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HEPATIC STEATOSIS IN PATIENTS WITH CHRONIC VIRAL HEPATITIS C TREATED WITH DIRECT ACTING ANTIVIRALS

Oana Irina Gavril[1], Irina Mihaela Esanu[1], Ioana Madalina Zota[1], Iolanda Valentina Popa[1], Lidia Iuliana Arhire[1], Diana Tatarciuc[1], Alexandra Mastaleru[1], Andrei Drugescu[1], Radu Sebastian Gavril[1], Mariana Graur, Florin Mitu[1,2]
[1]University of Medicine and Pharmacy "Grigore T. Popa" Iași (Romania)
[2]Academy of Medical Sciences of Romania
Corresponding author: Irina Mihaela Esanu, Radu Sebastian Gavril
E-mail: esanu1925@gmail.com, rgavril87@yahoo.com

Abstract
Hepatic steatosis is a frequent pathological finding in patients with chronic viral C infection (HCV) and can be independently associated with increased alcohol consumption, type 2 diabetes, obesity and hyperlipidemia. All these factors can lead to the development of hepatic steatosis in patients with HCV. There are several noninvasive techniques and scores used for diagnosing and quantifying liver steatosis. Successful eradication of HCV with interferon-free treatment regimens has been suggested to improve the level of hepatic steatosis. The precise mechanisms responsible for these beneficial effects are currently under investigation, but it is thought that the decrease in hepatic inflammation and viral replication contribute to the resolution of hepatic steatosis. Moreover, the overall enhancement in liver health and metabolic factors may also have a significant impact.
Keywords*: hepatic steatosis, Steatotest, chronic viral C infection, metabolic syndrome.*

Rezumat
Steatoza hepatică reprezintă o patologie frecvent întâlnită în rândul pacienților cu infecție virală cronică cu virus C (VHC) și este asociată în mod independent cu diabetul zaharat de tip 2, consumul excesiv de alcool, obezitatea și hiperlipidemia. Toți acești factori pot duce la apariția și progresia steatozei hepatice la pacienții cu VHC. Există numeroase tehnici și scoruri non-invazive utilizate pentru diagnosticarea și cuantificarea steatozei hepatice. S-a observat că obținerea răspunsului viral susținut la pacienții cu VHC sub tratament antiviral oral poate duce la regresia gradului de steatoză hepatică. Mecanismele exacte responsabile pentru aceste efecte benefice sunt încă în curs de investigare, dar se pare că scăderea inflamației hepatice și a replicării virale joacă un rol important. În plus, ameliorarea afecțiunii hepatice și a parametrilor metabolici poate avea, de asemenea, un impact semnificativ.
Cuvinte cheie: *steatoză hepatică, Steatotest, infecție cronica virală C, sindrom metabolic.*



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Introduction

Hepatic steatosis represents a common histological feature in chronic viral hepatitis C subjects (HCV), but it can also occur independently, in association with obesity, excessive alcohol consumption, type 2 diabetes mellitus (T2DM), and hyperlipidemia. All these factors can lead to the development of hepatic steatosis in patients with HCV infection.

Hepatic steatosis can occur as a result of obesity, alcohol consumption, T2DM, protein malnutrition, total parenteral nutrition, certain treatments, excessive carbohydrate intake, and chronic HCV infection[1]. Imaging and biopsy-based evaluations suggest that approximately 20-30% of the adult population in the United States and Western countries have excess liver fat accumulation[2]. Approximately 10% of these individuals (2-3% of the general population) have non-alcoholic steatohepatitis (NASH). A study identified hepatic steatosis in 70% of obese subjects and 35% of non-obese patients[3]. The prevalence of steatosis in patients with altered liver tests (after excluding other causes of liver disease) was 64%. Among these patients, 50% had hepatic steatosis and 50% had NASH. Also, the vast majority of T2DM subjects are diagnosed with fatty liver disease.

In patients with HCV, the prevalence of steatosis ranges from 40 to 86% (average value 55%)[4]. The majority of patients with hepatic steatosis (78%) present a mild form, with less than 30% of hepatocytes affected. Therefore, steatosis occurs more frequently in patients with HCV infection (55%) compared to the general population (20-30%) of adults in Western countries.

The association between hepatic steatosis and obesity has been highlighted, particularly in patients with HCV genotype 1[4]. These findings led to the idea that in patients with HCV viral infection, there are two concepts which should be mentioned: "metabolic fat" (especially in patients with HCV genotype 1) and "viral fat" (especially among patients with genotype 3). Epidemiological studies also suggest a link between T2DM and HCV infection[5].

In 1849, the Austrian pathologist Carl von Rokitansky proved that hepatic cirrhosis could be a consequence of fat accumulation[6]. However, descriptions related to the relationship between fatty liver, caloric intake, and T2DM were determined only a century later[7]. Hepatitis within fatty liver was first described in 1962[8].

At that time, nonalcoholic fatty liver disease (NAFLD) was considered a benign condition, and patients with obesity-related comorbidities had other medical pathologies of interest. In 1990, it was recognized that NASH represents an independent medical condition associated with morbidity and

mortality[9]. The broader term NAFLD started being used in 2002 and includes a wide spectrum of pathologies from isolated hepatic steatosis to NASH and NASH-related cirrhosis[10]. Over time, the incidence and prevalence of NAFLD have dramatically increased along with the global obesity epidemic[11].

Biopsy-free scoring systems for hepatic steatosis

Several scoring systems for hepatic steatosis have been reported as early as 2005. Steatotest is the first proposed serum biomarker for quantifying hepatic steatosis and has been used in a cohort of 884 patients with various causes of chronic liver disease (chronic HCV/HBV infection, chronic toxic hepatopathy) using liver biopsy as the reference method[12].

The calculation of this algorithm within the range of 0-1 is based on 12 parameters including: alanine transaminase (ALT), alpha-2 macroglobulin, apolipoprotein A1, gamma-glutamyl transferase (GGT), total bilirubin, haptoglobin, total cholesterol, triglycerides, glucose, age, gender, and body mass index. The method has shown a sensitivity of 90% and a specificity of 88%[13]. Using ultrasound as the reference method for diagnosing hepatic steatosis, 4 scores have been proposed, including: Fatty Liver Index (FLI), Hepatic Steatosis Index (HSI), Lipid Accumulation Product (LAP), and Index of NASH (ION). FLI was developed in a cohort of 496 subjects suspected of having liver disease. It includes 4 components that are routinely and widely measured (body mass index, waist circumference, triglycerides, and GGT) and has values ranging from 0 to 100[14]. A FLI score below 30 excludes the presence of hepatic steatosis with a sensitivity of 87%, while a score above 60 confirms the presence of hepatic steatosis with a specificity of 86%[15].

HSI was evaluated in a population of 10,724 Koreans who underwent medical check-ups (5362 cases with NAFLD vs. 5362 control cases) and is composed of three variables (AST/ALT ratio, body mass index and T2DM)[16].

The LAP score, developed in a cohort of 558 patients, is calculated using three variables (waist circumference, triglycerides and gender)[17]. ION represents a proposed score, used in a cohort of 4588 patients with NAFLD and subsequently validated in a cohort of 152 patients with NAFLD confirmed by liver biopsy[18]. The ION score is calculated using different variables depending on gender: for males - waist-to-hip ratio, triglycerides, alanine transaminase (ALT), and insulin resistance (HOMA-IR - Homeostatic Model Assessment for Insulin Resistance), for females - triglycerides, ALT, and HOMA-IR.

Ultrasound is widely available, simple, inexpensive, non-invasive, and reproductible. It represents a non-invasive method for detecting hepatic steatosis in clinical practice. Steatosis appears as increased echogenicity of the hepatic parenchyma, giving the liver a brighter appearance compared to the renal cortex and spleen. Recently, a new parameter called the Controlled Attenuation Parameter (CAP) has been proposed for non-invasive evaluation of hepatic steatosis. Computed tomography (CT) and magnetic resonance imaging (MRI) are highly sensitive imaging methods, but are not routinely used for the diagnosis of hepatic steatosis[19].

The evolution of hepatic steatosis after achieving sustained viral response

Approximately 40-80% of patients with HCV infection have hepatic steatosis, defined as



excess triglyceride intrahepatic deposits[20]. The prevalence of hepatic steatosis is strongly genotype-dependent[21], and HCV genotype 3 infection is currently recognized as an independent cause of hepatic steatosis. The severity of hepatic steatosis correlates with a higher viral load, and HCV genotype 3-associated steatosis was proved after achieving sustained virological response (SVR) with direct-acting antiviral (DAA) therapy[22].

Although HCV genotype 3 infection is independently associated with accelerated fibrosis progression[23] and increased risk of hepatocellular carcinoma (HCC), these complications do not have a higher incidence in steatosis associated with genotype 3. While patients with genotype 3 exhibit increased fibrosis progression, increased risk of HCC development, and lower SVR rates after DAA treatment, patients with genotype 1 and hepatic steatosis may be at an increased risk for clinical outcomes.

Hepatic steatosis is not solely mediated by HCV infection, as SVR may not resolve liver damage and fibrosis progression, although some recent studies have shown improvements in lipid profiles after HCV treatment in genotype 1 patients[24].

Hepatic steatosis in individuals infected with HCV can also be determined by other well known causes. For example, metabolic syndrome, obesity, hypertriglyceridemia, chronic alcohol consumption, infections, or exposure to certain medications can contribute to hepatic steatosis[25].

Unlike genotype 3-related hepatic steatosis, fatty liver within metabolic syndrome or insulin resistance is associated with accelerated fibrosis progression, decreased treatment response, and increased risk of HCC[23]. In many subjects, both viral and non-viral factors contribute to the development of hepatic steatosis. Indeed, HCV replication relies on lipid metabolism for its replication cycle and leads to hepatic steatosis through several mechanisms, such as increased lipogenesis, impaired mitochondrial lipid oxidation, and decreased microsomal triglyceride transfer protein activity[26].

Steatosis itself can enhance HCV replication, which has been shown to be present in the dysregulation of lipid metabolism due to alcohol[27].

Regarding the impact of interferon-free treatment on hepatic steatosis in HCV patients, research and clinical trials have shown promising results. It is indicated that successful HCV eradication through interferon-free regimens can lead to improvements in hepatic steatosis. The exact mechanisms underlying this improvement are still being explored, but it is believed that the reduction in hepatic inflammation and viral replication contribute to the resolution of hepatic steatosis.

Additionally, the overall improvement in liver health and metabolic factors may also play a key role [28].

Conclusion

Interferon-free treatment for HCV has shown favorable outcomes regarding hepatic steatosis. Achieving SVR through these regimens has been associated with the improvement or even resolution of hepatic fatty load, highlighting the importance of early and effective HCV treatment in patients with coexisting liver steatosis. However, it is important to note that individual patient characteristics and comorbidities may influence the response to treatment, and further research is needed to fully understand the mechanisms and long-term effects of DAA treatment on hepatic steatosis in HCV patients.

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