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Assessment of carotid atherosclerosis in Egyptian chronic hepatitis C patients after treatment by direct-acting antiviral drugs

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Abstract

Background: Recent studies suggested association between hepatitis C virus (HCV) infection and cardiovascular disorders, including carotid atherosclerosis with evidence of an effect of HCV clearance on carotid atherosclerosis.

Objectives: We aimed to evaluate the impact of direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection on carotid atherosclerosis.

Subjects and methods: This is a prospective cohort study that was carried out in Internal Medicine and Hepatology Department, and outpatient clinics of the Ain Shams University hospitals included 80 Egyptian patients with chronic HCV infection who started treatment in the form of IFN-free DAA-based regimen and completed the course of treatment and 6-month follow-up period. All patients were subjected to detailed history taking, full physical examination, full laboratory investigations, radiological assessment by abdominal ultrasonography, and high-resolution B-mode ultrasonography of both the common carotid arteries.

Results: The mean age of cases was 58.13 ± 7.56 years, 49 (61.25%) males and 31 (38.75%) females. IMT was significantly decreased after treatment 1.24 versus 1.57 mm $p < 0.001$. The number of patients with $IMT \geq 1$ mm was significantly decreased after 6 months 45 (56.3%) versus 57 (71.3%). There was significant positive correlation between baseline carotid IMT and age, BMI, bilirubin, INR, CTP score, carotid plaques, and total cholesterol. Meanwhile, there was significant negative correlation between baseline carotid IMT and hemoglobin, platelets, albumin, and HDL. In patients who achieved SVR, total cholesterol, triglycerides, LDL, and HDL were significantly increased after treatment. IMT was significantly lower in SVR group compared to non-SVR group ($p = 0.016$).

Conclusion: Hepatitis C virus eradication by DAAs improves carotid atherosclerosis by decreasing carotid intima-media thickening.

Keywords: Carotid atherosclerosis, DAAs, Chronic hepatitis C

Introduction

The hepatitis C virus (HCV) is one of the most common causes of chronic liver disease, affecting an estimated 71 million individuals worldwide [1].

Despite its association with a reduction in serum concentrations of total cholesterol, LDL-C, and apolipoprotein B (apoB — the main protein element of LDL and very-low-density lipoprotein), chronic HCV infection has been linked to an increased risk of atherosclerosis and its clinical complications [2].

With HCV infection, the risk of carotid artery disease (CAD) increases. In addition, cardiac perfusion abnormalities were discovered in 87% of chronic

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hepatitis C patients, which improved after the virus was eradicated [3].

The carotid arteries are one of the most prevalent locations of atherosclerosis, which can lead to heart disease, stroke, and other complications. Ischemic stroke is the more common of the two major stroke subtypes, and it is caused mostly by carotid atherosclerosis [4].

A prolonged immunological assault and the development of pro-inflammatory cytokines were proposed as causes underlying carotid atherosclerosis. Persistent infection could so keep inflammation at a high level. These cardiovascular changes could be caused by a change in the cytokine balance seen in chronic hepatitis C patients [5].

Carotid intima-media thickness (CIMT) has been utilized as a surrogate of subclinical atherosclerosis, and studies have revealed that patients with chronic HCV infection have higher CIMT after accounting for traditional cardiovascular risk factors [6].

The recent introduction of direct-acting antivirals (DAAs) has changed hepatitis C virus (HCV) infection treatment. These treatments result in significantly high sustained viral response (SVR) rates (85–100%) after a brief treatment course (12–24 weeks) with no major side effects [7].

The available data on role of treatment of chronic HCV infection by new DAAs and improvement of carotid atherosclerosis are scarce and contradicting as study of Petta et al. revealed that HCV eradication by DAA improves carotid atherosclerosis in patients with severe fibrosis with or without additional metabolic risk factors [8].

The aim of the current study is to evaluate the impact of direct-acting antiviral (DAA) therapy for chronic hepatitis c virus (HCV) infection on carotid atherosclerosis.

Patients and methods

Subjects

This prospective study was carried out on eighty Egyptian patients recruited from the Hepatology and Gastroenterology Unit (Internal Medicine Department), Ain Shams University (ASU) Hospital, and from the Center for Treatment of Viral Hepatitis at Ain Shams University (one of the National Committee for the Control of Viral Hepatitis (NCCVH) centers in Cairo) from October 2019 to November 2021. Eligible patients were male and non-pregnant female patients, aged 18–75 years, with chronic HCV infection and positive HCV RNA by PCR.

During the study's population selection, we use a variety of exclusion criteria: patients with hepatocellular carcinoma, pregnancy, lactation, or inability to use an effective contraceptive method, and liver disease of various or mixed etiologies (such as hepatitis A, hepatitis B, autoimmune hepatitis, alcoholic liver disease, drug-induced hepatitis, hemochromatosis, Wilson's disease, or 1 antitrypsin deficiency); those with HIV infection, immunosuppressive medicines, or treatments that cause steatosis (valproic acid, tamoxifen, corticosteroids, amiodarone); and patients with a history of ischemic heart disease or cerebral disease.

The exclusion criteria for the administration of DAAs included (according to NCCVH protocol) the following: total bilirubin > 3 mg/dl, serum albumin < 2.8 g/dl, international normalization ratio (INR) > 1.7, platelet count < 50,000/mm^3, patients with any advanced systemic disease that could affect liver disease progression and the choice of antiviral regimen, and pregnancy or inability to use efficient contraception method in women.

Methods

According to the National Committee for the Control of Viral Hepatitis Egyptian treatment protocol, all patients were subjected to the following:

- Detailed history taking and full clinical examination
- Laboratory investigations at baseline: Complete blood count (CBC), liver profile (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total and direct bilirubin, serum albumin), serum creatinine, prothrombin time, INR, alpha-fetoprotein (AFP), random blood sugar, and HbA1c in diabetics
- Hepatitis viral markers: Hepatitis B surface antigen and HCV antibody using third-generation ELISA test and pregnancy test for females in the childbearing period
- Abdominal ultrasonography was done with special stress on liver echogenicity and size, portal vein diameter, the presence of any hepatic focal lesion (HFL), and splenomegaly.
- ECG for males above 40 years and females above 50 years and echocardiography for patients above 60 years
- Serum TG, total cholesterol, HDL, LDL, and VLDL
- Laboratory investigations at follow-up visits (every 4 weeks): CBC, ALT, AST, INR, and total bilirubin
- Serum HCV RNA level was measured before treatment, at the end of treatment (12 weeks and 24 weeks), and at 12 weeks after stopping of treatment.
- Sustained virological response (SVR12) defined as undetectable HCV RNA 12 weeks after completion of therapy by a sensitive HCV RNA assay [9]

We evaluated the following parameters:

- Recurrence rate: The percentage of patients has a detectable virus load by PCR 12 weeks after therapy ended.
- Response rate: The percentage of patients who achieved SVR12

Diagnosis of liver cirrhosis based on clinical, laboratory, and radiological study confirmed by FibroScan showed liver stiffness measurement more than or equal to 14.5 kPa [10].

Carotid artery evaluation

Carotid artery assessment is before and 6 months after completion treatment. An ultrasound machine (Toshiba Memo 30 scanner) coupled with a 7.5 MHz high-resolution transducer was used to perform high-resolution B-mode ultrasonography of both common carotid arteries. In the supine position, patients were examined. A professional physician analyzed the carotid artery in a blinded manner. The follow-up examination was performed by the same operators who performed the baseline examination. The carotid arteries of both the right and left sides were examined in longitudinal projections at the level of the common carotid artery, bulb, and internal carotid in each patient. The difference between the first (intima lumen) and second (media adventitia) interfaces on the far wall of the common carotid artery in a section free of plaque beginning 10 mm below their bifurcations and including the bifurcations for 10 mm was measured as the carotid intima-media thickness (CIMT). IMT 1 mm was used to define carotid thickening. A carotid plaque was described as a localized thickening of 1.5 mm or more at the common carotid artery's level.

In terms of the clinical significance of IMT measures, a larger IMT is a proven predictor of later coronary heart disease and stroke, the two major causes of cardiovascular death, while an IMT of less than 1 mm has been linked to a higher risk of cardiovascular events [11].

Antiviral therapy

All patients were treated according to therapeutic schedules suggested in national treatment program of hepatitis C guidelines in Egypt available at the time of the enrollment. HCV RNA measurements were repeated at the end of therapy and 12 weeks after stopping treatment.

The study was performed in accordance with ethical standards. The Faculty of Medicine, Ain Shams University ethical committee approval was taken before starting the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

Data was collected, coded, and then entered as a spreadsheet using Microsoft Excel 2016 for Windows and of the Microsoft Office bundle 2016 of Microsoft Corporation, USA. Data was analyzed using IBM Statistical Package for Social Sciences (SPSS) software (IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY, USA: IBM Corp.). The Kolmogorov–Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median, and IQR, while categorical data was expressed as numbers and percentage. A statistical value < 0.05 was considered as significant. Chi-square test was used to study the association between two qualitative variables. Wilcoxon signed-rank test was used for abnormally distributed quantitative variables, to compare two related samples, matched samples, or repeated measurements on a single sample to assess whether their population mean ranks differ. McNemar's test was used for paired nominal data. Mann–Whitney *U*-test was used when comparing two means that do not have normally distributed data.

Results

This study included 80 patients; the mean age in the studied cases was 58.13 ± 7.56 years and ranged from 43 to 70 years. Regarding gender, 49 (61.25%) patients were male, and 31 (38.75%) patients were female with male to female ratio 1.58:1. The mean BMI of patients was 27.93 ± 8.44 kg/m^2. Considering risk factors of carotid atherosclerosis, 8 (10%) patients were diabetics, 22 (27.5%) patients had hypertension, 24 (30%) patients were smokers, and 10 (12.5%) patients had dyslipidemia. Fifty-four (67.5%) patients were cirrhotic, 36 (45%) patients were Child class A, and 18 (22.5%) patients were Child class B (Table 1).

On comparing laboratory data before starting treatment and 6-month follow-up after treatment, it was noticed that platelets, total cholesterol, triglycerides, LDL, HDL, and albumin were significantly increased after treatment, while ALT, AST, bilirubin, INR, and RBS were significantly decreased after treatment. There was no statistically significant difference in Hb, WBCs, AFP, serum creatinine, and urea. Regarding HCV RNA, 96.25% became negative 6 months after treatment with DAAs. IMT was significantly decreased 6 months after treatment 1.24 vs. 1.57 mm, $p < 0.001$ (Table 2).

Seventy-seven (96.25%) patients achieved SVR, while 3 (3.75%) patients relapsed (Table 3). Fifty-six (70%) patients were treated by SOF/DAC regimen, while 24 (30%) patients were treated by SOF/DAC/RBV regimen (Table 4).

Table 1 Distribution of the studied cases as per sociodemographic characteristics, risk factors, and clinical data

		Studied patients (no. = 80)	
		No	**%**
Age (years)	**Mean ± SD**	58.13 ± 7.56	
	Range	43.0–70.0	
Gender	**Female**	31	38.75%
	Male	49	61.25%
BMI (kg/m^2)	**Mean ± SD**	27.93 ± 8.44	
	Range	22.40–35.30	
DM	**No**	72	90.0%
	Yes	8	10.0%
Hypertension	**No**	58	72.5%
	Yes	22	27.5%
Smoking	**No**	56	70.0%
	Yes	24	30.0%
Dyslipidemia	**No**	70	87.5%
	Yes	10	12.5%
Cirrhosis	**No**	26	32.5%
	Yes	54	67.5%
CTP score	**Class A**	36	45.0%
	Class B	18	22.5%

No. number, % percentage, *SD* Standard deviation, *CTP* Child-Turcotte-Pugh. The mean age in the studied cases was 58.13 ± 7.56 years and ranged from 43 to 70 years. Regarding gender, 49 (61.25%) patients were male, and 31 (38.75%) patients were female with male to female ratio 1.58:1. The mean BMI of patients was 27.93 ± 8.44 kg/m^2. Considering risk factors of carotid atherosclerosis, 8 (10%) patients were diabetics, 22 (27.5%) patients had hypertension, 24 (30%) patients were smokers, and 10 (12.5%) patients had dyslipidemia. Fifty-four (67.5%) patients were cirrhotic, 36 (45%) patients were Child class A, and 18 (22.5%) patients were Child class B

There was no significant difference between cases treated by double *SOF/DAC therapy* and cases treated by triple *SOF/DAC/RBV therapy* as regards carotid IMT at baseline and after 6-month follow-up. Meanwhile, there was significant decrease in carotid IMT at baseline compared to after 6-month follow-up in both double and triple therapy (Table 5).

The number of patients who had $IMT \geq 1$ mm was significantly decreased after 6-month follow-up 45 (56.3%) compared to baseline 57 (71.3%). There was no statistically significant difference between the presence of carotid plaques before and after treatment, $p = 0.063$ (Table 6) (Figs. 1 and 2).

Correlation between baseline carotid IMT and other parameters of the studied patients revealed that there was significant positive correlation between baseline carotid IMT and age ($p < 0.001$), BMI ($p = 0.019$), bilirubin ($p < 0.001$), INR ($p = 0.001$), CTP score ($p < 0.001$), carotid plaques ($p = 0.009$), and total cholesterol ($p = 0.001$). Meanwhile, there was significant negative correlation between baseline carotid IMT and hemoglobin ($p < 0.001$), platelets ($p < 0.001$), albumin ($p < 0.001$), and HDL ($p < 0.001$) (Table 6).

IMT at baseline and 6-month follow-up after initiation of anti-HCV therapy and the presence of cirrhosis revealed that there was no significant difference between cirrhotic (neither Child A nor B) and non-cirrhotic patients as regards carotid IMT at baseline and after 6-month follow-up. Meanwhile, there was significant decrease in carotid IMT at baseline compared to after 6-month follow-up in the three groups individually (Table 7).

In non-SVR patients, there was no statistically significant difference in total cholesterol, triglycerides, LDL, and HDL at baseline and follow-up ($p > 0.05$), while in SVR group, total cholesterol, triglycerides, LDL, and HDL were significantly increased after follow-up compared to baseline ($p < 0.001$). It was noticed that LDL was significantly higher in SVR group compared to non-SVR after treatment ($p = 0.034$). Also, carotid IMT was significantly lower in SVR group compared to non-SVR ($p = 0.016$) (Table 8).

Discussion

HCV is a leading cause of chronic liver disease and cirrhosis all over the world. It is linked to a variety of hepatic and extrahepatic symptoms, including cardiovascular changes. Hepatic steatosis and metabolic abnormalities,

Table 2 Comparison between laboratory data and IMT before treatment and 6 months after treatment

	Baseline			Follow-up			Test value[a]	*p*-value
	Mean	± SD	Median	Mean	± SD	Median		
Hb (g/dL)	11.89	1.32	11.55	11.85	1.48	11.50	0.227	0.821
WBCs (10^9/L)	5.26	1.38	4.80	5.32	1.36	4.80	0.241	0.809
Platelets (10^9/L)	178.85	51.93	183.00	204.60	53.70	210.00	8.77	**< 0.001**
TC (mg/dL)	175.88	39.06	165.00	199.96	39.22	189.50	8.83	**< 0.001**
TGs (mg/dL)	126.79	21.19	121.00	141.32	21.48	133.50	8.45	**< 0.001**
LDL (mg/dL)	100.54	8.35	101.50	116.99	8.63	118.00	8.82	**< 0.001**
HDL (mg/dL)	48.00	4.23	48.00	56.74	4.66	57.00	8.82	**< 0.001**
ALT (IU/L)	58.85	15.64	56.00	36.40	9.27	35.50	7.67	**< 0.001**
AST (IU/L)	62.47	17.63	57.50	41.89	12.38	39.50	7.13	**< 0.001**
Albumin (g/dL)	3.46	0.66	3.27	3.64	0.66	3.45	8.45	**< 0.001**
Bilirubin (mg/dl)	1.36	0.41	1.36	1.27	0.46	1.25	7.51	**< 0.001**
INR	1.28	0.28	1.17	1.22	0.31	1.10	7.19	**< 0.001**
HCV RNA	812,219.3	730,374.3	659,500.0	30,062.50	165,954.3	0.00	7.65	**< 0.001**
AFP (ng/mL)	9.88	6.25	9.30	9.26	5.91	8.25	0.722	**0.470**
S. creatinine (mg/dl)	0.94	0.18	0.90	0.92	0.18	0.90	0.609	**0.542**
Blood urea (mg/dl)	21.45	7.83	19.00	22.73	9.44	19.50	0.887	**0.375**
RBS (mg/dl)	146.19	60.39	126.00	130.00	31.25	121.00	8.61	**< 0.001**
IMT	1.57	0.73	1.36	1.24	0.57	1.07	7.823	**< 0.001**

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$ is considered highly statistically significant. [a]Wilcoxon signed-rank test. *SD* Standard deviation, *TC* Total cholesterol, *TGs* Triglycerides, $p \leq 0.05$ is considered statistically significant, $p \leq 0.01$ is considered highly statistically significant, *AFP* Alpha-fetoprotein, *RBS* Random blood sugar, *IMT* Intima-media thickness. On comparing laboratory data before starting treatment and 6-month follow-up after treatment, it was noticed that platelets, total cholesterol, triglycerides, LDL, HDL, and albumin were significantly increased after treatment, while ALT, AST, bilirubin, INR, and RBS were significantly decreased after treatment. There was no statistically significant difference in Hb, WBCs, AFP, serum creatinine, and urea. Regarding HCV RNA, 96.25% became negative 6 months after treatment with DAAs. IMT was significantly decreased 6 months after treatment 1.24 vs. 1.57 mm $p < 0.001$

Table 3 Descriptive analysis of different DAAs treatment regimens received by the studied cases

	Studied patients (no. = 80)	
	No	%
SOF/DAC	56	70.0%
SOF/DAC/RBV	24	30.0%

Seventy-seven (96.25%) patients achieved SVR, while 3 (3.75%) patients relapsed

Table 4 Distribution of the studied cases as per SVR

		Studied patients (no. = 80)	
		No	%
SVR	**Nonresponders**	3	3.75%
	Responders	77	96.25%

Fifty-six (70%) patients were treated by SOF/DAC regimen, while 24 (30%) patients were treated by SOF/DAC/RBV regimen

such as insulin resistance, are caused by chronic HCV infection, as are elevated inflammatory markers, which may contribute to endothelial dysfunction and coronary artery disease [12].

Carotid intima-media thickness (CIMT) has been used to assess subclinical atherosclerosis. It is a simple and inexpensive tool to assess the cumulative effect of atherosclerotic risk factor and is recommended by the American Heart Association as a noninvasive tool for assessment of cardiovascular risk [13].

HCV treatment outcomes have improved dramatically in recent years as a result of the introduction of new DAAs, with more than 90% of patients achieving an SVR after 12 weeks of treatment. Because of the improved efficacy of HCV treatment, there is now optimism for a considerable reduction in CIMT, carotid atherosclerosis, and even cardiovascular and cerebrovascular complications in these patients [14].

Previous studies had conflicting results about the effect of DAA on carotid atherosclerosis. This study was performed to highlight this effect especially on Egyptian patients who started treatment in form of INF-free, DAA-based regimen and completed the course of treatment according to the National Committee for Control of Viral Hepatitis in patients with or without cirrhosis.

The main finding of this study is that DAAs used in the national Egyptian treatment protocol for HCV infection

Table 5 Relation between IMT (at baseline and 6-month follow-up after initiation of anti-HCV therapy) and protocol of treatment

		Non-cirrhotic (no. = 26)			Child A (no. = 36)			Child B (no. = 18)			Test value[a]	*p*-value[a]
		Mean	± SD	Median	Mean	± SD	Median	Mean	± SD	Median		
IMT	**Baseline**	1.18	0.46	0.95	1.17	0.32	1.04	1.46	0.61	1.42	4.75	0.093
	6-month follow-up	0.95	0.39	0.76	0.97	0.35	0.90	1.06	0.49	0.88	2.61	0.271
***p*-value[b]**		**< 0.001**			**< 0.001**			**0.001**				

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$ is considered highly statistically significant. [a]Mann-Whitney *U*-test. [b]Wilcoxon signed-rank test. *SD* Standard deviation, *IMT* Intima-media thickness. No significant difference between cases treated by double *SOF/DAC therapy* and cases treated by triple *SOF/DAC/RBV therapy* as regards carotid IMT at baseline and after 6-month follow-up. Meanwhile, there was significant decrease in carotid IMT at baseline compared to after 6-month follow-up in both double and triple therapies

Table 6 Comparison between baseline and 6-month follow-up as per the presence of *IMT* ≥ 1 mm and carotid plaques

		Baseline		Follow-up		*p*-value[a]
		No	%	No	%	
IMT	**≥ 1 mm**	57	71.3%	45	56.3%	< 0.001
	< 1 mm	23	28.7%	35	43.8%	
Carotid plaques	**No**	43	53.8%	48	60.0%	0.063
	Yes	37	46.3%	32	40.0%	

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$ is considered highly statistically significant. [a]McNemar's test. *SD* Standard deviation, *IMT* Intima-media thickness. The number of patients who had *IMT* ≥ 1 mm was significantly decreased after 6-month follow-up 45 (56.3%) compared to baseline 57 (71.3%). There was no statistically significant difference between the presence of carotid plaques before and after treatment, $p = 0.063$

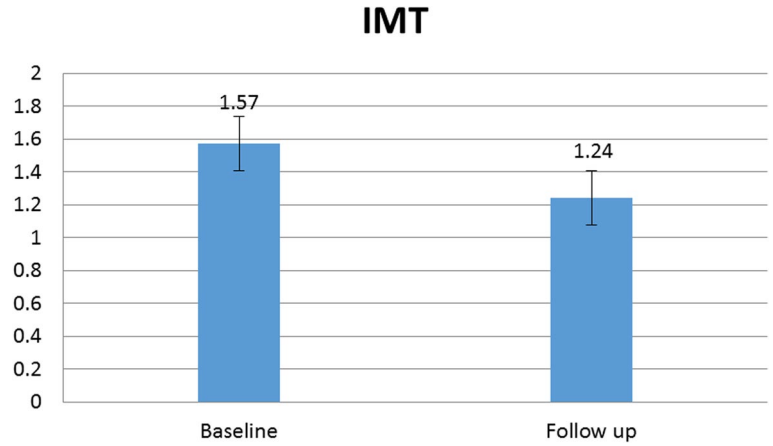

Fig. 1 Comparison between IMT at baseline and follow-up. The number of patients who had *IMT* ≥ 1 mm was significantly decreased after 6-month follow-up 45 (56.3%) compared to baseline 57 (71.3%)

treatment lead to reduction in CIMT, while no changes are noticed in patients who did not achieved SVR (Table 9).

Many studies have found that HCV-infected patients have higher carotid IMT than healthy control subjects, with the mean IMT of HCV-infected patients being significantly higher than healthy controls. This difference cannot be explained by differences in age, gender, BMI, or cardiometabolic risk factors [15].

To the best of our knowledge, there are still just a few studies that have looked into whether DAAs can reduce the risk of carotid atherosclerosis. Previous research into the role of INF-based therapy in hepatitis C viral eradication found that INF treatment was linked

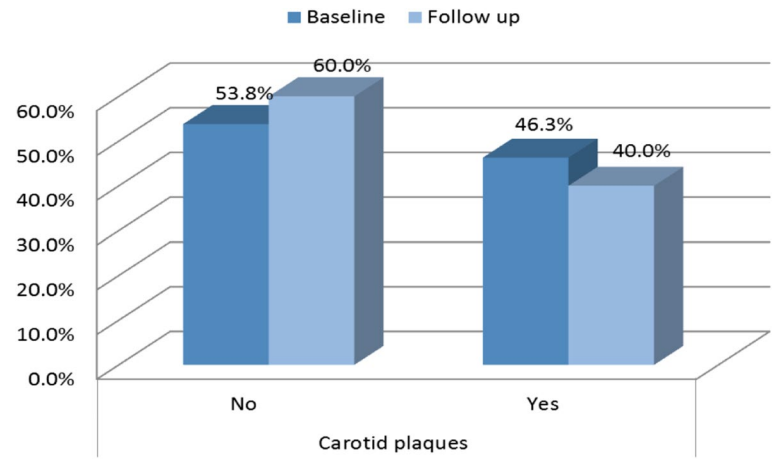

Fig. 2 Comparison between carotid plaques at baseline and follow-up. There was no statistically significant difference between the presence of carotid plaques before and after treatment, $p = 0.063$

Table 7 Relation between IMT at baseline and 6-month follow-up after initiation of anti-HCV therapy and the presence of cirrhosis

		Non-cirrhotic (no. = 26)			Child A (no. = 36)			Child B (no. = 18)			Test value[a]	*p*-value[a]
		Mean	± SD	Median	Mean	± SD	Median	Mean	± SD	Median		
IMT	**Baseline**	1.18	0.46	0.95	1.17	0.32	1.04	1.46	0.61	1.42	4.75	0.093
	6-month follow-up	0.95	0.39	0.76	0.97	0.35	0.90	1.06	0.49	0.88	2.61	0.271
***p*-value[b]**		**< 0.001**			**< 0.001**			**0.001**				

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$ is considered highly statistically significant. [a]Kruskal-Wallis test. [b]Wilcoxon signed-rank test. *SD* Standard deviation, *IMT* Intima-media thickness. IMT at baseline and 6-month follow-up after initiation of anti-HCV therapy and the presence of cirrhosis revealed that there was no significant difference between cirrhotic (neither child A nor B) and non-cirrhotic patients as regards carotid IMT at baseline and after 6-month follow-up. Meanwhile, there was significant decrease in carotid IMT at baseline compared to after 6-month follow-up in the three groups individually

to a lower risk of cerebrovascular and cardiovascular complications, but it is unclear whether the observed positive effect is due to virological clearance, IFN, or selection bias [16].

In the present work, IMT and the number of patients who had IMT ≥ 1 mm were significantly decreased 6 months after treatment compared to baseline (p-value < 0.001), while there was no statistically significant difference between the presence of carotid plaques before and 6 months after treatment (p-value 0.063). This problem could arise because, in the short-to-medium term, IMT may be more sensitive to changes in inflammatory and fibrogenic mediators caused by HCV infection than a stable plaque. HCV can enhance cardiovascular risk by causing insulin resistance [17], producing a systemic inflammatory state via natural killer and Th1-mediated responses, increasing TNF-a and IL-6 levels while lowering adiponectin levels and causing endothelial damage directly linked to HCV infection. However, with a longer follow-up, we cannot rule out the possibility of virological elimination having an influence on carotid plaques [18].

This came in agreement with Petta et al. [8] who found that mean IMT significantly decreased from baseline to 9–12 months after the end of antiviral therapy (0.94 ± 0.29 mm vs. 0.81 ± 0.27, $p < 0.001$), and both carotid thickening and carotid plaques were found in 42.8% of patients with no differences were reported for carotid plaques. None of the study subjects had clinically relevant carotid stenosis (i.e., less than 60%).

On the other hand, a prospective observational study by Revuelto et al. [19] reported that the eradication of hepatitis C virus by direct-acting antiviral agents does not improve the atheroma plaques and nor does it vary their composition.

In the current study, it was found that there was significant positive correlation between baseline carotid IMT and age of the patients ($p < 0.001$), BMI ($p = 0.019$),

Table 8 Correlation between and baseline carotid IMT and other risk factors

	Carotid IMT	
	r	*p*-value
Age	0.612	**< 0.001***
BMI	0.263	**.019***
Systolic BP	0.128	0.257
Diastolic BP	.031	0.782
Pulse	.023	0.837
Hb	− 0.400	**< 0.001***
WBCs	− .083	0.466
Platelets	− 0.638	**< 0.001***
ALT	.054	0.632
AST	.047	0.678
Albumin	− 0.790	**< 0.001***
Bilirubin	0.782	**< 0.001***
INR	0.352	**0.001***
CTP score	0.846	**< 0.001***
HCV RNA	.088	0.437
TC	0.357	**0.001***
TGs	− 0.129	0.254
LDL	− .070	0.539
HDL	− 0.418	**< 0.001***
S. creatinine	− .062	0.586
Urea	− .052	0.647
RBS	.002	0.989
AFP	.092	0.417
Carotid plaques	0.290	**0.009**

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$* is considered highly statistically significant. In non-SVR patients, there was no statistically significant difference in total cholesterol, triglycerides, LDL, and HDL at baseline and follow-up ($p > 0.05$), while in SVR group, total cholesterol, triglycerides, LDL, and HDL were significantly increased after follow-up compared to baseline ($p < 0.001$). It was noticed that LDL was significantly higher in SVR group compared to non-SVR after treatment ($p = 0.034$). Also, carotid IMT was significantly lower in SVR group compared to non-SVR ($p = 0.016$)

bilirubin ($p < 0.001$), INR ($p = 0.001$), carotid plaques ($p = 0.009$), and total cholesterol ($p = 0.001$). Meanwhile, there was significant negative correlation between baseline carotid IMT and hemoglobin ($p < 0.001$), platelets ($p < 0.001$), albumin ($p < 0.001$), and HDL ($p < 0.001$). This came in agreement with Petta et al. [8] who found that older age and lower platelet count were associated with higher IMT ($p < 0.10$ for both).

The results of this study also reported a positive correlation between baseline carotid IMT and Child score. This was consistent with Barakat et al. [20] who found that CIMT significantly increased with chronic hepatitis C virus patients especially in those with cirrhosis and correlated with Child–Pugh scoring of cirrhosis, but the results were not in agreement with those made by Bilora et al. [21] who have shown that chronic viral hepatitis may protect from atherosclerosis in the carotid arteries.

The current study addressed that the CIMT decrease significantly in the non-cirrhotic patients and patients with Child A who received Sof/Dac regimen and those with Child B who received Sof/Dac/Riba regimen with no significant difference between the 2 groups of patients. To our knowledge, the present study is unique in assessing CIMT in patients with Child B decompensated cirrhosis.

Interestingly, in the present study, we found that total cholesterol, LDL cholesterol, serum triglyceride, and HDL cholesterol were significantly increased 6 months after treatment compared to before treatment with (p-value 0.001); also, we demonstrated that lipid profile was significantly higher among patients who achieved SVR than non-SVR patients. Notably, the few number of relapsers makes actually difficult to draw firm conclusions about these subgroups.

These findings are consistent with those of Carvalho et al. [22], who observed a worsening of lipid profile with DAA treatment, highlighting the possibility of anti-HCV therapy having detrimental repercussions in patients with prior cardiovascular disease. They found a substantial rise in LDL, total cholesterol, and HOMA-IR in patients who achieved SVR after DAA treatment, implying that interferon-free therapy may have deleterious implications on cardiovascular risk. Pro-atherogenic lipid alterations during therapy were linked to improvements in insulin resistance, according to Gitto et al. [23]. They raised the issue of global cardiovascular balance in patients with amelioration of glucose metabolism and concurrent negative changes of lipid profile.

Another study by Ichikawa et al. [24] reported that the small low-density lipoprotein cholesterol was exacerbated after 1 year of treatment with direct-acting antiviral and concluded that atherosclerosis must be evaluated in patients achieving SVR.

The rapid suppression of HCV core proteins caused by DAA, according to Hashimoto et al. [25], may lead to a dysregulation of host lipid metabolism, manifested as a decrease in lipid droplet synthesis in HCV-infected liver cells and a substantial rebound of circulating LDL.

On comparing random blood sugar before and after DAAs therapy, of notice, random blood sugar showed significant decline after treatment (146.19 ± 60.36) and before treatment vs. (130 ± 31.25) after treatment, p-value < 0.001; these findings matched those of Hum et al. [26], who discovered that HCV eradication with DAAs improved blood glucose levels in individuals with type 2 diabetes. As a result, early HCV treatment may

Table 9 Concentration of lipid profile and IMT at baseline and 6-month follow-up after initiation of anti-HCV therapy in studied cases categorized according to whether or not they achieved SVR

	Non-SVR (no. = 3)			SVR (no. = 77)			Test value[a]	*p*-value[a]
	Mean	± SD	Median	Mean	± SD	Median		
TC (mg/dL)								
Baseline	180.67	18.45	176.00	175.69	39.70	165.00	1.17	0.243
Follow-up	181.33	18.23	178.00	200.69	39.70	190.00	1.04	0.298
***p*-value**[b]	0.655			**< 0.001**				
TGs (mg/dL)								
Baseline	129.67	23.59	132.00	126.68	21.26	121.00	0.076	0.939
Follow-up	132.33	30.44	120.00	141.68	21.26	136.00	1.05	0.293
***p*-value**[b]	1.00			**< 0.001**				
LDL (mg/dL)								
Baseline	103.00	7.00	106.00	100.44	8.43	101.00	0.827	0.402
Follow-up	105.33	5.86	103.00	117.44	8.43	118.00	2.12	**0.034**
***p*-value**[b]	1.00			**< 0.001**				
HDL (mg/dL)								
Baseline	48.00	3.61	47.00	48.00	4.28	48.00	0.216	0.829
Follow-up	50.00	9.64	46.00	57.00	4.28	57.00	1.36	0.173
***p*-value**[b]	1.00			**< 0.001**				
Carotid IMT								
Baseline	1.97	0.20	1.98	1.56	0.74	1.35	1.51	0.132
Follow-up	2.11	0.37	1.92	1.20	0.55	1.06	2.42	**0.016**
***p*-value**[b]	0.285			**< 0.001**				

$p \leq 0.05$ is considered statistically significant; $p \leq 0.01$ is considered highly statistically significant. [a]Mann-Whitney *U*-test. [b]Wilcoxon signed-rank test. *SD* Standard deviation, *TC* Total cholesterol, *TGs* Triglycerides. In non-SVR patients, there was no statistically significant difference in total cholesterol, triglycerides, LDL, and HDL at baseline and follow-up ($p > 0.05$), while in SVR group, total cholesterol, triglycerides, LDL, and HDL were significantly increased after follow-up compared to baseline ($p < 0.001$). It was noticed that LDL was significantly higher in SVR group compared to non-SVR after treatment ($p = 0.034$). Also, carotid IMT was significantly lower in SVR group compared to non-SVR ($p = 0.016$)

help to delay the start and progression of diabetic microvascular complications.

The current study has some limitations that should be considered. The study included a small number of patients, carotid IMT was not measured at different stages of treatment, and the follow-up period had to be extended.

Conclusion

This study suggests that hepatitis C virus eradication by direct-acting antiviral agents (DAA) improves carotid atherosclerosis by decreasing intima-media thickening of the carotid artery.

Abbreviations

HCV: Hepatitis C virus; DAAs: Direct-acting antiviral drugs; INF: Interferon; CAD: Carotid artery disease; CIMT: Carotid intima-media thickness; IMT: Intima-media thickness; SVR: Sustained virological response; ASU: Ain Shams University; NCCVH: National Committee for the Control of Viral Hepatitis; PCR: Polymerase chain reaction; BMI: Body mass index; TC: Serum total cholesterol; TG: Serum triglycerides; LDL: Serum low-density lipoprotein; HDL: Serum high-density lipoprotein; VLDL: Serum very-low-density lipoprotein; MS: Metabolic syndrome; U/S: Ultrasound; CBC: Complete blood count; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International normalized ratio; AFP: Alpha-fetoprotein; HFL: Hepatic focal lesion; ECG: Electrocardiography; TH1: T-helper 1; TNF: Tumor necrosis factor; IL6: Interleukin 6; ELISA: Enzyme-linked immunosorbent assay; ANOVA: Analysis of variance; PPV: Positive predictive value; NPV: Negative predictive value.

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Authors' contributions

MAM, EMB, MMS, and ASA conceived and planned the experiments. MAM contributed to sample preparation. All authors provided critical feedback and helped shape the research, analysis, and manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Ain Shams University Research Committee and with the 1964 Helsinki Declaration and its later amendments (

Ethics committee's reference number: 000017585.
Address: Faculty of Medicine, Ain Shams University, Cairo 11211, Egypt).
Informed written consent was obtained from each participant before enrollment in the study.

Consent for publication
Informed written consent to publish patient's data was signed by all participants prior to beginning of the research.

Competing interests
The authors declare that they have no competing interests.

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