Research Article

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

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therapy may come up owing to side effects in 10-20% of cases [15] and hypothyroidism may also be seen [14]. Early discontinuation of psychosis, convulsions, auto immune reactions, hyperthyroidism, leucopenia and thrombocytopenia. Although less frequently; acute of HCV is thought to be 20-39. The majority of CHC cases are [5,6]. As similar to other data in our country, GT1 was 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% [3,9]. HCV is responsible for 20% of acute anicteric and asymptomatic [3,9]. HCV is responsible for 20% of acute viral hepatitis, 40% of viral hepatitis ending with cirrhosis, 60% of Hepato Cellular Cancer (HCC) and 30% of cases requiring liver transplantation in developed countries [10]. It was interferon mono therapy that was the first agent 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 was limited due to fast clearance and short half-life. Thus, pegylated forms were developed to extend the short half-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-like symptoms, fatigue, hairloss, anemia, leukopenia and thrombocytopenia. Although less frequently; acute psychosisis, 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 and 72 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: poor follow-up, chronic renal failure, 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).

Clinical and laboratory assessments
Patients’ records including body weight, body mass index, waist circumference, uric acid, 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 Ishak system. Steatosis was defined as percentage of hepatocytes including fat droplets. Steatosis

INTRODUCTION
It is 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% [3,9]. HCV is responsible for 20% of acute viral hepatitis, 40% of viral hepatitis ending with cirrhosis, 60% of Hepato Cellular Cancer (HCC) and 30% of cases requiring liver transplantation in developed countries [10]. It was interferon mono therapy that was the first agent 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 was limited due to fast clearance and short half-life. Thus, pegylated forms were developed to extend the short half-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-like symptoms, fatigue, hairloss, anemia, leukopenia and thrombocytopenia. Although less frequently; acute psychosisis, 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]

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Abstract

**Introduction:** It was aimed in this study to evaluate the influence of uric acid levels on pegylated-interferon alpha (PEG-IFN-a) 2a/2b plus ribavirin therapy in patients with chronic hepatitis 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 uric acid and HCV-RNA (0, 12, 24, 48 and 72 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 owing to lack of uric acid levels and/or liver biopsies. Of the 137 included, 117 had no hyperuricemia while 20 did (cut-off levels were 7 and 6 mg/dL in males and females, respectively). In univariate analyses, no statistically significant association was established between hyperuricemia and age, waist circumference, HOMA-IR score, sustained virologic response, fibrosis and histologic activity index (p values were 0.61; 0.115; 0.437; 0.645; 0.235 and 0.166; respectively). However, significant association was found between hyperuricemia and body mass index, hypertension, existence of metabolic syndrome and grade of steatosis (p values were 0.045; 0.04; 0.045; 0.007; respectively). No significant relevance was noted between hyperuricemia and the parameters in multivariate analyses.

**Conclusion:** There has been detected a significant association between hyperuricemia and steatosis in patients with chronic hepatitis C. However, no influence on therapy has been found with regard to uric acid levels. Multicenter studies are required to enlighten the smetabolic chaos.

**Keywords:** Chronic hepatitis C; Uric acid; Steatosis
was stratified as “none”, “mild”, “mild to moderate” and “severe” corresponding to less than 5%, between 5-33%, 33-66% and more than 66%; respectively.

**Antiviral therapy schedule**

Patients administered PEG-IFN 2a (Pegasys; Roche, Basel, Switzerland) as 180 mcg/week and ribavirin (1000 mg/day for those with a body weight of less than 75 kg and 1200 mg/day for those more than 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 and chi-square tests 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 meaning “not severe (G0-G2)” and “severe (G3)”, respectively. It was “necroinflammatory activity” variable was “hyperuricemia” entered as 0 or 1 corresponding to “no” and “yes”, respectively. It was “necroinflammatory activity” the dependent variable in the second model which was entered as 0 or 1 corresponding to “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 was entered 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 mass index, ALT, thrombocyte, total cholesterol, LDL, HDL, triglycerides, glucose, insulin, HOMA-IR score, arterial hypertension, diabetes mellitus, creatinine, eGFR (glomerular filtration rate – assessed in hyperuricemia model only), HCV-RNA (denoted by Log10), viral genotype, uric acid levels, hyperuricemia, and steatosis, necroinflammatory activity and fibrosis.

HOMA-IR score, glucose, insulin, uric acid levels along with hyperuricemia were not included in the same model with ALT and necroinflammatory activity to avoid linear relationship effect. Regression-analyses were conducted using sub-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 the patients were normal weight while 44.2% (n = 73) were overweight and 27.3% (n = 45) were obese. 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 vast majority. It was genotype 1b the responsible agent in 154 (93.3%) patients while genotype 1a 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 (24.7%). Stage of fibrosis was 0 in 14 (9.3%), 1 in 53 (35.3%), 2 in 43 (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 waist circumference, uric acid level and hyperuricemia were found to be statistically related to degree of steatosis when it was divided into three as “none” (steatosis in less than 5% of hepatocytes), “mild” (steatosis in between 5-30% of hepatocytes) and “severe” (steatosis in more than 30% of hepatocytes) (p values were 0.005, 0.002, 0.007; respectively).

No significant association was found between fibrosis and uric acid 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, hyperuricemia 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 uric acid levels and/or liver biopsies. Of the 137 included, 117 had no hyperuricemia while 20 did (cut-off levels were 7 and 6 mg/dL in males and female, respectively). In uni-variate analyses, no statistically significant association 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;...
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                   | 0.715   |
| 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 < 25      | 34                  | 4                   | 3                     | 0.406   |
| 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   |
| Uric Acid-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*  |
| Diabetes Mellitus (Yes / No)     | 25 /86              | 7 /17               | 5 /10                 | 0.565*  |
| Arterial Hypertension (Yes / No ) | 23 /88             | 8 /16               | 4 /11                 | 0.395   |
| Metabolic Syndrome (Yes / No)   | 21 /90              | 6 /18               | 6 /9                  | 0.168   |
| Hyperuricemia (Yes %/ No)       | 9 /91               | 6 /17               | 5 /9                  | 0.007*  |
| Treatment (SVR/NonSVR)          | 66 /45              | 10 /14              | 7 /8                  | 0.219   |
| Viral genotype (1a /1b)         | 19 /64              | 21 /52              | 21 /38                | 0.253*  |
| Log HCV-RNA                     | 5.74 ± 0.88         | 5.47 ± 0.96         | 5.93 ± 0.81           | 0.067*  |
| Histology                       | 207.3 ± 71.8        | 196.2 ± 91.6        | 199.9 ± 57.6          | 0.753*  |

DISCUSSION

Hepatitis C infection is 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 uric acid levels and histology of non-alcoholic fatty liver disease [28]. In this context, some studies were performed handling the association between uric acid 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 recent study, 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 uric acid 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 uric acid levels as the greater degree 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 with high-grade steatosis. On the otherhand, adiponectin levels were found low in CHC patients [33]. Besides, in patients with non-alcoholic fatty liver disease, uric acid 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 diabetes mellitus [27]. There are a few theories about this; first, hyperuricemia may cause metabolic syndrome by making some inflammatory events, oxidative stress [27]; second, uric acid may cause metabolic syndrome by endothelial dysfunction [35]; third, 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. In this study, being different than others, frequency of metabolic syndrome and arterial hypertension was higher in hyperuricemic group. However, no significant difference was noted between hyperuricemic and normouricemic CHC patients in terms of insulin, glucose and HOMA-IR scores. This may be related to different metabolic pathways take place in development of metabolic syndrome in hepatitis C patients. Molecular studies are required to enlighten this issue.

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

| Parameter                        | Group 0-1 | Group 0-2 | Group 1-2 |
|----------------------------------|-----------|-----------|-----------|
| Body Mass Index (kg/m²)          | 0.237     | 0.173     | 0.757     |
| Waist Circumference (cm)         | 0.259     | 0.006     | 0.356     |
| Uric Acid (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.

| Parameter                  | R       | p       |
|----------------------------|---------|---------|
| Age (years)                | 0.148   | 0.068   |
| Body Mass Index (kg/m²)    | 0.213   | 0.009   |
| Waist Circumference (cm)   | 0.228   | 0.020   |
| Aspartate Aminotransferase I/U/L | -0.052 | 0.528 |
| Alanine Aminotransferase I/U/L | -0.010 | 0.907 |
| γ-glutamyltranspeptidase I/U/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  |
| Histologic Activity Index  | 0.168   | 0.049   |
| Fibrosis                   | 0.038   | 0.657   |

*Anova test; Pearsonchi-square; Others: Kruskall-Wallis.
*Mean ± Standard Deviation (median; minimum-maximum)

AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: γ-glutamyltranspeptidase; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; HbA1C: Hemoglobin A1C

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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)**            |                               |                            |                         |                                  |       |
|                            | 53.29 ± 11.3 (56)*            | 57 ± 10.9 (57)             | 0.163                   | (0.959-1.075) 1.063              | 0.610 |
| **Body Mass Index (kg/m²)**|                               |                            |                         |                                  |       |
| < 25                       | 27.18 ± 4.56 (28.6)           | 28.65 ± 3.29 (28.4)        | 0.045                   | (0.947-1.193)                    | 0.300 |
| 25-29.9                    |                               |                            |                         |                                  |       |
| ≥ 30                       | 27                            | 2                          | 0.114                   |                                  |       |
| **Waist Circumference (cm)**|                               |                            |                         |                                  |       |
| < 98                       | 98.18 ± 5.85 (98)             | 101.19 ± 7.51 (100)        | 0.115                   |                                  |       |
| **AST (IU/L)**             |                               |                            |                         |                                  |       |
| < 47                       | 60.66 ± 53.94 (47)            | 55.45 ± 24.09 (55)         | 0.604                   |                                  |       |
| **ALT (IU/L)**             |                               |                            |                         |                                  |       |
| < 47                       | 69.66 ± 53.09 (54)            | 77.35 ± 45.63 (74)         | 0.216                   |                                  |       |
| **GGT (IU/L)**             |                               |                            |                         |                                  |       |
| < 46                       | 75.47 ± 73.53 (46)            | 69.80 ± 43.75 (57)         | 0.367                   |                                  |       |
| **Total Cholesterol (mg/dL)**|                               |                            |                         |                                  |       |
| < 166                      | 157.32 ± 35.14 (157)          | 165.95 ± 30.55 (166)       | 0.304                   |                                  |       |
| **Triglyceride (mg/dL)**   |                               |                            |                         |                                  |       |
| < 122                      | 113.62 ± 64.09 (96)           | 125.55 ± 34.25 (122)       | 0.028                   | 1.002 (0.993-1.012)              | 0.616 |
| **LDL-Cholesterol (mg/dL)**|                               |                            |                         |                                  |       |
| < 90                       | 91.89 ± 35.09 (90)            | 98.75 ± 29.92 (89)         | 0.387                   |                                  |       |
| **HDL-Cholesterol**        |                               |                            |                         |                                  | 0.998 |
| < 44                       | 45.52 ± 15.36 (44)            | 42.30 ± 11.51 (41)         | 0.421                   | (0.952-1.047)                    | 0.949 |
| **Fasting Blood Glucose (mg/dL)** |                           |                            |                         |                                  |       |
| < 100                      | 111.06 ± 37.1 (98)            | 98 ± 14.2 (97)             | 0.369                   |                                  |       |
| **Insulin (μU/mL)**        |                               |                            |                         |                                  |       |
| < 11.6                     | 17.94 ± 14.44 (13.6)          | 23.39 ± 17.67 (17.9)       | 0.151                   |                                  |       |
| **HOMA-IR**                |                               |                            |                         |                                  | 0.988 |
| < 1.2                      | 5.22 ± 5.36 (3.42)            | 5.81 ± 5.18 (4.78)         | 0.437                   | (0.885-1.103)                    | 0.832 |
| **Platelet-microL**        |                               |                            |                         |                                  |       |
| < 182.5                    | 209.3 ± 75.4 (198)            | 181.2 ± 58.5 (182.5)       | 0.115                   |                                  |       |
| **Log10_HCVRNA**           |                               |                            |                         |                                  |       |
| < 0.73                     | 5.72 ± 0.73 (5.73)            | 5.90 ± 0.91 (6.1)          | 0.321                   |                                  |       |
| **Diabetes Mellitus (Yes/No )** |                           |                            |                         |                                  |       |
| Yes                        | 34/83                         | 2/18                       | 0.074                   | 2.383                           |       |
| **Arterial Hypertension**  |                               |                            |                         |                                  |       |
| Yes                        | 27/90                         | 9/11                       | 0.040                   | (0.453-12.542)                   | 0.306 |
| **Metabolic Syndrome**     |                               |                            |                         |                                  | 1.162 |
| Yes                        | 23/94                         | 8/12                       | 0.045                   | (0.177-7.625)                    | 0.876 |
| **Response (SVR/NonSVR)**  |                               |                            |                         |                                  | 0.645 |
| **Histology**              |                               |                            |                         |                                  |       |
| SteatosisDegree            |                               |                            |                         |                                  |       |
| 1 (5-33 %)                 | 91                            | 9                          |                         |                                  |       |
| 2 (> 33-66%)               | 17                            | 6                          |                         |                                  |       |
| 3 (> 68%)                  | 9                             | 5                          |                         |                                  |       |
| Histological Activity      |                               |                            |                         |                                  |       |
| Index                      | 0.007                         |                            |                         | 2.412                           |       |
| 0 (0)                      | 37                            | 6                          |                         |                                  |       |
| 1 (1-6)                    | 55                            | 6                          |                         |                                  |       |
| 2 (9-18)                   | 25                            | 8                          |                         |                                  |       |
| Fibrosis                   |                               |                            |                         |                                  | 0.876 |
| 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 Confidence Interval

AST: Aspartate Amino Transferase; ALT: Alanine Amino Transferase; GGT: γ- glutamyl Transpeptidase
It has been noted in literature that many factors including age, viral load, body mass index and insulin resistance may play a role in progression of fibrosis in patients with CHC [37]. However, studies handling association between uric acid and fibrosis are lacking. In a study conducted by Afrali 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 uric acid levels and fibrosis plus histologic activity index. This may be related to abundance of factor playing a role in development of fibrosis in hepatitis C patients [40]. Sustained virologic response can be achieved in more than 50% of patients with PEG-IFN plus ribavirin therapy in CHC. Treatment success can be influenced by numerous factors including genotype, viral load, age, gender, weight, insulin resistance and metabolic syndrome [41,42]. Petta, et al. [30] could not find any relation between uric acid levels and sustained virologic response rates. We achieved a SVR rate of 55.2%. Similar to the literature, 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. In parallel with the study of Petta et al., although low subject number, it can be inferred that uric acid level has no influence on therapy success in CHC patients. How can this be explained?

Infected cells are cycled by Th1 cell immunoreponse in CHC infection [43]. Uric acid may prevent cell damage by stimulating nitric acid synthase enzyme [44,45]. Besides, interferon may stimulate nitric acid synthase enzyme [46].

High uric acid levels may protect infected cell against Th1 cell immune response. In opposite, low serum uric acid levels may cause a more potent Th1 immune response against infected cells [19]. A third hypothesis to these twoos the TNF-alfa synthesis with purine pathway. Schulz et al. reported a positive correlation between TNF-alfa and uric acid levels [47]. High TNF-alfa levels lower success rates of antiviral therapy [48]. Despite these theories, no sufficient clarification has been documented regarding the relation between uric acid levels and therapy response in literature to date. 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 reveal any influence of uric acid level on success of therapy. Further multi-center studies are required to clarify the smetabolic chaos.

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