ejpmr, 2021,8(9), 754-757

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

DIABETES AND CIRRHOSIS: PREVALENCE AND IMPACT

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Article Received on 22/07/2021 **Article Revised on 12/08/2021** **Article Accepted on 01/09/2021**

ABSTRACT

Background: Abnormalities of glucose metabolism are common in cirrhosis. About 31% of cirrhotic patients have diabetes. Diabetes appears both as a consequence of cirrhosis and as an aggravating factor of its clinical course. **Aim:** The aim of the current study was to determine the prevalence of diabetes during cirrhosis and compare virological profile, as well as the severity of cirrhosis and its evolutionary modalities according to the prescence or not of diabetes. **Methods:** To meet these objectives we conducted a descriptive and retrospective study, including all patients followed for cirrhosis in the gastroenterology department B of the Rabta hospital in Tunisia. Patients were divided into 2 groups according respectively to presence or not of diabetes. **Results:** One hundred and thirty-two patients were included. Among the study population, 40.9% had diabetes. In uni-variate analysis, our results showed that liver disease was more severe in diabetic cirrhotics. In addition, complications of cirrhosis were significantly associated with diabetes, such as ascites, hepatic encephalopathy, esophageal variceal hemorrhage, hepatocellular carcinoma and infections. In multivariate analysis, same factors were associated with diabetes in cirrhosis except ascites and hepatic encephalopathy. **Conclusions:** Through this study, our results confirm that diabetes seems to worsen the evolutionary course of cirrhosis. Therefore, modalities of monitoring and management of a cirrhotic patient must be reconsidered in the presence of diabetes.

KEYWORDS: Diabetes, cirrhosis, hepatocellular carcinoma, prognosis, complications.

INTRODUCTION

The liver is the site of intense metabolic activity including the metabolism of carbohydrates. Its dysfunction during cirrhosis is frequently accompanied by diabetes. The overall prevalence of diabetes in cirrhosis is estimated at 31% according to a meta-analysis published in 2019.[1] Studies carried out in different regions of the world have shown that the association (diabetes- cirrhosis) was responsible for a higher incidence of complications of cirrhosis and reduced survival. Type 2 diabetes it self can cause non-alcoholic fatty liver disease which may be complicated by fibrosis then cirrhosis, or even hepatocellular carcinoma. Glycoregulation disorders during cirrhosis are a cofactor of severity and an independent pejorative prognostic element in the course of chronic liver disease, which implies specific diagnostic and therapeutic management.

The aim of the current study was to determine the prevalence of diabetes during cirrhosis and compare virological profile, as well as the severity of cirrhosis and its evolutionary modalities according to the prescence or not of diabetes.

METHODS

It was a descriptive, retrospective study, including all patients followed for cirrhosis. in the gastroenterology department B of the Rabta hospital in Tunisia.

During the 1-year period between january 2016 and january 2017, the diagnosis of cirrhosis was retained : Either on a set of clinico-biological and morphological arguments attesting to the presence of hepatocellular insufficiency and portal hypertension signs[2], or in front of a degree of advanced fibrosis attested by non-invasive fibrosis tests validated (Fibroscan, Fibrotest) or histologically by liver biopsy.

We have excluded incomplete records and cases of non-alcoholic fatty liver cirrhosis (because of the unavailability of diagnostic confirmation by liver biopsy for all patients).

For each patient following features were noted, recording epidemiological, anthropometric, clinical, biological, virological and morphological aspects of cirrhosis as well as the clinical course.

The diagnosis of diabetes was made according to the following diagnostic criteria reviewed by the American Diabetes Society in 2014.[3]

Patients were divided into 2 groups according to

presence or not of diabetes:
Group 1: Cirrhotic diabetic patients
Group 2: Cirrhotic patients without diabetes

The epidemiological and clinical characteristics of the two groups were compared as well as the severity of the disease and its evolutionary modalities.

Statistical analysis was performed using Chi square test and student t test. In all statistical tests, p-value <0.05 was considered statistically significant.

RESULTS

One hundred and thirty-two cirrhotic patients were included. 40.9% among them were diabetics.

As seen in **Table I**, the majority of the patients in both groups were in age nearly 60 years. There was no statistically significant difference in both groups regarding age distribution.

Fifty-nine percent of diabetic cirrhotic patients were women versus 64% of non-diabetic cirrhotics with no statistically significant difference (p = 0.57) and an odds ratio of 0.815 (95% confidence interval [0.399 - 1.662]).

A family history of diabetes was noted in 5% of the cirrhotics so similar between diabetics and non-diabetics.

Body mass index (BMI) was higher in diabetics (28.7 kg / m² versus 22kg / m²) with a statistically significant difference (p = 0.001).

Table I: Comparison of general characteristics in diabetic and non-diabetic cirrhotics.

	Group 1 (n=54)	Group 2 (n=78)	P
Age (years)	60.6	58.4	NS
Female (%)	59	64	NS
Family history of diabetes (%)	5	5	NS
BMI(kg/m2)	**28.7**	**22**	**0.001**

NS: not significant

Based on comparison between diabetic and non-diabetic cirrhotics patients, the results in univariate analysis did not objectify statistically significant differences for the virological profile (viral C etiology was predominant in the 2 groups of patients). In addition, our results showed that liver disease was more severe in diabetic cirrhotic patients. In fact, 81.5% of diabetic cirrhotic patients and 29.5% of non-diabetic cirrhotic patients had Child B or C. This difference was statistically significant (p <0.001).

Complications of cirrhosis were significantly associated with diabetes. Indeed, in the group of diabetic cirrhotics, 72.2% presented at least one episode of ascites. This complication has been found in non-diabetic cirrhotics in 45.7% of cases with a significant difference (p=0.007), hepatic encephalopathy was found in 27.7% of diabetic cirrhotics versus 6.4% in non-diabetics (p = 0.001), gastrointestinal bleeding was noted in 57.4% of diabetic cirrhotics against 12.9% in non-diabetics (p<0.001), hepatocellular carcinoma (HCC) was found in 33.3% of diabetic cirrhotics versus 18% in non-diabetics (p = 0.04) and infections were more common in diabetic cirrhotics (70.4% VS 29.6%) (p = 0.003) as well as the need for hospitalization for an infectious episode (33.3% VS 42.6%) with a significant difference (p = 0.02).

There was no significant difference in duration of cirrhosis, etiologies of cirrhosis and laboratory assessment for hepatocellular failure.

In multivariate analysis, same factors were associated with diabetes in cirrhosis except ascites and hepatic encephalopathy.

Table II: Comparison of complications of cirrhosis in diabetics and those without diabetes.

	Group 1 (N=54)	Group 2 (N=78)	P
Ascites(%)	72.2	45.7	0.007
Encephalopathy(%)	27.7	6.4	0.001
Bleeding(%)	57.4	12.9	<0.001
Hepatocellular Carcinoma (%)	33.3	18	0.04
Infections(%)	70.4	29.6	0.003

DISCUSCION

The interaction between diabetes and chronic liver disease is now well established in the literature.[4,5] Indeed, in cirrhotic patients, the prevalence of diabetes varies from 17 to 65%, according to different authors.[5–7] In our study, the prevalence of diabetes was 40.9%.

Based on literature data, diabetes in people with cirrhosis was associated with age over 60 years, a family history of diabetes (60.6%) and a body mass index greater than 27 kg / m².[8]

Studies published in 2011, 2015 and 2017 showed that diabetics had lower albumin and cholesterol levels than

non-diabetics when they were at same advanced stage of cirrhosis.[9–11] On the other hand, in our series, we did not objectify a statistically significant difference between the two groups for laboratory assessment.

Many authors have studied the implication of the etiology of chronic liver disease in the development of carbohydrate metabolism disorders. This relationship has been fine established with hepatitis C virus (HCV). The mechanisms by which the HCV produces insulin resistance and diabetes is not clearly known. In a study conducted on an animal model, the mechanisms inducing insulin resistance by HCV included the production of TNF-α which appears to be the main mechanism, phosphorylation of insulin receptor substrates (IRS-1 and IRS-2) and overexpression of cytokine suppressors (SOC).[12] Some genotypes C virus may be involved in the occurrence of glucose metabolic disorders, genotypes 1 and 4 being significantly associated with insulin resistance more frequently than genotypes 2 and 3 (37% vs 17%).[13]

In our series, the main etiology of cirrhosis in diabetic patients was viral C infection (55.1%) genotype 1b (92%), followed by viral hepatitis B (21.7%) then autoimmune origin (6.4%). By comparing these results with the group of non-cirrhotics diabetics, HCV was also the main cause (55.5% of cases) genotype 1b (94%), followed by hepatitis B (22.2%), then autoimmune causes (12.9%). Without statistically significant difference.

In the literature, diabetes has emerged as an independent prognostic indicator pejorative of cirrhosis.[14] In our patients, a Child B or C score was present in 81.5% of diabetic cirrhotics, while only 29.5% of non-diabetic cirrhotics had the same score with a statistically significant difference ($p < 0.001$). What joins the data of the literature.

Ascites marks a turning point severe progressive in the natural history of cirrhosis, survival decreasing to 50-85% and 30-56% respectively 1 and 5 years after its onset.[15]

In several studies, the frequency of ascites depended on glycemic disorders.[16] This is due to several mechanisms. Systemic circulatory alterations specific to abnormalities in glycoregulation could be associated with alterations in hepatic architecture to major the mechanisms behind the formation of ascites in cirrhosis.[17] In our study, diabetes was significantly associated with the occurrence of edema-ascitic decompensation (72.2% in diabetics versus 45.7% in non-diabetics, $p = 0.007$). Our results were then consistent with the literature.

The combination of diabetes and hepatic encephalopathy during cirrhosis has been reported in several studies. Since diabetes can be associated with delayed gastrointestinal transit, its presence in patients with cirrhosis predispose to hepatic encephalopathy.[18] This same mechanism is also responsible for an increase in the intestinal production of toxic substances t particularly ammoniac, the high level of which in the blood induces and aggravates hepatic encephalopathy.[19] In our study, hepatic encephalopathy occurred in 27.7% of diabetic cirrhotics and 6.4% of non-diabetics cirrhotics. The difference was statistically significant ($p = 0.001$).

Variceal haemorrhage remains one of the most severe and immediate life-threatening complications in patients with cirrhosis and constitutes the second most frequent decompensating event after ascites.[20] It has long been established that diabetes can induce hepatic microangiopathy characterized by perisinusoidal fibrosis.[21] It is therefore possible that the liver damage specific to diabetes is in addition to that of initial hepatic disease to increase intrahepatic block and lead to worsening portal hypertension. In our study, diabetes was associated with the more frequent occurrence of digestive haemorrhage. In fact, diabetic cirrhotics had a higher prevalence digestive hemorrhage compared to non-diabetic cirrhotics with a statistically significant difference (57.4% versus 12.9% with $p < 0.001$.

Diabetes is considered to be an independent factor of HCC in cirrhotics.[22] With increased mortality linked to HCC in diabetic cirrhotic patients.[23] However, this association has not been confirmed by other studies.[24] In our series, a high prevalence of hepatocellular carcinoma was found in diabetic cirrhotic patients compared to non-diabetic patients with a statistically significant difference ($p = 0.04$).

Regarding the risk of infection, previous studies in patients with cirrhosis have shown an incidence of higher bacterial infections in people with diabetes, due to its immunosuppressive effects.[25] This is consistent with our results where bacterial infections were more frequent in the group of diabetics (70.37%) compared to the group of non-diabetics (45.71%), with a statistically significant difference ($p = 0.003$).

LIMITATION AND OUTLOOK

The major limitation of the study was the retrospective nature but the method comparative study allowed us to draw relevant conclusions.

Another limitation was the unavailability of the follow-up of our patients in endocrinology. From this in fact, the precision of the exact impact of cirrhosis on diabetes has not been mentioned.

The results of our research could also focus on other studies interesting ways of managing diabetes in this group of patients, leading to a better quality of life.

CONCLUSION

In conclusion, co-existent diabetes increases the

incidence of complications in patients with cirrhosis. These results should lead to early detection of diabetes in cirrhotic, and above all to propose preventive actions, particularly nutritional, in order to limit the risk of its occurrence and ensure that the balance of diabetes is maintained.

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