Direct Acting Antiviral and Glycemic Control In Patients with Hepatitis C

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Abstract: Background sustained virological response (SVR) can be achieved in high percentage of HCV patients with the availability of direct acting antiviral agents DAAs. However, the effect of DAAs on insulin resistance and glycemic control has to be clearly documented in patients with HCV infection and type 2diabtes mellitus.

We hypothesize that treatment of HCV with novel direct-acting antiviral medications may have effect on glycemic control and decreased requirement for DM-modulating medications at the time of SVR.

Patients and methods: the present study involved 50 patients with Chronic HCV attended to outpatient hepatology clinic of One Day Surgery Hospital for treatment with DAAs. Measurement of HbA1c, FPG, fasting insulin hormone, c-peptide and calculation of HOMA-IR before and 3 months after DDAs therapy is done.

Statistical analysis was done for these data. Results : After achievement of SVR; HbA1c decreased from 9.57±1.39 to 7.22 ± 0.7 in diabetic patients, HOMA-IR decreased significantly also there was a significant improvement of lipid profile after completion of therapy.

Conclusion: This study showed that eradication of HCV by DAAs cause a parallel decrease in IR and improve glycemic control in patients with established T2DM.

Keyword: HCV hepatitis c virus, DAA direct acting antivirus, DM diabetes mellitus

1. INTRODUCTION:

Throughout the world more than one million people die each year from hepatitis c virus (HCV) related diseases, and over 300 million people are chronically infected with hepatitis B or Hepatitis C virus (HCV). Most patients infected with HCV develop chronic hepatitis, and as many as one in five will develop cirrhosis and its complications in addition to a wide spectrum of extrahepatic manifestations (1) . Egypt is one of the highest countries with heavy HCV infection (2).

The prevalence of hepatitis C virus (HCV) infection in Egypt is the highest in the world. This became apparent early on, soon after the discovery of HCV (3). It is well recognized that HCV infection is associated with several metabolic derangements including hypolipidemia, hepatic steatosis and metabolic syndrome (4).also HCV may induce insulin resistance (IR) regardless of the severity of liver disease, and IR may be associated with severe hepatic fibrosis and contribute to fibrotic progression in chronic HCV infection (5).

This explain The association between type 2 diabetes mellitus (DM) and HCV infection (6), and this is associated with higher risk for the development of hepatocellular carcinoma (HCC). This was explained by the role of the virus in the development of insulin resistance (IR) by modulating cellular gene expression and interfering with insulin signaling pathways (7).so 30-70% of patients with chronic hepatitis C (CHC) show some form of IR. patients chronically infected with HCV are 3.8 times more likely to have T2DM than HCV-negative one (8). Finally It is estimated that 20% of chronic HCV patients will develop cirrhosis and as many as ~50% of these patients will have T2DM. This translates into 47 million people worldwide and 750,000 people in the USA alone who are expected to develop HCV-associated T2DM (9).

The present study hypothesized that treatment of HCV with novel direct-acting antiviral medications may lead to improved glycemic control and decreased requirement for DM-modulating medications at the time of SVR

Aim of work: The aim of this study is to evaluate the glycemic effect of DAAs in a series of HCV-positive diabetic patient receiving DAAs who achieved SVR.

2. METHODS:

The current study, prospective analytic case study was conducted on 50 persons, 42% (21) males and 58% (29) females of the same age group (35-65 yrs). They were selected from outpatient clinic of Hepatology unite of One Day Surgery Hospital from october 2018 to October 2019. All patients were diabetic . Diabetes was diagnosed if Hb A1C ? 6.5%,FPG ? 126 mg/dl, or random plasma glucose at any time of day without regard to time since last meal ? 200mg/dl plus symptoms suggestive of DM as (polyuria, polydepsia,and unexplained weight loss) ADA, 2018. All were +ve for HCV antibody that was confirmed by PCR with HCV-RNA levels >1000 IU/mL Ref .

Patient was exclude if had any of the following: decompensated liver disease, renal impairment, hepatitis B virus infection, HIV infection, Autoimmune disorders, Clinically significant cardiac or cardiovascular abnormalities, platelet counts < 50000 mm3. Methods: Examinations and investigations were done with complete respect of humanity and dignity.

All study group subjected to history taking , physical examination and investigations. Calculation of body mass index. Blood Samples collection: Blood was collected by venipuncture, and drown into; EDTA tube; Citrate tube for CBC; and into plain tube for other investigations; where serum was separated and can be frozen at -20C for 3 months prior to assay. Laboratory investigations including CBC , ALT, AST, serum albumin, total bilirubin, S. creatinine and Fasting blood glucose before and 3 months after HCV treatment , HCV antibody, HBs antigen by Elisa technique and Quantitative PCR for HCV RNA before treatment and 3 months later for SVR by Realtime PCR . HbA1c is done, before and 3 months

after the treatment, by using . Fasting insulin level before and 3 months after the treatment: It Was assayed by ELIZA.

Insulin resistance was calculated for all patients before and 3 months after the treatment by using homeostatic model assessment of insulin resistance (HOMA-IR) which is calculated by the following equation: Fasting insulin (uIu/l) x fasting plasma glucose (mg/dl) /405(10). c-peptide Was assayed by ELIZA., lipid profile was assed including serum Triglycerides (TG), Total cholesterol (TC), High density lipoprotein cholesterol (HDLc), and Low density lipoprotein cholesterol (LDLc). LDL was estimated by the following formula = Total cholesterol -HDLc /5 .

3. RESULT

✓ The present study involved 50 patients their ages range from 36- to 73 years, 58%(29) were female and 42% (21) mal, 70% had positive family history of DM, and majority of patients 68% were on oral hypoglycemic and 32% were treated with insulin (table 1).

✓ The study revealed that after 3 months of treatment by DAAVs SVR was achieved in 100% of those diabetic patients. Their blood glucose decreased significantly as FPG reduced from 347.4 mg/dl pretreatment to 143 mg/dl post treatment ($p < 0.001$) figure (1), HbA1c pretreatment was 9.5% reduced to 7.2%postreatment ($p<0.001$) figure (2) . this better glycemic control was associated with significant decrease in insulin resistant state in the form of a lower HOMA IR after treatment (30.06 ± 23.78 vs 8.09 ± 3.98 post treatment) Table (2), figure (3) (p value=0.001)). Also a significant decrease was achieved in the level of total cholesterol, triglycerides, and LDL, after treatment. table (3) figure (4).

Table (1): Demographic and clinical data of study patients (n=50)

	ean±SD ange)
Age (years) Mean±SD (Range)	.58±7.8 5-73)
Sex Male Female	(42%) (58%)
Age of onset DM (years) Mean±SD (Range)	.8±7.9 5-65)
Duration of DM (years) Mean±SD (Range)	.78±7.91 29)
Family history +ve -ve	(70%) (30%)
Type of therapy Oral Hypoglycemic	(68%)

Insulin	(32%)

Table (2): Blood glucose level and insulin resistant state of the study group:

	fore	ter		value
FBG	7.42±77.45 (7-538)	3.58±32.98 3-201)	.801	**.001***
PP	0.34±70.67 5-503)	8.48±36.03)1-294)	.44	**.001***
HBA1c	7±1.39 46-13.2)	2±0.7 1-9.1)	.621	**.001***
HOMA IR (total)	06±23.78 (4.19-90.6)	9±3.98 (2.4-19.95)	39	**.001***
OMA IR (oral hypoglycemics (n=34)	3±21.8 (4.2-90.6)	1±3.9 (2.4-19.95)	65	**.001***
HOMA IR (insulin (n=16)	43±21.8 (18.5-88.9)	1±3.95 (3.68-16)	16	**.001***

Numerical data displayed as mean, standard deviation and range, analyzed by paired t-test, *: Significant level at P value < 0.05.

Table (3): Lipid Profile of the study group:

	fore	ter		value
Cholesterol	6.82±54.92 4-381)	6.96±56.52)2-329)	.072	**.001***
TG	7.33±43.45 7.7-296)	0.64±40.73 -246)	.656	**.001***
HDL	24±7.71 2-59)	8±4.07)-53)	326	91
LDL	7.11±55.61 3-305.2)	5.03±56.78 3.2-262.6)	.134	**.001***

Numerical data displayed as mean, standard deviation and range, analyzed by paired t-test *: Significant level at P value < 0.05
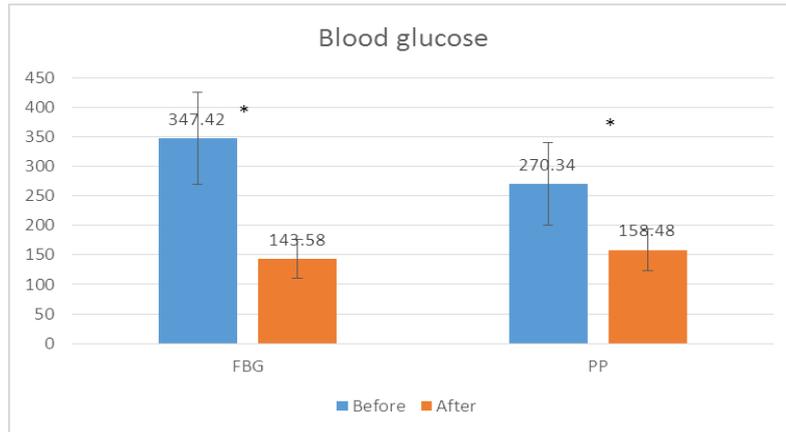
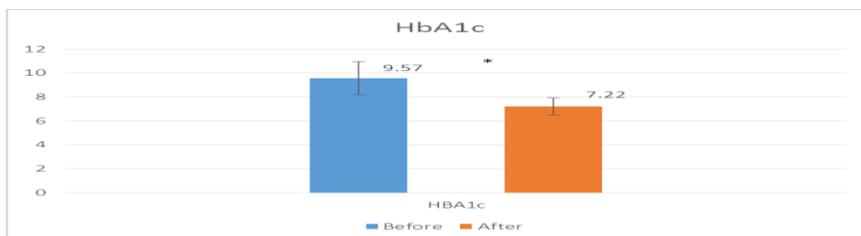Figure (1):effect of DAAVS on blood glucose level

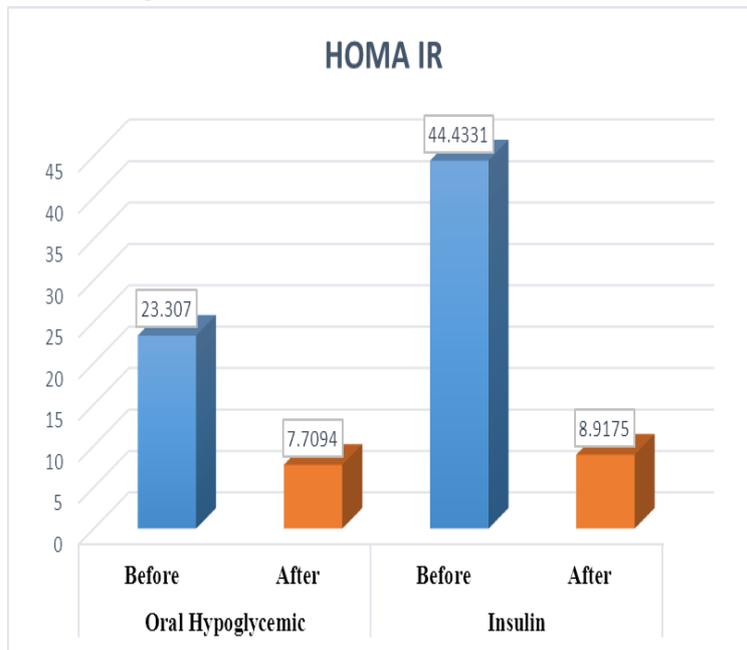Figure (2): effect of DAAVS on Hb A1c

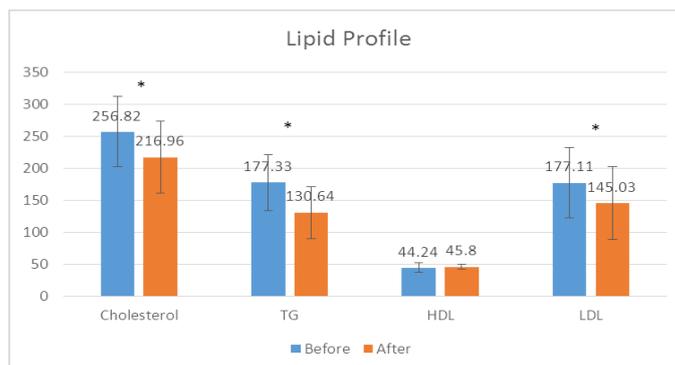Figure (3) effect of DAAVS on insulin resistant state

Figure (4) effect of DAAVS on lipid profil

4.   DISCUSSION:

Egypt has a high prevalence of HCV infection (3). HCV infection is associated with several metabolic derangements including hypolipidemia, hepatic steatosis and metabolic syndrome (4). There is also a multifold increase in the prevalence of glucose abnormalities in patients with HCV this can be explained by the role of the virus in the development of insulin resistance (IR) by modulating cellular gene expression and interfering with insulin signaling pathways (7).

Clearance of the virus was proved to improve IR as measured by reduction in homeostasis model of assessment (HOMA) value, suggesting that the virus itself plays a significant role in mediating IR. 11 . The present study revealed that better glycemic control was achieved after DAAs treatment of 100 diabetic patients as mean HbA1c before treatment was 7.4 to 13.2 and reduced to 6.1 to 9.1.after treatment. Hashim et al., 2017 (12) reported similar results as HbA1c and blood glucose in studied populations at the end of 3 months therapy by DAAs was ranging 7.4%. to 8.7 .Hum et al., 2017 (13) ,also demonstrated that eradication of HCV infection with DAAs agents is associated with improved glycemic control in diabetic patients and reduction of HbA1c level was greater in those who achieved SVR (0.98%) than in those with sustained treatment failure (0.65%).

These findings are important given prevalence rates of insulin resistance in patients with chronic HCV In contrary to our results, the study of Stine et al., 2017 (14) that was done in Virginia United States and demonstrated that HbAlc was largely unaffected by DAAs treatment of chronic HCV infected patients. However, this may in part be attributable to clinical management of diabetes and hyperglycemia with pharmacologic therapy rather than a primary process of viral clearance itself as nearly one-third of this cohort had increasing dosages of their anti-hyperglycemic therapy.

The present study demonstrated higher prevalence of female gender with 58% in comparison to 42% male and this is in consistent with the study of Hashim et al., 2017 (12) that demonstrated the effect of new DAAs drugs, used for treatment of HCV, on insulin resistance and glycemic control at the end of treatment in patients with type 2 diabetic mellitus (T2DM) and reported that females had higher prevelence (52%) than males (48%).

Our finding may be explained by the higher prevelance of obesity in patients with T2DM and obesity is more common in women than men (12) 0ur study was in disagreement with Niu et al., 2016 (15) who found the prevalence of HCV infection in males significantly higher than

that of females (male 56.62 % vs female 43.38 %). . Regarding duration of diabetes, the present study involved patient with diabetes duration ranged from 1 to 29 years. This was consistant with the study of Dawood et al., 2017 (16). T2DM with prolonged duration may be associated with more ?-cell failure and so improvement in IR does not lead to marked improvement in glycemic control. Shorter duration was reported in the study of Hashim et al., 2017 (12) in which disease duration ranged from 1 to 11 years.

The present study demonstrated that the percentage of patients with positive family history of T2DM was 70% this is consistent with one case-control study that showed a similar percent of 67% , among 45 non-cirrhotic HCV-seropositive patient. (16). Although Hashim et al., 2017 (12) revealed that the percentage of patients with positive family history of T2DM was significantly lower than our findings.

In patients without family history of T2DM, the possibility of IR is likely due to HCV infection only, so the eradication of HCV infection helps to improve IR and glycemic control, unlike those with inherited IR. It might be useful to classify patients with hereditary IR mostly those with positive family history for DM or HCV-induced IR to define better the effect of HCV eradication on these distinct populations (17).

Regarding physical examination, the present study revealed that most of the patient were above the normal weight as mean BMI was 27.9 ±4.7 (26% of normal weight, 42% were overweight and 32% were obese). Similar result was that of stine et al.,2017 (14) which reported that Mean cohort BMI was 29.9±6.8 m2. Some theories can explain the inter play between insulin resistance and obesity in diabetic patients (18).

Of those is the portal/visceral hypothesis theory which gives a key role in elevated non-esterified fatty acid concentration .also the ectopic fat storage syndrome(deposition of triglyceride in muscle, liver, and pancreatic cells). There is a great changes in PCR level before and after treatment by DAAs as it was ranged from 11.500-10.900.000, and became negative (below detection level) in 50 patients (100%). Similar results was obtained by Abada et al., 2017 (19) who reported that the viral load of patients before DAAs treatment was 1,283,288±2,165,432IU/mL and became below detection level after treatment, regardless of the regimen prescribed. The present study demonstrated that the mean ALT was 85.12±23.15. Ciancio et al., 2018 (20) showed similar results as ALT (IU/mL) was 81.2?±?77.2. as hepatocytes is natural target of HCV so elevation of ALT level can be explained (21). The current study revealed that blood glucose is reduced statistically significant after DAAs also mean HbA1c after treatment reduced to 6.1 to 9.1 g/dl. Similarly , Hashim et al., 2017 (12) reported that Improvement of HbA1c and blood glucose in studied populations at the end of 3 months therapy was ranges from 8.7 to 7.4%. Hum et al., 2017 (13) investigate whether eradication of HCV infection with DAAs agents is associated with improved glycemic control in patients with diabetes.

They found that the decrease in HbA1c associated with antiviral treatment was greater in those who achieved SVR (0.98%) than in those with treatment failure (0.65%) . although the study of Stine et al., 2017 (14) that was done in Virginia United States demonstrating that HbAlc was largely unaffected by treatment of chronic HCV with DAA in patients with and without cirrhosis. As nearly one-third of this cohort had increasing dosages of their anti-hyperglycemic therapy so this can be in part attributable to clinical management of diabetes and hyperglycemia with pharmacologic therapy rather than a primary process of viral

clearance itself.. lower level of cholesterol, triglycerides, HDL and LDL was observed after treatment by DAAs. in contrary to our results, the study of Batsaikhan et al., 2018 (22) demonstrated that all serum lipid levels have been significantly increased in all patients with SVR groups but not in non SVR group. It is well known that Liver plays fundamental role in lipid metabolism and hepatitis C virus (HCV) is linked to the lower lipid profiles and predisposes to dyslipidemia, liver steatosis or advanced fibrosis and progression of the chronic liver disease (21).

In the other hand Lipids also play an important role in HCV life cycle or its structure. However hypobetalipoproteinemia caused by HCV binding to lipoprotein was already reported and it may be one of the main pathways to lowering lipid profiles during HCV infection.

Several studies have reported dysregulated serum lipid levels in HCV infection, especially low levels of low-density lipoprotein cholesterol (LDLC) and little is known about the serum triglyceride (TG) (23). In this sample of Egyptian patients treated for 3 months by DAAs there is a significant reduction of insulin resistant state represented in HOMA IR level.

HOMA IR is reduced for those on oral hypoglcemics or insulin therapy. (p value < 0.001) .also the study demonstrated that there was a positive correlation and statistical significant difference between HOMA IR of patients on insulin therapy and each of cholesterol (p value = 0.012) and LDL (p value =0.03) after DAAs. These results differed than those of Shehab-Eldin et al., 2017 (24) who found marked increase in fasting insulin and HOMA-IR after study of glucose homeostasis in 80 patients chronically infected with HCV at end of therapy by DAAs drugs. Pre-hepatic ?-cell insulin secretion can be estimated by plasma C-peptide level . C-peptide may be a good index because it doesn't undergo hepatic extraction, so C-peptide may more accurately reflect pre-hepatic ?-cell secretion. .

Second, C-peptides has more steady clearance than insulin as Insulin clearance is influenced by various factors. In insulin resistant state, activity of insulin degrading enzyme is increased. Also Hepatic extraction of insulin is increased. . Third, C-peptide has lower variability within subject and between-subjects than insulin, so C-peptides were more reproducible for the determination of ?-cell function . Also C-peptide acts as a bioactive peptide. As it can inhibit nuclear factor ?B, reduce reactive oxygen species, and activate AMP-activated protein kinase . So C-peptide has the insulinomimetic effect and may also interact synergistically with insulin (25). In conclusion there is a higher prevalence of DM among HCV-associated hepatitis compared to other viral hepatitis. The underlying mechanisms for the development of diabetes can be listed as HCV-associated glucose intolerance, insulin resistance (IR), increased inflammatory response, liver fibrosis, and the direct effect of HCV on insulin signaling. This link is more clear by the improvement of DM after antiviral treatment (26). These findings raise the question as to whether the HCV eradication may also impacts the future morbidity and mortality due to T2DM. For this reason, close T2DM follow up post?HCV treatment is warranted and large prospective studies are needed to validate these results.

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