# THE ROLE OF HOST LIPIDS IN THE PATHOGENY OF CHRONIC HEPATITIS C

**Asist. Univ. Dr. Mihaela Andreea Rădulescu[1,2], Dr. Irina Duport[1], Prof. Dr. Victoria Aramă[1,2]**

*[1]Universitatea de Medicină şi Farmacie „Carol Davila" Bucureşti*

*[2]Institutul Național de Boli Infecțioase „Prof. Dr. Matei Balş", Bucureşti*

## ABSTRACT

Despite the innovations in the past years in the field of chronic hepatitis C treatment, Hepatitis C virus (HCV) infection remains an important global burden with elevated healthcare costs and high morbidity and mortality due to its complications – liver cirrhosis and hepatocellular carcinoma. The interrelation between HCV and host's lipid metabolism is widely accepted, as it has been proved in many clinical and research studies. HCV infection is associated with different types of metabolic disorders such as liver steatosis and insulin-resistance. On the other side these metabolic disturbances induce an accelerated progression of liver disease. HCV interacts with host lipids in every step of viral life cycle: viral transport in the blood stream, cell entry, replication, assembly and transport to the extra-cellular space. This review focuses on the complex link between HCV and host lipids, emphasizing the clinical implications of these interactions. Although the pathogenic mechanisms of HCV infection are incompletely understood, recent literature data elucidates some important aspects which opened a road to innovating therapeutic approaches such as host targeting agents, with a pan-genotypic antiviral effect and high genetic barrier. Targeting parts of the pathogenic pathways of HCV infection represents a new kind of therapeutic approach, hopefully with higher treatment success rates and lowering morbidity and mortality related to this infection.

**Keywords:** chronic hepatitis C, lipid metabolism, pathogenesis

## BACKGROUND

Despite remarkable progress over the past few years regarding diagnostic tools and treatment options for chronic hepatitis C, this infection remains an important public health problem which affects 150 million individuals worldwide and approximately 350 000 deaths annually are attributed to its complications – liver cirrhosis and hepatocellular carcinoma. (1) Romania has a moderate prevalence of HCV infection, of 3.23% according to a study published by L Gheorghe et al in 2010. (2)

It is well established that certain factors, such as older age, male gender, chronic ethanol abuse, co-infection with hepatitis B virus or human immunodeficiency virus, co-existence of other chronic hepatic conditions, lead to an accelerated progression of HCV infection to liver cirrhosis. (3) Over the past years, apart from these traditional risk factors, multiple studies reported the influence of some metabolic disorders on fibrosis progression. The liver plays a key role in regulating lipid and carbohydrate homeostasis and at the same time represents an obvious target of different metabolic disorders. Also, HCV seems to be tightly connected to the host's lipid and carbohydrate metabolism. HCV infection is associated to a wide range of metabolic disorders, including hepatic steatosis, insulin resistance and diabetes mellitus, dyslipidemia. On the other hand these metabolic factors are associated to an accelerated progression of HCV infection to hepatic cirrhosis and hepatocellular carcinoma.

Moreover, over the past century, human society has evolved to a new lifestyle that has a progressive tendency to reducing physical activity, while food resources became more available and varied, which explains the increasing prevalence of metabolic syndrome. Furthermore, the lifespan has increased over time and hypertension, obesity, dyslipidemia and diabetes mellitus have a higher rate of occur-

Coresponding author:
Dr. Irina Duport, Institutul Național de Boli Infecțioase „Prof. Dr. Matei Balş", Str. Dr. Grozovici nr. 1, sect. 2, Bucureşti
E-mail: irina_duport@yahoo.com

rence in older people. These aspects explain why the metabolic syndrome has spread to an epidemic range, especially in well developed countries. For example, in the Unites States, the NHANES program (The National Health and Nutrition Examination Survey) which contains a series of surveillance studies on health issues and nutrition related conditions, reported an increasing incidence of the metabolic syndrome from 23-25% between 1988 and 1994 to 34 % between 2003-2006 (4). Also it has been reported a higher incidence of metabolic syndrome components: abdominal obesity, elevated arterial blood pressure, hypertrygliceridemia and fasting hyperglicemia.

## LIPID PROFILES IN HCV INFECTED PATIENTS

Currently, the relationship between HCV and the lipid metabolism is widely accepted, as it has been proved in many clinical and experimental studies. Hence, in a large study led by Li et al (5), which included over 26000 patients, of which over 1000 HCV infected, LDL and HDL values were significantly lower in infected patients and the prevalence of the metabolic syndrome was considerably higher in infected patients over 45 years old. Another study, published by Nogueira et al (6), which evaluated 150 HCV infected patients genotypes 1, 2 and 3 respectively, showed that serum triglycerides, VLDL and HDL values were significantly lower in infected patients, while LDL and apolipoprotein (apo) B were higher. Although these variations were more pronounced in patients with genotype 3, they were significant for all genotypes. In addition, the authors reported a correlation between serum levels of apoB and the viral load in genotype 1 infected patients. Another study from Egypt, on 150 genotype 4 HCV infected patients, also reported low levels of total cholesterol, triglycerides and LDL in infected patients, with an increase of the serum lipids following antiviral treatment in patients who obtained sustained virological response (7). These data suggest that the interaction between HCV and lipid metabolism is available for all viral genotypes.

Other authors reported an influence of the antiviral therapy on serum lipids as well. On that account, Kuo and col reported a rebound of serum cholesterol and triglycerides in patients with sustained viral response (SVR), but not in those with different non-response types (8).

## THE ROLE OF LIPID METABOLISM IN THE PATHOGENY OF HCV INFECTION

A large amount of literature data emphasize the complex interactions between HCV and different parts of the host lipid metabolism, which are used in several steps of the viral life cycle. HCV circulates in the blood as two types of particles, which are classified based on their densities: high density particles which are associated to immunoglobulins and are less infective, and low density particles, associated with lipids and lipoproteins, highly infective.(9) These lipoviral particles contain HCV-RNA, core protein, LDL, VLDL and apolipoproteins B and E. (10)

The virus adheres and enters the hepatocyte via numerous receptors, including CD81, scavenger receptor B type 1 (SR-B1), glycozaminoglycans, claudin 1, occludin and the LDL receptor (LDLr). Two of these receptors will be further discussed because of their role in the lipid metabolism. SR-B1 is a lipoprotein part of the hepatocyte membrane and also of steroid producing cells that has a physiological role as an HDL receptor, but also for VLDL and oxidized forms of LDL, in order to extract cholesterol from these lipoproteins for subsequently cell internalization. (9, 11) As Lindenbach et al emphasized, the SR-B1 is a mandatory receptor for HCV. It binds to E2 envelope glycoprotein, mediates the efficiency of cell entry using its lipid transfer ability and finally exposes certain segments of the E2 protein which facilitates the CD81 binding. (11)

The LDL receptor is the ligand for LDL on the surface of the hepatocyte and has a role in the endocytosis of these particles. Although HCV has a low affinity for the LDLr and this receptor is not absolutely necessary for HCV entry, it is important for optimal replication of the virus. (12) A recent study published by Nakamuta et al (13) showed that in HCV infected hepatocytes, the LDL receptor transcription is inhibited and has a negative correlation with serum level of LDL and HCV core protein. The authors postulated that inhibiting the transcription of LDLr might be a consequence of intracellular lipid accumulation, by suppressing the microsomal triglyceride transfer protein by HCV. Furthermore, certain genotypes of LDLr correlate with high levels of viral load, (14) while low expression of LDLr gene seems to correlate with lack of antiviral treatment response. (15)

The Niemann-Pick C1-like 1 is a transmembranous protein involved in cholesterol transport, which is expressed on the surface of hepatocytes

and enterocytes. This protein has recently been described as a co-factor required for HCV entry in the hepatocyte, and also has been proposed as a therapeutic target. (16)

Apolipoproteins also play a key role in the penetration of HCV into the hepatocyte. Apo B and E are part of the lipoviral particles, while Apo-C1 appears to have a role in the fusion of the endosome after HCV entry. (9) On the other hand, Apo CIII inhibits the internalization of VLDL and inhibits the stimulating effect of Apo E in VLDL capture, (17) with a possible beneficial effect in HCV infection. Thus, Apo CIII seems to correlate to spontaneous viral clearance, (18) whilst low levels of Apo CIII were associated to viral persistence and advanced fibrosis. (19) Apo A1 seems to play a part in HCV replication and lowering its expression leads to an inhibition of viral replication and a decrease in viral particle production in cell cultures. (20)

Certain lipid components also play an important role in the replication and assembly of HCV. After internalization of HCV into the cell, it loses its capsid, discharging a single stranded positive RNA chain, which then enters the endoplasmic reticulum where the translation of the viral poli-protein will take part. Releasing the positive chain of RNA induces a permutation of the intracellular membranes which is necessary for further organization of replication complexes, which contain nonstructural viral proteins – NS4B, NS5A and NS3, viral RNA and other cellular components. (21) The replication complex is rich in cholesterol and fatty acids, whose esterification degree influences HCV replication. (22) Furthermore, in the replication vesicles, fatty acid synthase stimulates the activity of the NS5B protein which acts as an RNA polymerase, thus influencing replication. (23)

Moreover, newly synthesized viral particles are transported to the cell membrane by inclusion into lipid droplets which are then released into the extracellular space through VLDL excretion pathways. (24) Nepomnyashchikh et al (25) described a particular type of fat load in the hepatocyte with small lipid vesicles rich in NS3, corresponding to the replicative phase of HCV, located subcytolemal, which suggest a role in the transportation of virions towards the extracellular space.

## CLINICAL ASPECTS OF THE HCV-HOST LIPIDS INTERRELATION

Multiple studies demonstrated that chronic HCV infection is associated to a high prevalence of hepatic steatosis. Steatosis is considered to be a direct consequence of the viral factors for patients carrying genotype 3,\ in whom hepatic steatosis is almost customary and frequently present as high degrees of liver fat load. For the other genotypes, including genotype 1, which is almost exclusevely present in Romania, steatosis is related to both viral and metabolic factors. (26) Thus, Lerat et al showed in a murin model that HCV induces liver lipogenesis by activating the fatty acid synthase complex and stimulating certain sterol transcription factors and at the same time inhibits triglyceride secretion to extracellular space by inhibiting the microsomal triglyceride transfer protein. (27) Increased synthesis and low excretion obviously lead to an accumulation of lipids in the intracellular space, with liver steatosis as a direct consequence. Similary, Lambert et al showed that HCV increases liver synthesis of free cholesterol, also proved HCV role in systemic lipid dysregulation by increasing free and esterified cholesterol production in infected patients. (28)

Hepatic steatosis in HCV infected patients seems to be an important predictor for disease progression. Zubair et al (29) found a significant correlation between steatosis and the fibrosis score, but not with necroinflammatory score, while Syed et al (30) reported a correlation between steatosis and fibrosis score, also between steatosis and liver necroinflammation in HCV infected patients. Also, a meta-analysis published by Leandro et al (31) which included over 3000 HCV infected patients enrolled in 10 clinical studies, demonstrated an independent association between steatosis and the presence of fibrosis and liver necroinflammation. Furthermore, steatosis was associated with hepatic iron load, which is considered a contributing factor to disease progression. (32)

Steatosis appears to play a role in hepatic carcinogenesis in infected patients. A retrospective Japanese study, which evaluated over 1300 HCV infected patients, followed for a period of 11 years, showed that hepatic steatosis is an independent risk factor in developing hepatocellular carcinoma, with an odds ratio of 3.04. (33) Moreover, hepatic steatosis is a risk factor for hepatocarcinoma recurrence in patients with liver resection. (34)

Hepatic steatosis is considered an negative prognostic factor for treatment response. In a study on 574 infected patients, Patton et al (35) showed that steatosis is associated to a lower probability of obtaining undetectable viral load after 12 weeks of treatment and a lower incidence of sustained virological response. Another recently published study, on 150 infected patients showed that liver steatosis

is associated to less favorable viral kinetics under treatment. (36) Also, Restivo et al reported an association between hepatic steatosis and virological relapse in genotype 3 infected patients, but not in genotype 2 infected patients. (37) Although metabolic factors seem to play a key role in pegylated Interferon and ribavirin treatment response, it seems this is not the case for triple therapy with protease inhibitors. (38)

Lipid profile before treatment also seems to play a role in treatment response. In a study that included over 300 HCV infected patients published by Ramcharan et al, (39) the probability for sustained virological response correlated with lower values of serum triglyceride and higher values for LDL. Another study from Japan on 108 infected patients showed that treatment response is influenced by VLDL composition. Thus an increased cholesterol/ triglycerides ratio was proved as an independent predictor for SVR. (40) Similarly, Lange et al (41) demonstrated the role of hypocholesterolemia as a negative predictor for SVR, also in the study lead by Mawatari et al, patients who obtained SVR had higher pretreatment concentration of serum cholesterol, triglyceride and LDL, while hypercholesterolemia and hypertriglyceridemia were predictors for SVR. (42)

Genetic profile of IL28B, considered an important predictor for antiviral treatment response, (43) seems to have certain connections with the lipid metabolism in HCV infected patients. A study conducted on 377 infected patients compared to over 400 controls reported that the favorable IL28B-CC genotype was associated to higher serum levels of cholesterol and LDL in HCV infected patients with genotype 1, but not in those with genotypes 3 and 4. (15) Another recent study which evaluated 434 infected patients with genotype 1 reported that the IL28B CC genotype correlated with higher levels of LDL, lower triglycerides, also with low prevalence of insulin-resistance and moderate / severe liver steatosis (44) – metabolic profile described by other authors as favorable for SVR rate.

Liver steatosis is frequently in HCV infected subjects and seems to influence the disease progression and treatment response. The interaction between the virus and the host cellular components implies complex alterations in lipid metabolism with consequence and common factor liver steatosis.

Multiple data published in the literature in the past 15 years lead to a better comprehension of the complex interaction between viral and host factors, highlighting certain steps in HCV infection pathogenesis that can be approached as therapeutic targets.

Molecules against host factors represent a new therapeutic approach for HCV infection with certain advantages compared to direct antiviral agents. (45) By acting on host factors and not on viral factors, the probability of the virus developing resistance mutations is low, which confers a higher genetic barrier. Moreover, their action does not depend on the viral genotype, unlike interferon and direct antiviral molecules. Furthermore, by acting on complete different targets, it is expected a synergic action with direct antiviral agents and it might even permit the use of reduced doses and/or a shorter therapy course with direct agents in combination schemes – with direct effect on reducing adverse effects and drug interactions, which is especially useful for HIV co-infected patients. Multiple molecules targeting different components of the lipid metabolism involved in the HCV life cycle are currently in different phases of research, from membranous receptors used for virus attachment and penetration into host cell, to different host molecules involved in viral replication. (46)

Although the pan-genotypic antiviral effect and high genetic barrier represent two of the major advantages of these molecules, an important obstacle could be the possible adverse reactions, as consequence of altering some important cellular processes. On the other side, statins, which belong to this therapeutic area, have been widely utilized for treatment of hypercholesterolemia without major adverse reactions. Future research will show how many of these molecules will become part of the therapeutic arsenal against HCV infection.

Although the exact pathogenic mechanisms of the interaction between HCV and host lipid metabolism are not fully comprehended, many aspects have been clarified in recent published data, and certain aspects of these interactions are investigated as therapeutic targets which may help in managing the metabolic disorders associated to HCV infection, also with an antiviral effect.

An overwhelming amount of data from fundamental and clinical research emphasized the complex interactions of hepatitis C virus host lipid metabolism, with a high impact over disease activity and progression, also on antiviral treatment response. Furthermore, these interactions lead to a high cardiovascular risk, by increasing the incidence of diabetes and insulin resistance, which implies the necessity of a complex interdisciplinary approach of these patients.

All this data suggest that HCV infection must not be seen as a simple liver infection, but as a complex metabolic condition, and understanding the underlying pathogenic mechanisms will lead to an improvement in managing these patients.

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