RESEARCH

Open Access

Effect of different direct-acting antiviral regimens for treatment of nondiabetic hepatitis C virus–infected Egyptian patients on insulin resistance and sensitivity

Tarek Yosef[1] , Wesam Ahmed Ibrahim[1] , Ahmed El-Ghandour[1] , Soha Attia[2] and Sarah El-Nakeep[1*]

Abstract

Background: The association between hepatitis C virus (HCV), insulin resistance (IR), and metabolic syndrome has been extensively investigated. Direct-acting antivirals (DAAs) have a high sustained virologic response (SVR) rate, reaching > 90%. The effect of SVR after DAA treatment on metabolic parameters and IR in nondiabetic patients could be an important factor in the patient's long-term outcome. The aim of the study is to evaluate the impact of different DAA regimens on IR and sensitivity in naïve chronic HCV-infected nondiabetic patients (before and after 12 weeks of treatment).

Methods: This prospective cohort study was conducted on 100 HCV-infected Child A nondiabetic patients eligible for DAA treatment in the Department of Gastroenterology and Hepatology, Ain Shams University, and Kobry El-Kobba Military Hospital among patients attending the outpatient clinic.

Patients were categorized into four groups according to the HCV regimens they received for 12 weeks.

All patient were subjected to the following tests before and 12 weeks after treatment: HCV quantitative PCR, Fibros-can, fasting insulin level (using insulin quantitative test kit), fasting and postprandial blood glucose (PPG), lipid profile, liver enzymes, BMI, and waist circumference.

Results: All patients achieved SVR at 12 weeks. In all treatment groups, lab was assessed before and after treatment, the 2-h PPG, high-density lipoprotein, and low-density lipoprotein levels showed statistically significant increases, whereas triglyceride, fasting glucose, hemoglobin A1C, and fasting plasma insulin levels showed statistically significant decreases. The homeostasis model assessment of insulin resistance (HOMA-IR) exhibited statistically significant decreases, whereas the quantitative insulin sensitivity check index (QUICKI) and Matsuda index showed statistically significant increases, across the four groups.

Conclusions: DAA treatment in naïve nondiabetic HCV-infected patients affects metabolic profile and insulin resistance/sensitivity, with similar effect among different DAA regimens.

Keywords: Hepatitis C virus, Direct-acting antivirals, Insulin resistance, Insulin sensitivity, HOMA-IR, Matsuda index, QUICKI index

*Correspondence: sarahnakeep@yahoo.com
[1] Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Full list of author information is available at the end of the article

Background

Hepatitis C virus (HCV) has a known diabetogenic- and insulin-resistance effect on the infected patients, which could be explained by the activation of various inflammatory pathways [1]. HCV affects approximately 200 million

people worldwide; however, with the introduction of the highly curative direct-acting antivirals (DAAs), several nations have organized eradication plans for the disease. Nevertheless, questions still remain about the effectiveness for the eradication of the associated metabolic effects of the virus [2]. HCV genotype 4 is the most dominant in Egypt, differing from other genotypes in its effect on liver steatosis and response to DAAs [3, 4].

Metabolic syndrome comprising steatosis, insulin resistance, and hyperlipidemia is associated with HCV, even in the absence of obesity or diabetes [5, 6]. Non-alcoholic steatohepatitis (NASH) was a common finding in liver biopsies collected before the initiation of HCV interferon treatment, and they were incorporated into the scoring system that predicted the antiviral response [7].

The standard method for evaluating insulin resistance is obviously the oral glucose tolerance test (OGTT). Another method widely used in clinics is the hyperinsulinemic-euglycemic clamp [8].

Insulin resistance is associated with a higher risk for cardiovascular disease [9]. Various insulin resistance/sensitivity scores could be measured using the insulin level. They are surrogate markers for the actual insulin resistance. Multiple validated scores for evaluating insulin resistance/sensitivity are suitable for clinical use, including the quantitative insulin sensitivity check index (QUICKI), homeostasis model assessment of insulin resistance (HOMA-IR), and Matsuda index [10]. The effect of HCV treatment on insulin resistance has been delineated by a recent meta-analysis conducted by Hu et al., which reported that HOMA-IR is decreased after achieving a sustained virologic response (SVR) [11].

Diabetes, which by the time diabetes is diagnosed, it may be too late, is preceded by a prediabetic phase, which could be detected through OGTT and fasting plasma glucose levels [12].

The aim of this study was to evaluate the efficacy of new DAAs for the treatment of chronic HCV infection in treatment-naïve nondiabetic patients on insulin resistance and insulin sensitivity using the following primary parameters for insulin resistance and sensitivity: HOMA-IR, QUICKI, and Matsuda index. Another aim was to investigate the effect of viral eradication on glucose levels and lipid profile, as a component of the complete metabolic profile of the patient.

Methods

This study was conducted at the Gastroenterology and Hepatology Department, Ain Shams University, and Kobry El-Kobba Military Hospital on 100 patients with chronic HCV infection who attended the outpatient clinic between September 2018 and June 2019.

The patients were scored as Child A according to the Child–Pugh score diagnosed based on HCV-Ab by enzyme-linked immunosorbent assay (ELISA) and HCV ribonucleic acid (HCV RNA) by PCR and received treatment with DAAs.

The patients were divided into the following four groups according to the drug received:

- Group A: 25 patients who received treatment with sofosbuvir (400 mg) and daclatasvir (60 mg) daily for 12 weeks
- Group B: 25 patients who received treatment with sofosbuvir (400 mg) and simeprevir (150 mg) (OLYSIO) daily for 12 weeks
- Group C: 25 patients who received treatment with sofosbuvir (400 mg) and ledipasvir (90 mg) (Harvoni) daily for 12 weeks
- Group D: 25 patients who received treatment with ombitasvir (12.5 mg), paritaprevir (75 mg), and ritonavir (50 mg) single dose of two tablets (QUREVO) daily for 12 weeks
- The treatment regimens and administration followed the most recent European Association for the Study of the Liver (EASL) guidelines [13] and the National Egyptian guidelines.

Inclusion criteria

1. Patients with positive quantitative HCV RNA as assessed by polymerase chain reaction (PCR)
2. Patients with the international normalized ratio INR < 1.7
3. Patients with serum albumin level > 2.8 g/dl
4. Patients with direct bilirubin level < 2 mg/dl
5. Patients with platelet count > 100000/mm^2
6. Patients with serum creatinine level < 2 mg/dl

Exclusion criteria

1. Coinfection with HBV
2. Patients with autoimmune hepatitis
3. Patients with bilharzial infection
4. Patients with metabolic disorders or genetic disorders, e.g., hemochromatosis or Wilson's disease
5. Patients with decompensated cirrhosis with the following conditions:

   a. INR > 1.7
   b. Serum albumin level < 2.8 g/dl
   c. Total bilirubin level > 2 mg/dl
   d. Platelet count < 100/mm^3

    e. Ascites
    f. Splenomegaly

6. Patients with high level of serum total cholesterol > 240 mg/dL or triglycerides (TG) level (> 200 mg/dL)
7. Patients with diabetes diagnosed by fasting blood glucose, 2-h postprandial blood glucose, and glycated hemoglobin (HbA1C) levels
8. Patients with renal failure
9. Patients with hypertension
10. Patients with malignancy, either primary hepatocellular carcinoma (HCC) or secondary, or a previous history of malignancy and chemotherapy
11. Patients with hypothyroidism or hyperthyroidism

All patients were subjected to the following examinations:

1. Appropriate history-taking and clinical examination, including the following:

    a. Waist circumference to exclude metabolic syndrome

    Waist circumference $\geq$ 102 cm in men or $\geq$ 88 cm in women

    b. Measuring body mass index (BMI) = weight in kg/height in m^2

2. Laboratory investigations, including the following:

    a. HCV RNA by PCR before and 3 months after treatment. Assessment was done using the Roche COBAS TaqMan HCV assay V.2.0 (lower limit of detection 15 IU/m).
    b. Liver function tests, including ALT, AST, albumin, and total bilirubin levels
    c. Kidney function tests, including urea and serum creatinine levels
    d. Complete blood count
    e. Prothrombin time and INR
    f. Alpha-fetoprotein tumor marker (AFP)
    g. Lipid profile, including TG, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and cholesterol levels, we included borderline and normal levels of cholesterol & TG, but excluded high levels, according to Mayo clinic serum levels.
    h. Fasting blood sugar, 2-h postprandial blood glucose, we used OGTT; each patient fasted for 8 h and was then administered 75 g glucose in the form of soluble sugar, and HbA1C levels.

    i. Fasting serum insulin was measured using the insulin quantitative test kit, which is based on a solid-phase ELISA. The assay system uses first an anti-insulin antibody for solid-phase (microtiter wells) immobilization and then an anti-insulin antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution. The standards and test specimen (serum) were added to the insulin antibody-coated microtiter wells. Then, the anti-insulin antibody labeled with horseradish peroxidase (conjugated) was added. The presence of human insulin in the test tube causes the formation of a molecular aggregate by the combination of the antibody on the well and the enzyme conjugate, where the insulin molecules are sandwiched between the solid-phase and enzyme-linked antibodies. The wells of the labeled but unbound antibodies were washed after 1 h of incubation at room temperature. A blue color developed due to the addition of TMB solution and incubation for 20 min. The color development stopped after the addition of the stop solution, and then the color changed to yellow, at which time point it was measured spectrophotometrically at 450 nm. The color intensity in the test sample is directly proportional to the insulin concentration.
    j. Radiological investigations, including pelvic–abdominal ultrasound examination to assess the homogeneity, echogenicity, and brightness of the liver, as well as the liver and spleen dimensions, portal vein diameter and splenic vein diameter, and the presence of thrombosis or focal lesions
    k. Electrocardiogram (ECG) and echocardiography for patients aged > 70 years
    l. Assessment of insulin resistance: HOMA-IR was evaluated before and after treatment.
    HOMA-IR = Fasting serum insulin $\times$ Fasting serum glucose (mg/dl)/405 [14].
    m. Assessment of insulin sensitivity: QUICKI and Matsuda index were measured before and after SVR.

      1. QUICKI: Quantitative insulin sensitivity check index

      QUICKI = 1/(log fasting insulin + log fasting glucose) [10].

      2. Matsuda index: This is used to assess the level of insulin sensitivity, which is calculated using plasma glucose and insulin levels [15].

$$\text{Matsuda index} = 1000/\sqrt{(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin})}$$

Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 4 of 14

A level of> 4.3 predicts insulin resistance [10].

After obtaining approval from the local institutional ethics committee, and an individual agreement of each participant in the study, an informed and written consent was obtained from each participant (Ethical Committee Approval number FMASU-MD-321/2017).

Statistical methods

1. Data analysis was conducted using the SPSS program version 23.
2. Quantitative data were expressed as mean and SD.
3. Qualitative data were presented as count and percentage.
4. One-way ANOVA was used to compare quantitative data between different groups followed by post hoc test when significant.
5. Fisher's exact test was used to compare qualitative data between groups.
6. Paired samples *t* test was used to compare data before and after treatment.
7. Repeated measures ANOVA was used to compare changes in quantitative data before and after treatment between different groups.
8. *P* < 0.05 was considered to be statistically significant.

Results

SVR was achieved at 12 weeks in all the 100 patients (100%), irrespective of the type of medications they received (groups A, B, C, and D).

Tables 1 and 2 show the comparison between the four groups according to the demographic data (age and gender). Group A consisted of 23 men (92%) and 2 women (8%) aged (mean ± standard deviation) 57 ± 9 years. Group B consisted of 25 men (100%) aged 58 ± 7 years.

In group C, there were 23 men (92%) and 2 women (8%) aged 59 ± 9 years. Group D comprised 24 men (96%) and 1 woman (4%) aged 58 ± 7 years showing no statistical significance across groups. Among the study patients, there were 95 men and 5 women with age ranging from 34 to 72 years (mean age = 58.16 years). Patients with chronic HBV coinfection, HIV coinfection, schistosomiasis, and autoimmune hepatitis were excluded. Figure 1 shows the demographic data (height, weight, and BMI) of the four groups.

Table 3 shows the comparison between the four groups according to laboratory data. At baseline, the TG level was highly significant (*P* < 0.001). Platelet count, total bilirubin, serum albumin, and INR showed positive statistical significance (*P* < 0.05). The remaining laboratory data (hemoglobin level, total leukocyte count, neutrophil count, lymphocyte count, ALT, AST, PT, serum creatinine, urea, total cholesterol, HDL, LDL, and AFP levels and PCR findings) showed no statistical significance.

The "a" and "b" post hoc test revealed statistically significant differences between groups A and C and between groups A and D in terms of TG level. The Kruskal–Wallis test revealed a statistically significant difference between the groups; however, it did not identify the groups that were different.

The liver dimensions showed no changes in groups A and B, but a statistically significant difference was detected in groups C and D between the dimensions at baseline and those after achieving SVR, as shown in Table 4.

Lipid profiles showed statistically significant increases in total cholesterol (mg/dl) from baseline to SVR at 12 weeks as follows: group A (from 172.6 ± 30.99 to 189.36 ± 27.25), group B (from 163 ± 20.37 to 184.16 ± 26.61), group C (from 166.52 ± 20.42 to 182.12 ± 27.86), and group D (from 166.52 ± 20.42 to

Table 1 Demographic data of the study groups (age)

	Drug type								F [a]	*P* value
	Group A		**Group B**		**Group C**		**Group D**			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Age	57	9	58	7	59	9	58	7	0.32	0.81

[a] One-way ANOVA

Table 2 Demographic data of the study groups (gender)

		N	%	N	%	N	%	N	%	X^{2} [b]	*P* value
Gender	**Male**	23	92.0%	25	100.0%	23	92.0%	24	96.0%	2.38	0.75
	Female	2	8.0%	0	.0%	2	8.0%	1	4.0%		

[b] Fisher's exact test

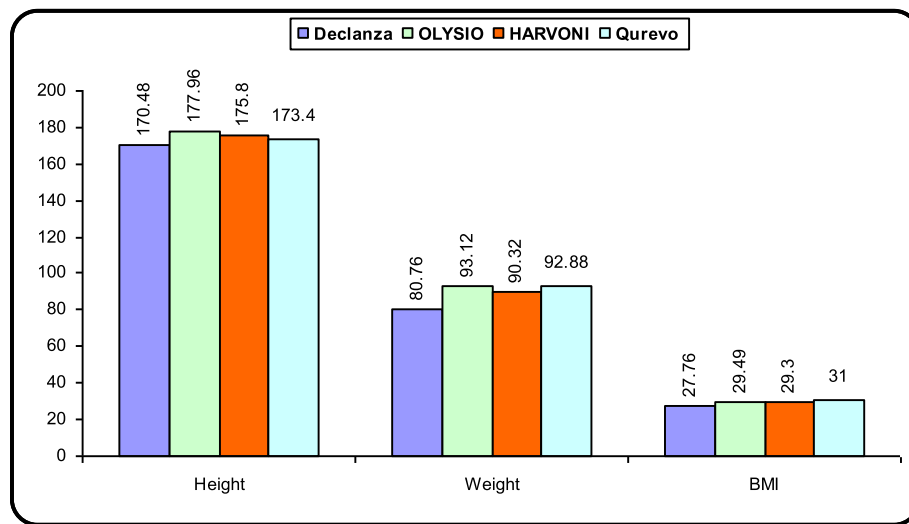Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 5 of 14

Fig. 1 Comparison of demographic data (height, weight, and BMI) between the study groups

Table 3 Laboratory investigations for the study groups before treatment

Variable	Drug type								F*	P value
	Group A		Group B		Group C		Group D			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Hb (13.5–17 g/dl)	13.82	1.64	13.52	1.12	13.96	1.17	13.52	1.23	0.72	0.54
PLT (150–450/mm^2)	208.52[a]	73.73	243.08	64.12	258.52[b]	61.28	262.92[b]	65.18	3.47	**0.02**
TLC (4.5–11/mm^3)	7.62	2.65	7.40	1.66	7.28	1.79	7.32	1.65	0.15	0.93
Neutrophil count	4675.24	1610.78	4714.32	1500.19	5032.16	1559.97	4824.16	1529.27	0.27	0.85
Lymphocyte count	3198.84	1605.99	2676.4	761.32	2772.36	763.2	2787.32	687.75	1.28	0.29
ALT (up to 50 IU/L)	57.37	50.46	60.92	16.72	57.60	19.35	59.40	19.10	0.08	0.97
AST (up to 50 IU/L)	52.08	38.10	47.76	20.31	50.32	19.99	59.68	20.78	0.98	0.41
Total BIL (0.1–1.2 mg/dl)	0.86[a]	0.32	1.10[b]	0.27	1.02	0.32	0.96	0.28	2.99	**0.04**
ALB (3.5–5.4 mg/dl)	4.78[a]	.59	4.44	0.45	4.25[b]	0.56	4.38	0.49	4.57	**0.01**
PT (11–13.5 s)	13.18	1.29	12.83	1.51	12.88	1.81	12.73	1.70	0.38	0.77
INR (0.8–1.2 mg/dl)	0.99[a]	0.14	0.88	0.19	.85[b]	0.21	0.84[b]	0.20	3.35	**0.02**
Creatinine (0.8–1.2 mg/dl)	0.98	0.21	0.88	0.19	0.96	0.18	0.92	0.16	1.26	0.29
Urea (7–20 mg/dl)	31.20	10.33	30.08	6.57	30.60	7.40	29.08	6.91	0.32	0.81
Total Chol (200–239 mg/dl)	172.60	30.99	163.00	20.37	166.52	20.42	167.64	20.95	0.71	0.55
TG (< 150 mg/dl)	119.76[a]	44.73	164.96[b]	19.82	167.64[b]	19.58	157.40[b]	20.65	15.41	**<0.001**
HDL (40–59 mg/dl)	44.48	11.08	40.04	5.56	39.84	6.91	41.08	4.35	2.10	0.11
LDL (< 100 mg/dl)	98.40	30.09	78.00	26.08	90.44	25.23	85.16	25.98	2.56	0.06
AFP# (10–20 ng/ml)	2.30	3.90	2.80	2.00	2.60	1.80	2.90	2.30	0.23	0.97
PCR#	374000	541000	653000	500000	473000	280000	529000	400000	3.83	0.28

*One-way ANOVA (a,b, post hoc test)

Median and IQR (Kruskal–Wallis test)

182.12 ± 27.86). These data are shown in Figs. 2A, 3A, 4A, and 5A, respectively.

HDL levels exhibited statistically significant increases from baseline to SVR at 12 weeks as follows: group A (from 44.48 ± 11.08 to 50.92 ± 8.84), group B (from 40.04 ± 5.56 to 44.64 ± 6.93), group C (from 39.84 ± 6.91 to 42.68 ± 7.05), and group D (from 39.84 ± 6.91 to 42.68 ± 7.05). These results are illustrated in Figs. 2A, 3A, 4A, and 5A, respectively.

Yosef *et al. Egypt J Intern Med* (2021) 33:45

Page 6 of 14

Table 4 Insulin sensitivity before and after SVR at 12 weeks among patients in group A

Insulin sensitivity/ resistance index	Mean	SD	t^a	P value
HOMA-IR before	3.19	1.35	8.28	**< 0.001**
HOMA-IR after	2.17	.96		
QUICKI before	.33	.02	5.78	**< 0.001**
QUICKI after	.35	.03		
Matsuda index before	5.57	2.03	3.37	**0.003**
Matsuda index after	6.57	2.31		

[a] Paired samples *t* test

The HOMA-IR, QUICKI, and Matsuda indices were highly significant in group A before and after treatment ($P < 0.001$)

Similarly, LDL levels (mg/dl) showed statistically significant increases from baseline to SVR at 12 weeks in groups A, B, C, and D as follows: from 98.4 ± 30.09 to 105.96 ± 28.56, from 78 ± 26.08 to 86.96 ± 25.65, from 90.99 ± 25.23 to 99.64 ± 26.9, and from 85.16 ± 25.98 to 93.76 ± 26.92, respectively. However, TG levels showed statistically significant decreases from baseline to SVR at 12 weeks in the four groups as follows: from 119.76 ± 44.73 to 89.28 ± 27.6, from 164.96 ± 19.82 to 115.04 ±18.94, from 176.64 ± 19.58 to 122.2 ± 24.45, and from 167.64 ± 19.58 to 122.2 ± 24.45, respectively. These data are shown in Figs. 2A, 3A, 4A, and 5A, respectively.

Regarding blood glucose (mg/dl), the fasting levels were significantly decreased from baseline to SVR at 12 weeks in the four groups as follows: in group A, from 92.64 ± 8.84 to 91.12 ± 8.55; in group B, from 87.28 ± 8.29 to 86.64 ± 8.55; in group C, from 88.68 ± 9.48 to 87.16 ± 10.08; and in group D, from 91.4 ± 8.15 to 90.16 ± 8.51 (Figs. 2B, 3B, 4B, and 5B, respectively).

However, the 2-h postprandial blood glucose levels showed statistically significant increases from baseline to SVR at 12 weeks in the four groups as follows: from 151.72 ± 16.34 to 181.16 ± 10.55, from 160.8 ± 11.47 to 184.48 ± 9.84, from 153.08 ± 31.69 to 184.52 ± 10.91, and from 163.24 ± 13.37 to 183.84 ± 11.25, respectively. A comparison of results could not reveal the effect of DAAs on 2-h postprandial blood glucose levels. These findings are illustrated in Figs. 2B, 3B, 4B, and 5B, respectively.

HbA1c levels were statistically significantly decreased from baseline to SVR at 12 weeks in group A (from 5.98 ± 0.54 to 5.22 ± 0.86), group B (from 5.7 ± 0.41 to 5.28 ± 0.74), group C (from 5.75 ± 0.48 to 4.91 ± 0.7), and group D (from 5.65 ± 0.48 to 5.15 ± 0.69). These data are shown in Figs. 2C, 3C, 4C, and 5C, respectively.

Regarding fasting serum insulin, the levels showed statistically significant decreases from baseline to SVR at 12 weeks in group A (from 14.04 ± 6.09 to 9.77 ± 4.44), group B (from 15.36 ± 5.69 to 11.14 ± 3.88), group C (from 13.32 ± 5.61 to 9.58 ± 3.73), and group D (from 15.76 ± 6.48 to 10.75 ± 4.75), as shown in Figs. 2C, 3C, 4C, and 5C, respectively.

The HOMA-IR values also showed statistically significant decreases from baseline to SVR at 12 weeks in group A (from 3.19 ± 1.35 to 2.17 ± 0.96), group B (from 3.33 ± 1.31 to 2.38 ± 0.9), group C (from 2.9 ± 1.22 to 2.04 ± 0.76), and group D (from 3.55 ± 1.48 to 2.38 ± 1.09), as shown in Fig. 6A. The overall data and statistical differences are shown in Table 4.

The QUICKI values in our study exhibited significant increases from baseline to SVR at 12 weeks in group A (from 0.33 ± 0.02 to 0.35 ± 0.03), group B (from 0.32 ± 0.02 to 0.34 ± 0.02), group C (from 0.33 ± 0.02 to 0.35 ± 0.02), and group D (from 0.32 ± 0.03 to 0.34 ± 0.03), as shown in Fig. 6B. The overall data and statistical differences are shown in Table 4.

Regarding the Matsuda index, the values showed significant increases from baseline to SVR at 12 weeks in group A (from 5.57 ± 2.03 to 6.57 ± 2.31), group B (from 5.53 ± 2.4 to 6.34 ± 2.16), group C (from 6.02 ± 1.92 to 6.91 ± 2.34), and group D (from 5.17 ± 2.22 to 6.43 ± 2.91), as shown in Fig. 6C. The overall data and statistical differences are shown in Table 4.

Regarding the ultrasound findings, the values showed significant decrease in the liver dimensions from baseline to SVR at week 12 in group B and D only while the other groups showed no change (Tables 5 and 6). All groups did not show any change in spleen dimensions.

Discussion

The effect of DAAs on insulin resistance and sensitivity is an important subject in the post-HCV eradication era, where insulin resistance and hepatic steatosis remain new unresolved dilemmas. Although various studies have been conducted in this regard, each study concentrated on only one facet of the problem, i.e., either HOMA-IR, HOMA-β, or glucose levels and HbA1C or lipid profile and liver steatosis. In the present study, we evaluated the effect of treatment on *all* these parameters to assess the metabolic problem of the patients in general. Furthermore, we excluded all patients with abnormalities in their glucose tolerance test to ensure that there is no previous metabolic imbalance or an apparent prediabetic risk. Surprisingly, we found that even this strict category of patients (with normal OGTT) benefited from the eradication of HCV infection and showed a marked decrease in their lipid, glucose, and insulin levels.
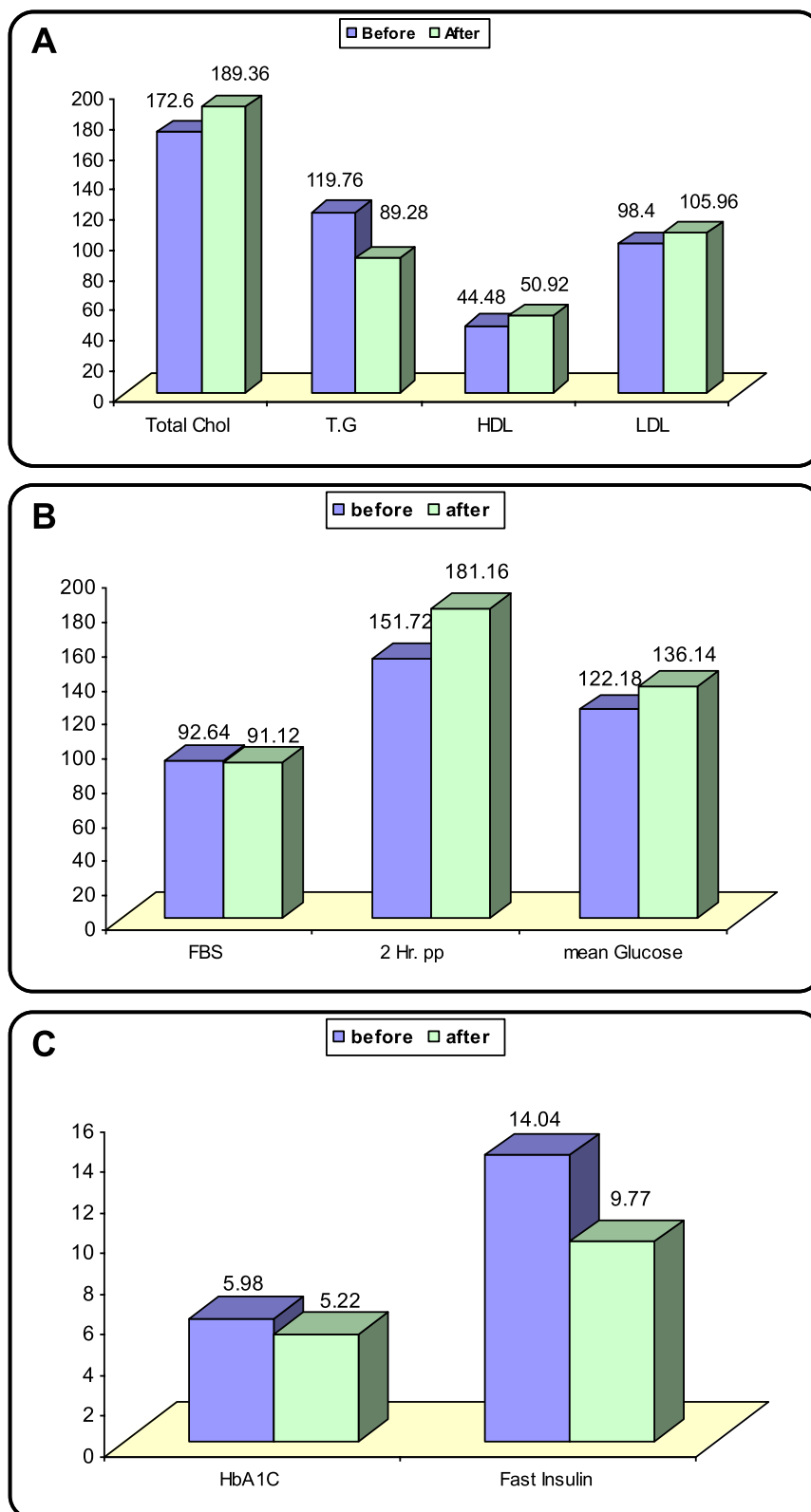
Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 7 of 14

Fig. 2 A Comparison between lipid profiles at baseline and after SVR at 12 weeks among patients in group A. **B** Comparison between FBS, 2-h postprandial blood glucose, and mean glucose levels at baseline and after SVR at 12 weeks among patients in group A. **C** Comparison between HbA1C and fasting serum insulin levels at baseline and after SVR at 12 weeks among patients in group A
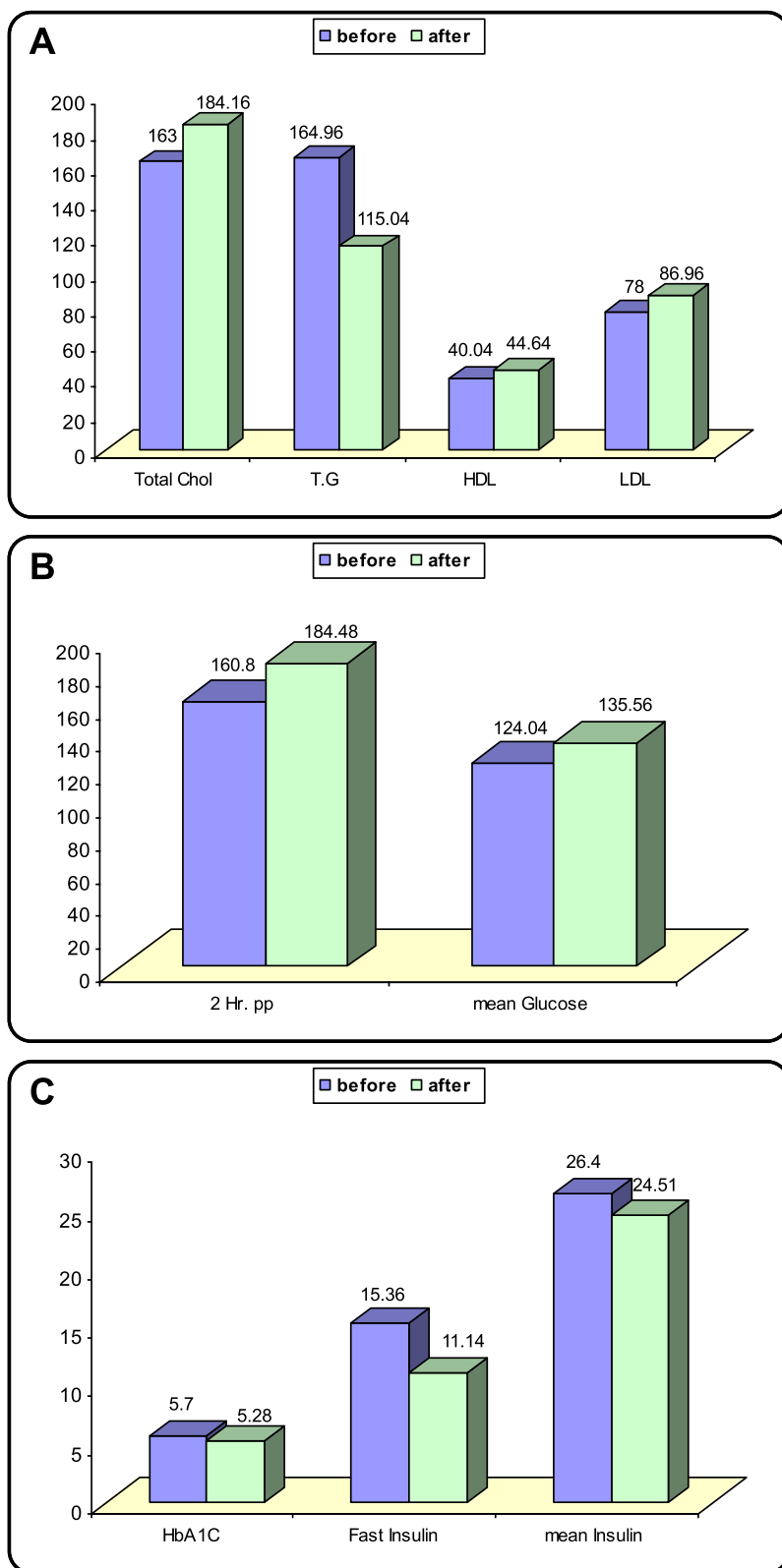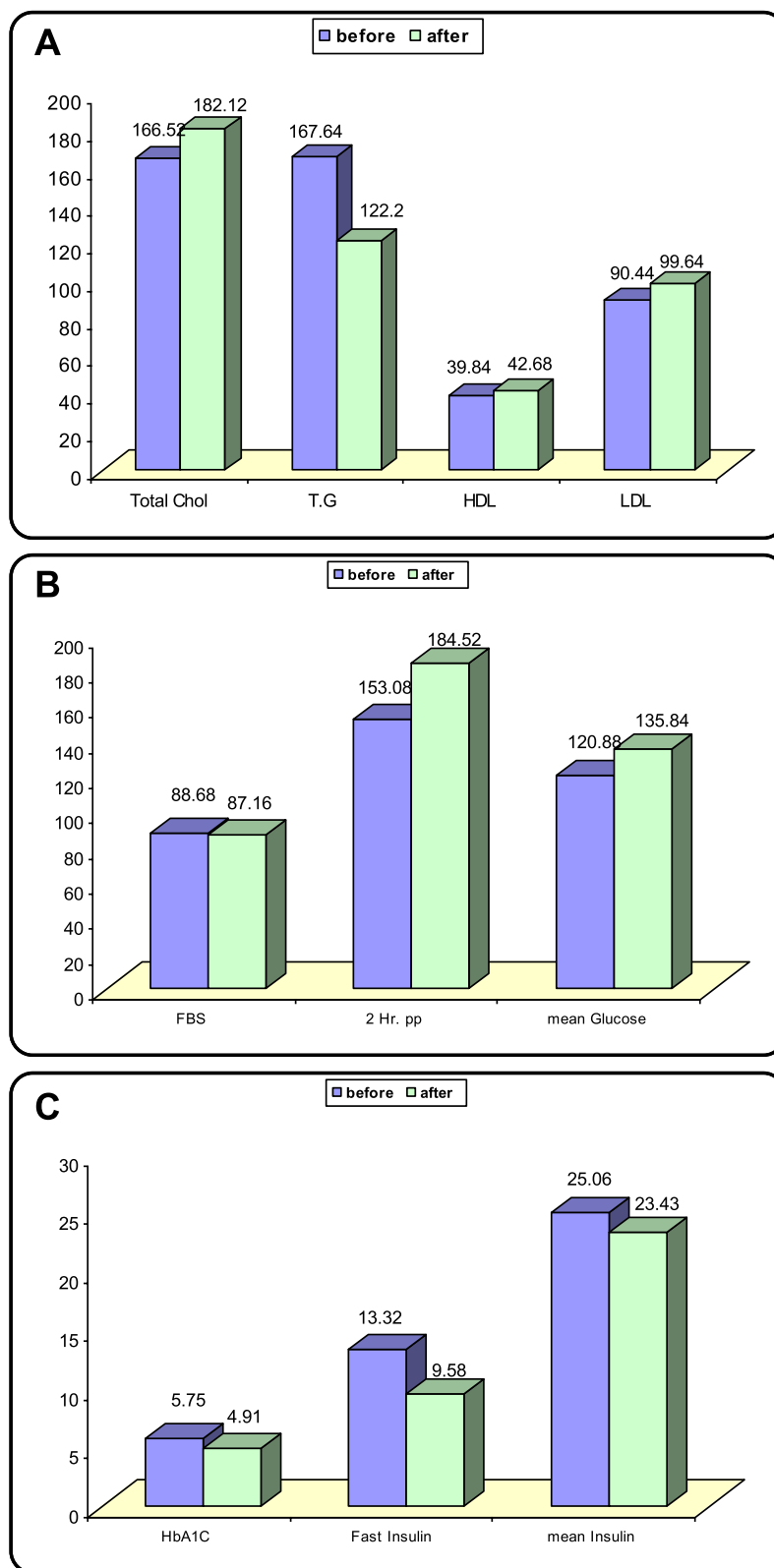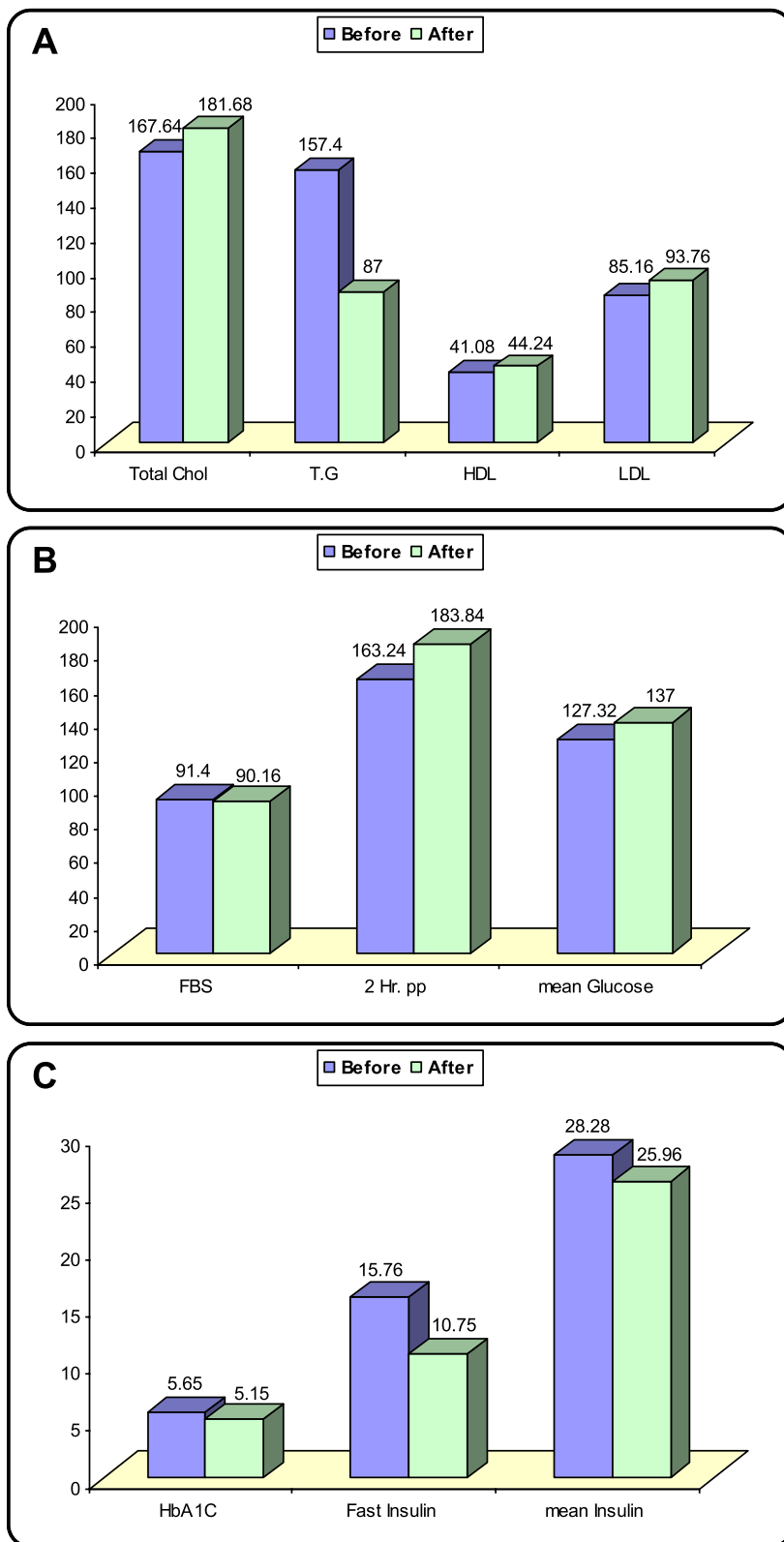
Fig. 3 **A** Comparison between lipid profiles at baseline and after SVR at 12 weeks among patients in group B. **B** Comparison between 2-h postprandial blood glucose and mean glucose levels at baseline and after SVR at 12 weeks among patients in group B. **C** Comparison between HbA1C, fasting insulin, and mean insulin levels at baseline and after SVR at 12 weeks among patients in group B

Fig. 4 **A** Comparison between lipid profiles at baseline and after SVR at 12 weeks among patients in group C. **B** Comparison between FBS, 2-h postprandial blood glucose, and mean glucose levels at baseline and after SVR at 12 weeks among patients in group C. **C** Comparison between HbA1C, fasting insulin, and mean insulin levels at baseline and after SVR at 12 weeks among patients in group C

Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 10 of 14

Fig. 5 **A** Comparison between lipid profiles at baseline and after SVR at 12 weeks among patients in group D. **B** Comparison between FBS, 2-h postprandial blood glucose, and mean glucose levels at baseline and after SVR at 12 weeks among patients in group D. **C** Comparison between HbA1C, fasting insulin, and mean insulin levels at baseline and after SVR at 12 weeks among patients in group D

Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 11 of 14
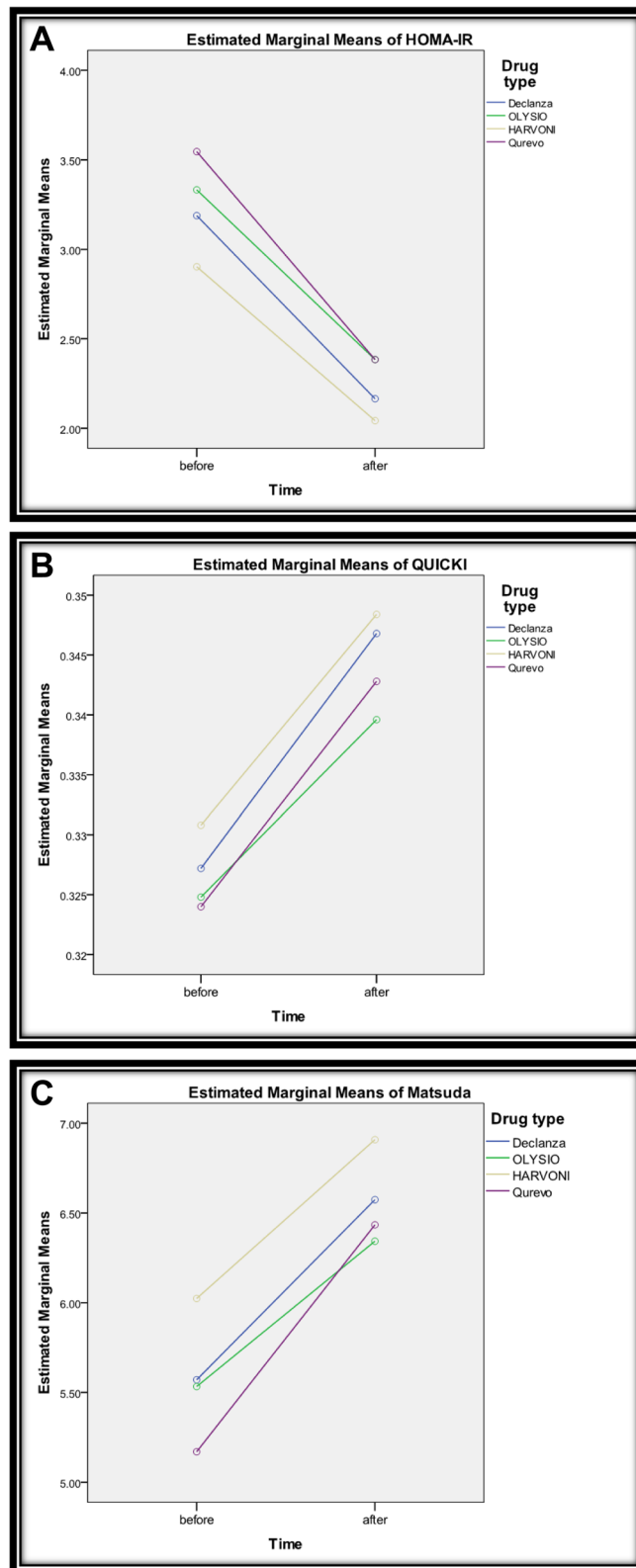
Fig. 6 A Estimated marginal mean values of HOMA-IR over time between the four groups. **B** Estimated marginal mean values of QUICKI over time between the four groups. **C** Estimated marginal mean values of Matsuda index over time between the four groups

Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 12 of 14

Table 5 Pelvic–abdominal ultrasound examination before and after SVR at 12 weeks among patients in group C

Ultrasound finding	Mean	SD	t^a	P value
Liver dimensions before	13.34	1.24	2.37	0.03
Liver dimensions after	13.00	1.09		
Spleen dimensions before	12.79	0.69	0.47	0.64
Spleen dimensions after	12.74	0.69		

[a] Paired samples *t* test

Table 6 Pelvic–abdominal ultrasound examination before and after SVR at 12 weeks among patients in group D

Ultrasound findings	Mean	SD	t^a	P value
Liver dimensions before	13.54	0.92	4.09	< 0.001
Liver dimensions after	13.12	0.98		
Spleen dimensions before	12.64	0.60	0.15	0.89
Spleen dimensions after	12.66	0.51		

[a] Paired samples *t* test

In a recent study conducted by Mada et al., achieving SVR by DAAs was shown to result in a significant improvement of HbA1C levels in diabetic patients [16]. In our study, the HbA1C level was similarly significantly decreased after SVR at 12 weeks, although the patients were nondiabetic.

In the present study, LDL levels showed a statistically significant increase in all the four groups after achieving SVR. This finding is consistent with previous studies on LDL levels after achieving SVR at 12 weeks, where the levels were found to increase with viral eradication [17, 18]. This could be explained by the decreased production of lipid droplets from hepatocytes due to the rapid decline in the core HCV protein, consequently followed by an increase in "rebound" LDL levels [19]. Hashimoto et al. [20] reported a rapid increase in LDL-C and TG levels in the early treatment phase (first 28 days), which was higher in patients treated with LDV/SOF than in patients treated with DCV/ASV.

In our study, cholesterol, LDL, and HDL levels were increased in all the four groups. The highest cholesterol increase was observed in group B, and the highest HDL increase was observed in group A, whereas LDL increase did not differ between the groups. TG levels were declined across all the study groups, but the highest level was found in group C. Glucose, HbA1C, and insulin levels were decreased with no difference across the study groups. This finding could help guide our choice of the DAA combination for treating patients with insulin resistance and/or with a special type of hyperlipidemia.

Liver dimensions were decreased after treatment with DAAs in our study, which could be due to the resolution of chronic hepatitis and the decline in the associated inflammatory response [21].

Regarding the HOMA-IR values, we detected a significant "within-subjects" effect, indicating a significant change in score over time. The "between-subjects" effect was not statistically significant, indicating that the mean score did not differ significantly between the study groups. There was no interaction between the variables time and drug type.

Hashim et al. [22] demonstrated that of the 75 patients treated for HCV infection by DAAs, the HOMA-IR value improved in 72% and 73.3% of patients after 12 weeks and 6 months, respectively. Compared with the interferon treatment era, the eradication of HCV infection showed a decline in HOMA-IR, fasting insulin, and glucose levels in the patients [8]. Adinolfi et al. found that HOMA-IR levels were decreased in nondiabetic patients treated for HCV genotype 1, with the viral-clearing effect being irrespective of BMI or baseline liver fibrosis [23].

In another Egyptian study conducted in the National Liver Institute, Menoufia University, the researchers found that different DAA regimens were associated with an increase in insulin secretion as evaluated by HOMA-β, an increase in insulin sensitivity as assessed by HOMA-S, and a decrease in insulin resistance as determined by HOMA-IR when SVR was achieved at 12 weeks [24]. Russo et al. examined the effect of DAAs on nondiabetic patients with HCV infection and found that insulin levels were decreased even in cirrhotic patients, or in those with high BMI, but the levels of BMI, fasting glucose, and HOMA-IR showed no significant changes after 12 weeks of treatment. This could be attributed to the baseline heterogeneity of the examined population, i.e., although they were nondiabetic, OGTT was not performed before treatment to analyze their glucose tolerance. However, their study showed similar effects on lipid profile as those observed in our study. Hu et al. [11] conducted a meta-analysis to investigate the effect of HCV treatment on insulin resistance in interferon-containing regimens and found that HOMA-IR and HOMA-β levels were significantly decreased in patients who achieved SVR compared with those who did not achieve SVR.

We could not find a comparative study regarding the QUCKI and Matsuda indices in patients before receiving DAAs and after achieving SVR at 12 weeks.

Our study showed that for HOMA-IR, QUICKI, and Matsuda index scores, there were significant "within-subjects" effects, indicating significant changes in score over time. The "between-subjects" effects were not statistically significant, indicating that the mean scores did not differ significantly between the study groups. There

was no interaction between the variables time and drug type, implying that the improvement in all indices occurs irrespective of the DAA regimen administered to the patients, with mild variations.

The QUICKI and Matsuda index scores could be used to detect insulin sensitivity interchangeably with other surrogate scores used for the same calculation as HOMA-S.

In our study, the improvement in insulin sensitivity and resistance was also reflected in the improvement in fasting and postprandial glucose levels after achieving SVR at 12 weeks. Moreover, there was an improvement in HbA1C levels in all the study groups. Our study population did not have diabetes, and their GTT result was within normal range, yet the improvement in glucose indices was apparent. This finding shows that even in nondiabetic patients, HCV treatment might affect the long-term quality of life of the patient by decreasing the risk for diabetes and metabolic imbalances. The effect of DAAs on glycemic control was also apparent in a recent Egyptian study conducted on 32 diabetic patients with HCV infection. El-Badry et al. found that achieving SVR decreased the HbA1C level by > 1% [25], which could be explained by the elimination of HCV that causes downregulation of glucose transporter (1 and 2) along with decreased glucose uptake, accompanied by upregulation of hepatic gluconeogenesis [26, 27].

The fasting blood sugar has improved which is an important parameter when diagnosing DM. In addition, it is documented that the metabolic profile of patients post treatment may worsen at first few months as LDL increase and then after a longer period of follow-up, the levels return to normal; this is explained by the effect of HCV on LDL receptors. Moreover, despite the increased level of postprandial blood sugar, they did not exceed the limit for overt diabetes diagnosis. We expect this elevation to be temporary as proved by previous studies on interferon therapy, but our study is limited to 3 months follow-up after treatment.

In our study, there were only 5% of female patients, which is consistent with previous studies that reported that women are more likely to clear the virus than men among Egyptian populations [28], indicating the variability of the infection in women along with geographical distribution [29]. Moreover, hepatic markers, including liver enzymes, coagulation profiles, albumin, and bilirubin, were improved after achieving SVR at 12 weeks, which is consistent with a systematic review conducted by Zeng et al. who stated that "liver function repair" is associated with DAAs in at least two-thirds of the treated patients [30].

Conclusions

Lipid profile, except LDL, insulin sensitivity/resistance, and glucose parameters improved after achieving SVR after treatment with different anti-HCV DAAs in patients with normal glucose tolerance. Using various surrogate indices to detect insulin sensitivity/resistance after achieving SVR showed no difference, and hence, they could be used interchangeably.

We recommend a strict follow-up for all patients post-HCV treatment at least for 6 months. Special attention to patients with basal metabolic disturbances is also recommended.

Author details
[1]Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt. [2]Kobry El-Kobba Military Hospital, Cairo, Egypt.

Yosef *et al. Egypt J Intern Med*   (2021) 33:45

Page 14 of 14

References

1. Hassan MS, Mourad YH, Elghobary MA (2016) Diabetogenic effect of hepatitis C virus and insulin resistance among chronic hepatitis C patients. Egypt J Intern Med 28:149–154
2. Kaur H, Singh P, Pannu HS, Sood A, Jain NP, Bhoday HS (2015) To study the prevalence of impaired glucose tolerance in patients with hepatitis C virus related chronic liver disease. J Clin Diagn Res 9:OC16-OC20
3. Talaat A, Fatin A, Elsawy A (2012) Hepatic steatosis in HCV infection genotype 4 in Egypt. Egypt Liver J 2:16–21
4. Ahmed OA, Safwat E, Khalifa MO, Elshafie AI, Fouad MHA, Salama MM et al (2018) Sofosbuvir plus daclatasvir in treatment of chronic hepatitis C genotype 4 infection in a cohort of Egyptian patients: an experiment the size of Egyptian village. Int J Hepatol 2018:9616234
5. Oliveira LPM, Jesus RP, Boulhosa RSSB, Mendes CMC, Lyra AC, Lyra LGC (2012) Metabolic syndrome in patients with chronic hepatitis C virus genotype 1 infection who do not have obesity or type 2 diabetes. Clinics (Sao Paulo) 67:219–223
6. Lim T (2014) Metabolic syndrome in chronic hepatitis C infection: does it still matter in the era of directly acting antiviral therapy? Hepat Med 6:113–118
7. Patel A, Harrison SA (2012) Hepatitis C virus infection and nonalcoholic steatohepatitis. Gastroenterol Hepatol (N Y) 8:305–312
8. Kim JK (2009) Hyperinsulinemic-euglycemic clamp to assess insulin sensitivity in vivo. Methods Mol Biol 560:221–238
9. Harrison SA (2008) Insulin resistance among patients with chronic hepatitis C: etiology and impact on treatment. Clin Gastroenterol Hepatol 6:864–876
10. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A (2015) Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metab 19:160–164
11. Hu JH, Chang ML, Liu NJ, Yeh CT, Huang TJ (2019) Effect of HCV treatment response on insulin resistance: a systematic review and meta-analysis. Exp Ther Med 18:3568–3578
12. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y (2019) From pre-diabetes to diabetes: diagnosis, treatments and translational research. Medicina (Kaunas) 55:546
13. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver (2018) EASL recommendations on treatment of hepatitis C 2018. J Hepatol 69:461–511
14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
15. Matsuda M, DeFronzo RA (1999) Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
16. Mada PK, Malus ME, Parvathaneni A, Chen B, Castano G, Adley S et al (2020) Impact of treatment with direct acting antiviral drugs on glycemic control in patients with hepatitis C and diabetes mellitus. Int J Hepatol 2020:6438753
17. El Sagheer G, Soliman E, Ahmad A, Hamdy L (2018) Study of changes in lipid profile and insulin resistance in Egyptian patients with chronic hepatitis C genotype 4 in the era of DAAs. Libyan J Med 13:1435124
18. Jain A, Kalra BS, Srivastava S, Chawla S (2019) Effect of sofosbuvir and daclatasvir on lipid profile, glycemic control and quality of life index in chronic hepatitis C, genotype 3 patients. Indian J Gastroenterol 38:39–43
19. Gitto S, Cicero AFG, Loggi E, Giovannini M, Conti F, Grandini E et al (2018) Worsening of serum lipid profile after direct acting antiviral treatment. Ann Hepatol 17:64–75
20. Hashimoto S, Yatsuhashi H, Abiru S, Yamasaki K, Komori A, Nagaoka S et al (2016) Rapid increase in serum low-density lipoprotein cholesterol concentration during hepatitis C interferon-free treatment. PLoS One 11:e0163644
21. Salas-Villalobos TB, Lozano-Sepúlveda SA, Rincón-Sánchez AR, Govea-Salas M, Rivas-Estilla AM (2017) Mechanisms involved in liver damage resolution after hepatitis C virus clearance. Med Univ 19:100–107
22. Hashim AM, Kandeel H, Hendy O, El-Mola K, El-Raey F, Attia MM (2017) Effect of new direct-acting antiviral drugs on insulin resistance and glycemic control after treatment of chronic hepatitis C virus infection in type 2 diabetic patients. Al-Azhar Assiut Med J 15:187–195
23. Adinolfi LE, Nevola R, Guerrera B, D'Alterio G, Marrone A, Giordano M, Rinaldi L (2018) Hepatitis C virus clearance by direct-acting antiviral treatments and impact on insulin resistance in chronic hepatitis C patients. J Gastroenterol Hepatol 33:1379–1382
24. Alsebaey A, Elhelbawy M, Abdel-Razek W, Hashim M, Elshenawy H, Waked I (2019) HCV treatment with direct acting antivirals improves the insulin sensitivity. Expert Rev Anti-Infect Ther 17:749–754
25. El Badry MM, Ali DA, Eltaweel NH, Abdel-Wahed MA (2020) Effect of eradication of HCV infection by direct-acting antivirals in diabetic HCV-infected patients as regards glycemic control. Egypt Liver J 10:54
26. Kasai D, Adachi T, Deng L, Nagano-Fujii M, Sada K, Ikeda M, Kato N, Ide YH, Shoji I, Hotta H (2009) HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. J Hepatol 50:883–894
27. Deng L, Shoji I, Ogawa W, Kaneda S, Soga T, Jiang DP, Ide YH, Hotta H (2011) Hepatitis C virus infection promotes hepatic gluconeogenesis through an NS5A-mediated, FoxO1-dependent pathway. J Virol 85:8556–8568
28. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, Esmat G, Hamid MA, Mohamed MK, Fontanet A (2006) Higher clearance of hepatitis C virus infection in females compared with males. Gut 55:1183–1187
29. Clifford GM, Waterboer T, Dondog B, Qiao YL, Kordzaia D, Hammouda D, Keita N, Khodakarami N, Raza SA, Sherpa AT, Zatonski W (2017) Hepatitis C virus seroprevalence in the general female population of 9 countries in Europe, Asia and Africa. Infect Agent Cancer 12:1–8
30. Zeng H, Li L, Hou Z, Zhang Y, Tang Z, Liu S (2020) Direct-acting antiviral in the treatment of chronic hepatitis C: bonuses and challenges. Int J Med Sci 17:892–902

Publisher's Note