The Effect of Antiviral Therapy on Lipid Metabolism in Patients with Viral Hepatitis C

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The liver is the main metabolic organ, having complex physiological and biochemical roles, many of these functions being in a close relationship. It is also well known that hepatitis C virus infection is associated with changes in lipid metabolism. This is evident in liver dysfunctions, when liver functions are disturbed simultaneously. The aim of this study is to evaluate the effect of antiviral therapy on serum lipid level in patients with viral hepatitis C before and at the end of the 48 weeks of treatment compared patients treated with Interferon vs Interferon + Ribavirin and relation with sustained virological response, from North East Romania. We evaluated patients hospitalized in Emergency Hospital for Children St. Mary Iasi between 2009-2017. The result of our study show that the mean age of patients from group 1 was 11.85±3.65 years, vs 11.52±3.1 years in group 2 (p=0.171). We found changes in cholesterol metabolism in both groups of patients, increases in total cholesterol level, 21.43% of patients in the group 1 vs 32.3% in group 2 (p=0.258) and decreases 17.86% vs 14.7% (p=0.131). At initiation of antiviral therapy mean serum cholesterol level were 155.78±36.30 mg/dL, in group 1 vs 149.88±47.22 mg/dL, for group 2. At 48 weeks of treatment in the both groups revealed significantly decreased of total cholesterol levels 136.46±41.63mg/dL, for group 1 vs 109.26±41.05, for patients in group 2 (p=0.003). Triglycerides, HDL cholesterol and LDL cholesterol did not show significant changes in the patients of the two groups. Total cholesterol level after antiviral therapy were significantly different between patients who achieved SVR and non SVR (p=0.014), group 1 vs (p=0.001), group 2. Total serum cholesterol level showed significant changes during the antiviral therapy in both monotherapy and combination therapy group.

Keywords: viral hepatitis C, cholesterol, trygliceride, antiviral therapy

Hepatitis C virus (HCV) was discovered about 30 years ago and this has been an important step in the treatment of hepatitis [1]. Globally, about 180 million people are infected with hepatitis C virus, and 3-4 million are new cases every year in the world. Obviously, the actual incidence of new HCV infection is much higher, most cases being asymptomatic. The source of infection in HVC are the infected patients with asymptomatic, chronic and acute forms [2].

Hepatitis C virus is a small, enveloped, with approximately 9.6 kb positive-sense single-stranded RNA virus of the family Flaviviridae, the genus Hepaciviridae. It has at least 6 genotypes and over 50 subtypes, error-prone RNA polymerase associated with the high rate of virus replication, being responsible for the high diversity of HCV [3,4].

Lipid metabolism is in a close association with HCV infection. Has implication in structural analysis of HCV virions which is very limited because the virus is difficult to cultivate in cell cultures. In fact, viral particles obtained from the serum are associated with low serum density lipoproteins, which makes it difficult to isolate by centrifugation the serum/plasma virions of the infected patients. Depending on their density, lipoproteins are classified in four groups: high, low and very low density lipoproteins (HDL, LDL, VLDL and chylomicrons) and each of them has a distinct protein and lipid structure, defining its structure and function [5].

Another aspect is that the entrance of HCV into the hepatocyte involves certain cell surface receptors and cofactors that play an important role in the transport of cholesterol and the metabolism of lipoproteins therefore cholesterol metabolism can be disturbed. Other mechanisms that alters cholesterol homeostasis in HCV infection is interference with the mevalonate pathway, which leads to a decrease in cholesterol synthesis [6,7].

There are studies that have demonstrated that for HCV entry, replication and secretion are required lipid metaboling pathways. During entrance of HCV into hepatocytes due to lipid receptors, the lipid metabolic profile of these cells can be altered, therefore therapies that targeting these receptors would be useful in the treatment of viral hepatitis C [8-10].

Experimental part

Material and methods

The aim of this study is to evaluate the effect of antiviral therapy on serum lipid level in patients with viral hepatitis C before and at the end of the 48 weeks of treatment compared patients treated with Interferon vs Interferon + Ribavirin and relation with sustained virological response (SVR).
We performed a retrospective and prospective study, during 2009-2017, of 62 children, diagnosed with viral hepatitis C, aged 6-18, admitted to Clinic II Pediatrics, St. Mary’s Hospital, Iasi. The study included 2 groups of patients, group 1, 28 patients, received monotherapy (Interferon) and group 2, 34 children who received combination therapy (Interferon + Ribavirin). The patients originated from North East Romania.

Inclusion criteria was: positive diagnosis with viral hepatitis C and detectable HCV-RNA, age bigger than 3 years, and parents consent. Informed consent were obtain from the parents, containing permission to do laboratory tests. All patients were clinically examined at each admission and were followed including weight and Body Mass Index (BMI). Lipid parameters (cholesterol, triglycerides, HDL, LDL) were followed at the initiation and at the final of antiviral therapy, 48 weeks.

The sustained virological response is defined as the absence of HCV-RNA at 24 weeks after completion of antiviral therapy for HCV infection. The value of lipid parameters were determined in serum samples, in the morning, before breakfast. Triglyceride and cholesterol measurement was performed by an enzymatic spectrophotometric method, in which serum separation was performed in maximum 1 hour after harvesting. For the measurement of LDL cholesterol a direct enzymatic chlorimetric method was used which is based on selective micellar solubilization of LDL-cholesterol with a non-ionic detergent and the interaction of a saccharide-like compound with lipoproteins (VLDL and chylomicrons). This method accomplish the requirements of the National Cholesterol Education Program (NCEP) to have a total analytical error ≤12%. The LDL lipoproteins from serum or plasma are precipitated by phosphotungstic acid in the presence of magnesium ions. After removed by centrifugation the clear supernatant containing high density lipoproteins (HDL) is used for the determination of HDL cholesterol [11,12].

In the study, the statistical analysis and graphical representations were performed in the EXCEL and SPSS program. The study was approved by the ethical committee, nr 2704/10.02.2017

Results and discussions

Age

The mean age of patients from group 1 was 11.85±3.65 years, with predominance of boys, compared to 11.5±3.1 years, and predominance of girls in group 2 (fig. 1). There are no statistically significant differences between patients from group 1 and group 2 (p=0.171).

Age is an important aspect in the acquisition of hepatitis C virus because it is a factor that gives information about the the most common route of transmission which differs in children compared to adults, the chances of spontaneous clearance, and possible comorbidities associated that play an important role in progression to cirrhosis and hepatocarcinoma [13]. As the most common route of transmission in children is vertical, it is important to educate mothers about measures that can reduce the risk of transmission during and after birth [14]. In children and adolescents fulminant forms of hepatitis are rare compared to adults. The evolution of viral hepatitis C in children differs from the adult in many ways including spontaneous clearance, which is more common in younger age. Spontaneous clearance occur in children under the age of 2 years in 25-40% of cases compared with adults 20% of cases [15].

Body weight

We observed a predominance of overweight status in group 2, 52.94% vs. 46.43% in group 1 (fig. 2). Analyzing patients distribution by sex and BMI, we noticed preponderance of girls in both groups, 25% in group 1 and 29.41% in group 2, but without statistically significant differences (p=0.347).

Obesity is one of the main nutritional disorders of the child and adolescent [17]. The association between BMI, lipid metabolism, weight loss and response to the treatment is controversial. Obesity leads to an association of events from which results an increased intake of free fatty acids in the liver. When capture of free fatty acids in plasma and their de novo synthesis exceeds their oxidation and export from hepatocyte as triglycerides, the excess of triglycerides it accumulates in the hepatocytes leading to steatosis. In the presence of steatosis, intracellular concentrations of fatty acids in excess can cause oxidative stress, leading to apoptosis of hepatocytes and activation of stellate cells, and ultimately lead to fibrosis [18,19].

Lipid parameters

We found that 21.43% of patients in the group 1 vs 32.3% of patients in the group 2 had an elevated total cholesterol level and 17.86% vs 14.7% of patients had low level of total cholesterol, but without statistically significant differences (p=0.258) and (p=0.131) respectively. We also noticed that 7.14% patients from group 1 and 8.8% patients from group 2 had elevated level of triglyceride, with no statistically significant differences (p=0.90) (fig. 3).

Total cholesterol levels were significantly changed during antiviral therapy in both groups of patients. At initiation of antiviral therapy mean serum cholesterol level were 155.78±36.30 mg/dL, in group 1 vs 149.88±47.22 mg/dL, for patients in group 2. At 48 weeks of treatment in both groups revealed significantly decreased of total cholesterol levels 136.46±41.63mg/dL, for group 1 vs 109.26±41.05, for patients in group 2. Comparative analysis using T test show that changes of total cholesterol levels at 48 weeks of antiviral therapy were significantly different between the two groups (p=0.003).
Analyzing the total triglyceride level in the two groups, we observed a mean trygliceride level of 111.32±39.55 mg/dL in group 1 vs 112.17±35.06 mg/dL in group 2, without important changes during antiviral therapy. All patients included in the study had HDL and LDL cholesterol level in normal limits without significant changes during antiviral therapy (table 1).

Lipid metabolism may show changes in viral hepatitis C compared to other types of hepatitis because the HCV outer membrane has a lipid affinity.

Treatment of viral hepatitis C with Interferon and Ribavirin may influence lipid metabolism by several mechanisms. The first is resolution of hepatic inflammation after successful HCV eradication, which may normalize hepatocellular function and hepatic production of serum lipoproteins. The second is that antiviral therapy may alter lipid metabolism by receptors on hepatocytes, which have important roles in the regulation of serum lipid concentrations [20]. The activity of hepatic triglycerides, an enzyme that degrades serum triglycerides, is inhibited during Interferon therapy, and hepatocellular triglyceride synthesis is stimulated by treatment. Therefore, high levels of triglycerides during Interferon therapy could be caused by Interferon action in triglyceride degradation, such as impaired synthesis of hepatic triglycerides and through transcriptional activation of lipogenic genes favoring lipid synthesis in patients [21].

Antiviral treatment has multiple actions, not only helps to eradicate HCV in the body but has implications in lipid metabolism and because this disease is often asymptomatic, it is often difficult to diagnose and treat immediately [22]. Therefore, monitoring of patients with viral hepatitis C requires both the specialist’s and the patient’s family’s attention because the changes that occur may affect the quality of life of these patients [23, 24].

In the present study, the SVR were achieved by 64.29% of patients, in group 1, vs 88.2% in group 2. Analyzing the changes of total cholesterol during antiviral therapy we found that the changes of total cholesterol after antiviral therapy were significantly different between patients who achieved SVR and non SVR in both groups by measure ANOVA analysis (p=0.014), group 1 vs (p=0.001), group 2. The effect of antiviral therapy on lipid metabolism was also confirmed in a study in Korea of 203 patients with viral hepatitis C who reported a decrease in total cholesterol during antiviral therapy and increases in serum triglycerides [25].

**Conclusions**

Because lipid metabolic processes occur in the liver, serum total cholesterol level is closely related to the severity of liver diseases and response to the treatment. The result of our study show that patients with viral hepatitis C may present changes in lipid metabolism before and during antiviral therapy, therefore total cholesterol level, an investigation that can be done in any laboratory, can be used as a prediction factor for the therapeutic response.

**References**


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