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IMPACT OF DIABETIC CONTROL ON ACHIEVING SUSTAINED VIROLOGIC RESPONSE IN CHRONIC HCV PATIENTS RECEIVING DIRECT-ACTING ANTIVIRALS

By

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Abstract

This study evaluated the effect of diabetic control on achieving sustained virologic response in patients with chronic hepatitis C virus infection who received direct-acting antivirals (Daclatasvir + Sofosbuvir ± Ribavirin). It included 100 patients with chronic HCV infection (Treatment naive patients). Patients were classified into 3 groups according to diabetic control; GI: non diabetics, GII: well controlled diabetics & GIII: poorly controlled diabetics. All were subjected to clinical and laboratory examinations, abdominal ultrasonography and calculation of FIB-4 score. PCR for HCV RNA was assessed prior to treatment, post treatment and 12 weeks post-treatment**.**

The results showed insignificant differences between all groups as regards sustained virologic response. Overall sustained virologic response was achieved in 91% of patients including 91.8% of patients treated with Daclatasvir + Sofosbuvir and 89.7% of those treated with Daclatasvir + Sofosbuvir + Ribavirin.

Keywords: hepatitis C, type-2 DM, diabetic control, direct-acting antivirals.

Introduction

Egypt was confronted with HCV disease burden of historical proportions that distinguished it from others (Gomaa *et al*, 2017). A massive HCV epidemic at the national level must have occurred with substantial transmission still ongoing today (Mohamoud *et al*, 2013). On the other hand, the International Diabetes Federation (IDF) identified Egypt as the ninth leading country in the world for the number of patients with T2D. Prevalence of T2D in Egypt was almost tripled over the last 2 decades (IDF, 2015). Hepatitis C virus infection proved to be linked to a higher prevalence of type 2 diabetes (Zhou *et al*, 2010). Association was due to Beta-cell dysfunction together with insulin resistance (IR) that occurred early in the course of the disease even in patients without or with minimal fibrosis (Negro and Alaei, 2009). The mechanisms for HCV-induced IR are only partly understood and include a direct inhibitory effect of HCV on insulin signaling pathway (Chehadeh *et al*, 2009). Insulin resistance in chronic HCV caused increased rate of progression of hepatic fibrosis, cirr hosis & HCC (Hammerstad *et al*, 2015). IR reduces response rate to pegylated interferon (PEG-IFN) & Ribavirin (RBV) combination therapy. IR effects on response to direct-acting antivirals (DAAs) based regimens was unknown (Knobler and Malnick, 2016).

Patients and Methods

This study was conducted in the Gastroenterology and Hepatology Unit, Internal Medicine Department, Ain Shams University Hospitals, from February 2017 to August 2017, on 100 patients with chronic HCV infection (treatment naive, Child's A patients). The study was carried out according to the ethical standards for human experimentation approved by the human research committee of Ain Shams University Hospitals and informed consents were obtained from them.

Patients were classified in to 3 groups according to diabetic control: GI: 40 non diabetic patients, GII: 30 with well controlled type-2 DM, HBA1C<7 and GIII: 30 with poorly controlled type-2 DM, HBA1C>7. Patients were subjected to history taking, clinical and laboratory examinations, abdo-

minal ultrasonography & calculation of FIB 4 score. Significant fibrosis= FIB4 score > 2.67 (≥F3). Qualitative PCR for HCV/RNA was assessed prior to treatment, post treatment and 12 weeks post-treatment to evaluate sustained virologic response (SVR).

Results

The results were shown in tables (1 to 12)

Table 1: Comparison between studied groups regarding the demographic data

Variable		GI		GII		GIII		P-value
		No	%	No	%	No	%	
Sex	Male	20	50.00	15	50.00	10	33.33	0.308
	Female	20	50.00	15	50.00	20	66.67	
Age (Years)	Range	20 - 73		34 – 70		30 - 69		0.001
	Mean ±SD	46.450 ±13.873		55.773 ± 9.373		56.133 ± 9.666		
TUKEY'S Test								
GI & GII		GI & GIII		GII & GIII				
0.003		0.002		0.990				

Insignificant differences between all as to sexes, a significant difference as to age between GI & GII, and GI & GIII.

Table 2: Comparison between groups regarding BMI

Groups	BMI (kg/m2)		ANOVA	
	Range	Mean±SD	F	P-value
GI	21.7 - 28.9	27.04± 2.13	4.156	0.019
GII	21.6 - 30	27.04± 2.49		
GIII	21.4 - 29.7	27.04± 2.54		
TUKEY'S Test				
GI & GII	GI & GIII	GII & GIII		
0.348	0.014	0.353		

Significant difference regards BMI between GI & GIII.

Table 3: Comparison between groups regarding liver function tests

Items	GI	GII	GIII	F	P-value
ALT (U/ml) Range	10 – 142	24 – 216	15 – 99	1.257	0.289
Mean ±SD	48.125 ± 29.784	56.167 ± 38.215	43.700 ± 23.515		
AST (U/ml) Range	12 – 149	22 – 141	11 – 143	0.832	0.438
Mean ±SD	45.675 ± 27.631	54.900 ± 33.400	48.133 ± 29.733		
Albumin (mg/dl) range	3.3 – 4.8	3 – 4.6	3.3 – 5	0.348	0.707
Mean ±SD	4.015 ± 0.383	4.017 ± 0.357	3.947 ± 0.395		
T. Bilirubin (mg/dl) range	0.3 – 1.2	0.3 – 1.5	0.4 – 1.5	1.378	0.257
Mean ±SD	0.768 ± 0.241	0.707 ± 0.302	0.827 ± 0.305		
INR range	1 -1.4	1 - 1.4	1 - 1.4	0.142	0.868
Mean ±SD	1.075 ± 0.097	1.081 ± 0.115	1.066 ± 0.103		

Insignificant differences between all groups regards liver function tests

Table 4: Comparison between groups regarding lipid profile

Item	GI	GII	GIII	F	P-value
Fasting Triglycerides (mg/dl) range	60 - 191	70 – 251	84 - 322	7.240	0.001
Mean ±SD	112.075±29.505	133.267 ± 49.405	157.833±68.495		
TUKEY'S Test					
GI &GII	GI & GIII	GII & GIII			
0.188	0.001	0.141			
Fasting Total Cholesterol (mg/dl) range	69 - 208	90 – 233	91 - 255	10.588	<0.001
Mean ±SD	127.725±26.071	143.000 ± 31.237	168.167±50.524		
TUKEY'S Test					
GI &GII	GI & GIII	GII & GIII			
0.197	<0.001	0.024			
Fasting HDL (mg/dl) range	25 – 71	29 – 91	28 - 76	0.747	0.477
Mean ±SD	49.65 ± 11.116	49.47 ± 14.002	46.27 ± 12.357		
Fasting LDL (mg/dl) range	45 – 195	53 – 168	52 – 203	0.455	0.636
Mean ±SD	95.85 ± 37.817	96.6 ± 29.478	103.767 ± 34.136		
Fasting VLDL (mg/dl) range	12 – 38.2	14 – 50.2	16.8 – 64.4	7.240	0.001
Mean ±SD	22.415 ± 5.901	26.653 ± 9.881	31.567 ± 13.699		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
0.188	0.001	0.141			

Significant differences regard fasting triglycerides between GI & GIII, fasting total Cholesterol between GI & GIII and GII & GIII, and fasting VLDL between GI & GIII.

Table 5: Comparison between groups regarding fasting blood sugar, 2 hours post prandial blood sugar and HbA1c

Variable	GI	GII	GIII	F	P-value
FBS (mg/dl) Range	65 - 102	97 – 183	130 - 245	143.750	<0.001
Mean ±SD	89.950 ±8.006	134.367 ± 17.567	178.867 ± 34.522		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
<0.001	<0.001	<0.001			
PPBS (mg/dl) Range	92 - 132	130 – 209	154 - 315	185.530	<0.001
Mean ±SD	115.55 ±10.32	163.167 ± 17.050	230.367 ± 40.045		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
<0.001	<0.001	<0.001			
HBA1C (%) Range	4 – 5.7	5.7 – 6.9	7.2 - 11	234.815	<0.001
Mean ±SD	4.958 ± 0323	6.537 ± 0.34	8.203 ± 1.018		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
<0.001	<0.001	<0.001			

Significant difference regards fasting blood sugar, 2 hrs post prandial blood sugar and HbA1c between groups.

Table 6: Comparison between groups regarding fasting insulin & HOMA-IR

Variable	GI	GII	GIII	F	P-value
Fasting Insulin (mU/mL) range	7.6 – 19.1	6.5 – 21.5	6.5 – 22.5	4.489	0.014
Mean ±SD	13.825±3.032	15.133 ± 4.138	16.517 ± 4.119		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
0.318	0.010	0.326			
HOMA-IR range	1.63 – 4.47	2.11 – 7.54	2.23 – 12.09	59.177	<0.001
Mean ±SD	3.089± 0.812	4.988 ± 1.437	7.350 ± 2.418		
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
<0.001	<0.001	<0.001			

Highly significant difference regards fasting insulin between GI & GIII and HOMA-IR between all groups.

Table 7: Comparison between groups regarding FIB4 Score

Fibrosis	GI		GII		GIII		Total		Chi-Square	
	No	%	No	%	No	%	No	%	X2	P-value
FIB-4 <1.3 (≤F1)	23	57.50	11	36.67	9	30.00	43	43.00	6.446	0.168
FIB-4 1.3:2.67 (>F1:<F3)	10	25.00	10	33.33	10	33.33	30	30.00		
FIB-4 >2.67 (≥F3)	7	17.50	9	30.00	11	36.67	27	27.00		
Total	40	100.00	30	100.00	30	100.00	100	100.00		

insignificant differences between all groups as regards number of patients with significant fibrosis

Table 8: Comparison between groups regarding pretreatment viral load

Groups	HCV before treatment by PCR			ANOVA	
	Range	Mean ± SD		F	P-value
G I	146 - 4448000	536014.400 ± 894027.587		3.532	0.033
GII	10580 - 4000000	958939.433 ± 1234992.368			
G III	7811 - 4374000	1224352.700 ± 1186702.449			
TUKEY'S Test					
GI & GII	GI & GIII	GII & GIII			
0.251	0.029	0.617			

Significant difference regards pretreatment viral load between GI & GIII.

Table 9: Comparison between groups regarding end of treatment response (ETR)

Group	ETR	SOF+DAC TTT Option		SOF+DAC+RBV		Total		Chi-Square	
		No	%	No	%	No	%	X^2	P-value
GI	Negative	29	96.67	9	90.00	38	95.00	0.702	0.402
	Positive	1	3.33	1	10.00	2	5.00		
GII	Negative	15	83.33	12	100.00	27	90.00	2.222	0.136
	Positive	3	16.67	0	0.00	3	10.00		
GIII	Negative	12	92.31	15	88.24	27	90.00	0.136	0.713
	Positive	1	7.69	2	11.76	3	10.00		

Insignificant difference between groups regards ETR.

Table 10: Comparison between groups regarding SVR

Group	SVR	TTT Option						Chi-Square	
		SOF+DAC		SOF+DAC+RBV		Total			
		No	%	No	%	No	%	X^2	P-value
GI	Negative	29	96.67	9	90.00	38	95.00	0.702	0.402
	Positive	1	3.33	1	10.00	2	5.00		
GII	Negative	15	83.33	12	100.00	27	90.00	2.222	0.136
	Positive	3	16.67	0	0.00	3	10.00		
GrIII	Negative	11	84.62	15	88.24	26	86.67	0.084	0.773
	Positive	2	15.38	2	11.76	4	13.33		

Insignificant difference between groups regards SVR.

Table 11: Multivariate analysis for achieving SVR (done for all patients)

All patients	Odd ratio	95.0% C.I. for Odd ratio	P-value
Sex	2.670	0.484-14.733	0.260
Age	1.013	0.941-1.091	0.725
Treatment Option	0.920	0.148-5.734	0.929
HOMA-IR	1.155	0.732-1.825	0.536
HBA1C	1.006	0.493-2.053	0.987
FIB4	0.783	0.392-1.564	0.489
Pretreatment viral load	1.000	1.000-1.000	0.754
SVR for all patients			

Insignificant impact of sexes, age, treatment option, HOMA-IR, HbA1c, FIB4 & pretreatment viral for achieving SVR among all patients.

Table 12: Multivariate analysis for achieving SVR done for diabetic patients (GII & G III)

Diabetic patients	Odd ratio	95.0% C.I. for Odd ratio	P-value
Sex	2.330	0.311-17.440	0.410
Age	0.962	0.881-1.050	0.382
Treatment Option	0.573	0.067-4.901	0.611
HOMA-IR	1.079	0.680-1.712	0.748
HBA1C	1.004	0.413-2.437	0.993
FIB4	0.804	0.360-1.796	0.595
Pretreatment viral load	1.000	1.000-1.000	0.854
SVR for diabetic patients			

Insignificant impact of sexes, age, treatment option, HOMA-IR, HbA1c, FIB4 & pretreatment viral for achieving SVR among diabetic patients.

Discussion

Epidemiological data have revealed a clear link between HCV infection and disturbed glucose homeostasis (Negro and Alaei, 2009). The prevalence of both DM and IR was higher among patients chronically infected with HCV when compared with either general population or with those with other causes of chronic liver disease (Hammerstad *et al*, 2015).

Both IR and DM are associated with a higher risk for worse outcomes of HCV infection, including progression to fibrosis and cirrhosis, and higher risk for development of HCC (Hammerstad *et al*, 2015). There is also great evidence of a central role for insulin resistance, a fundamental finding in type 2 DM, in failure to achieve SVR in HCV patients receiving PEG-INF based regimens (Shintani *et al*, 2004; Sung *et al*, 2004; D'Souza *et al*, 2005; Dharancy *et al*, 2005; Romero-Gomez *et al*, 2005; Konishi *et al*, 2007; Conjeevaram *et al*, 2007).

As regards the liver function tests (LFTs), the present study showed insignificant difference between the 3 studied groups. This finding agreed with Chehadeh *et al.* (2009) who found insignificant differences regarding LFTs between HCV diabetic patients and non-diabetic patients. However, Abdelaziz *et al*. (2016) found that HCV infected patients with type2 DM had a higher incidence of LFTs abnormalities than the non-diabetic patients.

Regarding fasting Triglycerides, fasting total cholesterol and fasting VLDL, HCV poorly controlled diabetic patients had significantly higher mean values than other

groups. These results agreed with Irazola *et al.* (2017) who found a significant association between hypercholesterolemia and hypertriglyceridemia with DM.

The HCV-DM association is mainly due to IR that occurs early in the course of the disease. The current study revealed a significant difference regarding HOMA-IR score between the 3 studied groups. Hyperinsulinemia is the hallmark of IR. Thus, the current study revealed a significant difference regarding fasting serum insulin between HCV non-diabetics and HCV poorly controlled diabetic patients. These findings agreed with Moucari *et al.* (2008) they found that IR proved to be a specific feature of chronic HCV infection especially among patients with genotypes 1 & 4 and those with high serum HCV/RNA level.

The present study showed insignificant differences between the three groups as regards fibrosis stage. This finding agreed with Elgouhari *et al.* (2009) who found insignificant association between DM and stage of fibrosis after accounting for other confounding variables. On the other hand, Moucari *et al.* (2008) reported contradictory results stating that significant fibrosis was independently associated with IR after exclusion of patients with decompensated cirrhosis. The discrepancy between the reported results could be attributed to differences in host, metabolic and viral factors, ethnicity, number of patients included in each study and other co-morbidities.

Regarding pretreatment viral load, poorly controlled diabetic patients were more likely to have higher viral loads. This finding agreed with Moucari *et al.* (2008) they reported a significant association between IR and higher viral loads. Knobler and Malnick (2016) suggested that with such effective DAA-based regimens; the previously reported effect of DM and IR on lowering SVR rates would be less evident. The present study showed that diabetic control patients had no effect on achieving ETR or SVR in chronic HCV genotype 4 infected patients who received DAAs (DCV + SOF ± RBV for 12 weeks). This finding matched with Willemse *et al.* (2016), as type2 DM had no effect on virological response to sofosbuvir/ simeprevir combination. Both Serfaty *et al.* (2012) and Younossi *et al.* (2013) also reported that HOMA-IR had no effect on virological response to telaprevir-based regimens. But, Nasrollah *et al*. (2015) reported contradictory results stating that metabolic factors such as DM and hyperlipidemia still compromised the effect of DAAs treatment.

The present study revealed an overall SVR of 91% including 91.8% of patients treated with DCV + SOF and 89.7% of those treated with DCV + SOF±RBV. These results agreed with Welzel *et al.* (2016) who reported that SVR was achieved by 91% of the 460 patients, including 92% of whom were treated with DCV + SOF and 89% of those treated with DCV+ SOF+ RBV. However, the higher SVR rates were reported by Eletreby *et al.* (2016) with an overall SVR rate of 94.0%.

Abdel-Razek and Waked (2015) suggested that the potency of second generation DAA might minimize the role of predictors of response to PEG-IFN/RBV therapy.

In the present study, multivariate logistic regression analysis was done to assess different pretreatment confounding factors that may affect the SVR. Insignificant effects were found as regards gender, age, treatment option, HOMA-IR, HbA1c, FIB-4 score and pretreatment viral load.

This observation disagreed with Elsharkawy *et al*. (2017), who reported that male gender, lower baseline serum albumin, platelet count and higher baseline INR and AST were significantly associated with treatment failure as these factors might be associated with more advanced liver fibrosis. Also, Eletreby *et al.* (2016) found that low serum albumin and higher Fib-4 score were associated with the greater likelihood of not achieving SVR in the patients with HCV infection who received DAAs.

Conclusion

The outcome data showed that Daclatasvir + Sofosbuvir ± Ribavirin combination for 12 weeks proved an effective and well tolerated regimen for patients with chronic HCV. Diabetic control did not affect SVR rate in these patients.

However, management of metabolic alterations remains a relevant strategy to limit progression of liver disease.

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