Risk of microangiopathy in type 2 diabetes mellitus patients with or without chronic hepatitis C: Results of a retrospective long-term controlled cohort study

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RISK OF MICROANGIOPATHY IN TYPE 2 DIABETES MELLITUS PATIENTS WITH OR WITHOUT CHRONIC HEPATITIS C. RESULTS OF A RETROSPECTIVE LONG-TERM CONTROLLED COHORT STUDY

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Running head: microangiopathy in HCV-positive diabetics

ABSTRACT

Background: patients with chronic hepatitis C have an increased risk of diabetes mellitus but the type and risk of developing diabetes-related complications have not yet been evaluated.

Methods: in order to compare the incidence of diabetic microangiopathy in patients with new onset diabetes without microangiopathy we recruited 54 hepatitis C virus positive and 119 negative patients from January 2005 to December 2006. All patients were followed-up every 6 months for liver and diabetic complications and incidence of cardiovascular diseases up to December 2012 when data were retrospectively analyzed.

Results: the 2 cohorts were comparable at enrolment except for mean body mass index, obesity rate and family history of diabetes (p=0.007). After 7.2 years of follow-up, 13 (24.1%) positive and 37 (31%) negative patients showed at least one microangiopathic complication (p= 0.34), 5 (9.3%) positive and 13 (10.8%) negative patients reported cardiovascular diseases (p=0.2). Fourteen (24.5%) positive compared to none negative patient developed liver-related complications (p=0.0003). One positive patient died due to HCC, 1 negative patient died for myocardial infarction (p= 0.3). Increasing age (HR= 1.04, 95%CI: 1.00-1.07, p= 0.04) and being smoker (HR= 2.94, 95%CI: 1.06-8.17, p= 0.04) were positively associated to diabetic complications.

Conclusions: incidence of microangiopathy is not significantly different in diabetics with or without chronic hepatitis C.

Key words: diabetes mellitus, chronic hepatitis C, cirrhosis, microangiopathy, macroangiopathy

INTRODUCTION

Type 2 diabetes mellitus (T2DM) which develops as a complication of advanced liver disease is a well-known condition defined “hepatogenous diabetes” (1). However, even if T2DM is considered clinically different from the “classical” DM, due to the fact that it is less frequently associated with microangiopathy (2-5), it is not recognized by the American Diabetes Association and the World Health Organization as a specific independent entity (2). This statement mainly derives from results of cross-sectional studies including patients with dissimilar etiologies of liver cirrhosis.

Hepatitis C Virus (HCV) seems to increase the risk of incident T2DM in predisposed individuals (6,7) as well as the risk of cardiovascular diseases (8), independently of stage of liver disease as reported by Knobler et al. who observed a prevalence of T2DM of 33% in non-cirrhotic patients with chronic hepatitis C (CHC) compared with 5.6% in a control group (9). The hypothesized mechanisms by which HCV can induce the development of T2DM are not clearly understood but these include the stimulus to the production of Tumor Necrosis Factor-α (TNF-α), the serine phosphorylation of the insulin receptors (IRS) and the overexpression of suppressor of cytokines (SOC-3) (10). Many studies (11-15) reported the clinical consequences of T2DM on CHC outcome but very few studies addressed the issue of microangiopathic complications among patients with CHC only, developing T2DM (16). The primary aim of our study was to assess the incidence of diabetic microangiopathy in a cohort of CHC patients with new-onset T2DM and without baseline microangiopathic complications throughout a 7-year follow up. In order to establish whether such incidence was different from that observed among diabetic patients without CHC, we compared the occurrence of diabetic complications in the CHC cohort with that of a similar control group of new-onset T2DM, HCV-negative patients without baseline microangiopathy, comparable for age, T2DM duration and length of follow up. Secondary aim was to compare the cumulative incidence rate of macroangiopathic complications (coronary artery disease (CAD), peripheral artery diseases) between the two cohorts.

PATIENTS AND METHODS

The medical records of 612 consecutive patients with CHC examined between January 2005 and December 2006 in two academic centers of North-Western Italy (the Gastrohepatologic Clinic of Molinette Hospital, Turin, Italy and the Gastroenterology Division of San Luigi Hospital, Orbassano, Italy) were retrospectively reviewed. Patients were included into the present study if they fulfilled the following criteria at baseline: age > 18 years; positive results for HCV-RNA by polymerase chain reaction (PCR); CHC at liver biopsy; new-onset T2DM; documented baseline informations regarding: gender, body mass index (BMI), viral load, genotype, liver histologic staging, glucose plasma level, glycosylated hemoglobin (HbA1c), smoking status, arterial hypertension (AH), family history for T2DM. Exclusion criteria were: known carriers of T2DM with or without chronic complications (CAD, stroke, retinopathy, nephropathy, neuropathy, peripheral artery disease), decompensated cirrhosis, active alcohol intake, presence of other concomitant diseases or conditions such as haemochromatosis, Wilson's disease, drug-related liver disease, autoimmune hepatitis, HBsAg carriership, HIV infection, primary biliary cirrhosis, α1-antitrypsin deficiency, neoplasia. Overall, 494 non-diabetic patients were excluded and of remaining 118 diabetic patients, 64 (54.2%) were known carriers of T2DM or showed T2DM-related chronic complications at diagnosis**.** Thus, 54 patients were enrolled in the CHC cohort. Of these 54 patients, 22 (40.7%) were treated during the follow up with Interferon (IFN)-based therapy and ribavirin (RBV) for 24 or 48 weeks according to HCV genotype. A sustained virologic response (SVR) was defined as the HCV-RNA clearance 6 months after the end of treatment. Patients who did not achieve this result were considered relapsers or non responders (NRs).

As control group, we considered 1212 patients with T2DM consecutively recruited at the Diabetic Clinic of the University of Turin, Italy, from January 2005 to December 2006. A detailed computerised database regarding demographic, clinical and pharmacological features of the entire cohort was available. Of 1212 patients, we selected for the study only HBsAg-negative, anti-HCV-negative patients with documented new-onset T2DM, without any chronic complication and

without alcoholic liver disease. One thousand patients (82.5%) were known carriers of T2DM and were excluded; of the remaining 212 patients with a newly diagnosed T2DM, 93 (43.8%) showed chronic diabetic complications at baseline. Thus, 119 patients were enrolled in the HCV-negative cohort as controls. Patients' flow is reported on Figure 1.

Each patient of both cohorts was examined at least every 6 months during follow up: they had their blood pressure and glycated haemoglobin measured at each visit. Liver function tests and abdominal ultrasound were also performed in HCV-positive patients. Moreover, all patients were screened yearly for chronic complications related to DM and were followed up for a mean time of 7.2 (standard deviation: 1.3) years; their clinical outcomes were recorded. At the end of a similar length of follow up, we performed a comparative analysis of the incidence of T2DM complications and liver cirrhosis adjusted for several potential confounders.

Definitions

Smokers were defined as persons smoking more than one cigarette per day or known to have smoked within three years before the study recruitment.

BMI was calculated as weight in kilograms divided by the square of the height in meters. Arterial blood pressure values reported were the means of the last three determinations. Hypertension was defined as a systolic and/or diastolic blood pressure of 140/90 mmHg or higher and/or a current anti-hypertensive treatment (17).

According to the criteria recommended by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, T2DM was defined as fasting plasma glucose ≥ 126 mg/dl (7 mmol/l) in two separate measurements (18).

Liver complications

Patients were considered to have liver failure if they met any of the following criteria: ascites confirmed by abdominal ultrasound or computed tomography (CT), bleeding oesophageal varices, jaundice with bilirubin > 35 µmol/L or hepatic encephalopathy. Patients were considered to have hepatocellular carcinoma (HCC) if the diagnosis was cyto-histologically confirmed, or if two coincident imaging techniques (ultrasound, CT or magnetic resonance imaging) showed a focal lesion > 2 cm with arterial hypervascularization or if one imaging technique showed a focal lesion > 2 cm with arterial hypervascularization in the presence of alpha-fetoprotein > 400 ng/ml.

Liver transplantation and mortality (classified as liver or non liver-related) were recorded.

Diabetes complications

The diagnosis of cardiovascular disease was based on documented events that were recorded by the diabetologists (i.e. angina, myocardial infarction, coronary artery by-pass graft or another invasive procedure to treat CAD, transient ischemic attack, stroke, gangrene, amputation, vascular surgery, intermittent claudication, absent foot pulses and abnormal brachial and posterior tibial blood pressure documented using Doppler techniques).

Retinopathy was diagnosed via an ophtalmoscopic examination and/or retinal photography. A fundoscopy was performed through dilated pupils by an ophthalmologist experienced with diabetic retinopathy. In case of retinopathy (any degree), a retinal photograph was taken, in accordance with the European protocol for diabetic retinopathy. Nephropathy was established by an albumin excretion rate (AER) higher than 20 µg/min in at least 2 out of 3 urine collections within 6 months (immunoturbidimetric method), gross proteinuria or elevated serum creatinine levels. Distal symmetric polyneuropathy was diagnosed by the presence of neuropathic symptoms, an abnormal vibration perception threshold, the absence of ≥ 2 ankle or knee reflexes and/or an abnormal

electromyographic test. Autonomic neuropathy was diagnosed by a loss of heart rate variability or postural hypotension.

Histology

The degree of liver fibrosis was assessed by one pathologist according to the Ishak scoring system (19). During the follow-up, subjects were classified as cirrhotic by a second liver biopsy or, in the absence of bioptic examination, if they showed unequivocal evidence of portal hypertension (presence of esophageal varices not associated with portal vein thrombosis), or a particular ultrasound pattern (nodular contour, diminished hepatopetal flow, collaterals) or a typical serology (platelets < 80000 x 10^9 /L, albumin < 3.5 g/l, clotting factors < 50%) or by liver elastography adopting the stringent recommendations suggested by Kettaneh et al. and showing a liver stiffness > 14.5 KiloPascal (20).

Statistical analysis

Baseline continuous variables were summarized with means (and standard deviations, SD); categorical variables were reported as frequencies (and percentages). The two cohorts were compared at baseline to identify meaningful differences for clinical or demographical characteristics by using either a t-test (for continuous variables) or a Chi-square (or Fisher) test (for categorical variables). The cumulative incidence of specific complications of T2DM was firstly compared as simple proportions by Chi-square (or Fisher) tests, considering all the events at the end of the follow up. To compare the risk of micro and macroangiopathic complications between the two cohorts, accounting for some known risk factors, the Cox proportional-hazard model was used. The estimated Hazard Ratios (HR), with their 95% Confidence Intervals (95% CI) were reported both as crude estimate and adjusted for age, gender, smoking habits and diabetes therapy.

RESULTS

The results of the comparison of the two cohorts are summarised in Table 1.

At baseline, the two cohorts were comparable for age, gender, disease duration and stage but they differed for BMI, obesity rate, liver disease, family history of T2DM, type of therapy and use of statins. Patients with CHC showed lower BMI ($p<0.0001$) and obesity rate ($p=0.008$); expectedly, pre-existing cirrhosis (61.4% vs 2.5%, $p<0.0001$) and alterations of ALT/GGT levels were more frequently found among HCV-positive patients ($p<0.0001$). A higher percentage of HCV-negative patients reported family history for T2DM compared with HCV-positive patients (86.3% vs 56.6%, $p= 0.003$). At baseline, a higher proportion of patients with CHC were treated with insulin (12.9% vs 1.6%, $p= 0.008$) but a significantly lower percentage of them were given statins (9.3% vs 58%, $p<0.0001$).

Among patients without cirrhosis at baseline, 2/116 (1.72%) in the HCV-negative cohort developed cirrhosis during the follow-up, while 2/20 (10%) in the HCV-positive cohort showed a cirrhotic evolution ($p<0.0001$).

After a mean follow-up of 7.2 years, 171 out of 173 patients were re-assessed; none was lost to follow up: one (0.84%) HCV-negative patient died for myocardial infarction and one (1.85%) HCV-positive patient died for HCC ($p= 0.3$). BMI did not significantly change among HCV-positive (mean difference from baseline: -0.58, SD: 1.88) and HCV-negative patients (-0.44, SD: 2.39), $p=0.69$, as well as mean HbA1c levels (- 0.42±1.48 vs – 0.82±1.84, $p= 0.21$) suggesting a comparable good glycemic control.

T2DM-related and liver-related complications observed during follow up are reported in Table 2.

Microangiopathy was found in 24.1% (95%CI= 14.6-36.9) of patients with CHC and in 31% (95%CI=23.5-39.9) of HCV-negative patients ($p= 0.34$); 3 (5.5%) HCV-positive patients experienced myocardial infarction compared to 2 (1.68%) HCV-negative patients ($p= 0.16$) while stroke was observed in 3.7% and 9.2% respectively ($p= 0.20$).

As expected, liver-related events were more frequently found among HCV-positive patients than among HCV-negative patients who did not show any hepatic complications; in the CHC cohort, 5 (9.25%, p= 0.001) patients had ascites, 6 (11.1%, p=0.0003) developed HCC and 2 (3.7%, p= 0.04) underwent orthotopic liver transplant.

Among HCV-negative cohort, 49 (58.3%) developed “de novo” AH compared to 3 (10%) HCV-positive diabetics (p=<0.0001).

At the end of follow up, therapy of T2DM was different between the two cohorts: significantly more HCV-negative diabetics were treated with insulin sensitizers (77.3% vs 54.3%, P= 0.007) compared with patients with CHC; conversely, a significantly higher proportion of HCV-positive patients was given insulin (21% vs 6.7%, p<0.0001) or diet only (24.5% vs 15.9%, p=0.003).

Out of 22 HCV-positive patients treated with Peg-IFN + RBV, 8 (36.3%) obtained a SVR: none developed micro/macroangiopathic complications.

In order to adjust the comparison between the two cohorts, accounting for known risk factors for T2DM-related complications, we used a Cox proportional hazard risk model; results are reported in Table 3.

Based on a multivariable Cox regression analysis, HCV positivity was not associated to an increased risk of developing T2DM-related complications (HR= 0.74, 95%CI=0.33-1.71, p= 0.49). The risk of complications was positively associated with increasing age (in years) (HR= 1.04, 95%CI: 1.00-1.07, p= 0.04) and being smoker at enrolment (HR= 2.94, 95%CI: 1.06-8.17, p= 0.04) were positively associated to micro/macroangiopathic complications.

DISCUSSION

The present study did not find any meaningful difference in the incidence of both microangiopathic and macroangiopathic complications between patients with newly diagnosed T2DM with or without CHC, after a comparable duration of disease and length of follow up and despite the lower BMI and obesity rate observed among HCV-positive patients. These data are apparently in contrast with those previously reported (2,4,5). Marchesini et al. (4) showed a lower prevalence of micro- and peripheral macroangiopathy in diabetic cirrhotics compared with non-cirrhotic diabetic patients; to explain the difference with our study, it should be considered that the study design was cross-sectional, the etiology of cirrhosis was heterogeneous (Hepatitis B Virus, HCV, alcohol, primary biliary cirrhosis, Wilson's disease, alfa1-antitrypsin deficiency, hemochromatosis) and the duration of diabetes was significantly longer in diabetic patients without cirrhosis. Holstein et al. (2) reported an overall rate of 8% regarding retinopathic complications in 52 patients with cirrhosis and T2DM; no T2DM-related complications were observed among 20 patients with newly diagnosed T2DM during the follow-up. However, the study design was not controlled, only 19% of patients were HCV-positive and the follow-up period was short (3.9 years). Kuriyama et al. (5) showed a significantly lower incidence of microangiopathy among diabetics with chronic liver disease (mainly HCV-positive) compared with a matched group of diabetic patients without liver disease. Main criticisms are the cross-sectonal study design and the fact that the diabetic disease duration was not reported. In contrast with the abovementioned studies, a recent study (16) reported a significantly higher prevalence of T2DM complications among HCV-positive diabetics compared with HCV-negative diabetics; however, no data regarding baseline liver histology, methods to assess microangiopathy/macroangiopathy and duration of T2DM were described. Duration of diabetic disease is crucial in determining the real incidence of T2DM-related complications; to date, no study recruited patients with only newly diagnosed T2DM making unreliable the comparison between two cohorts with different duration of disease. To the best of our knowledge, this is the first study which addressed this issue considering only patients with "de novo" diagnosis

of T2DM and without baseline micro/macroangiopathy. In spite of these strict selection criteria, we cannot exclude that some patients without HCV with newly diagnosed T2DM had pre-existing T2DM which remained undiagnosed due to a long lasting preclinical stage (4). On the contrary, patients with CHC were followed up with periodic glycemic controls; thus, in this cohort of patients the diagnosis of T2DM was made in the preclinical stage. In other words, it is likely that duration of diabetic disease is underestimated among ordinary diabetics compared with regularly followed up HCV-positive diabetics.

In our study, nearly 63% of HCV-positive patients with new onset T2DM were cirrhotic and 2 (10%) more patients developed cirrhosis during the follow up compared with 2 (1.7%) in the HCV-negative cohort ($p<0.0001$); it is possible, however, that incidence of liver cirrhosis among HCV-negative diabetics may be underestimated due to less stringent hepatologic follow up. We think that a considerable proportion of these patients are expected to never develop diabetic complications, because of a reduced, cirrhosis-related life expectancy; in fact, in cirrhotic patients with T2DM, the most recurrent cause of death is liver failure (3,21,22) . In a previous study (15) , we evaluated the impact of T2DM on the incidence of liver-related events and overall survival among patients suffering from CHC followed up for a mean period of 11 years after IFN-based plus RBV therapy. We showed that patients with baseline T2DM had a higher risk of HCC development and liver decompensation than non-diabetic patients; our results were recently confirmed by other studies (23,24).

It has been previously suggested that, in patients with viral cirrhosis, T2DM is not associated with an increased risk of peripheral macroangiopathy (4), CAD (2,4) and cerebrovascular disease (2,25); the coagulation abnormalities and thrombocytopenia (26,27) as well as the low serum cholesterol levels (28) and low arterial blood pressure frequently seen in cirrhosis have been proposed as possible protective factors. In our study, macroangiopathic complications were not different between the two groups but the relative small number of patients does not allow to draw definite conclusions.

Finally, 8/22 (36.4%) HCV-positive patients treated with Peg-IFN + RBV cleared the virus and none developed micro/macroangiopathic complications; our data confirm the results of a recent study (29) showing that antiviral treatment is associated with improved renal and cardiovascular outcomes in diabetic patients with concomitant HCV infection. Moreover, results and conclusions of our study did not change after exclusion of HCV-positive patients achieving SVR.

Certain methodological limitations should be taken into consideration when interpreting the results of the current study. Firstly, the retrospective nature of the study might be a potential source of selection bias. However, baseline discrepancies regarding HCV-positive diabetics/HCV-negative diabetics are not due to an arbitrary selection but represent well known differences between distinct populations and were carefully considered in the multivariate analysis.

Secondly, due to the small number of patients included, we can only exclude with a statistical power of 80% the existence of large differences (corresponding to HRs > 2.3) between the two groups regarding T2DM complications; for this reason, a larger prospective multicenter controlled study would be recommended.

In conclusion, according to our data the risk of microangiopathic complications in patients with CHC and new onset T2DM is similar to that observed among patients with newly diagnosed T2DM without CHC; however, the unfavourable natural history of HCV-positive cirrhotics due to liver complications is likely to make less evident the clinical impact of microangiopathy. There is still need for large prospective controlled studies in order to evaluate the outcome of T2DM in CHC.

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Figure legend:

Figure 1. Flow of recruited patients

DM: dibetes mellitus

HCV: hepatitis C virus

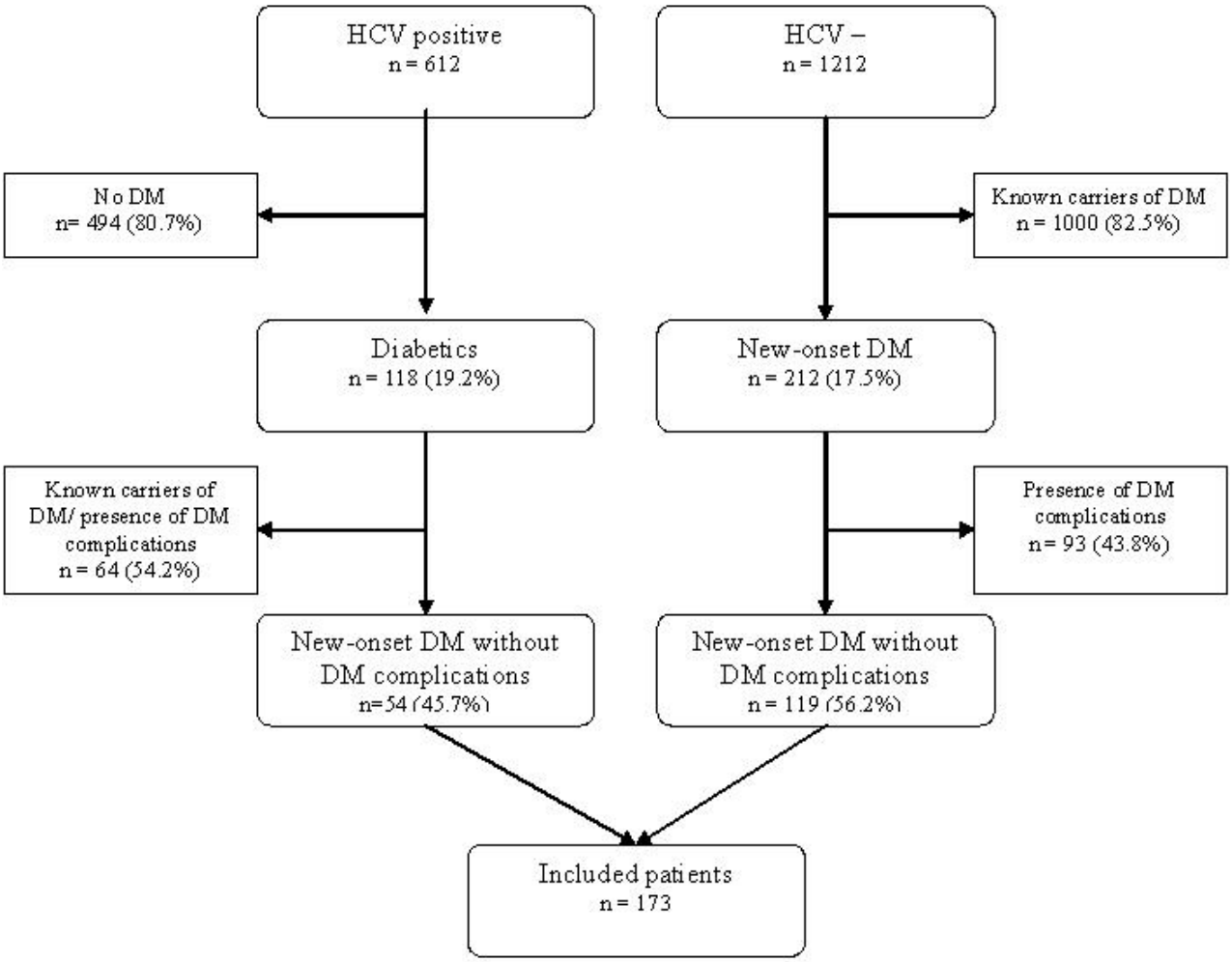
HCV positive
n = 612
HCV –
n = 1212
No DM
n= 494 (80.7%)
Known carriers of DM
n = 1000 (82.5%)
Diabetics
n = 118 (19.2%)
New-onset DM
n = 212 (17.5%)
Known carriers of DM/ presence of DM complications
n = 64 (54.2%)
Presence of DM complications
n= 93 (43.8%)
New-onset DM without DM complications
n=54 (45.7%)
New-onset DM without DM complications
n = 119 (56.2%)
Included patients
n = 173

Table 1. Comparison of Hepatitis C Virus positive vs Hepatitis C Virus negative cohorts of newly diagnosed type 2 diabetic patients

	HCV positive	HCV negative	p-value
N. of patients	54	119	
Mean age (± SD)	55.7 (±10.4)	57.7 (±10.8)	0.24
Male gender	32 (59.3%)	56 (47%)	0.14
Mean BMI (± SD)	26.6 (±4.2)	29.7 (±5.3)	<0.0001
Obese patients	12 (22.2%)	49 (41.2%)	0.008
Arterial hypertension (%)	14/54 (25.92%)	35/119 (29.41%)	0.64
Smokers (%)	11/54 (20.37%)	26/119 (21.85%)	0.41
Family history of DM (%)	56.67%	86.3%	0.003
Mean glycemic (mg/dl) values (± SD)	165.4 (±47.1)	151 (±45.4)	0.06
Mean Hba1c (g/dl) values (± SD)	7.4 (±1.5)	7.9 (±2.0)	0.14
Mild liver fibrosis (1)	9 (16.7%)	-	-
Severe liver fibrosis (2)	11 (20.3%)	-	-
Cirrhosis (%)	34/54 (62.9%)	3/119 (2.52%)	<0.0001
Mean ALT (UI/l) values (±SD)	121.1(±91.7)	36.3 (±28.4)	<0.0001
Mean GGT (UI/l) values (±SD)	134.5 (±266.5)	45.7 (±48.4)	0.003
Statins use	5 (9.3%)	69 (58%)	< 0.0001
DM therapy			0.008
Diet only (%)	23/54 (42.60%)	57/119 (47.9%)	
Oral hypoglycemic agents (%)	24/54 (44.44%)	60/119 (50.42%)	
Insulin (%)	7/54 (12.96%)	2/119 (1.68%)	

HbA1c= glycated hemoglobin ALT= Alanine Transaminase

GGT= Gamma Glutamyl Transpeptidase

(1) Ishak staging score = 0-3 (2) Ishak staging score = 4-5

Table 2. Incidence of diabetes mellitus related complications in Hepatitis C positive vs Hepatitis C negative cohorts of newly diagnosed type 2 diabetic patients

	HCV positive	HCV negative	p-value
N. of patients	54	119	
Overall microangiopathic events (%)	13 (24.1%)	37 (31.09%)	0.34
Retinopathy (%)	5 (9.26%)	15 (12.6%)	0.47
Nephropathy (%)	5 (9.26%)	12 (10.08%)	0.87
Neuropathy (%)	3 (5.56%)	6 (5.04%)	0.8
Ischaemic foot ulcer (%)	0 (0%)	4 (3.36%)	0.17
Coronary artery disease (%)	3 (5.55%)	2 (1.68%)	0 .16

Table 3. Association between chronic hepatitis C, other known risk factors and development of diabetes-related complications: multivariable Cox regression analysis

	hazard ratio	confidence intervals	p-value
Chronic hepatitis C	0.74	0.33-1.70	0.48
Male gender	1.23	0.57-2.66	0.58
Age	1.04	1.00-1.07	0.04
Body mass index	1.04	0.98-1.10	0.23
Current smokers (1)	2.94	1.06-8.17	0.04
Arterial hypertension	0.80	0.38-1.70	0.57
Oral hypoglycemic agents (2)	1.17	0.59-2.33	0.65
Insulin therapy (2)	0.90	0.11-7.38	0.92

(1) Reference category: never smokers

(2) Reference category: diet only