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### REVIEW

- 585 Current and novel modalities for management of chronic hepatitis B infection  
*Salama II, Sami SM, Salama SI, Abdel-Latif GA, Shaaban FA, Fouad WA, Abdelmohsen AM, Raslan HM*
- 609 Noninvasive biomarkers in pediatric nonalcoholic fatty liver disease  
*Jayasekera D, Hartmann P*

### MINIREVIEWS

- 641 Hypothyroidism and non-alcoholic fatty liver disease: A coincidence or a causal relationship?  
*Janota B, Szczepańska E, Adamek B, Janczewska E*
- 649 Sarcopenia in chronic viral hepatitis: From concept to clinical relevance  
*Coelho MPP, de Castro PASV, de Vries TP, Colosimo EA, Bezerra JMT, Rocha GA, Silva LD*
- 666 Fatty liver and celiac disease: Why worry?  
*Narciso-Schiavon JL, Schiavon LL*
- 675 Current guidelines for diagnosis and management of hepatic involvement in hereditary hemorrhagic teleangiectasia  
*Ielasi L, Tonnini M, Piscaglia F, Serio I*

### ORIGINAL ARTICLE

#### Clinical Trials Study

- 688 Respiratory muscle training with electronic devices in the postoperative period of hepatectomy: A randomized study  
*Pereira MG, Silva AMO, Galhardo FDM, Almeida BDM, Lopes RL, Boin IFSF*

#### Observational Study

- 699 Liver steatosis in patients with rheumatoid arthritis treated with methotrexate is associated with body mass index  
*Castiella A, Lopez-Dominguez L, Sanchez-Iturri MJ, Urreta I, De Diego A, Belzunegui J, Zapata E*

### CASE REPORT

- 707 Giant cavernous hemangioma of the liver with satellite nodules: Aspects on tumour/tissue interface: A case report  
*Fischer AK, Beckurts KTE, Büttner R, Drebber U*
- 715 Cerebrospinal fluid liver pseudocyst: A bizarre long-term complication of ventriculoperitoneal shunt: A case report  
*Yousaf MN, Naqvi HA, Kane S, Chaudhary FS, Hawksworth J, Nayar VV, Faust TW*

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## Observational Study

# Liver steatosis in patients with rheumatoid arthritis treated with methotrexate is associated with body mass index

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## Abstract

### BACKGROUND

Methotrexate (MTX) is the usual first-line treatment for rheumatoid arthritis (RA). Long-term use of MTX has been associated with liver steatosis (LS) and liver fibrosis (LF).

### AIM

To determine if LS in patients treated with MTX for RA is associated with MTX cumulative dose (MTX-CD), metabolic syndrome (MtS), body mass index (BMI), the male sex, or LF.

### METHODS

A single-center, prospective study of patients receiving MTX for RA was performed from February 2019 to February 2020. The inclusion criteria were patients aged 18 years or older diagnosed with RA by a rheumatologist and being treated with MTX (without limitation on the duration of treatment). The exclusion criteria were previous diagnosis of liver disease (hepatitis B or C virus infection, known nonalcoholic fatty liver disease), alcohol consumption greater than 60 g/d in males or 40 g/d in females, human immunodeficiency virus infection on antiretroviral therapy, diabetes mellitus, chronic renal failure, congestive heart failure, or BMI greater than 30 kg/m<sup>2</sup>. Patients receiving leflunomide in the 3 years prior to



the study were also excluded. Transient elastography (FibroScan, Echosens®, Paris, France) was used for fibrosis determination (LF > 7 KpA) and computer attenuation parameter (CAP) for LS (CAP > 248 dB/m). Demographic variables, laboratory data, MTX-CD (> 4000 mg), MtS criteria, BMI (> 25), transient elastography, and CAP scores were collected from all patients.

## RESULTS

Fifty-nine patients were included. Forty-three were female (72.88%), and the mean age was 61.52 years (standard deviation: 11.73). When we compared MTX-CD ≤ 4000 mg (26 patients; 14 with LS and 12 without) with > 4000 mg (33 patients; 12 with LS and 21 without), no statistical differences were found ( $P = 0.179$ ). We compared CAP scores stratified by MtS, BMI, sex, and LF. There were no significant differences in CAP scores based on the presence of MtS [CAP/MtS: 50 no MtS (84.75%); 9 MtS (15.25%);  $P = 0.138$ ], the male sex (CAP/sex: 8 male/18 female LS; 8 male/25 female no LS;  $P = 0.576$ ), or LF [CAP/fibrosis: 53 no LF (89.83%); 6 LF (10.17%);  $P = 0.239$ ]. LS determined by CAP was significantly associated with BMI > 25 (CAP/BMI: 22 BMI ≤ 25 (37.29%); 37 BMI > 25 (62.71%);  $P = 0.002$ ).

## CONCLUSION

LS in patients with RA treated with MTX was not associated with MTX-CD, LF, the male sex, or MtS. However, BMI was significantly related to LS in these patients.

**Key Words:** Methotrexate; Rheumatoid arthritis; Liver steatosis; Liver fibrosis; Transient elastography; Computed attenuation parameter

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**Core Tip:** Methotrexate (MTX) is the cornerstone of treatment for rheumatoid arthritis and has been associated with the development of liver fibrosis (LF) and liver steatosis (LS). The objective of this work was to study if LS in patients with rheumatoid arthritis treated with MTX and determine the association with body mass index, MTX cumulative dose, sex, LF, and metabolic syndrome. We concluded that LS in patients with rheumatoid arthritis on MTX treatment was not related to MTX-cumulative dose, LF, the male sex, or metabolic syndrome. In our study, body mass index was significantly associated with LS in these patients.

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## INTRODUCTION

Methotrexate (MTX) has been used in the treatment of oncological and chronic inflammatory diseases. It is also the cornerstone of treatment for rheumatoid arthritis (RA). The most concerning long-term adverse effect of this treatment is the development of liver fibrosis (LF)[1-5]. Liver steatosis (LS) has been associated with RA and with MTX treatment[6]. Liver biopsy has been the gold standard for the study of LF and LS, but it has several limitations[3]. There is a disparity of fibrosis values between biopsy samples, and it is an invasive technique accompanied by risks[3].

Recent studies have been carried out on non-invasive measurements of LF. Transient elastography (TE) is a non-invasive method without side effects that also allows the sequential determination of liver fibrosis measurements over time, which makes it of great interest for the follow-up of these patients[2-4].

MTX, as a risk factor for secondary LS, has been studied recently. RA has been associated with moderate to severe LS; predisposing factors such as higher body mass index (BMI), the male sex, and MTX cumulative dose (MTX-CD) have been published[7]. However, there have been conflicting results, and the impact of MTX on nonalcoholic fatty liver disease (NAFLD) is still unclear[6-11].

The computer attenuation parameter (CAP) measures carried out at the time of TE correlates with the histological LS[12]. The CAP algorithm calculates the ultrasound signal attenuation[12]. LS has been evaluated recently using CAP in chronic MTX users and was common with moderate and severe LS predicting moderate to severe LF[13].

The objective of our work was to determine if LS in patients with RA treated with MTX is associated with BMI, MTX-CD, sex, LF, and metabolic syndrome (MtS).

## MATERIALS AND METHODS

We performed a single-center, prospective study of patients receiving MTX for RA. The principle objective of this work was to study the presence of LF by TE and aspartate aminotransferase to platelet ratio index (APRI)[14] as well as the detection of LS by ultrasonography and CAP. Fibroscan® (FS) (Fibroscan®402, Echosens, France, [www.echosens.com](http://www.echosens.com)) was used for fibrosis determination (LF > 7 Kpa). CAP was used for LS (CAP > 248 dB/m)[11]. Demographic variables, laboratory data, MTX-CD (> 4000 mg), MtS criteria, BMI (> 25), TE, and CAP scores were collected from all patients.

Patients were recruited between February 1, 2019 and January 31, 2020 from the Gastroenterology-Rheumatology clinics of our hospital. The inclusion criteria were patients aged 18 years or older diagnosed with RA by a rheumatologist, and being treatment with MTX (without limitation on the duration of treatment). The exclusion criteria were previous diagnosis of liver disease (hepatitis B or C virus infection, known NAFLD), alcohol consumption greater than 60 g/d for males or 40 g/d for females, HIV infection on antiretroviral therapy, diabetes mellitus, chronic renal failure, congestive heart failure, or BMI greater than 30 kg/m<sup>2</sup>. Patients receiving leflunomide in the 3 years prior to the study were also excluded.

Demographic data analysis, treatment history, and MTX-CD were collected through computerized medical records. LF was defined by FS (measurement greater than 7 Kpa) and by APRI score (result greater than 0.7). The FS assessment was performed by a trained nurse. At the time of inclusion in the study, a blood test was performed to calculate the APRI score [aspartate aminotransferase level (upper limit of normal)/platelet level × 100]. High transaminase levels were defined as results above 33 U/L. Finally, disease activity was defined by a rheumatologist using the Disease Activity Score in 28 joints-c-reactive protein score. Data were collected by means of a questionnaire, a review of the computerized clinical history, and a visit to the gastroenterology clinic.

### Statistical analysis

Initially, a descriptive analysis was performed by calculating the mean and standard deviation (SD) (or median and interquartile range) for quantitative variables. For qualitative variables, absolute and relative frequencies were calculated as percentages. To compare the distribution of qualitative variables, the  $\chi^2$  test or Fisher's exact test was used. Similarly, the Student's *t*-test or the Mann-Whitney *U* test was used to compare quantitative variables. STATA 16.1 software was used for all the analyses. Statistical review of the study was performed by a biomedical statistician (IU).

### Ethics

The clinical research ethics committee of the Gipuzkoa health area (Código de Protocolo: ACLFSC-2018-01; Acta 01/2019) approved this study, and participants signed an informed consent form prior to inclusion.

## RESULTS

We included 59 patients in the study. There were 43 females (72.88%), and 61.52 years (SD: 11.73) was the mean age. Clinical characteristics are presented in Table 1 and laboratory data in Table 2 (Supplementary materials). The mean duration of the MTX treatment was 82.4 mo (SD: 65.1). The mean MTX-CD of the patients was 5214.5 mg (SD: 4031.9). Twenty-six patients presented an MTX-CD ≤ to 4000 mg. Thirty-three had an MTX-CD > than 4000 mg.

Treatment duration and times of disease progression were longer in the MTX-CD > 4000 mg group. MTX monotherapy was used in 46 patients (77.90%). Only 7 patients (11.80%) were on nonsteroidal anti-inflammatory drug therapy in association with MTX.

Ultrasonography was performed in 56 patients, of whom 39 presented no LS (69.64%), and 17 (30.36%) had LS. CAP was determined in all 59 patients, categorizing 33 patients without LS and 26 patients with LS.

We then compared both methods (56 patients in total). Ultrasonography presented a positive predictive value of 88.2% [95% confidence interval (CI): 63.6%-98.5%] and a negative predictive value of 76.9% (95%CI: 60.7%-88.9%), with a sensitivity of 62.5% (95%CI: 40.6%-81.2%) and a specificity of 93.8% (95%CI: 79.2%-99.2%) compared to CAP. When comparing MTX-CD ≤ 4000 mg (26 patients, 14 with LS and 12 without) with > 4000 mg (33 patients; 12 with LS and 21 without), we found no statistical differences in LS between low and high MTX-CD (*P* = 0.179) (Figure 1A). CAP scores were compared stratified by BMI, sex, LF, or MtS. No significant differences were observed based on the the male sex (CAP/sex: 8 males/18 females LS; 8 males/25 females no LS; *P* = 0.576), LF [CAP/Fibrosis: 53 no LF

**Table 1 Clinical characteristics**

Clinical characteristics	Value
Female/male	43 (73%); 16 (27%)
Age in yr	61.52 (11.73)
Height in cm	162.02 (7.66)
Weight in kg	67.33 (10.52)
Waist circumference in cm	88.81 (10.92)
BMI in kg/m <sup>2</sup>	25.55 (3.05)
BMI < 25 score	22 (37.29%)
BMI > 25 score	37 (62.71%)
Metabolic syndrome	9 (15.25%)
Type 2 diabetes	2 (3.57%)
DAS28 score	2.36 (1.14)
Treatment duration MTX in mo	82.43 (65.08)
MTX-CD in mg	5214.5 (4031.9)
FibroScan in kPa	5.02 (2.24)
APRI in score	0.32 (0.15)
CAP in dB/m	251.33 (51.13)

Data are *n* (%) or mean ± SD. APRI: Aspartate aminotransferase to platelet ratio index; BMI: Body mass index; CAP: Computed attenuation parameter; DAS28: Disease Activity Score in 28 joints; MTX-CD: Methotrexate cumulative dose.

**Table 2 Laboratory data**

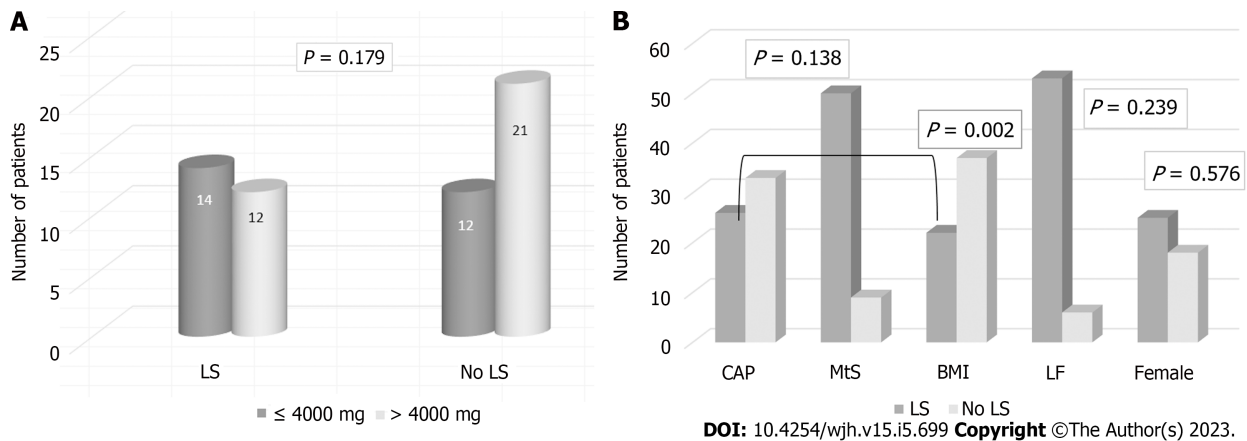
Classification	Value
AST in U/L	24.52 (12.56)
ALT in U/L	22.23 (12.15)
GGTP in U/L	23.42 (13.43)
AP in U/L	76.05 (23.72)
Bilirubin in mg/dL	0.50 (0.25)
Albumin in g/dL	4.39 (0.29)
Glucose in mg/dL	101.50 (16.08)
Triglycerides in mg/dL	99.43 (45.87)
Cholesterol in mg/dL	205.42 (43.57)
HDL-cholesterol in mg/dL	62.85 (14.74)

Data are mean ± SD. ALT: Alanine aminotransferase; AP: Alkaline phosphatase; AST: Aspartate aminotransferase; GGTP: Gamma glutamyl transpeptidase; HDL: High-density lipoprotein.

(89.83%); 6 LF (10.17%);  $P = 0.239$ ], or MtS [CAP/MtS: 50 no MtS (84.75%); 9 MtS (15.25%);  $P = 0.138$ ]. Nonetheless, LS measured by CAP was significantly related with BMI > 25 [CAP/BMI: 22 BMI ≤ 25 (37.29%); 37 BMI > 25 (62.71%);  $P = 0.002$ ] (Figure 1B).

## DISCUSSION

MTX is the gold standard of RA treatment, both in monotherapy and associated with biological therapies[15]. LF has been associated with chronic MTX use in this disease. There is increasing evidence



**Figure 1 Liver steatosis.** A: Liver steatosis by methotrexate cumulative dose; B: Liver steatosis by computer attenuation parameter compared with metabolic syndrome, body mass index, liver fibrosis, and sex. CAP: Computer attenuation parameter; MtS: Metabolic syndrome; BMI: Body mass index; LF: Liver fibrosis; LS: Liver steatosis.

that LF is broadly affected by other factors: Alcohol, other associated drugs, and MtS are directly related with the development of LF[16-19].

Drugs can affect LS development. The possible effect of MTX in the presence of LS in patients with RA is currently being studied. According to laboratory research, folate deficiency produced by chronic MTX treatment could promote liver fat accumulation[20], but folic acid supplementation has been recommended and is currently being used in treatment regimens. Studies have shown conflicting results, and the impact of MTX on LS is still unclear[6].

Choi *et al*[6] investigated whether MTX-CD in 368 RA patients led to LS determined by ultrasound, but they did not detect a significant association between LS development and MTX administration, suggesting that to adjust for individualized risk factors for NAFLD may be more efficient than MTX discontinuation in LS detection/management. Hypertriglyceridemia and higher BMI were associated with an increased risk of LS.

Erre *et al*[7] recently studied the independent association of LS and RA. In 223 patients with RA, they found that RA is independently associated with LS (moderate to severe), scored by ultrasound, and male sex, higher BMI, and MTX-CD are independent risk factors for the development of LS[7].

Mori *et al*[8] studied the association between NAFLD and liver injury during MTX treatment in 846 patients with RA. They did not observe a significant impact of MTX dose and duration on histological severity. On the other hand, Sakthiswary *et al*[9] concluded, in a retrospective study, that the MTX-CD was the only independent predictor of MTX-associated LS with transaminitis in a cohort of 978 patients with RA.

Recently, detection of LS by CAP in chronic MTX users was published for the first time. Tomaszewski *et al*[13] studied 172 patients on MTX (45 with RA). Diabetes mellitus, hypertension, and BMI ≥ 30 were predictors of LS. LS determined by CAP was frequent. Moderate and severe LS in this study predicted moderate to severe fibrosis of the liver.

Our prospective study was designed to determine in patients with RA treated with MTX if LS, as measured by CAP, was associated with BMI, sex, LF, or MTX-CD. When we compared MTX-CD ≤ 4000 mg with > 4000 mg, no statistical differences were found. There were no significant differences between the presence and absence of MtS, the male sex, or LF, but LS determined by CAP was significantly associated with BMI > 25 ( $P = 0.002$ ).

Our study had limitations. The sample size was relatively small, and we included all the patients with RA on MTX treatment, without a treatment duration limitation. More females than males were included in this study, and given the limited sample size, it is difficult to conclude that there is no relationship between sex and LS. The strengths of the study were that it was a prospective study and that LS was determined as measured by the CAP.

## CONCLUSION

We concluded that in our series of patients treated with MTX for RA, LS is not associated with MTX-CD, LF, the male sex, or MtS. In our study, BMI is significantly associated with LS. It seems that other factors, apart from MTX-CD or treatment duration, are more important for the development of LS in these patients.



## ARTICLE HIGHLIGHTS

### Research background

Methotrexate (MTX) remains the cornerstone of treatment for rheumatoid arthritis (RA), both in monotherapy and in association with other treatments. The most concerning adverse effect of this treatment, in the long term, is liver fibrosis (LF). Liver steatosis (LS) has been associated with RA and with MTX.

### Research motivation

MTX, as a risk factor for secondary LS, has been studied recently. RA has been independently associated with moderate to severe LS. Sex, higher body mass index (BMI), and MTX cumulative dose (MTX-CD) are predisposing factors. However, the studies have shown conflicting results, and the impact of MTX on LS is still unclear.

### Research objectives

The objective of our work was to study if LS in RA patients treated with MTX was related to BMI, MTX-CD, metabolic syndrome (MtS), sex, or LF.

### Research methods

We performed a prospective study of RA patients treated with MTX. The principal objective of this work was to study the presence of LF by transient elastography and aspartate aminotransferase to platelet ratio index as well as the detection of LS by ultrasonography and computer attenuation parameter (CAP).

### Research results

Fifty-nine patients were included in the study. When comparing MTX-CD  $\leq 4000$  mg with  $> 4000$  mg, we found no statistical differences in LS between low and high MTX-CD. We compared CAP scores with MtS, BMI, sex, and LF. There were no significant differences based on the presence or absence of MtS, the male sex, or LF. LS determined by CAP was significantly associated with BMI  $> 25$ .

### Research conclusions

We concluded that, in our series, LS in RA patients treated with MTX is not related to sex, MTX-CD, MtS, or LF. BMI  $> 25$  is significantly associated with LS in our study. Other factors, apart from MTX-CD or time in treatment, are more important for the development of LS in these patients.

### Research perspectives

The routine incorporation of FS for the study of LF and LS in RA patients with MTX treatment is critical and will aid in understanding the real impact of MTX on LS. More studies (larger and multicentric) are recommended to validate these results.

## FOOTNOTES

**Author contributions:** Castiella A and Lopez-Dominguez L were the guarantors and designed the study; Castiella A, Lopez-Dominguez L, Sanchez-Iturri MJ, Urreta I, De Diego A, Belzunegui J, and Zapata E participated in the acquisition, analysis, and interpretation of the data and drafted the initial manuscript; Castiella A, Lopez-Dominguez L, and Zapata E revised the article critically for important intellectual content.

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