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RESEARCH ARTICLE

The incidence of new-onset diabetes mellitus in patients with hepatitis C who finished the standard of care treatment

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Abstract

Background: The combined regimen of peg-interferon α2a plus ribavirin was considered as an effective therapy for hepatitis C infections. However, this combined therapy has been associated with a side effect that can make the course of the disease more complicated. The aim of this study is to quantify the risk of new-onset diabetes mellitus among patients who on-treatment and who finished the standard of care treatment in a large cohort of patients with chronic hepatitis C.

Materials and Methods: We used prospectively obtained data for 600 HCV-infected patients who finished their standard of care treatment within the previous one year, who were free of diabetes at baseline; diabetes is a study end point. Incidence of new-onset diabetes and impaired fasting glucose were assessed at follow-up at 6 months and 12 months. Baseline data for body-mass index (BMI) and other risk factors were recorded at baseline time.

Results: During the one year period of follow-up of the 600 HCV-infected patients who finished their standard of care treatment, 53 patients developed new-onset diabetes (8.9%) and 50 patients developed new-onset IFG (8.3%). Of the 53 patients who developed DM: 11 (1.8%) patients developed DM with the end of treatment, 22 (3.6%) patients developed DM at 6 months after the end of treatment, and 20 (3.5%) patients developed DM at one year of the end of treatment

Conclusion: The treated HCV patients have a higher incidence of new onset diabetes mellitus than the general population (8.9% versus < 0.1% per year).

INTRODUCTION

Hepatitis C is a single-stranded RNA virus which infects an estimated 170 million people worldwide. The prevalence of chronic hepatitis C (HCV) in Northern Europe and North America is 1.0 to 1.7 percent. The prevalence is higher in Southern Europe, in Asia and in Egypt [1].

There is growing evidence suggesting the mutual link between type 2 diabetes mellitus (DM) and chronic HCV infection. Based on case-control studies, the prevalence of DM had been reported in 21% to 24% of patients with HCV infection, which was significantly higher than that in the general population [2]. HCV can be found in pancreatic beta-cells leading to a reduction of glucose-stimulated insulin release [3].

Several clinical epidemiologic studies since 1994 have reported that HCV infection is linked to diabetes [4]. The association between HCV infection, in patients without cirrhosis (that is a well-known risk factor for type 2 diabetes (T2D)), and T2D has been first studied in in HCV positive patients with mixed cryoglobulinaemia by Antonelli A. et al. [5] and in patients with HCV-related chronic liver disease by Antonelli A. et al. [6]. There is one population study (National Health and Nutrition Examination Survey-NHANES III 1988–1994) that showed an adjusted odds ratio of 3.8 for T2D for those who were aged >40 years and HCV positive [7] and increased incidence of T2D [8]. There have been a few reports, too, that IFN treatment of HCV infection improves glucose tolerance [9] when HCV infection is eradicated; however, another study did not confirm these results [10]. Altogether the above mentioned data indicate that HCV chronic infection is a risk factor for developing T2D.

Interferon (IFN) exerts antiviral, antiproliferative, and immunomodulatory actions [11], and is used extensively for the treatment of HCV. Ribavirin (RBV), an antiviral agent, has been reported to reinforce the therapeutic effect of IFN in patients with chronic HCV [12]. In recent years, combined pegylated interferon (PEG-IFN) + RBV therapy has been used as a primary treatment for chronic HCV. However, IFN-induced autoimmune disease has been highlighted as one of the problems with this therapy. In 1992, Fabris et al. [13] reported the case of a patient with HCV who developed type 1 diabetes mellitus following treatment with IFN-α. Since then, cases of type 1 diabetes mellitus associated with IFN monotherapy or combined IFN + RBV therapy have been reported sporadically.

IFN-α therapy has been reported to induce multiple autoantibodies and type-1 diabetes mellitus in patients with chronic HCV infection [14], but Dicesare (1996) has reported that up to 13% of patients developed insulin autoantibody without the development of diabetes [15]. Most reports [7; 16] described the development of insulin-dependent diabetes mellitus during the early phase of therapy with interferon-alfa for HCV, although the disease can present up to 4 years after completion of therapy with interferon. These patients were found to be positive for one or more multiorgan antibodies such as ICA-IgG, anti-GAD antibody, anti-insulin antibodies, anti-insulin receptor antibody and thyroid microsomal autoantibodies. HLA tissue typing demonstrates an autoimmune disease phenotype of HLA-DR 1, 3, 8-allele type.

The incidence of newly onset diabetes related to PEG-IFN-α plus RBV therapy has not been analyzed in recent studies which monitored side effects. Our study is a one of the first studies which try to find the true incidence of DM related to chronic HCV treatments.

Materials and Methods

This observational prospective study was carried out at the internal medicine, faculty of medicine, Zagazig University from September 2013 till Jan 2015. This study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the Institutional Review Board of each participating facility. Informed consent was obtained from all patients. Eligible subjects were previously treated adults who are already finished the standard of care treatment to chronic HCV and are not diabetic before the starting of treatment.

The current analysis included 670 patients aged 18 to 62 years. Patients were treated with standard PEG-IFN- α and RBV therapy according to the American Association for the Study of the Liver Diseases (AASLD) guidelines [17]. Upon enrollment, data were resumed as follows: height, weight, BMI (kg/m2), personal and family history, and ongoing therapies. Exclusion criteria were as follows: previously known T1DM and untreated or treated T2DM; hormone treatments; suspected thyroid diseases; any therapy capable of influencing our data, chronic kidney disease, liver cirrhosis and other liver diseases, gastroenteropancreatic disturbances, and autoimmune disorders.

Glucose metabolism was assessed by fasting plasma glucose; oral glucose tolerance test (OGTT) for glucose; glycated haemoglobin (HbA1c). Lipid analysis included total-cholesterol (t-CHO), HDL-cholesterol (HDL-CHO), low density lipoprotein-cholesterol (LDL-CHO) and triglycerides levels. ADA recommendations [18] were used for the definition of glucose metabolism and T2DM, as follows: normal fasting plasma glucose (FPG) if < 100 mg/dl (5.6 mmol/l); impaired FPG(IFG) if FPG was 100–125 mg/dl (6.9 mmol/l); impaired glucose tolerance (IGT) if 2-h post-OGTT plasma glucose was 140–199 mg/dl (7.8-11.0 mmol/l); T2DM if FPG was ≥ 126 mg/dl (≥7 mmol/l) on two days apart, or if 2-h post-OGTT plasma glucose was ≥ 200 mg/dl (≥11.1 mmol/l). HbA1c values of 5.7 and 6.5% were considered as the threshold of normal glucose metabolism and T2DM, respectively.

Anthropometric and body fat assessment

The following anthropometric measurements were obtained: Weight was assessed by a balance-beam scale while the participant was wearing lightweight clothing. Standing height was assessed by a stadiometer. Body mass index (BMI) was calculated by the Quetlet index: weight in kilograms/height in meters squared (kg/m^2) [19]. WC was measured by use of a metal tape measure at the maximum WC between the lower rib and the iliac crest.

Participants were asked to stand with their weight equally distributed on both feet, with arms hanging at their sides and head facing straight ahead, relaxing their abdomen and breathing normally. The abdominal circumference was measured at eye level directly over bare skin, and the measurement was made at the end of a normal expiration to the nearest 0.1 cm. The measurement was taken twice. If the difference between the first 2 measurements was 1 cm, third and fourth measurements were obtained. The final abdominal circumference value used was the mean of the 2 or 4 recorded values.

Biochemical tests

Blood chemistry analyses were performed in Zagazig University laboratories. Venous blood samples were collected after fasting for 14 hour and 2 hours after the ingestion of 75 gram glucose. Plasma glucose was assayed by an automated glucose oxidase method. HbA 1c were measured by enzymatic methods (Roche Molecular Biochemicals, Mannheim, Germany). Tests for triglyceride were performed on Hitachi Chemistry analyzers with Roche chemistry reagents; settings were as specified by the manufacturer. HDL cholesterol was determined by precipitation with phosphotungstic acid, Sigma Chemical Reagent for in vitro diagnosis. Glomerular Filtration Rate (GFR) was estimated from serum creatinine using the MDRD formula and was expressed as ml/min/1.73 m2 [20].

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc, Chicago, IL). Data are expressed as mean ± SD, or geometric mean and 95% confidence interval (CI) for variables requiring logarithmic transformation. Statistical significance was defined as $P \leq 0.05$.

Results

A total of 670 patients participated in this study. Only 600 patients aged 40.86 ± 22.48 years continue our study and the others discontinue the follow up. The main characteristics of the study population are presented in Table 1. Ranking the participants based on their glucose tolerance status resulted in 497 patients (82.8%) of the studied patients had normal glucose tolerance tests (NGT), 50 patients (8.3%) of the studied patients had developed impaired fasting glucose (IFG) at some time during the period of follow up and 53 (8.9%) patients had developed new onset DM at some time during the period of follow up. Of the patients who developed DM: 11 (1.8%) patients developed DM with the end of treatment, 22 (3.6%) patients developed DM at 6 months after the end of treatment, and 20 (3.5%) patients developed DM at one year of the end of treatment. Table 2 shows the results of these groups.

Table 1: Clinical and metabolic characteristics of the total studied population

Characteristic	Average ± STDEV (min to max)
Number (M to F)	600 (405/195)
Age (years)	40.86 ± 22.48
BMI (kg/m^2)	23.34 ± 3.37
Hemoglobin (gm/dl)	12.9 ± 1.65
White Blood Cells (×10^3/µL)	6.93 ± 1.8
Platelets (×10^3/µL)	219.3 ± 67.7
INR	1.02 ± 0.06
Creatinine (mg/dl)	0.96 ± 0.28
Urea (mg/dl)	29.76 ± 9.4
AST (IU/L)	70.3 ± 16.2
ALT (IU/L)	68.58 ± 17.8
Albumin (gm/dl)	4.46 ± 0.6
Bilirubin (mg/dl)	1.29 ± 0.49
AFP (ng/ml)	2.98 ± 3.9
TSH (mIU/ml)	1.8 ± 1.6
CholesterolHDL (mg/dl)	190.3 ± 37.8
Triglyceride (mg/dl)	114.9 ± 24.24
PCR (iu/ml)	2586106 ± 4504506
Fasting blood glucose (mg/dl) at 0 week	90.18 ± 13.98
Post prandial blood glucose (mg/dl) at 0 week	137.7 ± 77.9
HbA1c (%) at 0 week	5.02 ± 0.61
Fasting blood glucose (mg/dl) at 24 week	91.07 ± 20.3

Post prandial blood glucose (mg/dl) at 24 week	120.5 ± 39.1
HbA1c (%) at 24 week	5.3 ± 0.69
Fasting blood glucose (mg/dl) at 48 week	94.7 ± 25.9
Post prandial blood glucose (mg/dl) at 48 week	141.7 ± 89.2
HbA1c (%) at 48 week	5.26 ± 0.86

BMI= Body mass Index; INR=International normalized ratio; AST=Aspartate Aminotransferase; ALT= Alanine Aspartate Aminotransferase; AFP= alpha feto protein; TSH= Thyroid stimulating hormone; PCR= Polymerase chain reaction; HbA1c= glycated hemoglobin

Table 2: the number of patients developed DM or IFG

DM			IFG		
At end of treatment	**At 6 months after treatment**	**At one year after treatment**	**At end of treatment**	**At 6 months after treatment**	**At one year after treatment**
11	**22**	**20**	**24**	**15**	**11**
Total = 53			**Total = 50**		

All of the 53 patients developed type 2 DM with a mean age equal to 41.91 ± 8.04 (SD); BMI equal to 24.56 ± 3.55; and male to female ratio equal to 39: 14 which is not highly significant different from that of NGT group (table 3).

Table 3: Clinical and metabolic characteristics of the normoglycemic patients in comparison to patients with DM or IFG

Characteristic	NGT	DM	IFG	p
Number (M to F)	547 (366 to 181)	53 (39 to 14)	50 (34 to 16)	
Age (years)	40.75 ± 23.41	41.91 ± 8.04	40.7 ± 10.4	P1=0.689 P2=0.969
BMI (kg/m^2)	23.22 ± 3.33	24.56 ± 3.55	23.14 ± 3.37	P1=0.019 P2=0.846
Hemoglobin (gm/dl)	12.9 ± 1.7	13.23 ± 1.21	12.55 ± 1.37	P1=0.001 P2=0.351
White blood Cells ($\times 10^3/\mu L$)	6.9 ± 1.8	7 ± 1.8	6.7 ± 1.7	P1=0.000 P2=0.001
Platelets ($\times 10^3/\mu L$)	222.9 ± 68.3	182.3 ± 48.74	231 ± 75.5	P1=0.000 P2=0.459
INR	1.02 ± 0.06	1.03 ± 0.45	1 ± 0.14	P1=0.153 P2=0.826
Creatinine (mg/dl)	0.94 ± 28	1.1 ± 0.3	0.93 ± 0.27	P1=0.136 P2=0.127
Urea (mg/dl)	29.7 ± 9.4	30.3 ± 9.34	29.7 ± 8.8	P1=0.303 P2=0.549
AST (IU/L)	69.1 ± 15.6	82.44 ± 17.6	68.4 ± 16.06	P1=0.000 P2=0.007
ALT (IU/L)	68.6 ± 17.9	68.11 ± 16.72	66.4 ± 20.3	P1=0.970 P2=0.717
Albumin (gm/dl)	4.5 ± 0.61	4.19 ± 0.45	4.78 ± 0.65	P1=0.001 P2=0.061
Bilirubin (mg/dl)	1.3 ± 0.51	1.25 ± 0.28	1.3 ± 0.29	P1=0.947 P2=0.302
AFP (ng/ml)	2.79 ± 3.28	4.96 ± 5.3	2.74 ± 3.3	P1=0.029 P2=0.529
TSH (mIU/ml)	1.8 ± 1.6	2.32 ± 1.3	1.64 ± 0.8	P1=0.040 P2=0.172
Cholesterol (mg/dl)	188.55 ± 37.03	207.98 ± 41	184.8 ± 38.2	P1=0.004 P2=0.988
Triglyceride (mg/dl)	113.23 ± 23.3	132.4 ± 27.4	113.24 ± 24.4	P1=0.000 P2=0.136
PCR (iu/ml)	2252506 ± 4075826	4789606 ± 2992686	1704506 ± 2561085	P1=0.000

				P2=0.280
Fasting blood glucose (mg/dl) at 0 week	88.5 ± 9.16	108.04 ± 31.85	102.3 ± 9.9	P1=0.000 P2=0.000
Post prandial blood glucose (mg/dl) at 0 week	135.5 ± 78.95	160.8 ± 62.09	138 ± 7.04	P1=0.002 P2=0.074
HbA1c (%) at 0 week	4.97 ± 0.5	5.55 ± 1.12	4.9 ± 0.56	P1=0.000 P2=0.530
Fasting blood glucose (mg/dl) at 24 week	86.4 ± 8.3	139.2 ± 37.6	91.4 ± 11	P1=0.000 P2=0.008
Post prandial blood glucose (mg/dl) at 24 week	111.43 ± 13.6	214.6 ± 75.8	117.3 ± 15.6	P1=0.000 P2=0.010
HbA1c (%) at 24 week	5.14 ± 0.44	6.54 ± 1.3	5.19 ± 0.42	P1=0.000 P2=0.648
Fasting blood glucose (mg/dl) at 48 week	87.5 ± 8.65	168.9 ± 28.6	97.22 ± 12.7	P1=0.000 P2=0.000
Post prandial blood glucose (mg/dl) at 48 week	128.03 ± 80.2	282.8 ± 41.5	126.68 ± 16.02	P1=0.000 P2=0.002
HbA1c (%) at 48 week	5.03 ± 0.47	7.54 ± 0.55	5.01 ± 05	P1=0.000 P2=0.688
Biopsy activity (A1:A2:A3)	513: 34: 0	31: 20: 2	47: 3: 0	
Biopsy fibrosis (F1:F2:F3))	492: 55: 0	32: 21: 0	42: 8: 0	

* P1=comparison of NGT and DM; P2= comparison of NGT and IFG; BMI= Body mass Index; INR=International normalized ratio; AST=Aspartate Aminotransferase; ALT= Alanine Aspartate Aminotransferase; AFP= alpha feto protein; TSH= Thyroid stimulating hormone; PCR= Polymerase chain reaction; HbA1c=glycated hemoglobin

Discussion

According to the World Health Organization about 150–200 million people worldwide are HCV-infected. The World Health Organization estimate published in 2013 is already more pessimistic. In fact, today more than 300 million people are estimated to be affected [21]. The Egyptian Demographic Health Survey (EDHS), a cross sectional survey including hepatitis C virus (HCV) biomarkers, was conducted in 2008 on a large nationally representative sample. It estimated HCV prevalence among the 15–59 years age group to be 14.7% [22]. Accordingly, Egypt has the highest HCV prevalence in the world [23]. Also the prevalence of diabetes mellitus is alarming. In fact, in 2008 almost 177 million people were estimated to be affected by diabetes worldwide, and this number is expected to double in 2030, and to increase in young people especially in developing-countries [24]. HCV infection can cause cirrhosis, which, through insulin resistance, predisposes the patient to diabetes mellitus. Cross sectional studies performed worldwide suggest that they are indeed closely linked [25]. Whereas this link between HCV and diabetes mellitus is well-established, the association between HCV-related treatment and glucose metabolic disorders and its actual incidence is still debated.

Our study demonstrated that a high incidence of NODM in chronic HCV infected patients who finished the standard of care treatment during the first year after the end of treatment response by a ratio of 8.9% of total patients. This incidence percentage found in our study is very high in comparison to the average annual incidence rate which was 2.42 per 1,000 U.S. Population (0.242%), but rates ranged from 1.79 per 1,000 per year at age 25-44 years to 8.63 per 1,000 per year at age 65-74 years (0.863%). This increase with age is also found in community surveys. Women have slightly higher incidence rates for diagnosis of diabetes than men [26]. In accordance to our results, a nationwide survey of patients with diabetes that developed during or shortly after interferon therapy was published. The survey found that diabetes occurred rapidly after a short duration of interferon therapy (mean 0.68 years). The onset time of diabetes was significantly shorter in patients receiving both interferon and ribavirin than that in patients with interferon monotherapy [27].

Several observational studies have shown a higher incidence of NODM in HCV infected patients. A recent metanalysis that reviewed 7 studies concluded that HCV infection increased the risk of NODM [OR = 1.39 (95%CI: 1.06, 1.83)] [28].

Ali S. et al. [29] also suggest three times higher prevalence of T2D in HCV seropositive patients. Also, data from the literature show a strong association between HCV and T2D. Several reasons can explain the association of T2D with HCV. One of the explanations is that the pathophysiology of HCV-associated T2D consists of a defect in insulin secretion, increased hepatic tumor necrosis factor alpha, excessive hepatic glucose production, and insulin resistance, because the core-encoding region of HCV is sufficient to induce insulin resistance by the previously

defined mechanism via either direct or indirect way [30]. Secondly, a major contribution of already present risk factors of diabetes such as positive family history and advancing age also plays an important role among HCV infected persons [31].

Metabolic evaluation has shown that HCV-infected patients are hyperinsulinemic and have increased peripheral insulin resistance, mainly at hepatic level, in analogy to what happens in T2D and with the characteristic insulin resistance observed in patients with cirrhosis and obesity [32]. Hepatic insulin resistance has been shown in liver biopsy specimens from HCV infected patients, which exhibit diminished signaling through the insulin receptor; furthermore human hepatoma cells expressing HCV core protein show suppression of insulin-induced glucose uptake [33].

It has also been suggested that patients with HCV infection have impaired beta-cell responsiveness, possibly because of direct viral effects on beta-cell function, increasing the risk of diabetes [34]. However, the cause of beta-cell dysfunction in chronic HCV infection, if this really occurs, remains unclear. An autoimmune process, directed against the pancreas, mediated by the virus along with an increased prevalence of other markers of autoimmunity in patients with HCV infection and diabetes, has also been proposed [35]. However, this hypothesis has not been confirmed, since anti-islet cell antibodies have rarely been detected in patients with HCV infection and diabetes [2]. Another possible mechanism may be represented by a direct cytopathic effect of HCV on pancreatic cells, since HCV-RNA has been identified in pancreatic cells [36].

The incidence of newly onset diabetes related to interferon therapy has not been analysed in recent studies which monitored side effects. The first case of type 1 DM related to α-interferon treatment was reported by Fabris et al in 1992 [13]. In 1996, Fatovich et al and Okanoue et al appreciated that the incidence of DM related to interferon treatment was 0.08% (10 of 11241 patients) and 0.7% (5 of 677 patients) respectively [37-38]. Mehta SH. Et al [7] described the development of insulin-dependent diabetes mellitus during the early phase of therapy with interferon-α for HCV, although the disease can present up to 4 years after completion of therapy with interferon. Also, Schreuder et al. [39] showed that the incidence of development of type 1 and type 2 DM during combination therapy were 2.6%, and 1.6% respectively.

In course of interferon therapy, the frequency of glucose intolerance is estimated to be about 0.1-0.6%, while insulin dependent diabetes mellitus (IDDM) with anti-pancreatic islet cell (ICA) antibody or antiglutamic acid decarboxylase (GAD) are described as rare cases [40]. Uto et al. [41] describe a case of IDDM with various autoantibodies including anti-insulin receptor antibody (AIRA). Three are the possible mechanisms supposed to explain the effects of α-IFN on pancreatic dysfunction in patients suffering from HCV infection: 1) viral dsRNA should induce apoptosis in pancreatic beta-cells and also production of α-INF, directly cytotoxic to pancreatic beta-cells; 2) α-IFN should activate apoptosis through oligoadenylate synthase -RnaseL and the protein kinase R; 3) INF should increase regulatory hormone secretion, such as growth hormone, glucagon and injure glucose tolerance [42]. It may suggest that the emergence of IR in chronic HCV is evolved from the multi-factorial, complex context encompassing viral proteins, cytokine cascades, native and adaptive immune responses and environmental factors.

These results underline the importance of periodic plasma glucose monitoring in patients during and after PEG-IFN and ribavirin therapy and weighting the benefits against the near and remote side effects. Also, the candidate patients for interferon treatment should therefore be investigated, in addition to thyroid autoimmunity, also for pancreatic autoantibodies before starting therapy.

Conclusion

Our study is the first in the published literature that focuses on the actual incidence of new-onset diabetes mellitus or glucose intolerance after finishing the standard of care treatment of HCV as a late complication for this treatment during a short period of follow-up. Further research is needed to determine the incidence during a long period of follow up and its pathophysiologic mechanism in this unique population. An appreciation for the incidence of and costs attributable to post-treatment NODM is important for several reasons. In some situations, the risk and cost of diabetes could affect the treatment decision and the need for alternative treatment with morbidity that may reduce the incidence of NODM. Finally, the data provide a baseline against which the effects of new medications may be compared.

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