Impact of direct-acting antiviral on subclinical atherosclerosis in chronic hepatitis C infected patients

Impact des antiviraux à action directe sur l'athérosclérose subclinique chez les patients atteints d'une hépatite C chronique

Sarra Laabidi[1], Mouna Medhioub[1], Amal Khsiba[1], Asma Bach Ali[2], Asma Ben Mohamed[1], Lamine Hamzaoui[1]

1. Gastroenterology department. Mohamed Taher Maamouri Hospital, Nabeul, Tunisia
2. Biology department. Mohamed Taher Maamouri Hospital, Nabeul, Tunisia

Abstract

Introduction: The impact of direct antiviral drugs (DAAs) on extrahepatic manifestations in chronic hepatitis C (CHC) has been poorly studied.
Aim: To assess the prevalence of subclinical atherosclerosis in patients with CHC and the impact of DAAs on atherosclerotic lesions.
Methods: A 5-year prospective evaluative study, including patients followed for CHC at hepato-gastroenterology department. The subclinical atherosclerosis was assessed by ultrasound measurement of carotid intima-media thickness (IMTc) and the highest IMTc measurements from the left and right side defined the IMTc maximum (IMTc max). IMTc>75th percentile (IMTc75) define subclinical atherosclerosis with high cardiovascular risk. Patients were evaluated before (T0) and one year after DAAs therapy achievement (T1).
Results: At time T0, forty patients (median age: 55 y.; sex ratio M / F = 0.48), were included. Average value of IMTc max was 0.68 ± 0.16 mm. Subclinical atherosclerosis was noted in 82.5 %. At time T1, 28 patients were evaluated, all of whom completed sustained virological response (SVR). Compared to time T0, there was a significant increase in cholesterol (p = 0.001) and triglyceride (p = 0.009) levels. IMTc max was significantly higher at time T1 compared to T0 (0.75 Vs 0.67 mm, p = 0.04). Prevalence of IMTc75 was 82.1% at time T0 and 75% at time T1 (p=0.5).
Conclusions: SVR, in CHC patients treated with DAA, was associated with worsening of carotid atherosclerotic lesions.

Key words: Hepatitis C virus, Chronic viral hepatitis, atherosclerosis, Antiviral therapy

Résumé

Introduction: L'impact des médicaments antiviraux à action directe (AAD) sur les manifesta-tions extra-hépatiques de l'hépatite C chronique (HCC) est peu étudié.
Objectif: Evaluer la prévalence de l'athérosclérose subclinique chez les patients atteints de HCC et l'impact des AAD sur les lésions athérosclérotiques.
Méthodes: Une étude évaluative prospective de 5 ans a été menée, incluant les patients suivis pour une HCC. L'athérosclérose subclinique a été évaluée par la mesure échographique de l'épaisseur intima-média carotidienne (IMTc), et les mesures IMTc les plus élevées ont défini l'IMTc maximum (IMTc max). Une IMTc >75e percentile (IMTc75) a été définie comme une athérosclérose subclinique à haut risque cardiovasculaire. Les patients ont été évalués avant (T0) et un an après la réalisation de la thérapie par les AAD (T1).
Résultats: Au moment T0, quarante patients (âge médian : 55 ans ; ratio homme/femme = 0,48) ont été inclus. La valeur moyenne de l'IMTc max était de 0,68 ± 0,16 mm. Une athérosclérose subclinique a été observée chez 82,5 % des patients. Une réponse virologique soutenue (RVS) est obtenue. Par rapport au moment T0, il y a eu une augmentation significative des taux de cho-lestérol et de triglycérides. L'IMTc max était significativement plus élevée au moment T1 par rapport à T0. La prévalence de l'IMTc75 était de 82,1 % au moment T0 et de 75 % au moment T1 (p = 0,5).
Conclusions: La RVS chez les patients atteints de HCC traités par AAD était associée à une aggravation des lésions athérosclérotiques carotidiennes.

Mots clés: hépatite virale C, Hépatite virale, athérosclérose, Thérapie antivirale

Correspondance
Sarra Laabidi
Gastroenterology department. Mohamed Taher Maamouri Hospital, Nabeul, Tunisia
Email: sarralaabidi2022@gmail.com

LA TUNISIE MEDICALE-2024; Vol 102 (03): 170-175

Introduction

Hepatitis C virus (HCV) infection remains one of the most important etiologies of chronic liver disease throughout the world [1]. Additional to liver damage, HCV infection causes a variety of systemic disorders as atherosclerosis [2]. Currently, few data are available on relationships between atherosclerosis pathogenesis and HCV. Some authors suggest that HCV would be associated with several atherogenic conditions such as insulin resistance, hepatic steatosis and chronic inflammation [3,4]. Furthermore, HCV has been shown to colonize and replicate in carotid plaques causing local vascular inflammation responsible for endothelial insult [5].
The sustained virologic response (SVR) was associated with improvement of extrahepatic manifestations linked to HCV [6]. This effect has been proven above all with interferon and few studies have been conducted on the impact of direct-acting antivirals (DAAs) on extra-hepatic manifestations and in particular atherosclerosis [7,8].
In this work, we were interested in evaluating atherosclerosis prevalence in patients infected with HCV, and in assessing the impact of DAAs on atherosclerotic lesions.

Methods

This is a prospective cohort study over a 5-years period from March 2015 to January 2020 including consecutive patients, followed for CHC at hepato-gastroenterology department.
The inclusion criteria were: the presence of anti-HCV and detectable HCV RNA without any features of acute hepatitis C. All patients met the following exclusion criteria: 1) Age <18 years, 2) advanced liver cirrhosis (CHILD Pugh B or C), 3) hepatocellular carcinoma ,4) another associated cause of chronic liver disease such as alcoholic hepatitis, hepatitis B, auto -immune hepatitis, primary biliary cholangitis, Wilson's disease, hemochromatosis,alpha antitrypsin deficiency viral B ,5) human immunodeficiency virus co- infection ,6) using drugs inducing hepatic steatosis (corticosteroid, tamoxifen, amiodarone) or interfering with lipid metabolism (statins, fibrates), 7) previous hepatitis C anti-viral treatment 8) previous history of symptomatic atherosclerotic disease, 9) illicit drug addiction.
We included patients who meet the above criteria. they were evaluated at time 0 (T0), and one year after stopping the treatment (T1), Patients received DAAs therapy and achieved SVR.
SVR refers to the eradication of the HCV from the bloodstream, typically assessed by the absence of detectable viral RNA in the blood for a 12 weeks after the completion of antiviral treatment [9,10].

Clinical and biological data

Clinical, anthropological and biological data were collected at T0 and T1. Blood pressure was taken manually in a subject who had been at rest for at least 20 minutes and the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) are noted.
The body mass index (BMI) was calculated according to the following formula: BMI = weight (kg) / height (m^2). Patients were classified as obese if BMI> 30 kg / m^2.
Biochemical analyses were performed in the same central laboratory for all patients, including complete blood count, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ glutamyl transpeptidase (GGT), Alkaline phosphatase (ALP), prothrombin time (PT), triglycerides (TG), total cholesterol (TC), high/low density lipoprotein cholesterol (HDL / LDL) and fasting plasma glucose (FPG).
The criteria of the International Diabetes Federation were adopted for the definition of the metabolic syndrome and the diabetes mellitus [11].

Virological data

The viral load of HCV (HCV –RNA) was measured by quantitative PCR in real time and expressed in IU/ml. The viral genotype C was determined by the viral sequencing method.
Evaluation of CHC fibrosis and inflammatory necrotic activity of hepatitis C was determined with fibrotest actitest [12]. It was performed only in patients with no clinical and biological signs of cirrhosis. Fibrosis was considered significant if ≥ F2, severe if ≥ F3 and the inflammatory necrotic activity was considered significant if ≥ A2 according to Metavir score. Hepatic steatosis was evaluated by ultrasound.

Evaluation of subclinical atherosclerosis

The carotid intima-media thickness (IMTc) represents a simple, non-invasive and reproducible parameter for detecting this anomaly at an early stage [13]. It was evaluated by a single expert radiologist, using a high-resolution B-mode ultrasonography equipped with a 9-MHz linear probe [13]. It was assessed, manually, at the left and right distal common carotid artery at 1 cm from the carotid bifurcation, on a segment measuring at least 10 mm. The IMTc maximum (IMTc max) was defined as the highest IMTc measurements from the left and right side. Subclinical atherosclerosis with high cardiovascular risk was defined by an IMTc max >75thpercentile (IMTc75) [14].

Statistical study

Data was analyzed by IBM SPSS Statistics software. Continuous variables were expressed on average ± standard deviation and the categorical variables were expressed on frequency. To look for subclinical atherosclerosis with high cardiovascular risk associated factors and to compare results at times T0 and T1, we used Mann Whitney test for independent variables and Wilcoxon for related variables. The dependent variable was IMTc max. Differences were statistically significant if $p < 0.05$. The study was performed in accordance with the principles of the Declaration of Helsinki and its

appendices and with local and national laws. Informed consent was secured from all participating patients.

Results

At time T0, forty patients (median age: 55 y. (23-87 y) with sex ratio = 0.48, were included in the study.
Eligible participants had hypertension in 25% of cases and diabetes mellitus in 17.5% of cases. No case of hperlipidemia was noted. A third of patients was obese, 46.6% of patients fulfilled the metabolic syndrome criteria. The epidemioclinical parameters of the patients are detailed in Table 1.

Table 1. Epidemiological and clinical profile of patients at T0

Parameter	Patients (n=40)
Median age (years)	55
Sex ratio	0.48
Hypertension(n) %	10 (25)
Diabetesmellitus(n)%	7 (17.5)
Dyslipidemia (n) %	0
Smokers (n) %	9 (22.5)
SBP(mmHg)	121.6 ± 12
DBP(mmHg)	72.62 ± 9
Weight (Kg)	71.03 ± 14,98
BMI (Kg/m²)	27.26 ± 5.15
Waist circumference (cm)	91.92 ±14.2
Obese (n) %	12(30)
Overweight (n) %	18(48)
Syndrome metabolic (n) %	30 (46.4)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI = body mass index

Regarding CHC, 31 (77.5%) had genotype 1b, 3 patients were cirrhotic, 27 (67.5%) significant fibrosis, 15 (37.5%) severe fibrosis and 18 (45%) significant necrotic-inflammatory activity. At T0, average value of IMTc max was 0.68 mm ± 0.16 mm (0.36 - 1.17mm). It increased with stages of fibrosis (Figure 1).

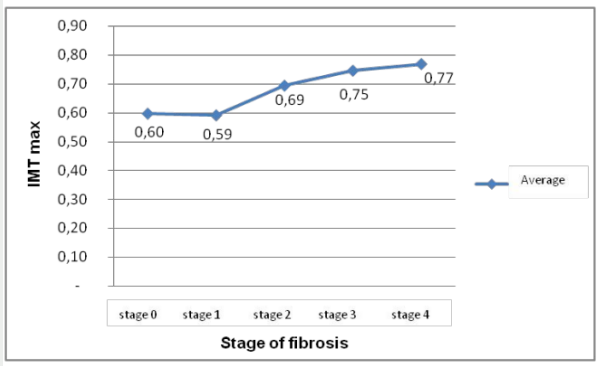

Figure 1. Variation of carotid intima-media thickness according to fibrosis stage at time T0

Thirty three patients (82.5%) of patients had subclinical high risk cardiovascular atherosclerosis which was significantly associated with a higher AST level (p = 0.03), with a lower platelet count (p = 0.03), hepatic steatosis (p = 0.02) and significant necrotico-inflammatory activity (0.04) (Table 2).

Table 2. Associated factors with carotid intima-media thickness

Parameter	IMTc 75 (+)	IMTc 75 (-)	P
Age ≥ 40	5 (12.5%)	29 (72.5%)	0.2
Female	4 (10%)	23 (57.5%)	0.5
Hypertension	2 (5%)	8 (20%)	0.8
Diabetesmellitus	1 (2.5%)	6 (15%)	0.8
Tobacco	2 (5%)	7 (17.5%)	0.6
BMI kg/m²	25.68 ± 6.3	27.6 ± 4.93	0.3
Obesity	1 (2.5%)	13 (32.5%)	0.2
Metabolic Syndrome	1	14	0.1
ALT (U/l)	85.62 ± 73.19	34.28 ± 18.27	0.07
AST (U/l)	**82.45 ± 77.85**	**36.71 ± 27.26**	**0.03**
GGT (U/l)	76.21 ± 94.84	58.71 ± 80.15	0.6
ALP (U/l)	107.84 ± 39.08	149.71 ± 158.15	0.1
Bilirubin (mmol/l)	12.95 ± 6.28	10.05 ± 6.6	0.2
PT (%)	84.63 ± 20.11	95.57 ± 5.94	0.1
Albumin g/l	37.79 ± 4.18	39.35 ± 5.03	0.3
Platelets (E/mm³)	**154848 ± 68459**	**216142 ± 55944**	**0.03**
FPG (mmol/l)	6.39 ± 2.51	5.31 ± 0.85	0.2
TC(µmol/l)	3.69 ± 0.93	4.09 ± 1.28	0.3
HDL(µmol/l)	1.25 ± 0.34	1.22 ± 0.32	0.8
TG (µmol/l)	0.95 ± 0.24	0.97 ± 0.47	0.8
Significantfibrosis	3(7.5%)	24(60%)	0.1
Significant necrotic-inflammatoryactivity	**1(2.5%)**	**17(42.5%)**	**0.04**

IMTc : carotid intima-media thickness, ALT : Alanine aminotransferase, AST: aspartate aminotransferase, GGT: γ glutamyl transpeptidase, ALP: Alkaline phosphatase, PT : prothrombin time, TG : triglycerides, TC: total cholesterol, HDL / LDL : high/low density lipoprotein cholesterol, FPG: fasting plasma glucose

At T1, 28 patients were included (median age: 61 y. (31-90 y) and sex ratio M / F = 0.33). There was no significant difference in anthropometric parameters at times T0 and T1 as well as in SBP and DBP (Table 3).

Table 3. Comparison of epidemiological and clinical features of patients

Parameter	T0	T1	P
Weight(Kg)	72.32 ± 14.98	70.75 ± 16.54	0.41
BMI (Kg/m²)	28.09 ± 5.16	27.83 ± 5.84	0.71
Obesity	11 (39 %)	10 (36 %)	0.55
Waist circumference(cm)	94.92 ± 14.11	94.57 ± 12.6	0.84
SBP mmHg	121.6	128.9	0.09
DBPmmHg	72.62	73.20	0.46
Metabolic syndrome%	46.4	21.4	0.03
ALT (U/l)	70.96 ± 58.36	22.72± 7.93	0.001
AST (U/l)	71.7 ± 62.1	16.98 ± 7.74	0.001
GGT (U/l)	72.32 ± 101.48	31.46± 35.73	0.03
ALP (U/l)	109.28 ± 81.65	98.53 ± 30.51	0.44
Bilirubin (mmol/l)	11.83 ± 5.77	11.4± 6.14	0.7
PT (%)	38.34 ± 3.85	44.08± 3.45	0.001
Albumin g/l	85.6 ± 21.06	90.03 ± 13.27	0.26
Platelets (E/mm³)	164821 ± 72166	176250 ± 67209	0.19
FPG (mmol/l)	6.18± 2.28	5.93 ± 1.11	0.5
TC (µmol/l)	3.68 ± 1.16	4.39 ± 0.91	0.001
HDL (µmol/l)	1.26 ± 0.32	1.37 ± 0.25	0.1
TG (µmol/l)	0.9 ± 0.25	0.98 ± 0.22	0.009

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, ALT: Alanine aminotransferase, AST: aspartate aminotransferase, GGT: γglutamyltranspeptidase, ALP: Alkaline phosphatase, PT: prothrombin time, TG : triglycerides,TC: total cholesterol, HDL / LDL : high/low density lipoprotein cholesterol, FPG: fasting plasma glucose

For the prevalence of metabolic syndrome, there was a significant decrease at T1 compared to T0 (P=0.03) (Table III). Average values of different parameters of liver function tests were lower at time T1 compared to time T0. Difference was significant for AST (p= 0.001), ALT (p= 0.001) and GGT (p=0.03). Albuminemia was significantly higher at time T1 compared to time T0 (P= 0.001). Serum TC, HDL and TG levels were higher at time T1 compared to time T0. This increase was statistically significant for TC (p=0.001) and TG (p=0.009) (Table 3).

The IMTc max was significantly higher at time T1 compared to T0 (0.75 mm ± 0.18 VS 0.67 mm ± 0.15, p=0.04) and the prevalence of IMTc 75 was 82.1% at time T0 and 75% at time T1 (0.5). (Table 3).

Discussion

In this study, CHC was associated with a high prevalence of subclinical atherosclerosis at high cardiovascular risk assessed by measuring IMTc. The HCV role in atherosclerosis pathogenesis is now increasingly recognized as suggested some latest findings [15]. A review of recent studies published in 2021 found a significant association between HCV infection and an increased risk of subclinical and experiencing cardiovascular events besides the increased burden of atherosclerosis in individuals infected with HCV [16].Interestingly, a previous study by our team found a positive association between HCV infection and atherosclerosis [17].

However, results concerning measurement of IMTc and assessment of atherosclerosis risk in CHC remain discordant[18,19] (Table IV). Ishizaka et al were the first to report a positive association between carotid atherosclerosis and CHC. Indeed, they highlighted an increase in prevalence of CHC in patients with carotid plaques (3.7% vs 1.7%) and in those with elevated IMTc (6.3% vs. 1.6%) [19]. Likewise, in a meta-analysis including nine case-control studies,Petta et al found that carotid plaques occurrence risk in HCV-infected individuals was twice as high compared to healthy controls[20]. In addition, chronic HCV infection was also significantly associated with higher IMTc compared to controls (p<0.001)[21]. Similarly, Artigas et al found that HCV infection is an independent risk factor for subclinical atheromatosis. To assess this risk, they used ultrasonography of the carotid and femoral arteries [22]. However, other studies have not revealed a positive association between CHC and carotid atherosclerosis. Bilora et al followed the progression of atherosclerotic disease in 40 HCV-infected subjects and 40 controls for 5 years. Both were matched for various classic cardiovascular risk factors and had a comparable IMTc on inclusion. At the end of the study, HCV-infected patients showed no change in IMTc and prevalence of carotid plaques. While a significant increase in IMTc was observed in controls, suggesting a possible protective role of CHC [23]. These data have been approved by other studies, including end-stage renal disease patients on hemodialysis and patients with HIV (human immunodeficiency virus) co-infection [24].

In our study, the IMTc max, at time T0, was 0.68 mm ± 0.16 mm with a high prevalence of subclinical atherosclerosis with high cardiovascular risk (82.5%).

In the literature, mechanisms implicating HCV in atherosclerosis pathogenesis are not yet fully elucidated. The direct role of HCV has been suggested by demonstration of HCV ribonucleic acid sequences in carotid plaques and in cerebral endothelium supporting hypothesis of a pro-atherogenic role and by induction of arterial inflammation, probably via pro-inflammatory cytokine interleukin 1β [25,26].

Endothelial dysfunction induced by adhesion molecules s-ICAM-1, s-VCAM-1, sE-selectin and sP-selectin hyper expressed in patients followed for CHC seems to explain part of pathogenesis of atherosclerosis[27]. Concerning lipid factors, Nakhjavani et al found that serum level of oxidized LDL-cholesterol was significantly higher in HCV-infected patients compared to controls[28]. In contrast, HCV was associated with a good lipid profile, characterized by low levels of TG, TC and its fractions but which did not protect against atherosclerosis [29]. Regarding impact of DAAs on lipid profile, serum lipids seems to be increased in patients who achieved SVR.

We also found that DAA treatment was associated with increased IMTc max and lipid profile parameters. Prevalence of IMTc75 was 82.1% at time T0 and 75% at time T1 but without clinical significance given the small number of patients included at T1.

In the literature, eradication of virus C was associated with an improvement of hepatic function and a regression of certain extrahepatic manifestations of HCV. Few studies have focused on evaluating the effect of viral eradication on atherosclerotic disease and on the various factors involved in atherogenesis, with sometimes contradictory data. Interestingly, Petta et al, evaluated variations of IMTc in a group of patients with advanced fibrosis CHC and treated with DAAs and a group of patients with untreated CHC[30]. In treated group, IMTc was decreased significantly, 9-12 months after the end of treatment (0.94 ± 0.29 mm vs 0.81 ± 0.27, p <0.001). Than for untreated group, no significant change in IMTc was noted (0.88 ± 0.30 vs 0.94 ± 0.40, p = 0.29). Authors thus suggested that eradication of HCV would allow improvement of carotid atherosclerosis lesions. Similarly, Salomone et al evaluated variations of IMTc in 182 patients with CHC treated with DAAs [31]. Mean IMTc value after treatment was significantly lower compared to pretreatment (0.92 ± 0.2 vs 0.8 ± 0.21, p < 0.01).

However, other studies have not report a beneficial effect of antiviral treatment on subclinical atherosclerosis. In a Spanish prospective study published in 2020, Carrero et al assessed changes in IMTc in 168 patients co-infected with HCV/HIV. Of these patients, 55.2% were treated with the pegylated interferon, ribavirin and DAAs combination, 33.8% with the pegylated INF and ribavirin combination and 11% with DAAs alone. SVR was obtained in 62% of patients. IMTc was measured before treatment and 96 weeks after the start of treatment. No significant change in IMTc was observed in responders and non-responders (p= 0.32)[32]. But these results were not reported according to the type of treatment

used. In our study, a significant increase in IMTc max was observed after obtaining an SVR (0.75 mm± 0.18 VS 0.67 mm ± 0.15) (p=0.04). This suggested a worsening role of DAAs treatment on carotid atherosclerosis. Various results discordance presented in the literature could be explained by populations heterogeneity, small number of patients included as well as disparity in evaluation times after antiviral treatment [33].

The primary strength of this study is the prospective nature of the study and the use of a reproducible parameter to assess high cardiovascular risk. The key limitation is the small number of patients included.

Conclusions

This work showed a high prevalence of subclinical atherosclerosis with high cardiovascular risk in HCV-infected patients and that SVR was associated with increased IMTc. These findings suggest the need for an assessment of atherosclerosis risk in HCV-infected patients as soon as the disease is diagnosed and after SVR. Further larger, multicenter studies are needed to elucidate the underlying mechanisms of atherosclerosis pathogenesis in CHC and to assess the effect of antiviral C treatment on atherosclerotic lesions in the short, medium, and long term in order to offer these patients adequate management of the cardiovascular risk.

References

1. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22(34):7824 40.
2. Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic Morbidity and Mortality of Chronic Hepatitis C. Gastroenterology. 2015;149(6):1345 60.
3. Kukla M, Piotrowski D, Waluga M, Hartleb M. Review article Insulin resistance and its consequences in chronic hepatitis C. Clin Exp Hepatol. 2015;1:17 29.
4. Adinolfi LE, Restivo L, Zampino R, Guerrera B, Lonardo A, Ruggiero L, et al. Chronic HCV infection is a risk of atherosclerosis. Role of HCV and HCV-related steatosis. Atherosclerosis. 2012;221(2):496 502.
5. Boddi M, Abbate R, Chellini B, Giusti B, Solazzo V, Sofi F, et al. HCV infection facilitates asymptomatic carotid atherosclerosis: preliminary report of HCV RNA localization in human carotid plaques. Dig Liver Dis. 2007;39:S55 60.
6. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology. 2017;152(1):142-56.
7. Salama II, Raslan HM, Abdel-Latif GA, Salama SI, Sami SM, Shaaban FA, et al. Impact of direct-acting antiviral regimens on hepatic and extrahepatic manifestations of hepatitis C virus infection. World J Hepatol. 2022;27;14(6):1053-73.
8. Roguljic H, Nincevic V, Bojanic K, Kuna L, Smolic R, Vcev A, et al. Impact of DAA Treatment on Cardiovascular Disease Risk in Chronic HCV Infection: An Update. Front Pharmacol. 2021;11;12:67.
9. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153 94.
10. Société tunisienne de gastro-entérologie. Le nouveau consensus tunisien sur le VHC. Tunis: STGE; 2022.
11. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabet Med. 2006;23(5):469 80.
12. Boursier J, de Ledinghen V, Zarski J-P, Fouchard-Hubert I, Gallois Y, Oberti F, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology. 2012;55(1):58 67.
13. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. J Am Soc Echocardiogr. 2008;21(2):93 111.
14. Herinirina NF, Ny LH, Herijoelison AR, Ahmad A. Epaisseur de l'intima-média carotidienne et facteurs de risque cardio-vasculaires. PAMJ. 2015;21.
15. Butt AA, Xiaoqiang W, Budoff M, Leaf D, Kuller LH, Justice AC. Hepatitis C virus infection and the risk of coronary disease. Clin Infect Dis. 2009;49(2):225 32.
16. Bailey AL, Al-Adwan S, Sneij E, Campbell N, Wiisanen ME. Atherosclerotic Cardiovascular Disease in Individuals with Hepatitis C Viral Infection. Curr Cardiol Rep. 2021;23(5):52.
17. Medhioub M, Bouzaidi K, Bachali A, Khsiba A, Hamzaoui L, Azouz MM. The risk of subclinical carotidatherosclerosis in patients with chronic hepatitis C. Tunis Med. 2021;99(4):449 55.
18. Ishizaka N, Ishizaka Y, Takahashi E, Tooda E, Hashimoto H, Nagai R, et al. Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet. 2002;359(9301):133 5.
19. Adinolfi LE. Chronic hepatitis C virus infection and atherosclerosis: Clinical impact and mechanisms. World J Gastroenterol. 2014;20(13):3410.
20. Petta S, Maida M, Macaluso FS, Barbara M, Licata A, Craxì A, et al. Hepatitis C Virus Infection Is Associated With Increased Cardiovascular Mortality: A Meta-Analysis of Observational Studies. Gastroenterology. 2016;150(1):145-55
21. Petta S, Torres D, Fazio G, Cammà C, Cabibi D, Di Marco V, et al. Carotid atherosclerosis and chronic hepatitis C: a prospective study of risk associations. Hepatol Baltim Md. 2012;55(5):1317 23.
22. Revuelto Artigas T, Zaragoza Velasco N, Gómez Arbones X, Vidal Ballester T, Piñol Felis C, Reñe Espinet JM, et al. Infección crónica por el virus de la hepatitis C: un factor de riesgo independiente para la ateromatosis subclínica. Rev Clínica Esp. 2019;219(6):293 302.
23. Bilora F, Campagnolo E, Rinaldi R, Rossato A, Arzenton M, Petrobelli F. Carotid and femoral atherosclerosis in chronic hepatitis C: a 5-year follow-up. Angiology. 2008;59(6):717 20.
24. Zaki MS. The effect of Hepatitis C Virus infection on cardiovascular complications in end stage kidney disease patients on regular hemodialysis. Electron Physician. 2017;9(2):3857 61.
25. Fletcher NF, Wilson GK, Murray J, Hu K, Lewis A, Reynolds GM, et al. Hepatitis C virus infects the endothelial cells of the blood-brain barrier. Gastroenterology. 2012;142(3):634-43.
26. Owusu DO, Phillips R, Owusu M, Sarfo FS, Frempong M. Increased levels of circulating IL-10 in persons recovered from hepatitis C virus (HCV) infection compared with persons with active HCV infection. BMC. 2020;13(1):472.
27. Al-Jiffri OH. Adhesive molecules and inflammatory markers among hepatitis C virus Saudi patients. Electron J Gen Med. 2017;14(4).
28. Nakhjavani M, Mashayekh A, Khalilzadeh O, Asgarani F, Morteza A, Omidi M, et al. Oxidized low-density lipoprotein is associated with viral load and disease activity in patients with chronic hepatitis C. Clin Res Hepatol Gastroenterol. 2011;35(2):111 6.
29. Simon TG, Butt AA. Lipid dysregulation in hepatitis C virus, and impact of statin therapy upon clinical outcomes. World J Gastroenterol. 2015;21(27):8293 303.
30. Petta S, Adinolfi LE, Fracanzani AL, Rini F, Caldarella R, Calvaruso V, et al. Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis. J Hepatol. 2018;69(1):18 24.
31. Salomone F, Petta S, Micek A, Pipitone RM, Distefano A, Castruccio Castracani C, et al. Hepatitis C virus eradication by direct antiviral agents abates oxidative stress in patients with advanced liver fibrosis. Liver Int. 2020;40(11):2820 7.

32. Carrero A, Berenguer J, Hontañón V, Navarro J, Hernández-Quero J, Galindo MJ, et al. Effects of Eradication of HCV on Cardiovascular Risk and Preclinical Atherosclerosis in HIV/HCV-Coinfected Patients. J Acquir Immune Defic Syndr. 2020;83(3):292 300.

33. Ichikawa T, Miyaaki H, Miuma S, Motoyoshi Y, Narita S, Toda S, et al. Carotid Intima-media Thickness and Small Dense Low-density Lipoprotein Cholesterol Increase after One Year of Treatment with Direct-acting Antivirals in Patients with Hepatitis C Virus Infection. Intern Med. 2019;58(9):1209 15.