Journal of Diabetes and Metabolism
ISSN: 2155-6156

Shehab-Eldin et al., J Diabetes Metab 2017, 8:10
DOI: 10.4172/2155-6156.1000766

Research Article Open Access

The Effect of Hepatitis C Virus Eradication with New Direct Acting Antivirals on Glucose Homeostasis in Non-Diabetic Egyptian Patients

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Received date: September 15, 2017; **Accepted date:** October 03, 2017; **Published date:** October 09, 2017

Abstract

Introduction: Chronic hepatitis C (HCV) infection and Diabetes Mellitus (DM) are common health problems in Egypt. HCV treatment by the new Direct Acting Antiviral (DAA) drugs gives hope to eradicate HCV. However, its effect on glucose homeostasis is not studied.

Aim: Study of glucose homeostasis before and after treatment of HCV infected patients with DAA drugs.

Subjects and methods: Eighty patients chronically infected with HCV, diagnosed by quantitative PCR, were subjected to physical examination and anthropometric measurements. In addition, FBS, fasting insulin, CBC, bilirubin, AST, ALT, Serum Albumin and serum creatinine were assessed at the beginning of the study. HOMA-IR, β cell %, BMI and e GFR were calculated. All patients received DAA drugs ± ribavirin for 3 months. All parameters were reassessed at End of Treatment (EOT).

Results: FBS, Hb, AST, ALT and Platelet count were reduced at EOT. Serum bilirubin, fasting insulin and HOMA-IR were significantly increased at EOT. No significant difference as regarding body weight, serum creatinine, e GFR or β cell function. Correlation between insulin resistance at EOT with all basal and EOT measurements showed only a significant positive correlation with basal bilirubin.

Conclusion: Although eradication of HCV by DAA drugs improves glycemic control, it is associated with increased IR. Basal serum bilirubin can predict the development of IR. However, this predictive value is lost with viral eradication by DAA.

Keywords: Glucose homeostasis; Direct acting antivirals; Hepatitis C

Introduction

Chronic Hepatitis C (HCV) infection is a major cause of liver cirrhosis, hepatocellular carcinoma and increased mortality worldwide [1]. In Egypt, The prevalence of HCV infection is estimated to be 9.8% standing as the highest country worldwide infected with Hepatitis c [2].

Diabetes Mellitus (DM) is a devastating disease. The estimated 5 years mortality is estimated at 18.9% of patients with Type 2 Diabetes Mellitus (T2DM). Death is usually related to diabetic complications namely; cardiovascular diseases, nephropathy, and neuropathy with subsequent amputation [3]. Diabetes Mellitus is another major health and economic burden in Egypt. The International Diabetes Federation (IDF) reported Egypt as one of the top 10 countries having a number of patients with DM. It estimated that the prevalence of DM is 15.56% with 7.5 million Egyptian patients having the disease [4].

Glucose homeostasis is disturbed in patients infected with HCV [5]. Moreover, HCV is accused as a risk factor for the development of DM [6]. Several mechanisms were proposed to explain how HCV induces T2DM such as direct viral effects, insulin resistance, pro-inflammatory cytokines and other immune-mediated processes [7,8].

Although the effect of DM on the outcome of HCV infected persons is extensively studied, the effect of HCV infection on the development of DM is not clear. Moreover, no studies tried to study the effect of HCV eradication on the Insulin Resistance (IR) and β cell function with subsequent development of DM [9]. Therefore, the relationship between HCV and DM was described as a two way association [10].

Recently, there is a hope for total cure and eradication of HCV with the revolution of the new Direct Acting Antiviral (DAA) therapy [11]. However, the consequences of viral eradication and the safety of these medications are not yet established. Positive and negative metabolic changes were noted from small studies [12].

Aim of the work

Study the effect of HCV eradication using new DAA on insulin resistance and β cell function in non-diabetic Egyptian cohort.

Study design

This is a prospective intervention study done on 79 naiive chronic HCV infected patients. IR and β cell function were evaluated before and at End of Treatment (EOT) with DAA, namely Sofosbuvir 400 mg and Daclatasvir 60 mg once daily, with/without Ribavirin. The study design was accepted by the local Ethics Committee.

Subjects and Methods

For the purpose of this study, 80 non diabetic patients chronically infected with HCV were selected from Internal Medicine Department, Tropical Medicine Department and Hepatology Department (National Liver Institute), Menoufia University, Egypt. Informed consents were obtained from the shared subjects. Sampling and physical examination of the patients was carried out at the outpatient clinics and the lab workup was done at Medical Biochemistry Department, Menoufia University from October 2016 to Jan 2017.

Subjects

All picked subjects were diagnosed as HCV infected patients for the first time by rapid test using 4th Generation HCV TRI-DOT. Routine biochemical tests, including; FBS, total bilirubin, ALT, AST, creatinine, Hb, Platelets count were done. In addition, HBsAg, Insulin, and HCV quantitative PCR were estimated. All these investigations were redone again to the same individuals after three months of either dual or triple antiviral treatment. All subjects older than 18 years and accepting to share in the study were included. Patients who have DM, Hepatocellular carcinoma, co-infected with Hepatitis B or received previous anti-viral therapy for HCV were excluded from the study.

Methods

Sampling: Samples are taken under complete aseptic conditions, after an overnight fasting for 8 hours. 8 ml venous blood sample were collected from each subject. 4 ml were put in a sterile tube, allowed to clot and centrifuged at 3000 rpm for 15 minutes for separating the serum to assess ALT, AST, total bilirubin, creatinine, FBS and insulin. Two ml of blood were put in EDETA tube to assess Hb, platelets count and HCV quantitative PCR. All sampling procedures were repeated after three months of treatment.

Laboratory methods: Biochemical tests for detection of ALT, AST, total bilirubin, creatinine and FBS were done on Synchron CX9 autoanalyser using kit supplied by Beckman (Beckman Instrument. Inc. Fullerton, California USA). Hepatitis viral marker HCV Ab was done by "ECLIA" using Cobas 411 analyzers (Roche diagnostics, Germany) and RT-PCR for HCV; nucleic acid extraction was done by QIAGEN viral RNA Mini Extraction Kit. Serum Insulin was assayed by using Enzyme Linked Immune Sorbent Assay (ELISA), supplied by WKEA MED SUPPLIES CORP, NEW YORK, USA. ELISA is a solid phase two site enzyme immunoassay. It is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the insulin molecule. During incubation insulin in the sample reacts with anti-insulin antibodies bound to the microtitration well and with peroxidase conjugated anti-insulin antibodies. A washing step removes unbound enzyme labeled antibody. The bound conjugate is detected by reaction with 3,3',5,5' tetramethylbenzidine (TMB, a frequently used chromogenic in ELISAs). The reaction is stopped by adding acid to give a colorimetric endpoint that is read spectrophotometrically at a wave length of 450 nm using a microplate reader.

Calculations

For the purpose of this study the following parameters were calculated:

1. Body Mass Index (BMI) = Weight (Kg)/ Height $(M)^2$
2. Insulin Resistance (IR) was calculated using the following formula: HOMA-IR = Fasting Glucose (mg/dl) × Fasting Insulin (mU/L)/405 [13].
3. β cell function was calculated using the following formula: HOMA-β=360 × Fasting Insulin (mU/L)/ [Fasting Glucose (mg/dl)-63] [13].
4. Glomerular Filtration Rate (GFR) was estimated by the Cockcroft Gault formula: GFR= [(140-age) × body weight (Kg) × 0.85 if female] ÷ [72 × Scr (mg/dl)] [14].

Statistical analysis

Data were calculated using SPSS version 24 and given as the Mean ± Standard Deviation (SD). Statistical difference before and at EOT was analyzed by the Paired sample t test. Relationships between IR and other factors were assessed by Pearson correlation analysis.

Results

Eighty non diabetic chronically infected with HCV patients were subjected to the treatment with DAA. Only one patient did not respond to therapy and excluded from the study. 79 (98.75%) patients were cleared from the virus hence included in the study. Their basal descriptive statistics were included in Table 1.

Parameter	Minimum	Maximum	Mean	SD
Age (Years)	27	71	53.56	10.13
Sex (Male/Female)	29/50			
Weight (Kg)	55	110	74.7	10.27
Height (cm)	150	180	166.47	7.69
BMI Kg/M^2	21.55	42.97	26.99	3.68
Hb gm/dl	9	16	12.84	1.29
Platlet count	83000	478000	220303	71.89
AST (IU/ml)	15	100	41.57	16.55
ALT (IU/ml)	14	199	47.26	24.1
Bilurubin (mg/dl)	0.5	1.3	0.88	0.19
Albumin (gm/dl)	3.2	5.2	4.37	0.5
Creatinine (mg/dl)	0.6	1.4	0.89	0.17
E GFR (ml/min/1.73 m^2)	117.88	139.49	125.94	10.1
PCR of Hep C	5592	5330000	751175	1122769

Table 1: Descriptive statistics of the patients' basal data before start of Therapy.

Comparison before and at EOT showed a significant reduction in FBS, Hb, AST, ALT and Platelet count. On the other hand serum bilirubin, serum insulin and HOMA-IR were significantly increased at EOT (Figure 1). No significant difference as regarding body weight, serum creatinine, e GFR or β cell function (Table 2).

Correlation between insulin resistance at EOT with all basal and EOT measurements showed only a significant positive correlation with basal bilirubin (Figure 2 and Table 3).

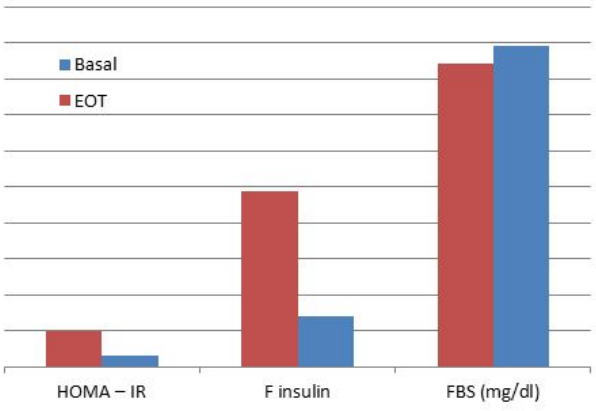

Figure 1: Comparison between basal and EOT results of FBS, fasting insulin and HOMA- IR.

Parameter	Basal	EOT	T Test	P value
Weight (Kg)	74.70 ± 10.27	74.39 ± 9.55	1.7	0.093
Hb (gm/dl)	12.84 ± 1.29	12.11 ± 1.16	6.49**	0
Platelet count	220303 ± 71.89	204.66 ± 68.30	2.63*	0.01
AST (IU/ml)	41.57 ± 16.55	33.30 ± 7.37	6.08**	0
ALT (IU/ml)	47.26 ± 24.10	36.58 ± 8.93	4.92**	0
Bilirubin (mg/dl)	0.88 ± 0.19	1.12 ± 0.24	8.08**	0
Creatinine (mg/dl)	0.89 ± 0.17	0.92 ± 0.18	1.66	0.102
E GFR (ml/min/1.73m^2)	125.94 ± 10.10	125.97 ± 10.11	1.48	0.144
FBS (mg/dl)	89.29 ± 16.66	84.18 ± 13.67	4.62**	0
F insulin	14.02 ± 19.63	48.81 ± 54.28	5.23**	0
HOMA – IR	2.99 ± 3.99	9.95 ± 11.02	5.06**	0
B cell %	278.22 ± 550	356.87 ± 7.67	1.28	0.205
* Significant ** Highly significant				

Table 2: Comparison between all parameters at the start of the study (basal) and at End Of Treatment (EOT).

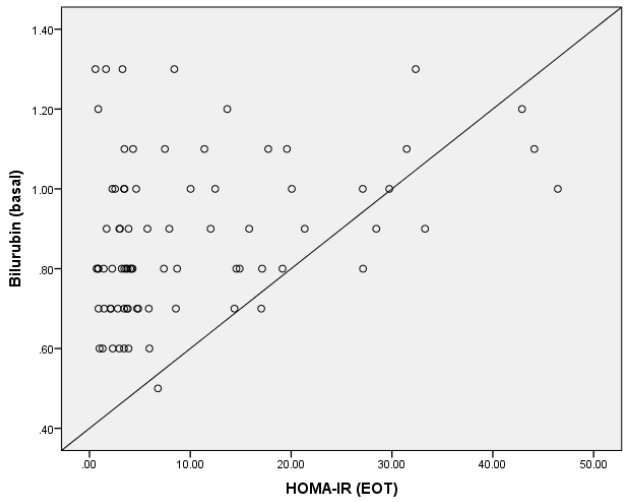

Figure 2: Correlation between Insulin Resistance (EOT) and basal bilirubin.

Parameter	Correlation	P value
Age (years)	0.085	0.455
Height (M)	0.105	0.358
Weight (Kg)	0.131	0.249
PCR of Hep C	-0.021	0.853
Albumin	-0.01	0.893
basal Hb (gm/dl)	-0.009	0.934
Hb (gm/dl) [EOT]	0.043	0.709
basal Platelet count	0.029	0.798
Platelet count [EOT]	0.019	0.867
basal AST (IU/ml)	0	0.999
AST (IU/ml) [EOT]	0.036	0.753
basal ALT (IU/ml)	0.104	0.364
ALT (IU/ml) [EOT]	0.072	0.527
basal Bilirubin (mg/dl)	0.341*	0.002
Bilirubin (mg/dl) [EOT]	0.204	0.071
basal Creatinine (mg/dl)	0.147	0.195
Creatinine (mg/dl) [EOT]	0.046	0.69
basal E GFR (ml/min/1.73m^2)	-0.005	0.964
E GFR (ml/min/1.73m^2) [EOT]	-0.006	0.96
EOT : End of Treatment		

Table 3: Correlation between HOMA-IR at EOT with all basal and EOT parameters.

Discussion

The outstanding finding of this work is the reduction of FBS at EOT. This is in agreement with several studies [12,15-17]. Abdel Alem et al., found a reduction in both FBS and HbA1c after HCV eradication [18]. Moreover, some cases were reported to stop insulin therapy after viral eradication [19]. Similarly, Morales et al., proved the reduction of HbA1c in patients with T2DM after treatment with DAA but they failed to explain this improvement [12]. They suggested an improvement of IR after eradication of HCV. Their work was a retrospective trial on only 52 patients with T2DM. Moreover, they didn't study the mechanisms of DM development. Contrary to their expectation, our work showed a marked increase in IR at EOT (Table 2). Meissner et al., also reported no improvement of IR after treatment with DAA despite lowering of HbA1c in non-diabetic patients [20].

According to our work, the improved glycemic control could be attributed to the increased insulin secretion at EOT (Table 2) which may reflect an improvement of β cell function. Increased insulin secretion could be explained in two ways. The first one is compensation from the pancreas to overcome the increased IR. This assumption is unlikely as the FBS was lower after treatment. Increased insulin secretion to overcome the IR would maximally keep FBS without change. The second assumption is direct inhibition of insulin secretion by HCV itself which improved after eradication. This assumption was proved before by several studies [21,22].

It should be referred to the deleterious cardiovascular outcome of hyperinsulinemia and IR. According to our findings, the call for treating hyperglycemia by eradication of HCV should be reevaluated [17].

The only parameter that correlated with HOMA IR at EOT was basal serum bilirubin. This is in agreement with Lee et al., who discovered recently that serum bilirubin can predict the future development of IR [23]. They explained this association through the link between bilirubin and heme oxygenase-1. Although serum bilirubin was increased significantly at EOT, its correlation with IR was lost which may reflect the effect of DAA treatment on the insulin sensitivity state.

Conclusion

Although eradication of HCV by the new DAA drugs improves glycemic control, yet it increases IR. The value of serum bilirubin to predict future development of IR is lost with this group of drugs.

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