

# THE REVERSE OF THE COIN: METHOTREXATE AND LIVER FIBROSIS IN A GROUP OF PSORIATIC ARTHRITIS PATIENTS

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## Abstract

**Objectives.** We aimed to assess the presence of liver fibrosis using transient elastography in a group of PsA patients, compared to controls, and its possible relationship with MTX treatment.

**Methods.** We performed a prospective study on 41 patients diagnosed with PsA admitted to the Rheumatology Department of the Emergency County Hospital Craiova and a control group, of 20 sex and age-matched subjects. Patients data included demographic, clinical and laboratory parameters and were collected from every patient in accordance to the study protocol. Liver stiffness was evaluated using transient elastography, by an experienced investigator, using Fibroscan system (Echosens, Paris, France).

**Results.** After assessing liver fibrosis (LF) by transient elastography, we obtained statistically significant values compared to controls (6.04+1.65 kPa vs 4.16 +0.93 kPa, p = 0.002); liver fibrosis was found in 11 patients (26.81%), 9 of them undergoing MTX treatment.

Analyzing the impact of MTX treatment, we found statistically significant values between the two groups (6.04+1.65 kPa for MTX treated group vs 5.35+1.30kPa, p = 0.03 for non-MTX patients). Analyzing the differences between patients with/without liver fibrosis, we reckoned the following data: no differences for sex, age, alcohol consumption, hypertension, diabetes or hepatic function; significant differences were observed for BMI, dyslipidemia and fatty liver.

**Conclusions.** Hepatic involvement, especially liver fibrosis might be underestimated in PsA patients, and it is necessary to be properly and periodically evaluated in order to prevent further complications and maintain the efficient and safe dose of MTX, the first line therapeutic agent chosen for these patients. Non invasive hepatic imaging methods, such as transient elastography should certainly be considered for screening, along with a proper monitoring of comorbidities.

**Keywords:** psoriatic arthritis, liver fibrosis, methotrexate, transient elastography

## INTRODUCTION

Methotrexate (MTX) is the main therapeutic choice in inflammatory rheumatic diseases, such as rheumatoid arthritis (RA) or psoriatic arthritis (PsA) [1,2]. Long term treatment with low doses, used in rheumatology, is usually associated with mild side effects but occasionally, potentially severe events may appear, including hepatic toxicity. Liver involvement is histologically revealed by the presence

of steatosis, stellate cells hypertrophy, hepatocyte anisonucleosis and fibrosis. Liver fibrosis has been reported related to MTX treatment in different percentages, between 0-33%, and there are several studies that evaluated its prevalence in PsA [2-8]. Patients with PsA who develop MTX induced-liver injury after long term therapy, often have related risk factors for fatty liver disease, such as high alcohol intake, obesity, diabetes and administration of other

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potentially hepatotoxic agents. Periodic evaluation of the parameters related to hepatic function (amino-transferases, albumin, alkaline phosphatase etc.) doesn't offer sufficient data regarding liver fibrosis and their values may be found in normal ranges, despite the presence of this process [8-11]. The golden standard investigation is considered to be the liver biopsy, but it may be associated with significant morbidity and mortality. As methotrexate-induced liver injury is not frequent in our current practice, the risk/benefit ratio of liver biopsy has been questioned [12,13]. Several new technologies have been developed in order to establish the diagnosis of chronic liver disease, including transient elastography (TE), a type of shear wave ultrasound elastography, using Fibroscan system that measures the speed of shear waves to estimate hepatic tissue stiffness. This is not considered an operator dependent technique, and it allows a fast evaluation, without producing any discomfort for the patient. Using such techniques, along with a proper periodic evaluation of each patient, individualized depending on the symptoms and associated conditions, enables an early detection of any possible adverse events that might appear during the treatment and allows an appropriate therapeutic management [7,14-16].

We aimed to assess the presence of liver fibrosis using transient elastography in a group of PsA patients, compared to controls, and its possible relationship with MTX treatment.

## MATERIAL AND METHODS

We performed a prospective study on 41 patients diagnosed with PsA according to CASPAR criteria [17], admitted to the Rheumatology Department of the Emergency County Hospital Craiova, between October 2019-June 2020, and a control group, of 20 sex and age-matched subjects, without acute or chronic inflammatory diseases. Patients data included demographic, clinical and laboratory parameters and were collected from every patient in accordance to the study protocol. Disease Activity in Psoriatic Arthritis (DAPSA) and Psoriasis Area Severity Index (PASI) scores were calculated in all PsA patients. We excluded the patients with any recent infection, history of hepatitis B or C infection, treatment with hepatotoxic drugs, besides current treatment for the rheumatic condition, alcohol abuse, autoimmune live diseases or recently diagnosed neoplasia.

Liver stiffness was evaluated using transient elastography, by an experienced investigator, using Fibroscan system (Echosens, Paris, France), composed of an ultrasound probe and a vibration attachment. Elasticity is calculated in kilopascals (kPa) and is measured at a depth between 25 and 65 mm, over an area of 1x4 cm ; the results can vary between 2.5 kPa and 75 kPa. A value over 7kPa is considered as hepatic fibrosis [6]. The patient positioning implies the right arm being in abduction, in order to increase the intercostal space and allow a better access to the right liver lobe. The measurements are performed at the cross section point of the medium axillar axis and the line that crosses the xiphoid process; there are 10 measurements to be performed, with the final result represented by their mean, in kPa, and can be interpreted as the equivalent of METAVIR score (F0-F4). The machine displays the interquartile range (IQR) and the success rate for the examinations (the number of measures depending on the applied impulses). This method offers the advantage of being non invasive, a fast technique and without pain or discomfort for the patients.

The study was performed in accordance with the ethics and deontology principles of the Helsinki Human Right's Declaration and approved by the Local Ethics Comitee. All patients provided their written informed consent, after receiving a standard form which mentioned that the results would be used for research purposes.

For statistical analysis we used GraphPad Prism 5.5 and the results are presented as mean  $\pm$ SD; in order to compare groups, we used t-test and One-way ANOVA, and for evaluating correlations, the Pearson/Spearman's coefficient. A level of  $p < 0.05$  was considered statistically significant.

## RESULTS

We enrolled 41 PsA patients, with a mean age of  $53.44 \pm 0.91$  years and a mean disease duration of  $6.63 \pm 4.26$  years, and 20 controls, with similar demographic characteristics.

All of the patients received DMARD therapy, most of them MTX monotherapy (26 subjects); for 16 of the patients the management option included a combination of a synthetic and a biologic DMARD . Disease activity reckoned a mean value of  $11.80 \pm 4.91$  (min.2, max. 25.8); for PASI, we calculated a mean of  $15.32 \pm 7.12$ , with limits between 0 and 28. Inflammatory markers were found with a mean value of

9.66±16.6 mg/dl for C reactive protein (CRP) and 23.27±15.59 mm/h for erythrocyte sedimentation rate (ESR).

Regarding comorbidities, we found dyslipidemia to be present in a percentage of 68.29 (28 patients), with altered values of total cholesterol and its fractions in all 28 and hypertriglyceridemia for 25 of them. High blood pressure was found in 21 patients (53.65%), all of them treated and periodically monitored, diabetes in 8 (19.52%) of them and non-Alcoholic fatty liver disease (NAFLD) in almost half of the patients (20).

The main characteristics of the study group are presented in table 1.

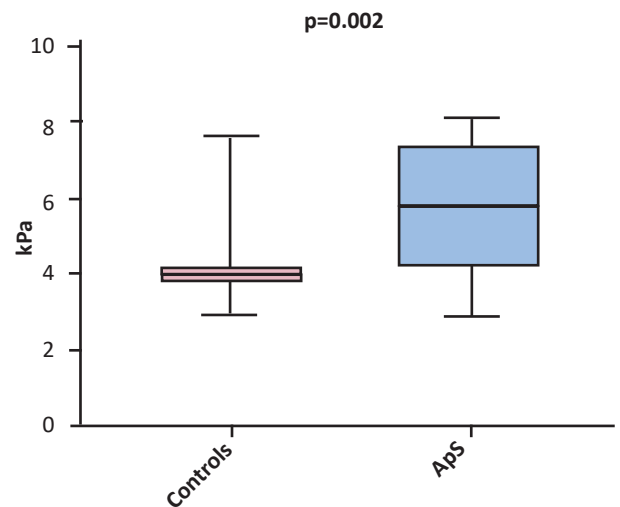
**TABLE 1.** General data of the study group

Patients (N)	41
Female (N; %)	27 (65.86)
Male (N; %)	14 (34.14)
Age (years)	54.34 ± 0.91
Disease duration (years)	6.63 ± 4.26
Type of psoriasis (N; %)	
- Nail	24 (58.53)
- Skin	35 (85.36)
- Nail and skin	24 (58.53)
- Sine psoriasis	5 (12.19)
Type of psoriatic arthritis (N; %)	
- Peripheral	32 (78.04)
- Axial and peripheral	9 (21.95)
CRP (mg/dl)	9.66 ± 16.6
ESR (mm/h)	23.27 ± 15.59
DAPSA	11.80 ± 4.91
PASI	15.32 ± 7.12
BMI (kg/m <sup>2</sup> )	27.44 ± 6.35
UA (mg/dl)	4.77 ± 1.48
Current medication	
- DMARD non biologic (N; %)	41 (100)
- DMARD biologic (N; %)	16 (39.02)
- MTX (N; %)	26
- Non-MTX DMARD (N; %)	15
NAFLD (N; %)	20 (48.78)
Hypertension (N; %)	21 (53.65)
Diabetes (N; %)	8 (19.52)
Smoking (N; %)	20 (48.78)
Dyslipidemia (N; %)	28 (68.29)
Alcohol consumption (N; %)	7 (17.07%)

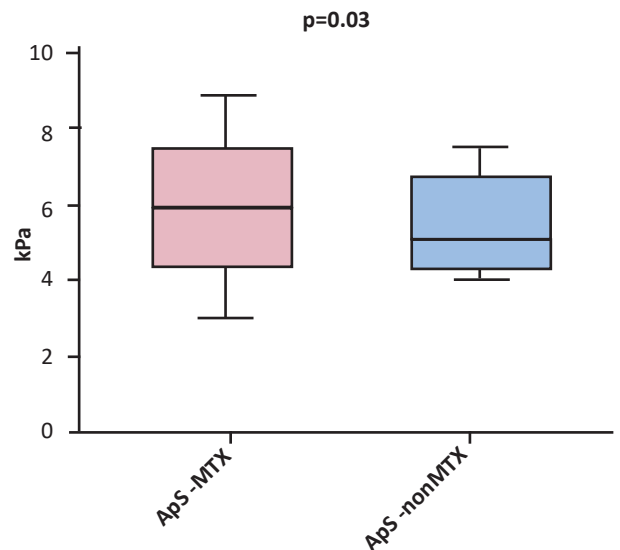
BMI – body mass index; UA – uric acid

After assessing liver fibrosis (LF) by transient elastography, we obtained statistically significant values compared to controls (6.04±1.65 kPa vs 4.16 ± 0.93 kPa,  $p = 0.002$ ) (figure 1); liver fibrosis was found in 11 patients (26.81%), 9 of them undergoing MTX treatment.

Analyzing the impact of MTX treatment, we found statistically significant values between the



**FIGURE 1.** Liver stiffness for controls and patients



**FIGURE 2.** Liver stiffness depending on treatment (MTX/non-MTX)

two groups (6.04±1.65 kPa for MTX treated group vs 5.35±1.30 kPa,  $p = 0.03$  for non-MTX patients) (figure 2).

Analyzing the differences between patients with/without liver fibrosis, we reckoned the following data: no differences for sex, age, alcohol consumption, hypertension, diabetes or hepatic function; significant differences were observed for BMI, dyslipidemia and fatty liver (table 2).

**TABLE 2.** Comparative parameters in the study group depending on the presence/absence of liver fibrosis

	Fibrosis (11)	Non fibrosis (30)	$p$
Age (years)	55.73 ± 10.68	50.55 ± 11.12	0.69
BMI (kg/m <sup>2</sup> )	29.73 ± 6.27	26.60 ± 6.27	0.03

	<i>Fibrosis (11)</i>	<i>Non fibrosis (30)</i>	<i>p</i>
Alcohol consumption (N; %)	2 (18.18%)	5 (16.66%)	0.08
NAFLD (N; %)	6 (54.54%)	14 (46.46%)	0.01
Diabetes (N; %)	2 (18.18%)	6 (20%)	0.68
Hypertension (N; %)	5 (45.45%)	16 (53.33%)	0.21
Disease duration (years)	9.09+5.35	4.36+2.99	0.02
MTX average dose (mg/week)	13.33 +4.33	13.67+ 5.16	0.34
MTX cumulative dose (mg)	3340+2769	1834 +1551	0.15
DAPSA	9.56+4.94	12.62+4.62	0.29
PASI	13.11+8.34	14.11+4.94	0.59
ESR (mm/h)	21.45+22.11	20.80+10.35	0.82
CRP (mg/dl)	6.03+11.3	5.86 +5.28	0.05
ALT (IU/l)	23.7+13.8	21.8 +16.5	0.58
AST (IU/l)	21.9 +17.3	18.9+ 18.2	0.56
ALP (IU/l)	101.40+45.18	96.23+25.12	0.19
GGT (IU/l)	58.20+20.34	58.80+22	0.28
Blood glucose (mg/dl)	106.5+29.76	101.3+31.46	0.81
TC (mg/dl)	252.7+64.30	204.9+44.22	0.007
LDL (mg/dl)	115.9+21.10	110.5+15.10	0.02
HDL (mg/dl)	69.57+22.92	59.89+11.02	0.09
TG (mg/dl)	227.4+117.6	129.4+61.18	0.001
UA (mg/dl)	7.30+3.96	4.75+1.40	0.32

*BMI* – body mass index; *ALT* – alanine aminotransferase; *AST* – aspartate aminotransferase; *GGT* – gamma-glutamyl transferase; *TC* – total cholesterol; *LDL* – low-density lipoprotein; *HDL* – high-density lipoprotein; *TG* – triglycerides; *UA* – uric acid

Analyzing the possible relationship between the presence of LF and different variables, we found a moderately positive correlation between LF and UA levels ( $r = 0.50$ ,  $p < 0.001$ ), BMI ( $r = 0.43$ ,  $p = 0.03$ ) and the presence of NAFLD ( $r = 0.51$ ,  $p = 0.02$ ).

## DISCUSSION

Generally, low dose MTX administered in inflammatory rheumatic conditions are not associated to severe side effects, but a part of them may be potentially severe, especially in the presence of comorbidities and related risk factors. Although several studies aimed to evaluate MTX hepatotoxicity, the direct drug impact is difficult to separate in the context of multiple therapeutic options and additional risk factors [3,4,18,19].

Hepatic toxicity is still a special concern during MTX treatment and PsA patients are already exposed, due to an increased metabolic syndrome re-

lated liver disease risk, which limits therapeutic options and imposes careful and constant evaluation. Transient elastography has proved to be a useful and easily available method for this purpose [4,6].

Enhanced liver stiffness was demonstrated in a percentage of 26.81 of the cases, significantly different compared to controls, most of them being under MTX treatment. Our finding is similar to other reported studies that showed the presence of liver stiffness in different percentages between patients undergoing MTX treatment, significantly increased in case of PsA, compared to rheumatoid arthritis or Crohn disease [3,6,20].

Early researches considered long term treatment with MTX a central risk factor for liver fibrosis and liver biopsy was mandatory in cases of psoriasis and PsA with cumulative doses over 1,500 mg [21], observation that was not sustained by the results of later studies [16,22-26].

Still, a recently published review, that included 8 observational studies with over 400 patients with psoriasis, concluded that MTX treatment contributes to the development of liver fibrosis, without a clear association to the cumulative dose [8]. Other scientific reports have also reported a direct, positive correlation between the total cumulative dose and the presence and degree of liver fibrosis [8,22,24,27-29]. Our results firstly showed significant differences depending on MTX use, but carrying out further statistical analyses regarding the total dose and liver fibrosis, didn't point out noticeable differences of the cumulative dose between subjects with/without fibrosis. We are aware of some limitations of our study, related to small number of patients and the lack of the study group with PsA, but no MTX treatment, as the disease itself is associated to metabolic syndrome. Subsequently, different components of metabolic syndrome contribute to the development of hepatic disease, impacted by the concurrent use of MTX, and seemingly patients may develop fibrosis at lower cumulative doses in the presence of such comorbidities [29-31]. Indeed, the long term pro-inflammatory status in PsA patients contributes to overall risk of metabolic complications and can induce steatosis, condition that exposes the liver to inflammatory and oxidative injury, with consequent steatohepatitis and fibrosis [6,32]. Our data have also showed the presence of steatosis between PsA patients, in a higher percentage for the group of liver fibrosis, but not statistically different, possible to a relative reduced number of subjects.

Although our study included a relative low number of subjects, the data are significant and line with the ones published by several scientific publication and underline the necessity of a complete hepatic investigation, that can uncover a subclinical associated pathology and offer a better view of the possible outcome impact for these patients.

## CONCLUSIONS

Because PsA is a common inflammatory joint disease, associated with an increased risk of premature death, due to a frequent and high association with all the components of metabolic syndrome, it represents a challenge in the clinical practice, and it might be tricking regarding subclinical comorbidities and drug induced side effects.

Hepatic involvement, especially liver fibrosis might be underestimated, and it is necessary to be properly and periodically evaluated in order to prevent further complications and maintain the efficient and safe dose of MTX, the first line therapeutic agent chosen for these patients. Non-invasive hepatic imaging methods, such as transient elastography should certainly be considered for screening, along with a proper monitoring of comorbidities.

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