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Research Article

Influence of Uricacid Levels on Pegylated-Interferon Plus Ribavirin Therapy in Patients with Chronic Hepatitis C -

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Abstract

Introduction: Itwasaimed in thisstudytoevaluateinfluence of uricacidlevels on pegylated-interferon alpha (PEG-IFN-a) 2a/2b plusribavirintherapy in patientswithchronichepatitis C.

Methods: A total of 165 chronic hepatitis c patients applying to Izmir Ataturk Research and Training Hospital, Department of Gastroenterology between 01.01.2005 - 01.11.2012 with ages ranging from 20 to 75 years having pre-and post-treatment serum uricacid and HCV-RNA (0, 12, 24, 48 and72 weeks) levels available were included in the study. These parameters were assessed according to the groups based on response to therapy (sustained virologic response–SVR, relapse and non-responders).

Results: Of the 165 patients, 28 were excluded from hyperuricemia analyses owingto lack of uricacid levels and/or liver biopsies. Of the137 included, 117 had nohyperuricemiawhile 20 did (cut-offlevelswere 7 and 6 mg/dL in malesandfemale, respectively). In univariate analyses, no statistically significantassociation was established between hyperuricemia and age, waist circumference, HOMA-IR score, sustained virologic response, fibrosis and histologic activity index (p valueswere 0,61; 0,115; 0,437; 0,645; 0,235 and0,166; respectively). However, significant association was found between hyperuricemia and body massindex, hypertension, existence of metabolic syndrome and grade of steatosis (p valueswere 0,045; 0,04; 0,045; 0,007; respectively). No significant relevance was noted between hyperuricemia and theparameters in multivariate analyses.

Conclusion: There has beendetected a significant association between hyperuricemia and steatosis in patients with chronic hepatitis C. However, noinfluence on therapy has been found with regard to uric acid levels. Multicenter studies are required to enlighten thi smetabolic chaos.

Keywords: Chronic hepatitis C; Uric acid; Steatosis

INTRODUCTION

Itis reported in literature that approximately 3% of world population – which equals to 170 – 200 million people -is infected with Hepatitis C Virus (HCV) [1]. Our country being moderate endemic in terms of HCV has a HCV prevalence of 1-3% [2]. GT1, the most prevalent genotype in developed countries, is also the most prevalent worldwide and well respond to the second generation direct-acting antiviral therapies with the viral eradication rates of > 90% [3,4]. In Turkey, GT1 has been reported to account for the vast majority of HCV infection, with prevalence ranging 51.7%-97.1% [5,6]. As similar to other data in our country, GT1 was the most common genotype (82.5%). Subtype 1b is the most prevalent subtype in Turkey, with prevalence ranging 56.5%-100%[7,8]. Peakagegroup of HCV is thought to be 20-39. The majority of CHC cases are anicteric and asymptomatic [3,9]. HCV is responsible for 20% of acute vira lhepatitis, 70% of chronic viral hepatitis, 40% of viral hepatitis ending with cirrhosis, 60% of Hepato Cellular Cancer (HCC) and 30% of cases requiring liver transplantation in developedcountries [10]. It was interferon mono therapy that was the first agen used in treatment of CHC in 1990. In 1998, interferon and ribavirin combination was shown to be more effective than interferon alone. Efficacy of interferon alfa wa limited due to fast clearance and short halflife. Thus, pegylated forms were developed to extend the shorthalf life. Following head to head comparisons, PEG-IFN & ribavirin combination started to be the standard therapy. Response rates of 50-60% and 80-90% were achieved with this therapy in genotype 1 and genotype 2 & 3, respectively [11-13]. The combination therapy had shown to cause flu-likesymptoms, fatigue, hairloss, anemia, leucopenia and thrombocytopenia. Although less frequently; acute psychosis, convulsions, auto immune reactions, hyperthyroidism and hypothyroidism may also be seen [14]. Early discontinuation of therapy may come up owing to side effects in 10-20% of cases [15] Methods

A total of 165 chronic hepatitis c patients applying to Katip Celebi University Ataturk Researchand Training Hospital, Department of Gastroenterology between 01.01.2005 and 01.11.2012 with ages ranging from 20 to 75 years having pre-and post-treatment serum uric acid and HCV-RNA (0, 12, 24, 48 and72 weeks) levels available were included in the study. These parameters were assessed according to the groups based on response to therapy (sustained virologic response –SVR, relapse and non- responders). Inclusion and exclusion criteria are as follows;

- Inclusion criteria: having diagnosed with chronic hepatitis c, completion of therapy
- Exclusion criteria: poorfollow-up, chronic renalfailure, any solid organ or hematologic malignancy, HIV positivity,pregnancy

Our study was performed in accordance with Helsinki Declaration. The approval of Katip Celebi Ataturk Research and Training Hospital review board was obtained before the study (3 March 2012/73).

Clinicaland laboratory assessments

Patients' records including body weight, body massindex, waist circumference, uricacid, glucose, total cholesterol, triglyceride, HDL & LDL cholesterol, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), gamma-Glutamyl Trans Peptidase (GGT), creatinine, insulin levels, hematologic parameters, liver biopsy and upper abdominal ultrasonography reports were obtained via Probel patient recording system. Metabolic syndrome, ATP III criteria are defined as follows: waist circumference ≥ 102 cm and ≥ 88 cm for male and female respectively; blood pressure ≥ 130/85 mmHg or diagnosis of controlled hypertension under treatment; triglyceride ≥ 150 mg/dl; HDL < 40 and < 50 mg/dl for male and female, respectively; fasting plasma glucose ≥ 100 mg/dl or diagnosis of controlled diabetes mellitus under treatment.Statistical analyses were performed.

Histologic assessment

Pathologic samples were assessed by pathologists blind both to patients and histories. Adequate sample was defined as a biopsy material of more than 15 mm or at least 10 complete portal fields. Samples were classified with respect to Ishaksystem. Steatosis was defined as percentage of hepatocytes includingfatdroplets. Steatosis

was stratified as "none", "mild", "mildtomoderate" and "severe" correspondingtolessthan 5%, between 5-33%, 33-66% andmorethan 66%; respectively.

Antiviral therapy schedule

Patients administered PEG-IFN 2a (Pegasys; Roche, Basel, Switzerland) as 180mcg/week and ribavirin (1000 mg/dayforthosewith a body weight of lessthan 75kg and 1200 mg/dayformorethan 75 kg) during 48 weeks. Treatments were stopped once virologic response is achieved. Virologic response is defined as undetectable HCV-RNA via PCR at week 24 was achieved

Statistical methods

Continuous variables were denoted by +/- while categorical ones were by frequency and percentage. ANOVA, t-test andchi-squaretests were used appropriately. Multiple logistic regression model was used to assess independently associated factors with hyperuricemia, severe necroinflammatory activity, severe fibrosis and sustained virologic response. In the first model, the dependent variable was "hyperuricemia" entered as 0 or 1 correspondingto "no" and "yes", respectively. It was "necroinflammatory activity" the dependent variable in the second model which was entered as 0 or 1 correspondingto "not severe (G0-G2)" and "severe (G3)", respectively. In the third model, the dependent variable was "fibrosis" entered as 0 or 1 meaning "not severe (F0-F2)" and "severe (F3-F4)", respectively. In the fourth one, the dependent variable was "sustained virologic response" that wa sentered as 0 or 1 meaning "no" and "yes", respectively. Besides, multiple ordinal regression model was used to assess independently associated factors with severity of liver teatosis.

Probable risk factors were determined as age, gender, body massindex, ALT, thrombocyte, total cholesterol, LDL, HDL, triglycerides, glucose, insulin, HOMA-IR score, arterialhypertension, diabetesmellitus, creatinine, eGFR (glomerularfiltration rate – assessed in hyperuricemia model only), HCV-RNA (denotedby Log10), viralgenotype, uricacidlevels, hyperuricemia, steatosis, necro inflammatory activity and fibrosis.

HOMA-IR score, glucose, insulin, uricacidlevelsalongwithhyper-uricemiawere not included in thesame model with ALT and necro-inflammatory activity to avoid linear relationship effect. Regression-analyseswereconductedusingsub-softwares of PROC LOGISTIC, PROC REG and SAS.

RESULTS

Basic demographic data of our patients were shown in table 1. Of the 165 patients, 63 were male and 102 were female. Mean age was 53,4 +/- 11,5. 28,5% (n = 47) of thepatientswere normal-weightwhile 44,2% (n = 73) wereoverweightand 27,3% (n = 45) wereobese. Cholesterol parameters (total cholesterol, triglyceride, LDL and HDL) were in normal range on average. HOMA-IR mean ± SD was 5,33 +/- 5,59. Diabetes mellitus, arterial hypertension, metabolic syndrome and hyperuricemia were not found in vastmajority. It wa genotype 1b the responsible agent in 154 (93,3%) patients while genotype1a in 11 (6,7%). In 90,9% (n = 150) of the patients, steatosis was detected and of these, 74% had mild steatosis while 16% moderate and 10%severe. Histologic activity index was 0 in 46 (30,7%) patients whereas 1 in 67 (44,7%) and 2 in 37 (n = 24,7%). Stage of fibrosis was 0 in 14(9,3%), 1 in 53 (n = 35,3%), 2 in 43 (n = 28,7%) and 3 in 40 (26,7%) patients.

Table 2 includes data regarding comparison of degree of steatosis and various parameters. Of the numerous parameters; only waistcircumference, uricacid level and hyperuricemia were found to be statistically related to degree of steatosis when it was divided into three as "none" (steatosis in lessthan 5% of hepatocytes), "mild" (steatosis in between 5-30% of hepatocytes) and "severe" (steatosis in morethan 30% of hepatocytes) (p values were 0,005; 0,002; 0,007; respectively).

Table 1: Parameter and number of CHC patients.

Parameter	Mean ± SD or median (min, max) *n* = 165
Gender (M/F)	63/102
Age (years)	53,4 ± 11,5 (56; 21-71)*
Body Mass Index (kg/m²)	27,65 ± 4,54 (27,1; 17,6-42,2)
Body Mass Index (kg/m²)	
< 25	47 (28,5)
25-29,9	73 (44,2)
≥ 30	45 (27,3)
Waist Circumference (cm)	97,02 ± 11,94 (97; 69-130)
AST (IU/L)	59,13 ± 47,69 (48; 14-480)
ALT (IU/L)	69,55 ± 49,54 (56; 13-373)
GGT (IU/L)	73,82 ± 69,51 (47; 10-350)
Platelet (microL)	209 ± 72 (201; 21-440)
Total Cholesterol (mg/dL)	158,64 ± 33,89 (159; 76-246)
Triglyceride (mg/dL)	114,94 ± 58,51 (101; 23-400)
LDL-Cholesterol (mg/dL)	92,58 ± 33,45 (89; 22-220)
HDL–Cholesterol (mg/dL)	45,19 ± 14,71 (44; 15-106)
Fasting Blood Glucose (mg/dL)	108,49 ± 33,77 (98; 68-288)
Postprandial Glucose(mg/dL)	158,50 ± 95,63 (124; 66-591)
HbA1C	5,83 ± 1,53 (5,5; 3,1-11,2)

AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; Hba1c: Hemoglobin A1c

No significant associationwas found between fibrosis and uricacid levels, existence of hyperuricemia and degree of steatosis (p values 0,657; 0,235 and 0,281; respectively).

We detected that waist circumference showed a significant association between "severe steatosis" and "no steatosis" groups only (groups 2 and 0) (p value 0,006) where as uric acid did both between groups 0 - 1 and groups 0-2 (p values 0,044; 0,018; respectively) when steatosis groups were assessed with respect to three parameters between which a significant association was noted separately (Table 3a & 3b). Similarly, hyperuricemi as howed a significant association between groups 0-1 along with groups 0-2 (p values 0,031 and 0,019; respectively).

No significant association was found between degree of steatosis and sustained virologic response, histologic activity index and fibrosis (p values 0,219; 0,094 and 0,281; respectively).

Of the 165 patients, 28 were excluded from hyperuricemia analyses owing to lack of uricacid levels and/or liver biopsies. Of the 137 included, 117 had nohyperuricemia while 20 did (cut-offlevels were 7 and 6 mg/dL in males and female, respectively). In uni-variate analyses, no statistically significan tassociation was established between hyperuricemia and age, waist circumference, HOMA-IR score, sustained virologic response, fibrosis and histologic activity index (Table 4) (p values were 0,61; 0,115; 0,437; 0,645;

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Table 2: Comparison of degree of steatosis and various parameters.

Variable	None < %5 (*n* = 111)	Mild %5-30 (*n* = 24)	Severe > %30 (*n* = 15)	*P* value
Gender (M/F)	41/70	11/13	6/9	0.715ı
Age-years	53,37 ± 11,3	58,33 ± 8,3	56,12 ± 11,49	0.119
Body Mass Index-kg/m²	27,3 ± 4,5	28.0 ± 3.6	28.9 ± 4.7	0.050
Body Mass Index-kg/m²				0.406ı
< 25	34	4	3	
25-29,9	51	14	6	
≥ 30	26	6	6	
Waist Circumference (cm)	95.1 ± 11.1	99.3 ± 10.3	102.9 ± 15.2	0.005*
Aspartate Amino Transferase - IU/L	60.9 ± 50.5	53.4 ± 31.9	84.1 ± 86.9	0.614
Alanine Amino Transferase - IU/L	71.2 ± 47.3	66.4 ± 48.7	110 ± 124.4	0.459
γ-glutamyl transpeptidase IU/L	69.5 ± 67.1	80.3 ± 54.7	97.9 ± 92.7	0.131
Cholesterol-mg/dL	157.6 ± 31.4	166.3 ± 45.3	157.5 ± 34.8	0.867*
Triglyceride-mg/dL	112.3 ± 57.1	140.7 ± 82.7	114.3 ± 62.8	0.450
LDL-Cholesterol mg/dL	91.1 ± 31	96.5 ± 39.9	92.5 ± 33.3	0.771
HDL –Cholesterol- mg/dL	46.2 ± 14.8	42.2 ± 14.7	43.6 ± 15.6	0.113
Blood Glucose- mg/dL	106.6 ± 28.7	112.5 ± 42.2	110 ± 39	0.828
Insulin - µU/mL	17.7 ± 13.6	20.7 ± 18.9	15.9 ± 11.2	0.979
HOMA	4.75 ± 4.1	6.72 ± 8.1	4,56 ± 4.3	0.978
UricAcid-mg/dL	4.72 ± 1.3	5.42 ± 1.5	5.9 ± 2.1	0.002
Platelet (microL)	207.3 ± 71.8	196.2 ± 91.6	199.9 ± 57.6	0.753*
DiabetesMellitus (Yes / No)	25 /86	7/17	5/10	0.565ı
ArterialHypertension (Yes / No)	23/88	8/16	4/11	0.395ı
MetabolicSyndrome (Yes / No)	21/90	6/18	6/9	0.168ı
Hyperuricemia (Yes %/ No)	9/91	6/17	5/9	0.007ı
Treatment (SVR/NonSVR)	66/45	10/14	7/8	0.219ı
Viralgenotype (1a /1b)	19/64	21/52	21/38	0,253ı
LogHCV-RNA	5.74 ± 0.88	5.47 ± 0.96	5.93 ± 0.81	0.067*
Histology				
Histolojic Activity Index				0.094ı
0 (0)	32	11	3	
1 (1-8)	54	7	5	
2 (9-18)	24	6	7	
Fibrosis				0.281ı
0 (0)	14	0	1	
1 (1-2)	38	10	5	
2 (3-4)	29	9	4	
3 (5-6)	29	5	6	

0,235 and 0,166; respectively). However, significant association was found between hyperuricemi and body massindex, hypertension, existence of metabolic syndrome and grade of steatosis (p values were 0,045; 0,04; 0,045; 0,007; respectively) (Table 4). No significant relevance was noted between hyperuricemia and theparameters in multivariateanalyses (Table 4).

DISCUSSION

Hepatitis C infectionis one of crucial causes of chronic liver diseases. Recently, influence of some factors such as insulin resistance and steatosis on chronic hepatitis C infection has been handled [16,17]. Besides, these factors have also been shown to be associated with non-alcoholic fatty liver disease [18]. Some evidence advocating

influence of afore mentioned factors on the therapy has emerged [19,20].

Relationship between gout disease and hypertension, diabetes mellitus, renal and cardiovascular diseases have long been known [21-24]. In recent years, this relationship has also been shown in metabolic syndrome, coronary artery disease, cerebrovascular disease, dementia and preeclampsia [21-26]. Some culprit mechanisms include low glomerular filtration rate, renal vasoconstriction, alcohol use, ischemic events, oxidative stress [27]. Besides, an independent association was found between uricacid levels and histology of non-alcoholic fatty liver disease [28]. Inthis context, some studies were performed handling the association between uricacid levels and hepatitis C infection [19,29,30]. Grassi et.al. showed that steatosis was found in 66,1% of CHC patients and that steatosis is well correlated with uric acid, body mass index and GGT levels [29]. In a recentstudy, it was noted that steatosis was more severe if hyperuricemia was detected (OR = 3,176) and that hyperuricemia frequency was markedly high if steatosis existed (OR = 2,751). A significant association was also found between severity of steatosis and uricacid levels, body mass index, triglycerides, HOMA-IR score, genotype 3 infection and necroinflammatory activity in the same study. In parallel with the literature, although lack in numbers, we found a significant correlation between steatosis and uricacid levels as the greater degree

Insulin (µU/mL)	18,57 ± 14,90 (13,70; 2,0-88,2)
HOMA-IR	5,33 ± 5,59 (3,42; 0,40-32,60)
UricAcid –(mg/dL)	4,99 ± 1,55 (4,80; 2,1-10,9)
Diabetes Mellitus (Yes %/ No %)	39 (23,6) /126 (76,4)
Arterial Hypertension (Yes %/ No %)	38 (23)/127 (77)
Metabolic Syndrome (Yes %/ No %)	36 (21,8)/129(78,2)
Hyperuricemia (Yes %/ No %)	23/142
Viral genotype (1a /1b)	11/154
Log10 HCV-RNA	5,71 ± 0,85 (5,74; 3,11-7,54)
Rapid Virologic Response	48/117
Early Virologic Response	94/71
Histology (*n* = 150)	
Degree of Steatosis	n (%)
1 (5-33 %)	111 (74)
2 (> 33-66%)	24 (16)
3 (> 66%)	15 (10)
Histologic Activity Index	n (%)
0 (0)	46 (30,7)
1 (1-8)	67 (44,7)
2 (9-18)	37 (24,7)
Fibrosis Stage	n (%)
0 (0)	14 (9,3)
1 (1-2)	53 (35,3)
2 (3-4)	43 (28,7)
3 (5-6)	40 (26,7)

*Anova test; Pearsonchi-square; Others: Kruskall-Wallis.
*Mean ± Standard Deviation (median; minimum-maximum)
AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: γ-Glutamyl Transpeptidase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HbA1C: Hemoglobin A1c

Table 3a: Associations between degree of steatosis and some parameters.

	Group 0-1	Group 0-2	Group 1-2
Body Mass Index (kg/m²)	0.237	0.173	0.757
WaistCircumference (cm)	0.259	0.006	0.356
UricAcid (mg/dL)	0.044	0.018	0.414
Hyperuricemia (mg/dL)	0.031	0.019	0.707

Table 3b: Regression analysis between uric acid and other parameters.

	Uric Acid	
	R	***p***
Age (years)	0,148	0,068
Body Mass Index (kg/m²)	0,213	0,009
WaistCircumference (cm)	0,228	0,020
Aspartate Aminotransferase-IU/L	-0,052	0,528
AlanineAminotransferase-IU/L	-0,010	0,907
ɣ-glutamyltranspeptidase-IU/L	0,127	0,119
Cholesterol-mg/dL	-0,028	0,730
Triglyceride-mg/dL	0,170	0,036
LDL-Cholesterol-mg/dL	0,002	0,984
HDL-Cholesterol-mg/dL	-0,277	0,001
Blood Glucose-mg/dL	-0,124	0,128
Insulin-µU/mL	0,016	0,852
HOMA	-0,041	0,629
Log10 HCV-RNA	0,060	0,465
Platelet-microL	-0,019	0,812
Steatosis Degree	0,295	<0,001
Histolojic Activity Index	0,168	0,049
Fibrosis	0,038	0,657

of steatosis the greater the number of hyperuricemic patients [31,32]. The reason of this discrepancy might be our group to be composed of genotype 1 patients only, high number of overweight and obese patients or paucity of patients withhigh-grade steatosis. On the otherhand, adiponectin levels were found low in CHC patients [33]. Besides, in patients withnon-alcoholic fatty liver disease, uricacid was found high while adiponectin was low [28]. This discrepancy may be related to metabolic pathway in CHC patients to be different.

Association between uric acid levels and metabolic syndrome has been shown [34]. High uric acid levels seen in patients with metabolic syndrome may cause hyperinsulinemia. Besides, hyperuricemia usually precedes hyperinsulinemia, obesity and diabete mellitus [27]. There are a few theories about this; first, hyperuricemia may cause metabolic syndrome by endothelial dysfunction [35]; second, uric acid may cause metabolic syndrome by making some inflammatory and oxidative alterations on adipocytes [36]. There exists very few data on uric acid levels and metabolic factors in CHC patients in literature. Inthis study, being different than others, frequency of metabolic syndrome and arterial hypertension was higher in hyper uricemic group. However, no significant difference wasn oted between hyperuricemic and normouricemic CHC patients in terms of insulin, glucoseand HOMA-IR scores. Thi may be related to different metabolic pathways take place in development of metabolic syndrome in hepatitis C patients. Molecular studies are required to enlighten thisissue.

Table 4: Uni and multivariate comparisons between patients with and without hyperuricemia.

Variable	Hyperuricemia None (*n* = 117)	Hyperuricemia Yes (*n* = 20)	Univariate Analysis (*p*)	Multivariate Analysis (OR %95 CI)	*P*
Age (years)				1,015	
	53,29 ± 11,3 (56)*	57 ± 10,9 (57)	0,163	(0,959-1,075) 1,063	0,610
Body Mass Index (kg/m²)	27,18 ± 4,58 (26,6)	28,65 ± 3,29 (28,4)	0,045	(0,947-1,193)	0,300
Body Mass Index (kg/m²)			0,114		
< 25	38	2			
25-29,9	52	11			
≥ 30	27	7			
Waist Circumference (cm)	98,18 ± 5,85 (98)	101,19 ± 7,51 (100)	0,115		
AST (IU/L)	60,66 ± 53,94 (47)	55,45 ± 24,09 (55)	0,604		
ALT (IU/L)	69,66 ± 53,09 (54)	77,35 ± 45,63 (74)	0,216		
GGT (IU/L)	75,47 ± 73,53 (46)	69,80 ± 43,75 (57)	0,367		
Total Cholesterol (mg/dL)	157,32 ± 35,14 (157)	165,95 ± 30,55 (166)	0,304		
Triglyceride (mg/dL)	113,62 ± 64,09 (96)	125,55 ± 34,25 (122)	0,028	1,002 (0,993-1,012)	0,616
LDL-Cholesterol (mg/dL)	91,89 ± 35,09 (90)	98,75 ± 29,92 (89)	0,387		
HDL–Cholesterol				0,998	
(mg/dL)	45,52 ± 15,36 (44)	42,30 ± 11,51 (41)	0,421	(0,952-1,047)	0,949
Fasting Blood Glucose (mg/dL)	111,06 ± 37,1 (98)	98 ± 14,2 (97)	0,369		
Insulin (µU/mL)	17,94 ± 14,44 (13,6)	23,39 ± 17,67 17,9)	0,151		
HOMA-IR				0,988	
	5,22 ± 5,36 (3,42)	5,81 ± 5,18 (4,78)	0,437	(0,885-1,103)	0,832
Platelet-microL	209,3 ± 75,4 (198)	181,2 ± 58,5 (182,5)	0,115		
Log10_HCVRNA	5,72 ± 0,73 (5,73)	5,90 ± 0,91 (6,1)	0,321		
Diabetes Mellitus (Yes/No)	34/83	2/18	0,074	2,383	
Arterial Hypertension				(0,453-12,542)	0,306
(Yes/No)	27/90	9/11	0,040		
Metabolic Syndrome				1,162	
(Yes/No)	23/94	8/12	0,045	(0,177-7,625)	0,876
Response (SVR/NonSVR)	65/52	10/10	0,645		
Histology					
SteatosisDegree			0,007	2,412	
				(0,462-12,599)	0,297
1 (5-33 %)	91	9			
2 (> 33-66%)	17	6			
3 (> 66%)	9	5			
Histolojic Activity				2,779	
Index			0,166	(0,775-9,961)	0,117
0 (0)	37	6			
1 (1-8)	55	6			
2 (9-18)	25	8			
Fibrosis				0,676	
			0,235	(0,180-2,536)	0,561
0 (0)	14	0			
1 (1-2)	42	9			
2 (3-4)	34	4			
3 (5-6)	27	7			

*Mean ± Standard Deviation (median) **Student t Test Others: Mann Whitney u Test HOSMER-Lemeshow Test : P = 0,136 OR %95 CI: Odd'sratio, %95 ConfidenceInterval.

AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: γ- glutamyl Transpeptidase

It has beennoted in literature that many factors including age, viralload, body mass index and insulin resistance may play a role in progression of fibrosis in patients with CHC [37]. However, studies handling association between uricacid and fibrosis are lacking. In a study conducted by Afzali et.al., a significant association was found between uric acid levels and cirrhosis in chronic liver patients [38]. However, Petta et.al did not find any relation between uric acid and fibrosis in CHC patients [30]. However, the results were conflicting. In a large meta-analysis involving a total of five observational studies, no significant protective role of hyperuricemia against the development of advanced liver fibrosis in NAFLD patients was observed [39]. Consistent with these results, we did not note any association between uricacid levels and fibrosis plus histologicactivityindex. This may be related to abundance of factor splaying a role in development of fibrosis in hepatitis C patients [40]. Sustained virologic response can be achieved in more than 50% of patientswith PEG- INF plus ribavirin therapy in CHC. Treatmen tsuccess can be influenced by numerous factors including genotype, vira lload, age, gender, weight, insulin resistance and metabolic syndrome [41,42]. Petta, et al. [30] could not find any relation between uricacid levels and sustained virologic response rates. We achieved a SVR rate of 55,2%. Similar to theliterature, no significant difference was noted between hyperuricemic and normouricemic patients in terms of SVR rates. When compared SVR tonon-SVR group, no significant difference was shown in uric acid levels. Inparallel with thestudy of Petta et.al., although low subject number, it can be inferred that uricacid level has no influence on therapy success in CHC patients. How can this be explained?

Infected cells ar ecleared by Th-1 cell immuneresponse in CHC infection [43]. Uric acid may prevent cell damage by stimulating nitric acid synthase enzyme [44,45]. Besides, interferon mayal so stimulate nitric acid synthase enzyme [46].

High uric acid levels may protect infected cell against Th-1 cell immune response. In opposite, low serum uric acid levels may cause a more potent Th-1 immune response against infected cells [19]. A third hypothesis to these twois the TNF-alfa synthesis with purine pathway. Schulz et.al. reported a positive correlation between TNF-alfa and uricacid levels [47]. High TNF-alfa levels lower success rates of antiviraltherapy [48]. Despite these theories, no sufficient clarification has been documented regarding the relation between uricacid levels and therapy response in literature todate. Differences in host immune response such as IL28b genetic polymorphism may clarify this. Further multi-center studies handling IL28 genetic polymorphism including HCV patients with different genotype are needed.

CONCLUSION

There has been found a significant association between uric acid levels and steatosis in CHC patients. This study did not revealany influence of uricacid level on success of therapy. Furthermulti-center studies are required to clarify thi smetabolic chaos.

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