RESEARCH ARTICLE

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Assessment of the Effect of Psoriasis and Methotrexate Treatment on Liver Stiffness by ARFI Imaging

ABSTRACT

Objective: To investigate whether psoriasis and methotrexate used in its treatment cause liver fibrosis and eventually to evaluate the safety of methotrexate in treatment.

Methods: 44 cases were included in the study. Methotrexate-using (group 1, n=14) and methotrexate-not-using (group 2, n=13) psoriasis patients were compared retrospectively with a healthy control group (group 3, n=17) according to mean shear wave rates obtained from sonoelastographic examinations with Acoustic Radiation Force Impulse (ARFI) technique.

Results: Mean shear wave velocities were calculated as 2.57 ± 1.13 m/sec in the patients using methotrexate, 2.31 ± 1.16 m/sec in the patients who did not use methotrexate, and 1.56 ± 0.62 m/sec in the healthy control group. While the average shear wave velocity of the 3rd group was found to be significantly lower than that of the 1st and 2nd groups (p=0.032; p=0.012), no significant difference was observed between the 1st and 2nd groups (p=0.755).

Conclusions: Shear wave imaging with ARFI quantification findings revealed no evidence that methotrexate therapy is associated with liver fibrosis in psoriasis patients and we think that the increase in liver tissue stiffness in patients using methotrexate for psoriasis is secondary to the inflammatory process caused by psoriasis itself rather than methotrexate.

Keywords: ARFI, Methotrexate, Psoriasis, Shear Wave Elastography.

Psöriazis ve Metotreksat Tedavisinin Karaciğer Sertliğine Etkisinin ARFI Görüntüleme ile Değerlendirilmesi

ÖZET

Amaç: Psöriazisin ve tedavisinde kullanılan metotreksatın karaciğer fibrozisine neden olup olmadığını araştırmak ve böylelikle metotreksatın tedavideki güvenilirliğini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 44 olgu dahil edildi. Psöriasis tanılı olup metotreksat kullanan (grup 1, n=4) ve metotreksat kullanmayan (grup 2, n=13) hastalar ile sağlıklı kontrol grubunun (grup 3, n=17) Akustik Radyasyon Kuvveti İmpulsu (ARFI) tekniği ile yapılmış sonoelastografik incelemelerinde shear wave hız ortalamaları retrospektif olarak karşılaştırılmıştır.

Bulgular: Ortalama shear wave hızları metotreksat kullanan hastalarda 2,57 ± 1,13 m/sn, metotreksat kullanmayan hasta grubunda 2,31 ± 1,16 m/sn, sağlıklı kontrol grubunda ise 1,56 ± 0,62 m/sn olarak hesaplanmış olup 3. grubun shear wave hız ortalaması 1 ve 2. gruptan anlamlı derecede düşük bulunurken (p=0,032; p=0,012), 1 ve 2. gruplar arasında anlamlı farklılık gözlenmemiştir (p=0,755).

Sonuç: ARFI kuantifikasyon ile yapılan shear wave görüntüleme bulguları psöriasis hastalarında metotreksat tedavisinin karaciğer fibrozu ile ilişkili olmadığını ve psöriazis nedeniyle metotreksat kullanan hastalarda ortaya çıkan karaciğer doku sertliği artışının, metotreksattan ziyade, psöriazisin neden olduğu inflamatuar sürece sekonder olduğunu düşündürmüştür.

Anahtar Kelimeler: ARFI, Metotreksat, Psöriazis, Shear Wave Elastografi.

INTRODUCTION

Psoriasis is chronic skin disease which is characterized with an autoimmune inflammation and it affects 1-3% of the population. This disease is associated with an increase in local and systemic proinflammatory cytokines (1). It has been shown that proinflammatory cytokines can cause insulin resistance and as a result metabolic syndrome through various biochemical pathways (2, 3).

Metabolic syndrome, which is a multisystemic and multifactorial disease, is an important risk factor for non-alcoholic fatty liver disease (4). There are studies stating that psoriasis, which is a systemic disease, is associated with fatty liver disease and liver fibrosis through proinflammatory cytokines (5, 6).

Methotrexate is used as a first-line therapy in the treatment of psoriasis worldwide (7). However, there are also studies present indicating that the use of methotrexate in long-term treatment may lead to an important side effect of liver fibrosis (8, 9).

Methods such as radiological imaging methods, biochemical data and histopathological examination are used in the evaluation of liver fibrosis. The gold standard method is accepted as histopathological evaluation with liver biopsy (10, 11). However, albeit low, liver biopsy poses a risk of morbidity and mortality (12). This situation has led to the need for new methods for the evaluation of liver fibrosis.

Shear wave elastography (SWE) method is a relatively new and is increasingly used, non-invasive imaging method that allows the measurement of elasticity and stiffness in tissues (13, 14). SWE is used to evaluate pathologies such as thyroid nodules, breast lesions, intra-abdominal solid organ tumors and liver fibrosis. Although the gold standard method for the evaluation of liver fibrosis is liver biopsy, it is stated that SWE may be an alternative method in terms of distinguishing normal from fibrotic liver (15).

The aim of this study was to investigate whether psoriasis and methotrexate used in its treatment cause liver fibrosis and thus to evaluate the safety of methotrexate in the treatment in terms of this side effect.

MATERIAL AND METHODS

Patients: The study was conducted after the approval of the Ethics Committee of Duzce University and written informed consent was obtained.

Between January 2018 and September 2020, those who had a history of psoriasis for at least 10 years and who received methotrexate therapy due to moderate-to-severe involvement according to the Psoriasis Area Severity Index (PASI) score (A PASI score higher than 5 indicates moderate psoriasis.) (Group 1, n=14), during this period patients with a history of psoriasis and moderate-to-severe involvement who received systemic therapy other than methotrexate (Group 2, n=13) were included in the study. Mean shear wave velocity results from ARFI sonoelastographic examinations performed together with liver ultrasonographic examination, which was requested during routine follow-ups, were examined retrospectively.

A detailed medical history was obtained from medical history archive. Patients with history of alcohol consumption, abnormal liver function tests, chronic liver disease, diabetes, obesity, patients with grade 3 hepatosteatosis on sonographic examination, patients exposed to hepatotoxic agents were excluded from the study. No patient had any clinical sign of hepatic decompensation, such as hepatic encephalopathy, ascites, or variceal bleeding.

Control Group: Seventeen healthy adult volunteers (nine men, eight women) who did not have a history of metabolic syndrome or liver disease were examined with ARFI sonoelastography constituted the control group in which median shear wave velocity measurements were performed. These individuals did not consume any medication, drug and alcohol just before the ARFI imaging.

ARFI Sonoelastography: ARFI sonoelastography was performed by using a Siemens Acuson S2000 US System (Siemens Medical System, Tokyo, Japan). In all patients, ARFI sonoelastography was performed with a curved array US probe at 4 MHz for B-mode imaging. The right lobe of the liver was examined through the intercostal space with the patient lying in left lateral decubitus. A minimal scanning pressure was applied by the operator, while the patients were asked to stop breathing for a moment, in order to minimize the breathing motion. A measurement depth of 2 cm below the liver capsule was chosen to standardize the examination. Care was taken not to include any blood vessels or billiary structures. Ten successful measurements were performed in each patient, and the median values were calculated, the results were expressed in meters/second (m/s). In all patients, ARFI imaging was performed by one physician (D.G., 10 years of experience in sonography) who was blinded to the clinical data.

Statistical Analysis: Descriptive statistics of categorical variables were given as numbers and percentages, and descriptive statistics of numerical variables were given as mean, median, standard deviation, minimum and maximum.

The conformity of the numerical variables to the normal distribution was examined with Shapiro-Wilk test.

Relationships between categorical variables were examined with Pearson chi-square test. Mann-Whitney U test was used to compare two independent group means. One-way analysis of variance (ANOVA) and Kruskall-Wallis test were used to compare more than two independent group means. Dunn's test was used as a post hoc test in pairwise comparison of the groups for the variables found to be significant as a result of the Kruskal-Wallis test. The statistical significance level was taken as 0.05 and the SPSS (version 28) package program was used in the calculations.

RESULTS

The total sample of the present study was n = 44 patients. Among them, there were 14 patients (31.8 %) receiving ongoing methotrexate therapy and 13 patients (29.5 %) who were not using methotrexate. The mean age was 49.21 ± 10.68 years in group 1, 45.07 ± 11.51 years in group 2, and 41.94 ± 7.33 years in group 3. No significant difference was observed between the groups in terms of gender, age and BMI distributions, and it is presented in Table 1 (p>0.05).

Table 1. Gender, age and BMI distributions between groups

		1. Group (n=14)	2. Group (n=13)	3. Group (n=17)	p
Age (years)	Mean ± SD	49.21±10.68	45.07±11.51	41.94±7.33	0.133
Gender	Male (n (%))	7 (50)	9 (69.2)	8 (47.1)	0.442
	Female (n (%))	7 (50)	4 (30.8)	9 (52.9)	
BMI	Mean ± SD	25.92±1.41	26.92±2.71	25.55±3.37	0.383

*One way ANOVA, **Pearson chi square test was used.

No hepatosteatosis was detected sonographically in 21.4 % (n=3) in group 1, 46.2 % (n=6) in group 2, and 64.7 % (n=11) in group 3. While 50 % (n=7) in group 1 had hepatosteatosis grade 1, 23.1 % (n=3) in group 2 had grade 1, and 35.3 % (n=6) in group 3 had grade 1. In addition, while 28.6 % (n=4) in group 1 had hepatosteatosis grade 2, 30.8 % (n=4) in group 2 had grade 2, and there was no grade 2 hepatosteatosis in group 3. Shear wave measurement could not be performed in patients with Grade 3 hepatosteatosis in sonographic examination, so they were excluded from the study. A significant difference was observed between the groups in terms of shear wave velocity averages (p=0.022). When the differences were examined in detail, the average shear wave velocity of the 3rd group (mean: 1.56 ± 0.62 m/sec) was compared to the 1st and 2nd group (mean: 2.57 ± 1.13 m/sec, 2.31 ± 1 .16 m/sec) was found to be significantly lower (p=0.032; p=0.012), while no significant difference was observed between the 1st and 2nd groups (p=0.755) (Table 2).

Table 2. Shear wave mean velocity and comparison of psoriasis patients using methotrexate (group 1) and non-methotrexate (group 2) and healthy control group (group 3)

Group	n	Mean	Median	Std. Deviation	Minimum	Maximum	p
1	14	2.57	2.44	1.13	0.797	3.956	0.022
2	13	2.31	1.66	1.16	1.221	4.352	
3	17	1.56	1.24	0.62	0.897	3.190	

*Kruskall Wallis and Dunn test was used.

In the statistical analysis between the psoriasis patient group, which was formed by combining the 1st and 2nd groups, and the control group, the average shear wave velocity of the 1st group (mean: 2.45 ± 1.13 m/sec) was compared to the 2nd group (mean: 1.56). ± 0.63 m/sec) was found to be significantly higher (p=0.006) (Table 3).

Table 3. Average shear wave velocity and comparison of psoriasis patient group (group 1) and healthy control groups (group 2)

Group	n	Mean	Median	Std. Deviation	Minimum	Maximum	p
1	27	2.45	2.07	1.13	0.797	4.352	0.006
2	17	1.56	1.24	0.63	0.897	3.190	

*Mann Whitney U test was used

DISCUSSION

Methotrexate is a long-term used drug given in low dose in the treatment of many rheumatological diseases. In addition to its side effects such as nausea, mucositis, and pneumonitis, there are studies stating that it develops liver fibrosis (8, 16). There are also studies showing that the use of methotrexate has no effect on liver fibrosis (17, 18). Considering this information, the relationship between long-term methotrexate use and liver fibrosis is a process that has not been fully elucidated.

Although biopsy is the gold standard in the evaluation of liver fibrosis, it carries a risk of morbidity and mortality since it is an invasive method. The ARFI method is a SWE method, in which a specific ROI area can be evaluated without applying external pressure (15). There are many studies in the literature showing that the ARFI technique can be used in the detection of liver fibrosis (15, 19). In this study, it was investigated whether long-term methotrexate use due to psoriasis has an effect on the development of liver fibrosis by using SWE as a non-invasive method.

Feuchtenberger et al. investigated the development of liver fibrosis in patients using methotrexate for rheumatoid arthritis. In this study, in which 119 patients were evaluated with the ARFI method, it was shown that there was no relationship between long-term methotrexate use and the development of liver fibrosis (17). In another study conducted by Erre et al. with the 2D shear wave method, it was found that the use of methotrexate for rheumatoid arthritis did not pose a risk in terms of liver fibrosis (18). In this study, it was shown that the risk of developing liver fibrosis is higher in patients with rheumatoid arthritis compared to healthy population.The current study, like the previous two, found no evidence that methotrexate increased liver stiffness.. In another study, Conway et al. states that the use of methotrexate leads to elevation in transaminase levels, but that this is not a risk factor for fibrosis (20).

Horster et al. reported in their study on healthy volunteers that liver tissue stiffness was 1.19 ± 0.18 m/sec in measurements made with the ARFI method (21). In another investigation, Goertz et al. categorized the patients into five groups and set cut-off values based on the degree of liver fibrosis. (22). In our study, liver tissue stiffness was found in the healthy volunteer group at similar intervals obtained from these studies. Regardless of methotrexate use, liver stiffness values in the group of patients with psoriasis were found significantly higher than the normal cut-off values from the other study, compared to healthy volunteers. These findings show that the increase in liver tissue stiffness in the psoriasis patients group is in correlation with the data from the literature.

It is stated that psoriasis is associated with liver fibrosis due to metabolic and systemic disorders (23). Pongpit et al. reported in their study that 11% of patients with psoriasis had increased liver tissue stiffness or significant liver fibrosis. In this study, it is emphasized that the risk of liver fibrosis increases significantly in patients with increased waist circumference and diabetes. They stated that the cumulative methotrexate dose was not a risk factor for fibrosis (24). In our study, it was observed that liver stiffness increased in the psoriasis patient group compared to healthy individuals. We observed no significant differences in liver stiffness in the measurements made with ARFI between patients using methotrexate and the group of patients not using methotrexate. With these findings, it can be interpreted that the increase in liver tissue stiffness in patients using methotrexate for psoriasis is secondary to the inflammatory process caused by psoriasis itself rather than methotrexate.

Psoriasis can cause central obesity and metabolic syndrome with the pro-inflammatory processes it creates. As a result of this process, it increases the risk of non-alcoholic fatty liver disease (6, 23). In our study, we found that fatty liver was significantly more common in the psoriasis patient group than in the normal control group, as expected. However, similar to the study of Motosugi et al. (25), we found that hepatosteatosis grades and BMI did not cause an increase in liver tissue stiffness. In the light of these findings, it can be concluded that hepatosteatosis developing secondary to metabolic syndrome in the psoriasis patient group did not cause an increase in liver tissue stiffness and that patients with increased tissue stiffness should be evaluated in terms of the fibrosis process.

In conclusion, psoriasis is a chronic inflammatory disease and can affect the liver through proinflammatory cytokines. SWE, which is a noninvasive method, is a useful method in evaluating liver involvement. As a result of our study, it was concluded that long-term methotrexate use due to psoriasis has no effect on the development of liver fibrosis.

The main limitation of our study is the small number of patients. Another limitation is that the patients could not be histopathologically confirmed by liver biopsy, which is the gold standard method. Studies with larger patient series will shed light on the literature.

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