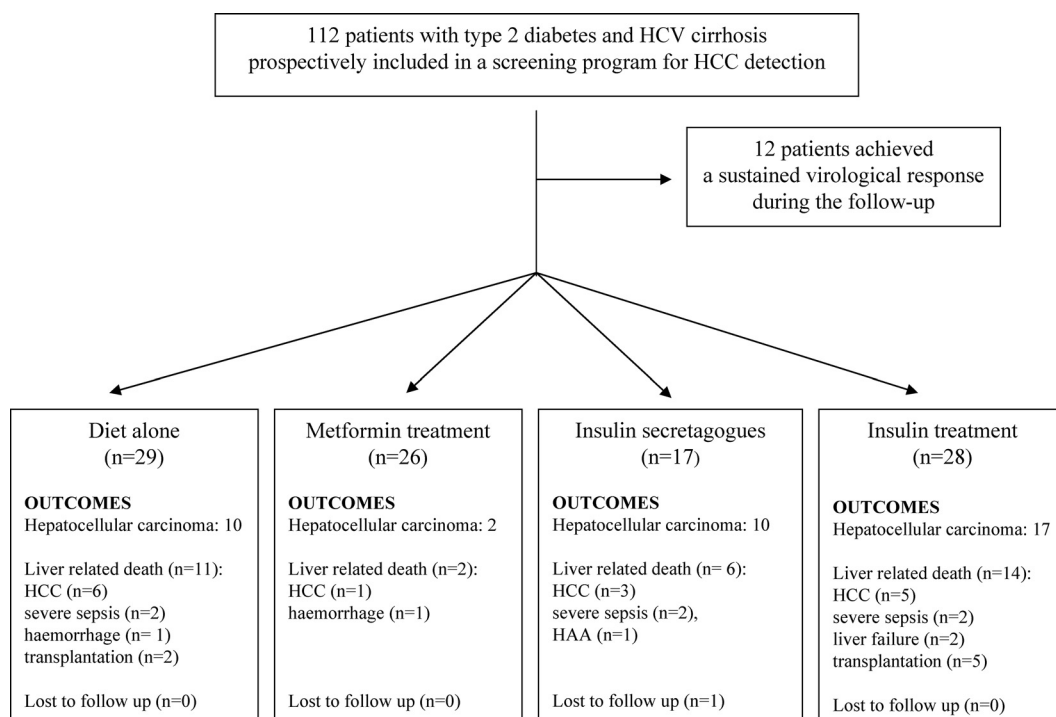


FIG. 1. Patient selection and outcomes. HAA, Acute alcoholic hepatitis.

**TABLE 1.** Baseline characteristics of the whole population and according to metformin treatment

Variables	Whole population	Metformin treatment	No metformin treatment	P value
n	100	26	74	
Age (yr)	61 ± 11	57 ± 8	62 ± 11	0.054
Male gender	53 (53)	13 (50)	40 (54)	0.72
BMI (kg/m <sup>2</sup> )	26 (24–29)	25 (24–28)	26 (24–29)	0.74
Diabetes duration at inclusion (yr) <sup>a</sup>	0 (0–2.7)	0 (0–1.7)	0 (0–2.7)	0.80
HbA1c (%)	6.9 (6.1–7.3)	7.0 (6.4–7.7)	6.9 (6.1–7.2)	0.42
Fasting glucose value (mmol/liter)	7.5 (6.5–9.4)	7.8 (7.0–10.0)	7.2 (6.4–9.3)	0.16
Creatinine clearance (ml/min)	84 (67–104)	89 (78–112)	82 (65–98)	0.09
Past or ongoing alcohol intake	23 (25)	2 (10)	21 (29)	0.09
Prothrombin activity (%)	88 (78–96)	90 (81–98)	87 (78–95)	0.23
Serum albumin (g/liter)	42 (39–44)	41 (40–43)	42 (38–44)	0.76
Serum AST (×ULN)	2.0 (1.3–3.0)	1.5 (1.2–2.2)	2.0 (1.3–3.0)	0.11
Serum ALT (×ULN)	2.5 (1.8–3.0)	2.0 (1.8–3.0)	2.5 (1.8–3.5)	0.52
AST/ALT ratio	0.9 (0.5–1.2)	0.7 (0.5–1.0)	0.9 (0.5–1.2)	0.18
GGT (×ULN)	2.8 (1.9–4.0)	2.6 (2.0–4.5)	3.0 (1.5–3.0)	0.53
Platelet count (Giga/liter)	121 (89–171)	149 (105–192)	117 (83–166)	0.04
Serum bilirubin (μl/liter)	14 (9–26)	13 (9–30)	15 (10–24)	0.28
AFP (ng/ml)	8 (4–12)	7 (4–10)	8 (6–14)	0.16
HCV genotype 1 or 4	86 (86)	23 (88)	63 (85)	1.00
Steatosis				
<10%	38 (42)	8 (31)	30 (46)	0.30
10–30%	36 (39)	11 (42)	25 (39)	
>30%	17 (19)	7 (30)	10 (15)	

Data are expressed as mean ± SD, median (interquartile range), or number (percentage). ULN, Upper normal limit range.

<sup>a</sup> Diabetes was diagnosed at the same time as cirrhosis in the majority of the patients.

AFP levels as independently associated with HCC occurrence (Table 2). We also performed two sensitivity analyses to confirm the association between metformin and the decrease in incidence of HCC. We built another multivariate model in which we adjusted by age, platelet count, BMI, past or ongoing alcohol abuse, and diabetes duration and the variables selected by the stepwise selection procedure (Table 2) and found that metformin treatment was still associated with a reduced incidence of HCC [HR, 0.22 (95% CI, 0.05–0.97);  $P = 0.046$ ]. In addition, using propensity score, we still found an association between metformin use and incidence of HCC [HR, 0.22 (95% CI, 0.05–0.98);  $P = 0.047$ ].

The patients treated with diet alone ( $n = 29$ ) had a similar incidence of HCC as compared with those treated with insulin or insulin secretagogues ( $n = 45$ ) [adjusted HR, 1.38 (95% CI, 0.61–3.17);  $P = 0.44$ ].

### Liver-related death or transplantation

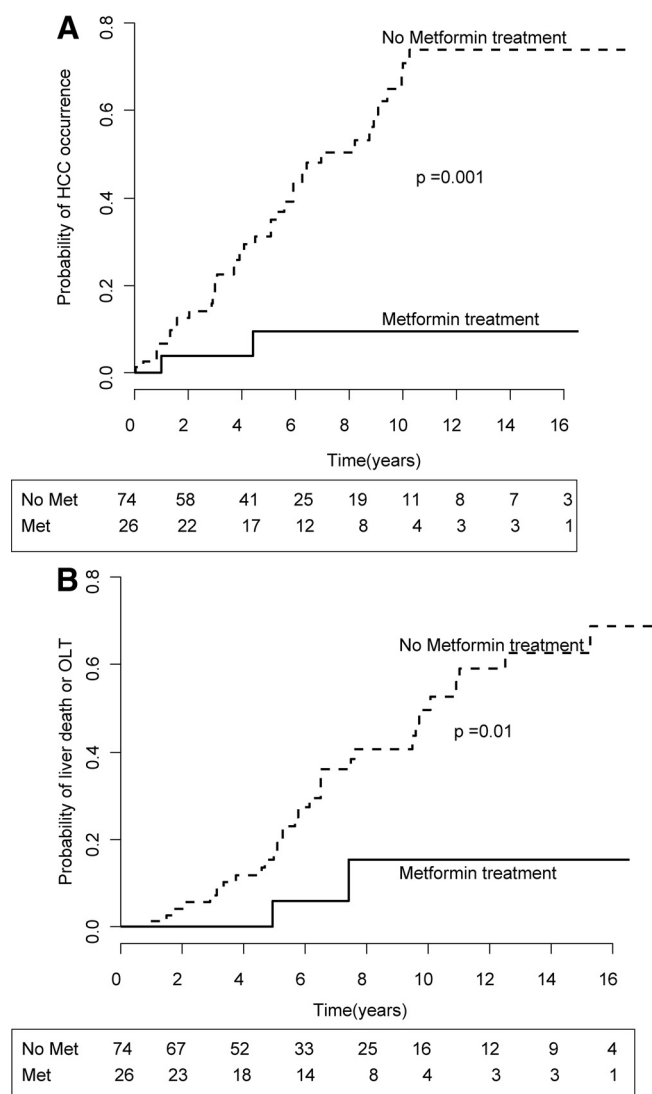
During a median follow-up of 5.7 (range, 3.8–9.5) yr, 26 patients died of liver cause, and seven patients were transplanted (Fig. 1). Liver-related death or transplantation was less frequent in metformin-treated patients than in those not treated with metformin ( $P \leq 0.01$  either considering log-rank or Gray test) (Fig. 2B). The 5-yr incidence of liver-related death/liver transplantation was 5.9 and 17.4% ( $P = 0.013$ ), respectively, in patients who received metformin and in those who did not.

Multivariate Cox regression analysis showed that high alcohol intake, high BMI, metformin treatment [HR, 0.22 (95% CI, 0.05–0.99);  $P = 0.049$ ], diabetes duration, and AST level were independently associated with liver-related death (Table 3). There were some non-liver-related deaths: one subdural hematoma in the diet group; one stroke in the insulin secretagogue group; and one cardiac failure, one breast cancer, and one road traffic crash in the insulin group. For all-cause mortality/liver transplantation, metformin use was associated after adjustment with a low mortality rate as compared with the other groups of patients [HR, 0.17 (95% CI, 0.04–0.70);  $P = 0.01$ ]. When taking into account non-liver-related death as a competing risk, the metformin use was still associated with fewer liver-related deaths [HR, 0.24 (95% CI, 0.06–0.97);  $P = 0.045$ ].

The patients treated with diet alone ( $n = 29$ ) had a similar 5-yr incidence of liver-related death or transplantation compared with those treated with insulin or insulin secretagogues ( $n = 45$ ), 18 and 16%, respectively ( $P = 0.96$ ).

### Discussion

In this cohort of patients with T2D and HCV cirrhosis who were prospectively followed, incident HCC and liver-related death were frequent, and this may be explained by insulin resistance (4). We found that metformin treatment



**FIG. 2.** Cumulative incidence of HCC (A) and liver-related death or liver transplantation (OLT) (B) in the 100 diabetic patients with HCV cirrhosis according to metformin (Met) treatment (n = 26) or no metformin treatment (n = 74).

was independently associated with a decrease in HCC occurrence and with a decreased rate of liver-related death. Our observation is in line with the case control study from Donadon *et al.* (18, 19) who have reported an 85% decrease in HCC in cirrhotic patients treated with metformin in comparison to those treated with insulin or insulin secretagogues. Recent longitudinal studies have shown a decrease in cancer occurrence, cancer mortality, or overall mortality in diabetic patients treated with metformin (16). However, the current study is the first one to show a statistically significant and independent impact of metformin on the prognosis of HCV cirrhosis in patients with T2D.

In addition to metformin, we found that male gender and high GGT and AFP levels were independently associated with HCC incidence, in line with previous studies (20). On the other hand, we did not find any association

of HCC incidence with age, BMI, or platelet count as it was previously reported (20). This is probably because our cohort of patients with T2D was selected and patients were older and had a higher BMI and more advanced cirrhosis than HCV cirrhotic patients without diabetes (1). We excluded patients who achieved a sustained virological response because insulin resistance was shown to decrease after viral clearance (24). Furthermore, sustained virological response strongly impacts the prognosis of those patients (25). In fact, in the present cohort, only one of 12 patients who achieved a sustained virological response (and were then not included) developed HCC.

Our observation has some limitations. Although highly statistically significant, our results are issued from a study including a relatively small and selected population of patients with HCV cirrhosis and T2D and need to be confirmed in larger studies, including patients with other causes of cirrhosis. Neither lipid parameters nor HbA1c change during follow-up was available for enough patients to allow statistical analyses. This study was longitudinal but observational, and the patients were not randomized for metformin treatment. Thus, confounding factors may introduce bias in our results. The choice of an antidiabetic treatment in cirrhotic patients has not been well defined, but usually metformin is less often prescribed in older patients and/or in those with liver or renal impairment or alcohol abuse. However, in the current study, the patients who had any condition that would not allow metformin use, such as renal or cardiac failure, were not included. When compared with metformin-treated patients, the patients who did not receive metformin had a lower platelet count and a trend for higher alcohol consumption and older age. There was no difference in HbA1c level or diabetes duration, which has been suggested to be associated with HCC development (26). However, a higher diabetes duration at inclusion was associated with liver-related death/transplantation. In our study, metformin was still associated with better outcomes after either adjusting on these parameters or using propensity score. Finally, we categorized our patients according to metformin use at inclusion only. It should be noted that none of the patients who were initially treated with metformin stopped this medication during follow-up, and none of those who were not treated with metformin at inclusion received metformin treatment subsequently. This point is partly explained by the fact that the patients were especially followed up by the hepatologist and that cirrhosis prognosis was considered as the priority.

In the past, severe complications such as lactic acidosis had been reported in patients with alcoholic or advanced cirrhosis who had renal failure or who were heavy drink-

**TABLE 2.** Univariate and multivariate analyses of predictors of HCC occurrence

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (yr)	1.01 (0.98–1.04)	0.44		
Male gender	3.15 (1.56–6.37)	0.001	2.66 (1.29–5.48)	0.008
Past and/or daily alcohol intake	2.04 (1.06–3.94)	0.033		
BMI (kg/m <sup>2</sup> )	1.06 (0.99–1.14)	0.09		
Metformin treatment	0.13 (0.03–0.55)	0.006	0.19 (0.04–0.79)	0.023
Diabetes duration at inclusion (yr)	1.05 (0.96–1.16)	0.27		
HbA1c (%)	1.03 (0.73–1.47)	0.85		
Fasting glucose (mmol/liter)	1.0 (0.88–1.14)	0.96		
Creatinine clearance ( $\mu$ mol/liter)	1.0 (0.99–1.0)	0.79		
GGT ( $\times$ ULN)	1.10 (1.02–1.19)	0.01	1.10 (1.01–1.20)	0.034
ALT ( $\times$ ULN)	0.96 (0.77–1.19)	0.70		
AST ( $\times$ ULN)	1.24 (1.01–1.55)	0.048		
Platelet count (Giga/liter)	1.0 (0.99–1.0)	0.15		
Prothrombin activity (5% units increase)	0.89 (0.86–0.93)	0.02		
Serum albumin (g/liter)	0.97 (0.90–1.05)	0.42		
Serum bilirubin ( $\mu$ l/liter)	0.98 (0.95–1.02)	0.38		
AFP (ng/ml)	1.02 (1.01–1.03)	0.003	1.02 (1.01–1.03)	0.006
Steatosis	0.91 (0.58–1.42)	0.68		

ULN, Upper normal limit range.

ers (27). This was especially reported in the patients with a high AST/ALT ratio, which was in the present study similar in the patients treated with metformin and in those who were not. In our study, no severe complication was observed with metformin treatment. This could partly be explained by the fact that patients with HCV cirrhosis stopped or strongly limited alcohol consumption after the diagnosis. Furthermore, the patients with severe life-threatening disease, especially cardiac and renal failures, were not included in this cohort.

Recent data have shown in different forms of cancer that metformin-treated patients exhibited better outcomes

than patients treated with other antidiabetic treatments (13). One may consider that insulin is a risk factor for HCC, rather than metformin being protective against HCC. However, we found in our study that the prognosis of patients treated with diet alone was similar to that of the patients treated with insulin or insulin secretagogues. The beneficial effect of metformin could be direct or indirect. Indirect effects of metformin include enhanced insulin sensitivity (9) and, for some, reduced hyperinsulinemia (7). In our study, no patient was treated with thiazolidinediones. Thus, further studies are needed to address the potential influence of this therapeutic class, which, like metformin,

**TABLE 3.** Univariate and multivariate analyses of predictors of liver-related death or transplantation

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (yr)	1.01 (0.98–1.05)	0.54		
Male gender	2.63 (1.25–5.55)	0.01		
Past and/or daily alcohol intake	2.00 (0.99–4.05)	0.054	3.80 (1.65–8.77)	0.002
BMI (kg/m <sup>2</sup> )	1.08 (1.01–1.16)	0.03	1.16 (1.06–1.26)	0.001
Metformin treatment	0.2 (0.05–0.83)	0.03	0.22 (0.05–0.99)	0.049
Diabetes duration at inclusion (yr)	1.11 (1.02–1.22)	0.020	1.21 (1.09–1.34)	<0.001
HbA1c (%)	0.99 (0.65–1.5)	0.95		
Fasting glucose (mmol/liter)	1.07 (0.93–1.23)	0.36		
Creatinine clearance ( $\mu$ mol/liter)	1 (0.99–1)	0.79		
GGT ( $\times$ ULN)	1.09 (1–1.2)	0.06		
ALT ( $\times$ ULN)	0.87 (0.67–1.12)	0.28		
AST ( $\times$ ULN)	1.31 (1.04–1.65)	0.024	1.11 (1.20–2.01)	0.001
Platelet count (Giga/liter)	0.99 (0.99–1.00)	0.09		
Prothrombin activity (5% units increase)	0.88 (0.84–0.93)	0.02		
Serum albumin (g/liter)	1.02 (1.01–1.04)	0.01		
Serum bilirubin ( $\mu$ l/liter)	0.95 (0.87–1.03)	0.20		
AFP (ng/ml)	1.01 (1.0–1.02)	0.12		
Steatosis	0.93 (0.58–1.49)	0.77		

ULN, Upper normal limit range.

decreases insulin resistance and hyperinsulinemia but can induce weight gain. At the cellular level, metformin, which is highly concentrated in the liver, activates AMP-activated protein kinase (AMPK), which plays a role in the linking between metabolic syndrome and cancer. AMPK is an essential mediator of the tumor suppressor LKB1 and could be suppressed in cancer cells containing loss-of-function mutations of LKB1 or in cancers associated with metabolic syndrome (28). Metformin also inhibits hepatic gluconeogenesis independently of the LKB1/AMPK pathway (8). The activation of AMPK reprograms cellular metabolism and enforces metabolic checkpoints by acting on mammalian target of rapamycin complex 1, p53, p27, cyclin D1, fatty acid synthase, and other molecules for regulating cell growth and metabolism (29). Recently, a pilot clinical trial has reported that a low dose of metformin suppresses colonic epithelial formation and rectal aberrant crypt foci formation in humans (30). Furthermore, metformin enhances CD8 T-cell immune response against cancer (31).

In conclusion, metformin treatment is associated with better outcomes in HCV cirrhotic patients with T2D. Limited by the observational study design, a conclusion of association by causality cannot be drawn. However, our findings add to the increasing body of evidence and may justify the initiation of clinical trials evaluating metformin in patients with hyperinsulinemia and HCV cirrhosis because it has been discussed and planned in chemoprevention of breast cancer recurrence.

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