Quest Journals
Journal of Medical and Dental Science Research
Volume 3~ Issue 8 (2016) pp: 42-48
ISSN(Online) : 2394-076X ISSN (Print):2394-0751
www.questjournals.org

Research Paper

IL-6 as biochemical Markers in diabetic patients infected with HCV type4a in Egyptian patients.

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Received 07 September, 2016; **A**ccepted 17 September, 2016 © The author(s) 2016. Published with open access at **www.questjournals.org**

Abstract
Background & Aims: *There is a controversy regarding whether hepatitis C virus (HCV) is associated with diabetic status and the corresponding level of specific cytokines. This work was designed to evaluate the level of IL-6, TNF-α and specified biochemical markers in HCV patients to evaluate the degree of liver dysfunction for prediction of type-2 DM occurrence.*
Patients & Methods: *This study comprised 60 Egyptian individuals aged from 21 to 65 years. They were classified equally into 4 groups; (Group 1 as a control, Group 2 as patients newly diagnosed with type-2 DM, Group 3 as patients suffering from HCV infection and Group 4 as patients suffering from HCV infection associated with type-2 DM). Laboratory measurements were performed to determine plasma IL-6, TNF-α as well as glucose, liver function tests and lipid profile.*
The results: *The main result shows that, the level of IL-6 was significantly increased ($p<0.05$) in diabetic HCV patients when compared with diabetic patients, while no significant difference when compared with HCV infected patients. However, TNF-α did not show any significant relevant among patients. Specified biochemical markers as (FBG, PBG, HbA1C, AST and ALT) were changed significantly.*
Conclusion: *in conclusion we find elevation of serum IL-6 in HCV patients with diabetes so it can used as diagnostic for diabetes susceptibility resulting from viral infection in Egyptian population.*
Keywords: *Hepatitis C, Diabetes mellitus, TNF-α, IL-6, Biochemical markers*

I. INTRODUCTION

Diabetes mellitus is considered one of the main threats to human health in Egypt **1**. The global epidemic of people with type-2 diabetes is largely due to population growth, aging, urbanization, and the scourge of obesity and physical inactivity **[1]**. The prevalence of diabetes in Egypt is 16.6%, according to (IDF) in 2012 whereas the prevalence of diabetes in the world is 8.3%**[2]**.

Hepatitis C virus (HCV) infections have been identified as one of the leading causes of chronic liver disease with serious sequelae such as end-stage cirrhosis and liver cancer [**3]**. HCV infection is affecting 3% of the world's population [**4]**. The highest HCV prevalence in the world occurs in Egypt at an estimated of 12% among the general population [**5]** and reached to 40% in persons 40 years of age and above in rural areas [**6]**.

Metabolic abnormalities are common in patients with HCV infection, there is considerable evidence that patients with chronic HCV are at a greater risk of developing insulin resistance (IR) and ultimately diabetes mellitus (DM) compared with non-infected individuals [**7]**. The suggestion that HCV may be associated with type 2 diabetes mellitus was first made by Allison on 1994 [**8]**. Several studies from different parts of the world have found that 13% to 33% of patients with chronic HCV have associated diabetes mostly type 2 diabetes mellitus [**9]**. In Egypt the prevalence of diabetes mellitus was 25.4% among HCV patients **[10]**.

Lastly, chronic HCV is characterized by a chronic inflammatory state in the liver with increased

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production of pro-inflammatory cytokines such as tumor necrosis factor (TNF) -α and interleukin 6 (IL-6) which can further potentiate IR [**11]**.

TNF-α has been shown by several studies to link obesity, a known major risk factor for type- 2 DM, and insulin resistance. In addition, TNF-α, is an integral part of inflammation in chronic HCV and acts as a link between chronic HCV infection and type-2 diabetes[**12]**.

Accumulating evidence indicates pathological roles for IL-6 in various disease conditions, such as chronic hepatitis and HCV-correlated liver cirrhosis **[13]**. A strong correlation between IL-6 with both insulin resistance and type-2 diabetes were previously recorded **[14]**. Circulating IL-6 has been shown to be elevated two- to threefold in insulin resistant states. The degree of correlation between these levels and severity of insulin resistance is actually higher in many reports than that of TNF-α **[14]**. Interestingly, recent evidence suggests that some of the observed effects of TNF-α may be mediated by its ability to induce IL-6 and IL-6 receptorexpression in tissues such as the liver and muscle **[14]**. Therefore, it seems that insulin resistance mediated by pro- inflammatory cytokines, but not a deficit in insulin secretion, is the main pathogenic mechanism involved in the pathogenesis of diabetes associated with HCV infection**[15]**.

Experimental

Sample collection

Blood was collected for all subjects by vein puncture. Each blood sample was divided into two tubes; The first plan tube used for FBG, PBG, liver function tests, lipid profile, TNF-α and IL-6. While the second one is EDTA tube for estimation of HbA1c.

Biochemical testes

Venous blood samples were taken in the morning after 12-h overnight fast.

Blood HbA1c were measured by using fast ion-exchange resin separation kit manufactured by Human Gesellschaft for Biochemical and diagnostics Germany, plasma glucose and serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), total bilirubin levels (Bil), cholesterol (Chol), and triglycerides (TG) were measured by using BioMed methods including in kits Benfleet's **[16].**

ELISA assays

All patients and controls samples were tested for HBsAg, anti-HBc and anti-HCV antibodies by ELISA, using third generation kits (DiaSorin, Italy) according to the manufacturer'sinstructions.TNF-α and IL-6 measurement Serum TNF-α and IL-6 tests were performed by ELISA using Ray Biotech, Inc, USA. according to the manufacturer's instructions.

HCV-PCR

HCV-PCR was performed in all patients' serum samples using Real Time PCR manufactured by Stratagene, Qiagen, USA.

HCV genotyping

HCV genotype was determined using INNO-LiPA II and III versant Kit (Innogenetics, Ghent, Belgium) according to manufacturer's directions

Statistical analysis

Data was analyzed using SPSSwin statistical package version 17 (SPSS Inc., Chicago, IL) [**17]**, Data were presented in the form of mean ± S.D, and Independent Sample t-test was applied to compare means of each two groups. All tests are two-tailed; a p-value<0.05 was considered significant

II. Results

The demographic findings of this study showed that Egyptian subjects aged ranging from 21 to 65 years, where out of 60 subjects 30 (50%) were females and 30 (50%) were males. Subjects used in this study were divided into equal four groups (Table 1) i.e. Control, Type-2 DM, HCV positive and HCV positive associated with type-2 DM. It was observed that systolic and diastolic blood pressure (SBP and DBP) means in diabetic HCV patients were the highest when compared with HCV infected patients, diabetic patients and control subjects.(Table1)

It was observed that FBG, PBG and HBA1C levels in diabetic HCV patients were highly significant increased ($P < 0.001$) respectively, when compared with HCV infected patients, while their levels were not statistically changed compared with diabetic patients. On the other hand, the levels of FBG and HBA1C in HCV infected patients were not significantly changed compared with control subjects; however the level of PBG was highly significant increased ($P < 0.03$) (Table2).

When liver function tests (LFTs) were analyzed (Table 3), it was found that ALT and AST levels were not significantly changed in diabetic HCV patients compared with HCV infected patients, while their levels were highly significant increased ($p<0.002$) and ($p<0.007$) respectively compared with diabetic patients.In addition, TB level was not significantly changed in diabetic HCV patients compared with either HCV infected patients or diabetic patients.In our study TP level was significantly decreased ($p<0.03$) in HCV infected patients compared with diabetic HCV patients, while its level was not significantly changed in diabetic HCV patients compared with diabetic patients. Our results proved that TA levels were not significantly changed between all groups of our study except that we found significant differences in diabetic patients compared with control subjects. Concerning lipid profile (TC, TG and LDL) levels were not significantly changed between all groups of our study. In addition, the level of HDL was not significantly changed in diabetic HCV patients compared

With eitherHCVinfectedpatientsordiabeticpatients.However,itslevelwassignificantlyincreasedineitherdiabetic HCV patients or HCV infected patients compared with control subjects. (Table 4). The results of this study clearly indicated that no significant differences in TNF-α levels between all groups of our study. (Table 5).It was observed that IL-6 level was not significant change in diabetic HCV patients when compared to HCV infected patients. However, its level was significantly increased ($P < 0.05$) in diabetic HCV patients when compared with diabetic patients. (Table 5) (Figure 1, 2).

Table (1): Demographic and clinical characteristics of study groups:

Groups	**Age**	**Blood pressure Mean ± SD**	
	Mean ± SD	**SBP (mmHg)**	**DBP (mmHg)**
G1	39 ± 11.4	117 ± 11	74.2 ± 6.4
G2	41 ± 12	122.6 ± 8.8	80 ± 6.5
G3	45 ± 13	126.6 ± 11.8	81.6 ± 7.9
G4	53 ± 4.7	126.6 ± 9.7	82.6 ± 7.9

Results are expressed in mean ± SE
a significant when compared to control group b significant when compared to group 2
c significant when compared to group 3

Table (2): Statistical analysis of Glucose parameters in studied groups:

	FBS (mg/dl)	**PP BG (mg/dl)**	**Hb A1c (%)**
G1	**84.4 ± 2.4a**	**103.8 ± 1.8 a**	**6.2 ± 0.05a**
G2	**213.9 ± 15.9a**	**267.1 ± 16.8a**	**9.9 ± 0.23a**
G3	**87.4 ± 3.09c**	**115.9 ± 2.8c**	**6.2 ± 0.08c**
G4	**221.4 ± 22.2a,b**	**283.3 ± 24.6 a,b**	**9.41 ± 0.27a,b**

Results are expressed in mean ± SE
a significant when compared to control group b significant when compared to group 2
c significant when compared to group 3

Table (3): Statistical analysis of Liver parameters on studied groups:

	AST (U\L)	**ALT (U\L)**	**TP (mg/dl)**	**ALB (mg/dl)**	**TB (mg/dl)**
G1	26.1 ± 0.9	25.4 ± 1	7.2 ± 0.15	3.6 ± 0.06	0.5 ± 0.02
G2	28 ± 2.5	27.6 ± 4.3	7.1 ± 0.13	3.8 ± 0.08a	0.7 ± 0.05a
G3	51.4 ± 5.2 **a, c**	59 ± 8 **a, c**	6.8 ± 0.12 **a**	3.8 ± 0.12	0.7 ± 0.08 **a**
G4	59.2 ± 10a,b	51 ± 4.9a,b	7.3 ± 0.20	3.7 ± 0.07	0.8 ± 0.1a,b

Results are expressed in mean ± SE
a significant when compared to control group b significant when compared to group 2
c significant when compared to group 3

Table (4): Statistical analysis of Lipid parameters in studied groups:

	T Cholesterol (mg/dl)	TG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
G1	178.2 ± 3.77	145.9 ± 7.1	31.8 ± 1.1	119.4 ± 2.5
G2	180.4 ± 6.4	126.1± 14.06	40.7 ± 2.6a	113.6 ± 4.1
G3	180.2 ± 8.2	138.5 ± 11.5	38 ± 1.9a	121.9 ± 4.4
G4	186.9 ± 7.1	139.4 ± 10.2	40.06 ± 1.4a	118 ± 4.7

Results are expressed in mean ± SE
a significant when compared to control group b significant when compared to group 2
c significant when compared to group 3

Table (5): Statistical analysis of TNF-α and IL-6 in studied groups:

	TNF- □ (pg/ml)	IL-6(pg/mL)
G1	0.14 ± 0.010	0.14 ± 0.117
G2	0.14 ± 0.017	0.14 ± 0.152
G3	0.13 ± 0.019	0.20 ± 0.024a,b
G4	0.12 ± 0.129	0.22 ± 0.034a,b

Results are expressed in mean ± SE
a significant when compared to control group b significant when compared to group 2
c significant when compared to group 3

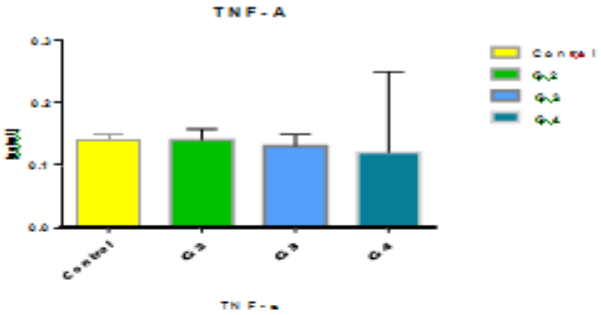

Figure 1. TNF-A concentration (pg/mL) among all groups

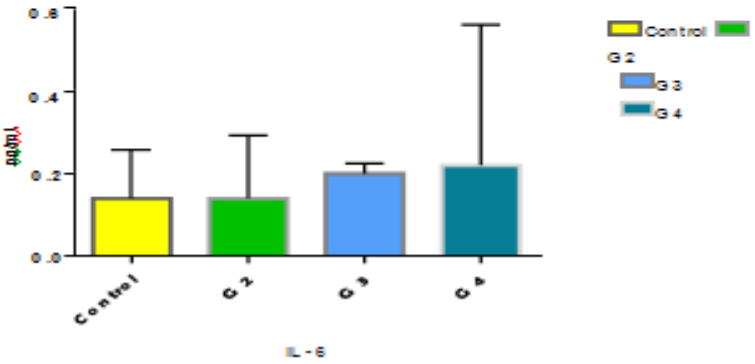

Figure 2. IL-6 concentration (pg/mL) among all groups

III. DISCUSSION

In this study, the mean of systolic and diastolic blood pressure (SBP and DBP) for diabetic HCV patients were (126.6 mmHg ± 9.7) and (82.6 mmHg ± 7.9) respectively, which is the highest in comparison with HCV infected patients, diabetic patients and control subjects, and this finding agreed with **Abdel Aziz *et al*. [18].** While **Nabil *et al*. [19]** reported that the mean systolic and diastolic blood pressure was significantly higher in diabetic patients in comparison with HCV diabetic or controls, and these results disagree with our findings.

Researchers have revealed that HCV eradication increase insulin sensitivity with reduced incidence of diabetes [**20]**. HCV core protein induces changes in signaling in the pathway of insulin [**21]**. Therefore, there is a decrease in the secretion of insulin and a rise in glucose level in blood [**21]**. In diabetic HCV patients FBG, PBG and HbA1C were significantly higher than in non-diabetic HCV patients **22, 23**, which are in agreement with our findings. It was observed that levels of PBG were highly significantly increased by 11% ($p<0.03$) in HCV infected patients compared with control subjects. Hence, HCV infection may adversely influence diabetes prognosis, where this result is in agreement with the result of **Naing *et al*. [24]** and **Lecube *et al.* [25]** found that HCV infected patients should be considered a high risk group for type-2 diabetes development. **Kawaguchi*et al.* [26]** reported that although fasting glucose levels were similar among all of the groups, fasting insulin and HOMA-IR levels, an indicator of insulin resistance, were significantly increased in patients with HCV infection compared to the other hepatobiliary disorders. β-Cell function evaluated by HOMA-β was also increased in patients with HCV infection compared to controls. These findings indicate that HCV infection induced insulin resistance and fasting glucose levels was compensated by hyperinsulinemia, and these findings are in agreement with our results, where the levels of FBG were not significantly increased in HCV infected patients compared with control subjects which can be explained by hyperinsulinemia compensation for fasting blood glucose

levels. Our results demonstrated that ALT and AST levels was not changed in diabetic HCV patients compared with HCV infected patients, where these results are in congruence with **Nassif*et al*. [27].** The cause of not significant findings for ALT and AST between diabetic and non diabetic HCV patients in our study can be explained by **Yano*et al*. [28]** found that the accuracy of ALT and AST for detecting hepatitis C is low. **Ramana*et al.* [29]** and **Nassif *et al*. [27]** concluded that ALT and AST were found to be significantly higher in diabetic HCV patients than diabetic only patients, which are in agreement with ourfindings.**Memon *et al*.[30]** and **Elhawary *et al*.[31]** found that TB level was not changed in diabetic HCV patients compared with HCV infected patients, where similar results obtained in our study**.** We found no difference between diabetic HCV patients compared with diabetic patients, where this result is disagreed with**Nabil *et al.* [19]**. The cause of not significant difference for bilirubin in HCV diabetic patients compared with diabetic patients in our study can be explained by **Fayyazi *et al*. [32]** stated that Bilirubin can be elevated in many liver-related and non-liver- related conditions, so the level of serum bilirubin is not a sensitive indicator of liver function and it may not accurately reflect the degree of liver damage.

In our study the level of total protein (TP) was significantly decreased ($p<0.03$) in HCV infected patients compared with diabetic HCV patients, while the level of TP was not changed in diabetic HCV patients compared with diabetic patients, and these results differ from **Bashir *et al.* [33]** reported that total protein has not shown any statistically significant result in all study groups. The total protein estimation may not be helpful to identify liver disease. Only 29 out of 50 liver disease patients had lower total protein, so no single parameter amongst Liver function tests can rule out liver disease **[34],** where these findings can explain the cause of not significant findings of TP in our study.

It was demonstrated that the level of TA was not changed in diabetic HCV patients compared with either HCV infected patients or diabetic patients [**33, 35],** where similar results obtained in our study. In the present study levels of TC, TG, LDL and HDL were not changed in diabetic HCV patients compared with either HCV infected patients or diabetic patients, which disagreed with **Liu *et al.* [35].** Cholesterol, triglycerides and LDL are significantly higher diabetic HCV patients than HCV patients, while HDL showed no significant difference [**36],** where these findings are different from our results. **Bashir *et al. [*33]** reported that among three groups, the diabetic HCV group showed a marked increase in serum cholesterol and triglyceride level than other two groups. On the other hand, LDL was slightly higher than normal in an HCV only group, relatively more raised in diabetes only groups while markedly raised in the diabetic HCV group. HDL was observed insignificant in all three groups of patients**,** where these findings are different from our results. The cause of not significant difference in total cholesterol, triacyl glycerol, LDL and HDL levels between diabetic HCV patients and non-diabetic HCV patients in our study can be explained by **Vincent *et al*. [38]** found that HCV infection was independently associated with diabetes only in subjects without hyperlipidemia.

It was observed that compared to non-diabetic patients with HCV infection, HCV patients with diabetes had increased serum and liver markers of increased inflammation and fibrosis. Thus, given the correlation between the activity of the liver disease and insulin resistance, a link between chronic HCV infection, TNF-α and type 2 DM is an attractive hypothesis **[39],** and these results are in opposition to our findings, where we did not find any significant result for TNF-α between diabetic and non-diabetic HCV. **Waleed *et al*. [40]** reported that there was no significant difference between patients with HCV and those with HCV+DM regarding the serum TNF-α, where these results in agreement with our findings. In our study, we found that levels of TNF-α were not changed in diabetic HCV patients compared with diabetic patients, which are disagreed with **Waleed *et al*. [40].** We didn't find any significant differences in TNF-α levels or results in our study; this may be due to a small sample size in our study.

Zuwa □a-Jagie □ □o*et al.* [41] reported that a high significant difference for patients with HCV+DM when compared with HCV regarding IL-6 plasma concentrations**,** where these results in opposition to our findings. Serum IL-6 was not significantly different between HCV patients with or without DM [**41],** which in agreement with our findings. In the present study the level of IL-6 was significantly increased by 57% ($p<0.05$) in diabetic HCV patients compared with diabetic patients, which maybe correlate with the severity of inflammation related to HCV infection. In addition the level of IL-6 was significantly increased by 57% ($p<0.04$) in diabetic HCV patients compared with control subjects, which in consistence with **Lecube *et al*. 16** reported that in HCV infected patients, IL-6 levels have been found to be higher than non HCV infected population and correlate with the histological severity of inflammation. **Zuwa □a-Jagie □ □o *et al*.41** and **Nagwa *et al.* [43]** demonstrated that serum levels of IL-6 were significantly higher in all HCV infected patients compared with control group, and these results in agreement with our findings, where the level of IL-6 was significantly increased by 42% ($p<0.01$) in HCV infected patients compared with control subjects.

IV. CONCLUSION

In conclusion, our findings are suggesting a potential role of IL-6 in association between HCV and type-2 DM so IL-6 must be followed-up. In addition, TNF-α and specified biochemical markers as (FBG, PBG, HbA1C, AST, ALT, SBP and DBP) can be used in HCV patients to evaluate the degree of liver dysfunction for prediction of type-2 DM occurrence.

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