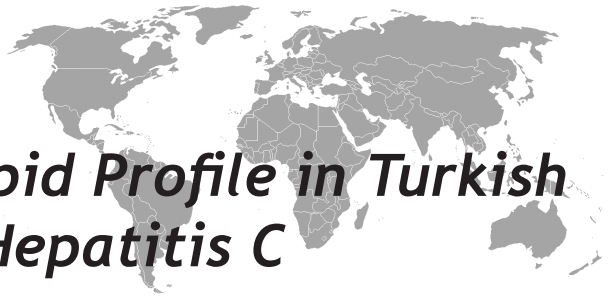

Evaluation of Serum Lipid Profile in Turkish Patients with Chronic Hepatitis C

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ABSTRACT

Aim: *In this study we researched the effect of chronic hepatitis C virus (HCV) infection on serum lipid profile.*

Method: *28 patients (age average: 58.2±7.9 years) 17 of them women and 11 of them men and 33 healthy people (age average: 51.1±7.4 years) 22 of them women and 11 of them men taking chronic hepatitis C diagnosis through liver biopsy and in that any treatment wasn't started yet were taken into the study. Liver biopsy samples were evaluated according to Knodell's histology activity index. As once in the patient and control group, Albumin, platelet, total cholesterol, Apolipoprotein A1, Apolipoprotein A2, Apolipoprotein B, Apolipoprotein E, total lipid and other biochemical parameters were measured in the serum.*

Result: *In patients with chronic hepatitis C, when compared with the control group, while alanine aminotransferase (104±11 and 21±11) IU/L, aspartat aminotransferase (74±5 and 19±7) IU/L and apolipoprotein A1 (137.68±38.46 and 119.27±19.84) mg/dl values were meaningfully high for each one (p<0.001), platelet (238±90 and 285±73) K/mm3, very-low density lipoprotein and total lipid values were found meaningfully low for each one (p<0.002). It wasn't determined any relationship between liver stage, histological activity index (HAI) and lipid profile.*

Conclusion: *HCV infection can lead to changes on serum lipid profile though its reason can't be enlightened absolutely.*

Key words: *Chronic hepatitis C, lipid, hepatosteatosis*

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Kronik Hepatit C'li Türk Hastalarda Serum Lipid Profilinin Değerlendirilmesi

Amaç: *Bu çalışmada kronik kronik hepatit C virus (HCV) enfeksiyonunun serum lipid profili üzerine etkisini araştırdık.*
Metod: *Karaciğer biyopsisi ile kronik hepatit C tanısı alan ve herhangi bir tedaviye başlanmamış 17 kadın 11 erkek 28 hasta (yaş ortalaması:58,2±7,9 yıl) ile 22 kadın 11 erkek sağlıklı 33 kişi (yaş ortalaması:51,1±7,4 yıl) çalışmaya alındı. Karaciğer biyopsi örnekleri Knodell'in histoloji aktivite indeksine göre değerlendirildi. Hasta ve kontrol grubunda bir kez olmak üzere serumda Albumin, trombosit, total kolesterol, ApolipoproteinA1, ApolipoproteinA2, ApolipoproteinB, ApolipoproteinE, total lipid ve diğer biyokimyasal parametreler ölçüldü.*
Bulgular: *Kronik hepatit C'li hastalar da kontrol grubu ile karşılaştırıldığında sırasıyla alanine aminotransferase (104±11 ve 21±11) IU/L, aspartat aminotransferase (74±5 ve 19±7) IU/L ve apolipoprotein A1 (137,68±38,46 ve 119,27±19,84) mg/dl değerleri her biri için anlamlı derecede yüksek iken (p<0.001), trombosit (238±90 ve 285±73) K/mm3, VLDL ve total lipid değerleri her biri için anlamlı derecede düşük bulundu (p<0.002). Karaciğer stage ve histoloji aktivite indeksi ile lipid profili arasında da bir ilişki saptanmadı.*
Sonuç: *HCV enfeksiyonu, nedeni tam olarak aydınlatılamamakla birlikte serum lipid profili üzerinde değişikliklere yol açabilir.*
Anahtar kelimeler: *Kronik hepatit C, lipid, hepatosteatoz*

INTRODUCTION

Chronic hepatitis C (CHC) and hepatitis C virus (HCV) leading to this state, as being different from many viral hepatitis factors, have a set of different properties in liver histopathologically. These are lymphoid follicle formations, bile duct damage and steatosis (fatty change) (1-3). In more than 50% of patients infected with HCV it is seen steatosis in liver. The reason of this situation can't be totally known and it can be probably due to both HCV and the host factor. As known, liver has a central role in the arrangement of the body's cholesterol balance. The synthesis realizes in cytosol with enzymes taking place both in cytosol and endoplasmic reticulum. The relation between HCV and lipid metabolism has been shown in many studies (4,5). In cell cultures a relation between HCV core protein and low density lipoprotein (LDL) receptor has been shown (6.7). In Europe, while HCV genotype 3a infection is related with steatosis, in far east countries like Japan, HCV genotype 1b infection is related with steatosis. In addition, in Europe it is observed hypocolesterolemia or hypobetalipoproteinemia not in 1b but in genotype 3a HCV infection (8). In apolipoproteins taking place in the structure of lipoproteins such as HDL, LDL, VLDL, it is shown that they have been affected by HCV infection in many studies. As known, apolipoprotein B takes place in the structure of VLDL and LDL. Apolipoprotein A1 and A2 take place in HDL structure. In contrast, apolipoprotein E and C take place in the structure of HDL and VLDL. In Japanese steatosis patients with HCV genotype 1b, it was determined serum total cholesterol, apolipoprotein B, CII and CIII levels meaningfully lower compared to genotype 2a and HBV infection (9). In the other side, it has been shown in the rat models with hepatic steatosis that HCV core gene decreases the level of microsomal triglyceride transfer protein and impairs VLDL secretion in liver (10). Also, while in liver the peroxisome proliferators-activated receptor-α (PPAR-α) activates the transcription of apolipoprotein AI and AII genes in human, it suppresses the transcription of apolipoprotein CII and CIII genes (11-12). In experimental studies a relation between HCV core protein and PPAR-α has been observed (11,12). As a result, HCV leads to steatosis in liver as being different from hepatitis B virus (HBV) and it is argued that steatosis is related with core antigen of HCV. In chronic hepatitis C, decreases in serum lipids have been reported. The relations between different HCV genotype and lipid metabolism disorder in the world have been defined. Our aim in this study is to determine serum lipid profile in Turkish HCV patients with chronic hepatitis C.

MATERIALS AND METHODS

Prior to the study, for this clinical study, the research confirmation numbered KA03/154 was taken from "Baskent University Medicine Faculty Research and Ethics Board". In the subjects taken into the study, the following criteria were taken into account:

1. Patient with CHC, these are patients in that antiviral treatment has not been started, who are not cirrhosis histologically and have HCV-RNA (+) in serum with PCR method.

2. There isn't any cirrhosis based on any etiology.

3. The body mass index <30 kg/m^2.

***Table 1**. Comparison of results of CHC patients and control group (Mean±S.D)*

	Patient	Control	p value
Age	*55.46±10.54*	*51.1±7.4*	*ns*
ALT	*104.21±11.203*	*21.58±11.27*	*<0.001*
AST	*74.18±5.318*	*19.76±7.59*	*<0.001*
PT	*12.56±1.04*	*12.10±0.61*	*0.036*
INR	*1.15±0.18*	*1.11±0.12*	*ns*
ALB	*4.01±0.48*	*4.12±0.30*	*ns*
TROM	*238214.3±90413.6*	*285303±73724.35*	*0.029*
TCOL	*172.96±39.03*	*185.76±36.89*	*ns*
VLDL	*25.29±16.67*	*36.15±18.47*	*0.005*
LDL	*98.5±31.03*	*113.88±38.46*	*ns*
HDL	*51.46±15.08*	*47.27±16.19*	*ns*
TG	*126.82±59.61*	*135.03±60.00*	*ns*
APOA1	*137.68±38.46*	*119.27±19.84*	*0.020*
APOA2	*411.68±124.47*	*343.62±87.08*	*0.015*
APOB	*74.87±24.14*	*81.76±19.28*	*ns*
APOE	*54.04±25.38*	*48.29±16.65*	*ns*
TLIP	*599.11±139.54*	*716.09±141.09*	*0.002*

ns: not significant mean±S.D: mean±standard deviation, (ALT: Alanine aminotransferase, AST:Aspartat amimotransferase, PT: Prothrombin time, INR: International normalization ratio, ALB: Albumin, TCOL:Total cholesterol, VLDL: Very low density lipoprotein, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG:Triglyceride, APOA1,A2,B,E: Apolipoprotein A1,A2,B and E , TLIP:Total lipid)

4. Alcohol uptake <40 gr/day.

5. They aren't using any medicines affecting lipid metabolism (such as lipid decreaser agents, nonsteroidal anti-inflammatory medicines).

6. Not being over that fasting blood glucose (FBG)≥126 mg/dl or random BG≥200 mg/dl.

7. HBsAg (-) availability in serum.

8. In addition, as being not included in the study or exception criterion, ones who have taken antiviral treatment before, used hepatotoxic medicines, consume regular or much amount of alcohol, have cirrhosis, have autoimmune and metabolic liver disease and have HBsAg (+) have not been taken into the study.

Liver biopsy was made on every patient with CHC. In biopsy samples, histological activity index (HAI) was made according to and phasing Knodell classification. In biopsy, HAI was scored in the way portal inflammation (0-4), lobular degeneration, necrosis (0-4) and periportal necrosis (0-10). In liver biopsy sample, absence of fibrosis was evaluated as stage 1, and bridging necrosis as stage 4. Also, in steatosis, the below of 5% in liver biopsy sample was accepted as normal fatting and the above of 5% as presence of steatosis. 17 female, 11 male, the total 28 patients (age average: 58.2±7.9 years) and 22 female, 11 male, the total healthy 33 people (age average: 51.1±7.4 years) having hepatitis C diagnosis through liver biopsy and on that any treatment wasn't started were taken into the study. Liver biopsy samples were evaluated according to Knodell's histology activity and whether there is steatosis. In serum, ALT, AST, PT, INR, Albumin, platelet, total cholesterol, VLDL, LDL, HDL, TG, Apolipoprotein A1, Apolipoprotein A2, Apolipoprotein B, Apolipoprotein E and total lipid were measured once in the patient and control groups. In addition, in patients with CHC, quantitative HCV RNA determination was made once with PCR.

Statistical Analysis

Statistical calculations were made using SPSS 9.05 (version 9.05; SPSS, Inc., Chicago, Illinois, USA) computer program. The results were got as mean±standard deviation (mean±SD). For statistical analysis, Student t and Mann-Whitnet U test were used and the relation between variables was examined with Pearson correlation. P<0.05 value was accepted meaningful statistically.

RESULTS

While ALT (104±11 and 21±11) IU/L, AST (74±5 and 19±7) IU/L and apolipoprotein A1 (137.68±38.46 and 119.27±19.84) mg/dl values of patients with CHC respectively were significantly high (p<0,001) compared

Table 2. *Comparison of results of CHC patients having liver steatosis and not having liver steatosis (Mean±S.D).*

	With steatosis	No steatosis	p value
Age	*58.24±7.49*	*51.18±13.31*	*ns*
HAI	*7.94±4.31*	*7.45±3.21*	*ns*
ALT	*90.23±71.18*	*125.81±157.89*	*ns*
AST	*74.59±39.39*	*73.55±71.78*	*ns*
PT	*12.80±1.06*	*12.16±0.91*	*ns*
INR	*1.19±0.18*	*1.09±0.18*	*0.036*
ALB	*3.94±0.41*	*4.11±0.59*	*ns*
TROM	*230529.4±104418.1*	*250090±66112.71*	*ns*
TCOL	*165.41±37.45*	*184.64±40.28*	*ns*
VLDL	*25.71±18.94*	*24.64±13.27*	*ns*
LDL	*91.35±28.79*	*109.55±32.42*	*ns*
HDL	*54.18±15.96*	*47.27±13.19*	*ns*
TG	*121.82±59.12*	*134.55±62.39*	*ns*
APOA1	*145.05±45.39*	*126.27±21.47*	*ns*
APOA2	*434.28±128.05*	*376.75±115.69*	*ns*
APOB	*69.79±24.01*	*82.73±23.22*	*ns*
APOE	*57.68±22.95*	*48.42±28.97*	*ns*
HCVRNACO	*427013.5±235332.6*	*252506.4±198591.9*	*ns*
TLIP	*601.24±145.51*	*595.82±136.65*	*ns*

ns: not significant

to the control group, platelet (238±90 and 285±73) K/mm3, VLDL and total lipid values were found out significantly low ($p<0.002$). Although the total cholesterol amount in patients with CHC is lower than that of healthy controls, this difference was not meaningful statistically ($p=0.194$). In addition, it wasn't determined any meaningful difference in both groups. Comparative results of the patients with CHC and the healthy group were given in Table 1.

In the other side, when lipid panels of 17 patients having steatosis (60.7%) and 11 patients having not steatosis (39.3%) were compared in liver biopsy among patients with CHC, any meaningful relation between them wasn't detected. In liver biopsy, 16 patients were in stage (fibrosis) 1, 7 patients in stage 2, 3 patients in stage 3, 2 patients in stage 4, and average HAI was 7.78±3.80. Any relation wasn't detected between stage, HAI and lipid profile as well. In CHC patients in liver biopsy sample other monitored parameters including quantitative PCR HCV RNA results of patients having and not having steatosis are shown in Table 2.

DISCUSSION

CHC is often associated with liver steatosis. Steatosis is reported in 31-72% of patients with CHC (13). However pathogenesis of steatosis in HCV infection hasn't been described clearly. In the literature the relation between lipid profile and steatosis, HCV infection in Turkish patients group hasn't ever been published. So it was aimed to contribute to the literature through this study. In CHC, steatosis can depend on HCV and the host factors. In different geographic regions there are relations between the discrimination of HCV genotype and steatosis and blood lipid profile. While in Europe HCV genotype 3a infection is related with steatosis, HCV genotype 1b infection in far east countries like Japan is related with steatosis. In addition, hypocolesterolemia or hypobetalipoproteinemia is observed not in HCV genotype 1b but in genotype 3a HCV infection in Europe (8). In Japan, nevertheless genotype 3a HCV infection is very rare, genotype 1b HCV infection is often. In this study in Japan steatosis patients infected with HCV genotype 1b it was determined meaningfully lower levels of serum total cholesterol, apolipoprotein B, CII and CII levels compared to genotype 2a and HBV infection (9). Furthermore, in patients with apolipoprotein AI, AII and E, HCV genotype 2a and HBV, the HCV was found out similar to patients with genotype 1b (9). That apolipoprotein B, CII and CIII are low and apolipoprotein AI, AII and E are normal has been described in that way: Both apolipoprotein CII and CII are present in HDL and

VLDL. Apolipoprotein B is available in VLDL and LDL. A disorder in synthesis and secretion of VLDL in liver explains these observations. In our study VLDL value was found out significantly low due to the decrease in serum in CHC namely in liver synthesis. Our this result shows parallelism with the literature studies in the way that HCV core gene impairs VLDL secretion in liver. This situation has been shown in the animal assays, and in rat models with hepatic steatosis, HCV core gene decreases the level of microsomal triglyceride transfer protein and impairs VLDL secretion in liver (10). In cell cultures a relation was shown between HCV core protein and low density lipoprotein receptor (LDL) (6,7). In our study LDL level in CHC patients was lower than that of control group (p=0.095). However this result was not meaningful. In addition, while another finding relating to HCV lipid interaction activates peroxisome proliferators-activated receptor-α (PPAR-α) in liver and transcription of apolipoprotein AI and AII genes in human, it suppresses transcription of apolipoprotein CII and CIII genes, and a relation between HCV core protein and PPAR-α was observed in experimental studies in literature (11,12). As a result, HCV, being different from hepatitis B virus (HBV), leads to steatosis in liver and it is argued out that steatosis is related with core antigen of HCV. For example, it is known that HCV genotype 3a stimulates fat storing in hepatocytes (14). Situations such as alcohol, diabetes and obesity which can lead to steatosis in liver were determined before the study and people being in this situation were not taken into the study. In our study in CHC patients the steatosis prevalence was found out 60.7 % and this finding is in harmony with the literature (13). However in many literatures this ratio is between about 30-40 % (14,15). It was shown that these differences can vary according to viral load and viral genotype (16). In contrast, in some studies in literature, it was stated that genotype 3a with steatosis was related with virus load amount but not related with other genotypes (16,17). In some studies it was stated that there wasn't any relation between virus load amount and hepatosteatosis (18). Results in our study is in harmony with this literature. However PCR and HCV RNA amount being approximately 427 thousand copies in serum in our steatosis patients in the group with CHC was approximately 252 thousand copies in the group without steatosis. This finding was not meaningful statistically (p=0.08). HCV genotype being very dominant in our country is genotype 1b and any relation between this quantitative load measured in our study and steatosis was not observed.

The relation of virus amount in hepatocyte with steatosis and changes in lipoprotein metabolism are possible mechanisms (8,14). In this subject there is need for advanced large-scale studies concerning patients. In hepatosteatosis, fat stores in hepatocyte increase and it has been argued out that in CHC treatment the interaction area between given antivirals and hepatocyte has decreased and consequently this has affected the treatment negatively (19,20). So liver steatosis is important in response to the treatment as well. In addition, HCV infection is generally associated with glucose tolerance disorder or diabetes and both these two situations are closely related with steatosis. Due to these two situations, HCV infection can be related with lipid metabolism indirectly.

Finally, that in our study we found total lipid, VLDL cholesterol and total cholesterol amounts as low and in the other side the increase in liver steatosis in CHC was shown shows that in CHC the lipid metabolism is affected also in Turkish patient population. CHC infection can lead changes on serum lipid profile although its reason can not be enlightened precisely. There is need for very well settled molecular and genetic studies to well understand HCV infection and lipid metabolism.

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