Prevalence and Predictors of Diabetes Mellitus in Chronic Hepatitis C Patients with and without Cirrhosis

Sahar A. El Gharabawy [1], Monir H.Bahgat [1] , Amira K. El Hawary [2]

[1] *Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.*

2 Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Corresponding Author
Sahar El-Garabawy

Mobile:
+21002382208

E mail: drselgharbawy @yahoo.com

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Background and study aim: The highest Hepatitis C Virus (HCV) prevalence in the world occurs in Egypt. The frequency of type 2 diabetes mellitus tends to be high in patients infected with HCV especially those with cirrhosis. We conducted this study to define the prevalence and predictors of diabetes mellitus (DM) in chronic hepatitis C patients with and without liver cirrhosis.

Patients and methods: Four hundred patients with HCV were enrolled (200 without cirrhosis [group I] and 200 with cirrhosis [group II]).Two hundred non hepatic disease subjects were enrolled as a control group [group III]. All patients were subjected to thorough history taking and physical examination. Investigations include liver function tests, viral markers (anti-HCV anti-bodies and polymerase chain reaction (PCR) for HCV), liver biopsy and abdominal ultrasound. Multiple logistic regression analysis was used to adjust for potential confounders.

Results: Prevalence of Type 2 diabetes was 30.25% in HCV patients as opposed to only 6.5 % of control group (p <0.0001, odds ratio [OR] = 2.7).Moreover the prevalence is significantly higher in HCV patients with cirrhosis than in non cirrhotic patients (51% vs. 9.5%), (OR= 9.9, P < 0.001). Partial correlation of prevalence of diabetes mellitus in HCV patients remain highly significant after adjustment for age, sex, family history of diabetes and BMI (r=0.291, P< 0.0001). Using logistic regression; older age, positive family history of diabetes, higher BMI, lower serum albumin level, higher activity and fibrosis score (OR= 1.3,19.4,1.8, 6.6,1.3 and 2.1 respectively) in patients with chronic hepatitis C were found to be associated with higher prevalence of DM (P <0.05), while activity by fibrosis was insignificant.

Conclusion: Chronic HCV is associated with increased risk of diabetes to 2.7-fold.Development of cirrhosis in patients with chronic HCV increases risk of diabetes to 10-folds. This association seems not to be related to the known risk factors for diabetes. Potential predictors for this association might include older age, positive family history of diabetes, higher BMI, lower serum albumin level, higher activity and fibrosis score.

INTRODUCTION

Chronic HCV infection is associated with an increased risk for the development of type 2 diabetes mellitus (DM) [1]. Therefore, type 2 diabetes is more prevalent among patients with chronic HCV compared to those with other liver diseases and the general population, irrespective of the presence or absence of liver cirrhosis [2–4].

An increased prevalence of glucose intolerance and diabetes mellitus among patients with chronic hepatitis C virus (HCV) infection has been reported in several studies [5-9]. An Egyptian study showed that the incidence of type 2 DM is increased two folds in patients who had HCV infection compared with those who did not, and reported that HCV-infected persons with type 2 DM were more likely to need insulin [10]. On the other hand, a higher prevalence of HCV infection has been reported in Spain in diabetic patients (11.5%) in comparison with non-diabetic blood donors (2.5%) [11].

Insulin resistance and progressive pancreatic β-cell dysfunction have been identified as the two fundamental features in the pathogenesis of type 2 DM in those patients [12]. Clinical and

experimental data suggested a direct role of HCV in the disturbance of glucose metabolism. Moreover, HCV can disturb glucose homeostasis via indirect mechanisms including cytokine stimulation [13]. HCV infection itself is a more important predictor of glucose intolerance than cirrhosis, and the combination of both factors further increases the risk of diabetes [14].

Type 2 DM has been suggested to enhance the development of HCC and to be associated with poorer prognosis of liver transplantation [15-17]. Thus, early intervention to prevent or improve type 2 DM seems necessary [18-21].

At the present time, investigating prevalence of type 2 DM in HCV patients in Egypt and whether potential risk factors as age, family history of diabetes, BMI, activity and fibrosis score contribute to it is not yet clear. So, the aims of this study were: *firstly*, to evaluate type-2 diabetes prevalence in chronic hepatitis C patients with and without liver cirrhosis; *secondly*, to investigate whether this relationship between HCV infection and type-2 diabetes could be modified by some risk factors of diabetes including age and obesity, and *thirdly* to study possible risk factors that may predict diabetes in such patients.

PATIENTS AND METHODS

This cross-sectional study was carried out on 400 patients with chronic HCV who were attending the outpatient clinic at Mansoura Specialized Medical Hospital over a 9-month period (January 2012 to September 2012). They were subdivided into two groups; group I which comprised 200 chronic HCV patients without liver cirrhosis and group II which comprised 200 chronic HCV patients with liver cirrhosis. A control group composed of 200 apparently healthy non-hepatic individuals were chosen to look for prevalence of DM.

Exclusion criteria:

- Associated other hepatic disorders as HBV, autoimmune liver disease, etc.
- Patients who had diabetes before or at the onset of diagnosing HCV.
- Patients with HCC or pancreatic tumor.
- Patients with systemic diseases as chronic renal failure.
- Patients using drugs known to alter glycemic state including, systemic steroids, and interferon.

All cases were subjected to the following:

1. Thorough history taking including family history of diabetes.
2. Physical examination including body weight and height to calculate body mass index.
3. Routine laboratory investigations including full blood count, prothrombin time, and liver function tests and blood glucose levels.
4. Diagnosis of HCV infection was based on positive testing for serum anti-HCV markers (Anti-body against HCV was detected with a third-generation enzyme-linked immunoassay).
5. Commercially available polymerase chain reaction assay was done to detect serum HCV RNA (Cobas Amplicor HCV Monitor Test, v2.0, Roche, Tokyo, Japan).
6. Diabetes mellitus was diagnosed according to the American Diabetes Association guidelines (ADA updated criteria, 2008& 2012) [22&23].
7. Abdominal ultrasonography.
8. Liver biopsy was available from all patients except those with advanced liver disease (Child B and Child C). Liver samples were scored for activity and fibrosis using METAVIR score [24&25].

Statistical Analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 17.0 for Windows). All quantitative variables were expressed as mean ± standard deviation. Comparison between groups was done using one-way ANOVA or the Student's t-test, whichever was applicable. Qualitative or categorical variables were described as proportions. Proportions were compared by use of the Chi-squared test or Fisher's exact test, whichever was applicable. Correlation was determined by Pearson's linear regression analysis. All P values are based on a two-sided test of statistical significance. P value of ≤ 0.05 will be considered as significant. Logistic regression analyses were used to evaluate the predictive variables that could be associated with the presence of diabetes.

RESULTS

Table (1): Clinical characteristics of the studied groups.

		Group 1 (n= 200)	Group2 (n=200)	Group 3 (n=200)	F	P value
Quantitative data		Mean ± S.D.				
Age (years)		38.33±9.75	51.25±10.51	46.08±9.87	83.652	<0.0001
BMI (kg/m^2)		21.7±2.55	24.9±2.75	23.6±2.98	70.457	<0.0001
Nominal data		Number (%)			X^2	P value
Sex	Male	131(65.5%)	169(84.5%)	106(53%)	19.253	<.0.0001
	Female	69(34.5%)	31(15.5%)	94(47%)		
FH of DM No. (%)		7 (3.5%)	2 (1%)	2 (1%)	4.630	>0.05

Group 1= HCV without cirrhosis Group2= HCV with cirrhosis

Group 3= control BMI= body mass index FH= Family history

The table showed a statistically significant difference between the 3 groups regarding age, sex, and BMI. On the other hand, positive family history of DM was insignificantly different between groups.

Table (2) : Frequency of diabetes mellitus in HCV & control patients.

Comparison groups		Diabetes mellitus		Chi square test $\chi 2$, p value	Binary logistic regression OR, p value
		N	%		
HCV vs control	HCV (*n* = 400)	121	30.25%	43.359, <0.0001	2.7, **<0.0001**
	Control (*n* = 200)	13	6.5%		
Group (1) vs Group (2)	Group (1) (*n* = 200)	19	9.5%	81.626, <0.0001	9.9, **<0.0001**
	Group (2) (*n* = 200)	102	51%		
Group (1) vs control	Group (1) (*n* = 200)	19	9.5%	1.223, >0.05	0.66, >0.05
	Control (*n* = 200)	13	6.5%		
Group (2) vs control	Group (2) (*n* = 200)	102	51%	96.671, <0.0001	15.6, **<0.0001**
	Control (*n* = 200)	13	6.5%		

OR= odds ratio

The table showed highly significant increased prevalence of diabetes mellitus in HCV patients versus control group, in group 2 versus control group and in group 2 versus group 1 (OR= 2.7, 15.6& 9.9 respectively). Partial correlation of prevalence of diabetes mellitus in all groups remain highly significant after adjustment for age, sex, family history of diabetes and BMI (r=0.291, P< 0.0001). A non significant increased prevalence was found on comparing group 1 with control group (P>0.05).

Table (3): Predictors for development of diabetes mellitus in HCV patients.

Factor	B	P value	OR
Age	0.299	< 0.01	1.35
FH. of DM	2.965	< 0.01	19.4
BMI	0.610	< 0.01	1.84
Serum albumin	0.76	<0.0001	6.6
Activity score	0.262	<0.05	1.3
Fibrosis score	0.755	< 0.001	2.1

B= Regression coefficient

The table showed that each one year more in age , positive family history of diabetes , each one unit higher of BMI , each one gram lower in serum albumin level than 4 grams / dl, each one grade of activity up, and each one stage of fibrosis up increase risk of diabetes by 1.3, 19.4, 1.8, 6.6, 1.3 and 2.1 folds respectively. Age by BMI is still significant (P <0.05{logistic regression}), while activity by fibrosis became insignificant.

DISCUSSION

Several studies have suggested a possible link between HCV infection and an increased prevalence of Type 2 DM [26, 27]. Diabetes mellitus was found to be more prevalent in patients with chronic hepatitis C than in patients with other liver disease [28]. Liver cirrhosis had a strong, independent association with Type 2 diabetes [29].

The present study showed that 30.25% of HCV patients had diabetes as opposed to only 6.5 % of control group (p <0.0001, OR 2.7). Prevalence of Type 2 diabetes was significantly higher in HCV patients with cirrhosis (51%) than in control group (6.5%), (OR 15.6, P < 0.001).Prevalence is also significantly higher in cirrhotic HCV patients (51%) versus non-cirrhotic patients (9.5%), (OR 9.9, P < 0.001). Non significant difference was found on comparing non-cirrhotic HCV patients with control group. This is consistent with previously published results of case-control studies, where the prevalence of DM had been reported in 21% to 50% (a two to ten fold increase in prevalence) among patients with chronic HCV infection, which was significantly higher than that in the general population or among patients with other forms of liver diseases [26,27&29]. However in our study a relatively larger number of patients were used to define the prevalence and predictors of DM in chronic hepatitis C patients. Also, in the present study we tried to define the effect of development of liver cirrhosis on diabetes prevalence in HCV patients. Prevalence was found to be significantly higher in cirrhotic versus non- cirrhotic patients.

Zein et al. [30] also reported that the prevalence of diabetes was significantly greater among patients with hepatitis C compared with those with cholestatic liver disease. They also mentioned that patients with cholestatic liver cirrhosis had a prevalence of diabetes similar to that of an age- and sex-matched general population suggesting that the mechanism of diabetes in patients with liver cirrhosis is related more closely to HCV. An association of type 2 DM and HCV was reported by Bahtiyar et al. [4] in a cohort of 100 patients with cirrhosis; 50% of those with HCV-related cirrhosis had type 2 DM as opposed to only 9% of those with cirrhosis from other etiologies (odds ratio = 10:5). In another cohort, diabetes was observed in 21% of patients with HCV infection, as compared with only 12% of HBV-infected patients [31].

However, the previous data were not adjusted for risk factors for Type- 2 diabetes such as family history of diabetes or BMI. Petit et al. [32] suggested that among individuals with HCV infection, those with diabetes are more likely to have traditional risk factors of diabetes. So, we examined whether this relationship between HCV infection and type 2diabetes could be modified by known risk factors of diabetes. In our study, it was found that the strong association between HCV and DM was not attributable to age, sex, family history of diabetes or BMI. This is comparable to that found by Wlazlo et al. [29] who reported that, classical risk factors such as family history of diabetes and BMI could not explain the association between HCV infection and Type 2 diabetes.

In our study, the frequency of diabetes in control group was 6.5%. This goes in line with that reported by Arafa & Amin [33] in Egyptian adults in 2010 (6.4%) and higher than that in 2008 (4.07%) However, the frequency in the present study might be lower than that expected by speculation in 2012 probably due to exclusion of patients with liver disease in our control group.

In this study, logistic regression analysis confirmed that age, family history of diabetes, BMI, serum albumin level, hepatitis activity and fibrosis score were independent predictors for diabetes mellitus. The study showed that positive family history of diabetes, each one year increase in age, each one unit higher in BMI, each one g/dl lower in serum albumin level, each one grade of activity up, and each one stage of fibrosis up increase risk of diabetes in HCV patients by 19.4, 1.3, 1.8, 6.6, 1.3, 2.1 folds respectively. However this effect disappeared on testing activity by fibrosis. In another study [34] age and residency in urban regions were the predictive variables that could be associated with the presence of diabetes in HCV patients.

Alavian et al. [31] also confirmed that age and HCV infection were independent predictors for diabetes mellitus. However, they found that HCV infection is a more important predictor of glucose intolerance than cirrhosis, and that the combination of both factors further increases the risk of diabetes. This is contradictory to our study which confirmed that cirrhosis is an even more important for the development of diabetes in HCV patients.

CONCLUSION

Chronic HCV is associated with increased risk of diabetes to 2.7-fold.Development of cirrhosis in patients with chronic HCV increases the risk to 10-fold. This association seems not to be related to the known risk factors for diabetes. Potential predictors for this association might include older age, positive family history of diabetes, higher BMI, lower serum albumin level, higher activity and fibrosis score. Further prospective trials are required to confirm these results.

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Peer reviewer: Elsaied Elbadrawy ;Professor of Tropical Medicine, Zagazig University , Egypt, Consultant Gastroenterologist and Hepatologist.
Editor: Tarik Zaher; Assistant Professor of Tropical Medicine, Zagazig University , Egypt, Consultant Gastroenterologist and Hepatologist