

Research Article



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Influence of pegylated interferon and ribavirin on insulin resistance and metabolic factors in chronic hepatitis C

Kronik hepatit C’de pegile interferon ve ribavirinin insulin direnci ve metabolik faktörler üzerine etkisi

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Abstract

Background: In this study it was aimed to evaluate the effect of pegylated interferon alfa-2a/2b and ribavirin, which are used for treatment of chronic hepatitis C (CHC), on insulin resistance and metabolic factors.

Materials and methods: A total of 104 CHC patients aged 20–75 years with available serum insulin data at 0 and 48 weeks, and hepatitis C virus (HCV)-RNA data at 0, 12, 24, 48 and 72 weeks were included in the study. All clinical parameters were assessed according to the therapy response.

Results: Among 104 patients, sustained virologic response (SVR) was achieved in 55 cases. A statistically significant difference was noted between SVR and non-SVR groups regarding γ -glutamyltranspeptidase (GGT), insulin level plus

homeostasis model assessment (HOMA) score and insulin resistance at week 48, log HCV-RNA and stage of fibrosis.

Conclusion: Insulin resistance is accepted to have a negative effect on SVR. Insulin resistance may improve once SVR is achieved. Presence of IR at week 48 has been found associated with SVR. In this context, it can be advocated that insulin resistance at week 48 may be a predictive factor for prediction of SVR at week 72.

Keywords: Chronic hepatitis C; HOMA; Insulin resistance.

Öz

Amaç: Bu çalışmada, kronik hepatit C tedavisinde kullanılan pegile interferon alfa 2a/2b ve ribavirinin insulin direnci ve metabolik faktörler üzerine etkileri incelenmiştir.

Materyal ve Metotlar: Çalışmaya yaşları 20 ile 75 arasında değişen, 0 ve 48. haftalara ait insulin değerleri ile birlikte 0, 12, 24, 48 ve 72. haftalardaki HCV-RNA değerleri mevcut olan toplam 104 kronik hepatit C hastası dahil edilmiştir. Tüm klinik parametreler tedavi yanıtına göre değerlendirilmiştir.

Bulgular: Kalıcı virolojik yanıt (KVY) 104 hastanın 55’inde elde edilebilmiştir. KVY elde edilen ve edilemeyen gruplar arasında GGT, HCV-RNA düzeyi, fibrozis evresi ve 48. haftadaki insulin düzeyi, insulin direnci ve HOMA skoru arasında istatistiksel olarak anlamlı ilişki tespit edilmiştir.

Sonuç: İnsulin direncinin KVY üzerinde negatif etkisi olduğu kabul edilmektedir. SVR elde edildiğinde ise insulin direnci düzelebilmektedir. İnsulin direncinin 48. haftadaki varlığı, KVY ile ilişkili bulunmuştur. Bu bağlamda; 48. haftada mevcut olan insulin direncinin, 72. haftadaki KVY konusunda öngördürücü olacağı söylenebilir.

Anahtar kelimeler: İnsulin direnci; Kronik hepatit C; HOMA.

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Introduction

As reported in the literature, approximately 3% of world population – which equals to 170–200 million people – is infected with hepatitis C virus (HCV) [1]. HCV is responsible for the indicated percentages of cases with acute viral hepatitis (20%), chronic viral hepatitis (70%), viral hepatitis ending with cirrhosis (40%), hepatocellular cancer (HCC) (60%) and cases requiring liver transplantation (30%) in developed countries [1–4].

Interferon was the first agent used in the monotherapy of chronic hepatitis C (CHC) in 1990. In 1998, interferon and ribavirin combination was shown to be more effective than interferon alone. Efficacy of interferon alpha was limited due to its fast clearance and short half-life. Thus, pegylated forms were developed to extend its short half-life. Following head-to-head comparisons, pegylated interferon (PEG-IFN) and ribavirin combination started to be the standard therapy. Response rates of 50–60% and 80–90% were achieved with this therapy in patients with genotype 1 and also genotype 2 and 3, respectively [5–7]. This combination therapy may cause flu-like symptoms, fatigue, hair loss, anemia, leucopenia and thrombocytopenia. Although less frequently; acute psychosis, convulsions, autoimmune reactions, hyperthyroidism and hypothyroidism may also be seen [8]. Early discontinuation of therapy may come up owing to side effects in 10–20% of the cases [9].

Hepatitis C virus adversely affects metabolic functions, primarily lipid metabolism [10]. It has also been shown that insulin resistance develops during treatment [11]. At the same time, the development of insulin resistance has been shown to have an adverse effect on sustained virologic response (SVR). Although there is a lot of work on the effects of combined treatment, it is not clear which patients can achieve SVR. In this study, we aimed to determine whether changes in insulin resistance at weeks 0 and 48 could predict SVR.

Materials and methods

A total of 104 CHC patients aged 20–75 years with available serum insulin (at 0 and 48 weeks) and HCV-RNA (at 0, 12, 24, 48 and 72 weeks) levels who applied to Izmir Atatürk Research and Training Hospital, Department of Gastroenterology between 01 January 2005 and 01 November 2012 were included in the study. Local Ethics Committee approval was taken. These parameters were assessed according to the groups categorized based on response to therapy (SVR, relapse and non-responders). Inclusion and exclusion criteria were as follows:

- Inclusion criteria: having diagnosed with CHC, completion of therapy
- Exclusion criteria: poor follow-up, diabetes mellitus, chronic renal failure, any solid organ or hematologic malignancy, HIV positivity, and pregnancy.

Clinical and laboratory assessments

For biochemical analyses, all the serum samples were drawn into gel separator tubes (Vacutainer SST, Beckton Dickinson, France) between 08.00 and 08.30 a.m. after a 12-h fasting. The blood samples were allowed to clot and then centrifuged at 2500 RCF for 10 min at room temperature. Routine biochemical measurements were performed in the with enzymatic method on the Abbott Architect c16000 Autoanalyzer (Abbott Diagnostics, Abbott Park, IL, USA). Insulin concentrations were measured by the electrochemiluminescence immunoassay (ECLIA) on an Elecsys E-170 analyzer (Roche Diagnostics Ltd., Basel, Switzerland). Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald's formula. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR), using the formula: fasting insulin ($\mu\text{IU/mL}$) $\times$ fasting glucose (mg/dL)/405.

Patients' records concerning body weight, body mass index (BMI), waist circumference, uric acid, glucose, total cholesterol, triglyceride, high-density lipoprotein (HDL) and LDL cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltranspeptidase (GGT), creatinine, insulin levels, hematologic parameters, liver biopsy and upper abdominal ultrasonography reports were obtained via patient recording system. Statistical analyses were performed.

Histologic assessment

Pathologic samples were assessed by pathologists blind both to patients and their histories. Adequate sample was defined as a biopsy material of more than 15 mm or those obtained from at least 10 complete portal fields. Samples were classified with respect to Ishak grading system. Steatosis was defined, and stratified based on the percentage of hepatocytes with fat droplets as: none: <5%, mild 5–33%, mild to moderate 33–66%, and severe >66%.

Antiviral therapy schedule

Patients were administered PEG-IFN-2a (Pegasys; Roche, Basel, Switzerland) as 180 $\mu\text{g/week}$ and ribavirin

(1000 mg/day, and 1200 mg/day for those with a body weight <75 kg, and >75 kg, respectively) during 48 weeks. Treatments were stopped if “virologic response” defined as undetectable HCV-RNA via PCR at week 24 was achieved.

Statistical methods

Continuous variables were denoted as mean $\pm$ standard deviation, while categorical ones as frequencies and percentages. ANOVA, t-test and χ^2 tests were used. Multiple logistic regression analysis was used to evaluate the effect of treatment on SVR. Age, BMI, insulin resistance (IR) at week 48, log HCV-RNA and fibrosis were used in this model. Presence of IR at week 48 and fibrosis were used as categorical variables. Hosmer-Lemeshow test was used for model consistency. Only one of the variables that are correlated with each other was included in the model. All analyses were performed in “Statistical Packages for the Social Sciences – SPSS 13.0 version”.

Results

Records of 182 patients who had successfully completed therapy were assessed. Patients with type II diabetes ($n=39$), genotype 2/3 HCV ($n=8$), missing data concerning insulin levels at week 48 ($n=17$), and those undergoing antiviral therapy ($n=14$) were excluded from the study. A total of 104 genotype I CHC patients including 93 with available liver biopsy results who successfully completed therapy were included in the study.

Basic demographic data of the patients are shown in Table 1. Patient population consisted of 40 male and 64 female patients with an overall mean age of 52.1 ± 11.8 years. Twenty-eight (26.9%) patients had normal body weight, while the remaining patients were overweight ($n=46$: 44.2%) or obese ($n=30$: 28.8%). Cholesterol parameters were within normal limits. Mean plasma glucose value at week 0 was 95.24 ± 11.83 mg/dL, while it was 92.84 ± 12.68 mg/dL at week 48. Insulin levels were 16.17 ± 11.45 mIU/L and 16.02 ± 16.27 mIU/L at weeks 0 and 48, respectively. Also, mean HOMA-IR scores were 3.81 ± 2.69 and 3.84 ± 4.45 – which were quite high – at weeks 0 and 48, respectively. IR was 53.9% ($n=56$) and 44.2% ($n=46$) at weeks 0, and 48, respectively. Arterial hypertension and metabolic syndrome were not noted in large majority of patients. Genotype 1b was responsible for in 98 (94.2%) patients while genotype 1a in 6 (5.8%).

Table 1: Demographic data of CHC patients.

Variable	HCV (n = 104)
Gender (M/F)	40/64
Age (years)	52.1 ± 11.8 (55; 22–71) ^a
Body mass index (kg/m ²)	27.93 ± 4.86 (27.1; 17.6–42.2) ^a
Body mass index	
<25	28 (26.9%)
25–29.9	46 (44.2%)
>30	30 (28.8%)
Waist circumference (cm)	96.97 ± 11.96 (97; 73–130) ^a
AST (IU/L)	53.40 ± 30.82 (47; 17–214) ^a
ALT (IU/L)	65.51 ± 43.57 (53.5; 13–316) ^a
GGT (IU/L)	61.10 ± 57.17 (43.5; 10–301) ^a
Platelet counts ($\times 10^3/\mu\text{L}$)	208.5 ± 68.2 (201; 21–424) ^a
Triglyceride (mg/dL)	160.02 ± 32.75 (160; 94–246) ^a
Total cholesterol (mg/dL)	109.78 ± 52.50 (96; 23–400) ^a
LDL-cholesterol (mg/dL)	92.59 ± 34.33 (89; 22–220) ^a
HDL-cholesterol (mg/dL)	46.35 ± 14.71 (44.5; 16–106) ^a
Blood glucose on week 0 (mg/dL)	95.24 ± 11.83 (95; 68–125) ^a
Blood glucose on week 48 (mg/dL)	92.84 ± 12.68 (94.5; 71–142) ^a
Insulin on week 0 (pU/mL)	16.17 ± 11.45 (12.5; 2.0–52.2) ^a
Insulin on week 48 (pU/mL)	16.02 ± 16.27 (12.3; 2.0–131) ^a
HOMA-IR at week 0	3.81 ± 2.69 (3.09; 0.40–12.53) ^a
HOMA-IR at week 48	3.84 ± 4.45 (2.69; 0.37–38.18) ^a
Insulin resistance at week 0 (%)	56 (53.9%)
Insulin resistance at week 48 (%)	46 (44.2%)
Arterial hypertension (yes %/no %)	20 (19.2%)/84 (80.8%)
Metabolic syndrome (yes %/no %)	20 (19.2%)/84 (80.8%)
Viral genotype (1a/1b)	6/98
Rapid viral response (yes/no)	29/75
Early viral response (yes/no)	58/46
SVR/non-SVR	55/49
Grade of steatosis (n = 93)	n (%)
1 (5–33%)	70 (75.3)
2 (>33–66%)	15 (16.1)
3 (>66%)	8 (8.6)
Histologic activity index (n = 93)	n (%)
0 (0)	31 (33.3)
1 (1–8)	41 (44.1)
2 (9–18)	21 (22.6)
Stage of fibrosis (n = 93)	n (%)
0 (0)	10 (10.8)
1 (1–2)	33 (35.5)
2 (3–4)	26 (28.0)

^aMean $\pm$ standard deviation (median; minimum–maximum).

Among 93 patients who underwent liver biopsy; mild, moderate and severe steatosis was noted in 75.3%, 16.1% and 8.6% of the patients, respectively. Histologic activity index was 0 in 31 (33.3%), 1 in 41 (44.1%) and 2 in 21 (22.6%) patients. Fibrosis stage was 0 in 10 (10.8%), 1 in 33 (35.5%), 2 in 26 (28.2%) and 3 in 24 (25.8%) patients. Correlation between pre-, and post-treatment HOMA scores and metabolic factors are shown in Table 2. HOMA score at week 0 was found to be correlated with levels of triglyceride, GGT

Table 2: Correlation between HOMA and variables.

	HOMA-IR at week 0		HOMA-IR at week 48	
	r	p-Value	r	p-Value
Age (years)	0.164	0.096	0.314	0.001
Body mass index (kg/m ²)	0.084	0.397	0.113	0.254
Waist circumference (cm)	0.061	0.602	0.464	<0.001
AST (IU/L)	0.149	0.132	0.192	0.050
ALT (IU/L)	0.095	0.336	0.123	0.215
GGT (IU/L)	0.224	0.022	0.369	<0.001
Total cholesterol (mg/dL)	-0.068	0.496	-0.103	0.298
Triglyceride (mg/dL)	0.320	0.001	0.243	0.013
LDL-cholesterol (mg/dL)	-0.125	0.208	0.030	0.759
HDL-cholesterol (mg/dL)	-0.187	0.058	-0.200	0.042
Log10 HCV-RNA	-0.003	0.972	0.068	0.494
Platelet counts ($\times 10^3/\mu\text{L}$)	-0.153	0.121	-0.142	0.150
Grade of steatosis	-0.024	0.817	0.058	0.579

Significant p-values are marked in bold.

and stage of fibrosis ($p=0.022$, 0.001 , and 0.001 , respectively). HOMA score at week 48 was found to be correlated with age ($p=0.001$), waist circumference ($p<0.001$), levels of GGT ($p<0.001$), triglyceride ($p=0.013$), HDL-cholesterol ($p=0.042$) and stage of fibrosis ($p=0.002$).

Among a total of 104 patients, 55 were in SVR, and 49 in non-SVR group. HCV-RNA levels of non-SVR group were higher than those of SVR group. No significant relationship was found between SVR and non-SVR groups regarding gender, age, BMI, and levels of total cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol, fasting plasma glucose, insulin, HOMA score at week 0, platelet counts, arterial hypertension, grades of steatosis and histologic activity index in univariate analyses (Table 3). However, also in univariate analyses, statistically significant associations were noted between the two groups regarding GGT, insulin levels, and presence of IR at week 48, log HCV-RNA levels and stages of fibrosis ($p<0.05$). In the majority of non-SVR groups, stage 3–4 fibrosis was detected, while fibrosis was absent or low in the majority of cases with SVR (Figure 1). In multivariate analyses; log HCV-RNA, triglyceride levels, and presence of IR at week 48 had influence on SVR ($p<0.05$) while age, BMI and stage of fibrosis did not.

Discussion

IR is prevalently seen in CHC patients [1, 2]. Hepatic inflammation, activated inflammatory cytokines and molecules disrupting insulin and lipid stimulation are the

factors that cause IR in CHC patients, while weight gain and lack of exercise in general population [3].

Many studies are conducted on efficacy of HOMA score – a test that assesses beta cell secretion functions and IR by measuring fasting blood glucose and insulin levels easily particularly in wide patient populations – on CHC patients [12–14]. In the literature, frequency of IR in CHC patients is reported between 29% and 56% with respect to HOMA (scores between 2 and 3) values [1, 14, 15]. We – as many other researchers advocated – agreed on a HOMA score of ≥ 3 to indicate IR [12–17]. Similar to literature, we found HOMA score more than 3 in 53.9% of our patients.

Hepatosteatois, which is frequently seen in patients with CHC, has been reported to be an independent risk factor for the progression of the disease [17]. HCV core protein stimulates lipid peroxidation and production of reactive oxygen radicals. It also regulates secretion of VLDL, triglyceride and apolipoprotein B. So that HCV directly promotes hepatic steatosis. It has been shown in transgenic mice that IR occurred before onset of hepatic steatosis. Besides, it is advocated that hepatosteatois may stimulate IR [18–20]. Steatosis of grade II and III was detected in 24.7% of our patients. No difference in grade of steatosis was detected between SVR and non-SVR groups.

It has been shown that IR negatively affects antiviral therapy in genotype I, II and III CHC patients. IR promotes HCV replication by increasing hepatic fat accumulation. HCV replication alter response to antiviral therapy negatively. On the other side, HCV core protein regulates suppressor cytokine signaling (SOCS-3). SOCS-3 causes IR by easing proteosomal degradation of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2). It also deteriorates response to antiviral therapy by inhibiting interferon- α expression [20–23]. SVR could not be achieved in 49 (47.1%) patients. During pretreatment evaluation increased number of patients with high HOMA scores were detected in non-SVR compared to SVR group.

IR is one of important markers that decrease response to therapy [1, 24, 25]. Eslam et al. [19] found that genotype I CHC patients with a HOMA score of less than 2 had higher response rates [OR: 2, 16 95% CI: 1.51–3.08] [19]. In different studies, IR rates were found to change with regard to therapy and to get better as HCV infection resolved [19–25]. In our study, similar to the literature, approximately 15% of the patients with IR in SVR group had their IR resolved while no change was noted in IR rate in non-SVR group.

Association between IR and progression of fibrosis in CHC patients was also shown [26]. Hepatocytes have

Table 3: Comparison of uni- and multivariate analyses in SVR and non-SVR groups (13.7).

Variable	SVR (n=55)	Non-SVR (n=49)	p-Value	Multivariate analysis, OR (95% CI)	p-Value
Gender (M/F)	22/33	18/31	0.733		
Age (year)	50.2±13.2 (53)	54.2±9.8 (57)	0.133	0.988 (0.943–1.035)	
Body mass index (kg/m ²)	27.2±5.2 (26.6)	28.7±4.3 (28.4)	0.117	0.951 (0.859–1.051)	0.325
			0.277		
<25	18	10			
25–29.9	24	22			
>30	13	17			
Waist circumference (cm)	94.96±12.1 (96)	100±12.3 (98.5)	0.073		
AST (IU/L)	52.16±26.66 (46)	54.80±35.13 (47)	0.945		
ALT (IU/L)	67.75±38.26 (56)	63.00±49.14 (52)	0.278		
GGT (IU/L)	47.1±42.1 (38)	76.8±67.42 (60)	0.003		
T. Cholesterol (mg/dL)	161.5±32.1 (162)	158.7±33.7 (150)	0.625		
Triglyceride (mg/dL)	118.0±63.5 (103)	100.5±34.8 (95)	0.275	1.012 (1.001–1.023)	0.039
LDL (mg/dL)	92.42±30.39 (90)	92.78±38.60 (87)	0.958		
HDL (mg/dL)	45.58±14.27 (43)	47.20±15.29 (46)	0.379		
Glucose at week 0 (mg/dL)	94.73±10.74 (96)	95.82±13.03 (93)	0.642		
Insulin at week 0 (IU/L)	17.9±14.4 (13.6)	23.4±17.7 (17.9)	0.062		
Glucose at week 48 (mg/dL)	94.3±12.4 (94)	95.4±13.0 (96)	0.700		
Insulin at week 48 (IU/L)	13.5±17.7 (9.3)	18.9±14 (13.7)	0.003		
HOMA-IR at week 0	3.54±2.80 (2.59)	4.09±2.5 6 (3.43)	0.906		
HOMA-IR at week 48	3.29±5.12 (2.45)	4.44±3.49 (3.23)	0.003		
IR – at week 0, n (%)	26 (47.3)	28 (57.1)	0.315		
IR – at week 48, n (%)	18 (32.7)	28 (57.1)	0.012	0.281 (0.099–0.796)	0.017
Platelet counts (×10 ³ /μL)	214.7±72.7 (207)	201.7±62.7 (197)	0.333		
Genotype (1a/1b)	2/53	4/45	0.286		
Lg10 HCV RNA	5.65±0.99 (5.65)	5.98±0.64 (6.05)	0.045	0.455 (0.253–0.820)	0.009
Hypertension (yes/no)	8/47	12/37	0.199		
Metabolic syndrome (yes/no)	12/43	8/41	0.478		
Histologic evaluation	(n=49)	(n=44)			
Steatosis (grade)			0.266		
1 (5–33%)	41	29			
2 (>33–66%)	6	9			
3 (>66%)	3	5			
Histologic activity index			0.310		
0 (0)	18	13			
1 (1–8)	18	23			
2 (9–18)	13	8			
Fibrosis (stage)			0.038	0.366 (0.120–1.116)	0.077
0 (0)	8	2			
1 (1–2)	21	12			
2 (3–4)	9	17			
3 (5–6)	11	13			

Significant p-values are marked in bold.

crucial role in degradation of insulin. It was noted that – as the fibrosis progresses – insulin clearance diminished which resulted in high insulin levels [25]. On the other side, IR stimulates connective tissue growth factor by influencing hepatic stellate cells. This rise in growth factor production may induce progression of fibrosis by increasing the amount of extracellular matrix [23]. Besides, increase in the concentration of hepatic lipids

also promotes progression of fibrosis by increasing free oxygen radicals [17]. In conclusion, it can be inferred that insulin – by numerous ways – accelerates development of fibrosis and as a paradox, fibrosis leads to an increase in insulin levels by inhibiting its degradation. Indeed, 53.8% of our patients had high grade fibrosis. Patients with high grade fibrosis was more numerous in non-SVR group (p=0.038).

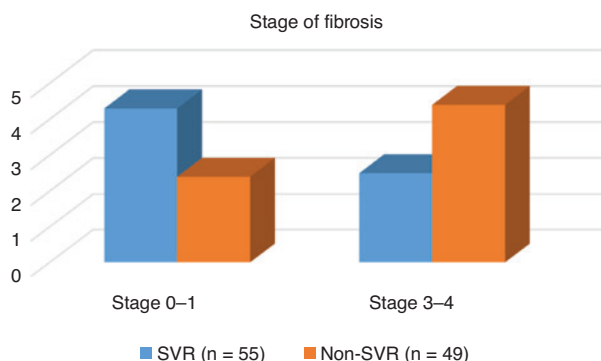


Figure 1: Comparison of fibrosis in SVR and non-SVR groups ($p = 0.038$).

Conclusion

IR is one of the factors that negatively affects SVR. IR may resolve as SVR is achieved. Although there is a lot of work related with the effects of IR on SVR, it is not clear which patients can achieve SVR. Presence of IR at week 48 has been found associated with SVR. In this context, it can be advocated that insulin resistance at week 48 may be a predictive factor for prediction of SVR at week 72. Thus, amelioration of IR detected before therapy at week 48 may predict SVR at week 72. Further multicenter studies with greater number of patients are needed to clarify this issue.

Abbreviations: BMI, Body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ -glutamyltranspeptidase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; metabolic syndrome, ATP III criteria are defined as follows: waist circumference >102 cm and >88 cm for male and female patients, respectively; blood pressure $>130/85$ mmHg or diagnosis of controlled hypertension under treatment; triglyceride >150 mg/dL; HDL <40 mg/dL and <50 mg/dL for male and female, respectively; fasting plasma glucose >100 mg/dL or diagnosis of controlled diabetes mellitus under treatment.

Conflict of interest statement: The authors declare no conflict of interest.

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