Hepatic steatosis as measured by the computed attenuation parameter predicts fibrosis in long-term methotrexate use

Marcel Tomaszewski MD1, Monica Dahiya BSc2, Seyed Amir Mohajerani MD, MSc3, Hanaa Punja Candidate BSc4, Hin Hin Ko MD5, Muxin Sun MD6, Alnoor Ramji MD7

ABSTRACT

INTRODUCTION: To determine predictors of hepatic steatosis by the computed attenuation parameter (CAP) and fibrosis via transient elastography (TE) in persons on methotrexate (MTX) therapy with rheumatologic and dermatologic diseases. METHODS: A single-centred retrospective cohort study was performed. Patients on >6 months of MTX for a rheumatologic or dermatologic disease who had undergone TE from January 2015 to September 2019 were included. Multivariate analysis was performed to determine predictors of steatosis and fibrosis. RESULTS: A total of 172 patients on methotrexate were included. Psoriasis was the most frequent diagnosis (n = 55), followed by rheumatoid arthritis (n = 45) and psoriatic arthritis (n = 34). Steatosis (CAP ≥245 dB/m) was present in 69.8% of patients. Multivariate regression analysis revealed that diabetes mellitus (OR 10.47, 95% CI 1.42–75.35), hypertension (OR 5.15, 95% CI 1.75–15.38), and BMI ≥30 kg/m² (OR 16.47, 95% CI 5.56–45.56) were predictors of steatosis (CAP ≥245 dB/m). Predictors of moderate to severe fibrosis (Metavir ≥F2 = TE ≥8.0 kPa) by multivariate regression analysis included moderate to severe steatosis (CAP ≥270 dB/m) (OR 8.36, 95% CI 1.88–37.14), diabetes mellitus (OR 2.85, 95% CI 1.09–7.48), hypertension (OR 5.4, 95% CI 2.23–13.00), dyslipidemia (OR 3.71, 95% CI 1.50–9.18), and moderate alcohol use (OR 3.06, 95% CI 1.2–7.49). CONCLUSIONS: In patients on MTX for rheumatologic and dermatologic diseases, hepatic steatosis as measured by CAP was common and moderate to severe steatosis predicted moderate to severe fibrosis.

KEYWORDS: liver diseases; methotrexate; psoriasis; psoriatic arthritis; rheumatoid arthritis

Author Affiliation

1 Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; 2 Faculty of Medicine, University of Alberta, Edmonton, Alberta, Canada; 3 Saint Paul’s Hospital, Gastrointestinal Research Institute, Vancouver, British Columbia, Canada; 4 Department of Biology, University of British Columbia, Vancouver, British Columbia, Canada; 5 Clinical Associate Professor of Medicine, Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; 6 Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; 7 Division of Gastroenterology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Marcel Tomaszewski, Department of Gastroenterology, University of British Columbia, 5153 - 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9 Canada. Telephone: 514-716-1761. E-mail: marcel.a.tomaszewski@gmail.com
INTRODUCTION

Low dose methotrexate (MTX) is used in the management of rheumatoid arthritis (RA), psoriatic arthritis (PsA), systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies, and vasculitis (1). Non-rheumatologic indications for MTX include severe psoriasis (PsO), lichen planus, Crohn’s disease, and autoimmune hepatitis. In RA, MTX is the preferred conventional disease-modifying anti-rheumatic drug (2). MTX is an inhibitor of dihydrofolate reductase and reduces the amount of folate cofactors that are necessary for nucleic acid synthesis. The clinical benefits of MTX in RA include slowing disease progression, preventing articular, extra-articular damage, comorbidities and decreasing mortality (2).

Long-term MTX users may develop hepatic fibrosis (3). Liver histology findings in MTX use include steatosis, stellate cell hypertrophy and anisonucleosis but the exact mechanism of fibrosis remains unknown. Risk factors for fibrosis among patients on MTX include increased BMI and metabolic syndrome (4). The observation that patients with PsO also have increased rates of metabolic syndrome and NAFLD shows the potential role that steatosis may play in the pathogenesis of hepatic fibrosis in this patient population (5–7). Additionally, the severity and prognosis of NAFLD are worse in PsO compared with RA (7). Systemic inflammation has been postulated to result in steatohepatitis contributing to the development of fibrosis in patients with PsO, PsA, and RA (8).

Previously liver biopsy was used to monitor for fibrosis in patients on MTX with PsO and RA (9). Currently, transaminases, complete blood count and albumin are performed serially to monitor patients with RA for hepatotoxicity (10). Transaminase levels, however, have a poor sensitivity and specificity for the detection of hepatic fibrosis (11).

Transient elastography (TE) is a non-invasive measure of hepatic fibrosis that has been used in patients on MTX (12–14). TE measures the stiffness (or elasticity) of the hepatic parenchyma using both ultrasound and low-frequency elastic waves produced by an ultrasound vibrator applied to the right upper quadrant to measure the propagation speed of a wave using a pulse-echo ultrasound (15). An Australasian position statement has suggested that TE be considered as a routine investigation to monitor patients with PsO on MTX (16). The AAD has suggested that TE can be for patients with PsO used in two contexts: 1) screening for fibrosis prior to initiating MTX and 2) routine surveillance after a cumulative dose of 3.5–4.0 grams of MTX (17). The computed attenuation parameter (CAP) measurement, performed at the time of TE, correlates with the histological degree of steatosis. The CAP algorithm calculates the attenuation of the ultrasound signal (18).

Although the presence of steatosis correlates with the extent of fibrosis in NAFLD, this could be different in patients receiving MTX (19,20). First, MTX independently stimulates hepatic stellate cells and myofibroblasts; therefore, there could be a discordance between the extent of steatosis and fibrosis in these patients. Second, immune-mediated disorders may attenuate the extent of hepatic fibrosis in NAFLD (21). Therefore, this patient population may have more extensive steatosis but less fibrosis.

To our knowledge, no studies have evaluated steatosis utilizing CAP in chronic MTX users. Our primary aim was to identify predictors of hepatic steatosis, as measured by CAP, and fibrosis, as measured by TE, in patients on MTX. Additionally, we assessed for a correlation between cumulative MTX dosing and the presence of steatosis and fibrosis.

MATERIALS AND METHODS

Study design

We performed a retrospective study of patients on MTX for rheumatologic or dermatologic conditions and who underwent TE (FibroScan, Echosens, Paris, France) from January 2015 to September 2019 at an academic tertiary care centre. Demographic and clinical data were collected from the electronic medical records. The study was approved by the University of British Columbia Providence Health Care Research Institute Research Ethics Boards (H19–02689). We included adults (>18 years old) diagnosed with RA, PsO, PsA, eczema, lichen planus, mixed connective tissue disease, systemic lupus erythematosus, and ankylosing spondylitis who underwent transient elastography. Patients with active hepatitis B (surface antigen positivity) and patients with excessive alcohol use (more than 15 standard drinks per week for men and more than 10 standard drinks per week for women) were excluded.

Assessment of transient elastography and computed attenuation parameter

Patients on chronic methotrexate therapy were referred to an academic hepatology centre in
Vancouver, British Columbia, Canada. TE and CAP are measured using FibroScan operated by a certified technician who had performed at least 100 prior scans. Patients fasted for more than 2 hours prior to TE and CAP measurement. For patients with a body mass index (BMI) above 30 kg/m², the XL probe was used. For all other patients, the M probe was used. Those with a TE score greater than 8.0 kPa were considered to have at least moderate fibrosis (≥F2) by the meta-analysis of histological data in viral hepatitis (Metavir) score. Patients with CAP ≥245 dB/m and CAP ≥270 dB/m were considered to have at least mild (≥S1) and moderate (≥S2) steatosis, respectively.

Demographics and clinical variables
For eligible patients, the following demographic and clinical variables were collected: age, gender, rheumatologic or dermatologic diagnosis, BMI, co-morbidities (diabetes mellitus, hypertension, dyslipidemia, and viral hepatitis), moderate alcohol use, MTX lifetime exposure, TE, CAP scores, probe type, and interquartile range. Liver enzymes, function and routine biochemistry were collected within 3 months preceding or following TE and CAP assessment. The Fibrosis-4 (FIB-4) index was calculated using the following formula:

\[
\text{FIB-4} = \frac{\text{age (years)} \times \text{AST}[\text{U/L}]}{\text{platelets}[10^9/\text{L}] \times (\text{ALT}[\text{U/L}])^{1/2}}.
\]

The aspartate aminotransferase to platelet ratio (APRI) was calculated using the formula

\[
\text{APRI} = \frac{\text{AST/upper limit of normal}}{\text{platelet count}[10^9/\text{L}] \times 100}.
\]

Statistical analysis
The IBM SPSS Statistics package, version 25 (IBM Corporation, Armonk, New York, USA), was used for analysis. The mean (SD) was used for descriptive quantitative variables. Two-sided t-tests were performed to determine significant between group differences between patients with and without steatosis. The Pearson correlation test was used to determine statistical association between cumulative MTX dose, steatosis, and fibrosis. Multivariate logistic regression analysis was used to determine predictors of steatosis and fibrosis.

RESULTS
A total of 172 patients on MTX were enrolled, of whom 82 were male (Table 1). PsO was the most frequent diagnosis (n = 55), followed by RA (n = 45) and PsA (n = 34). Steatosis (CAP ≥245 dB/m) was noted in 120 patients compared with 52 who did not have steatosis (CAP <245 kPa). TE score (7.67 kPa [SD 2.8] versus 4.6 kPa [SD 2.2]; p <0.05) and BMI (28.9 kg/m² [SD 6.2] versus 24.1 kg/m² [SD 3.4]; p <0.05) were higher in the steatosis group compared with the group without steatosis. The prevalence of steatosis was 69.8% in this population of patients on MTX. Most patients with PsA (85%), PsO (80%), and lupus (71%) had CAP evidence of steatosis.

Moderate to severe steatosis (CAP ≥270 dB/m) was identified in 48.3% of patients (n = 89) (Table 2). When compared with patients without moderate or severe steatosis, this group also had higher TE scores (8.3 kPa [SD 2.9] versus 4.6 kPa [SD 1.9]; p <0.05) and a higher mean BMI (29.8 kg/m² [SD 6.7] versus 24.7 kg/m² [SD 3.8]; p <0.05). Most patients with PsA (67%), PsO (66%), and lupus (52%) had CAP evidence of at least moderate steatosis. Conversely, only a minority of patients with RA had CAP evidence of at least moderate steatosis.

To analyze the correlation between steatosis as measured by CAP and lifetime MTX dose, we used Pearson correlation analysis (Figure 1). Higher CAP score was correlated with increased lifetime dose of MTX (r = 0.48, p = 0.001) (n = 85 patients).

Multivariate logistic regression analysis was used to determine clinical and demographic predictors of steatosis (Table 3). Predictors of steatosis (CAP ≥245 dB/m) included hypertension (OR 5.15, 95% CI 1.75–15.38), diabetes mellitus (OR 10.47, 95% CI 1.42–75.35), BMI ≥25 kg/m² (OR 10.1, 95% CI 1.88–37.14) and BMI ≥30 kg/m² (OR 16.47, 95% CI 5.56–45.56). Moderate alcohol use (OR 1.36, 95% CI 0.65–2.89), dyslipidemia (OR 2.25, 95% CI 0.70–6.65), male sex (OR 0.69, 95% CI 0.39–1.87), and past viral hepatitis (B or C) (OR 0.78, 95% CI 0.58–1.29) were not predictive of steatosis. Predictors of moderate to severe steatosis (CAP ≥270 dB/m) (shown in Table 4) included hypertension (OR 4.40, 95% CI 1.94–9.97), dyslipidemia (OR 3.75, 95% CI 1.48–9.50), diabetes mellitus (OR 4.60, 95% CI 1.47–14.49), and BMI ≥25 kg/m² (OR 1.98, 95% CI 1.58–2.50) in patients treated with MTX. Moderate alcohol use (OR 1.41, 95% CI 0.54–2.4), male sex (OR 1.02, 95% CI 0.54–1.92), and past viral hepatitis (OR 0.19, 95% CI 0.19–0.79) were not predictive of a higher risk of severe steatosis.

Multivariate logistic regression analysis revealed that predictors of moderate to severe fibrosis (Metavir ≥F2 = TE ≥8.0 kPa) among patients on MTX included moderate to severe steatosis.
Steatosis measured by CAP predicts fibrosis in long-term methotrexate use

Table 1: Demographic parameters of patients on methotrexate with CAP evidence of steatosis compared with no evidence of steatosis (N = 172)

| Variable                  | CAP <245 dB/m (n = 52) | CAP ≥245 dB/m (n = 120) | p-value |
|---------------------------|------------------------|-------------------------|---------|
| Age, y, mean (SD)         | 59.7 (13.5)            | 60.6 (12.5)             | >0.05   |
| Sex (male/female)         | 22/30                  | 60/60                   | >0.05   |
| Diagnosis, no. (%)        |                        |                         |         |
| PsA                       | 5 (10)                 | 29 (24)                 | <0.05†  |
| PsO                       | 11 (21)                | 44 (37)                 |         |
| RA                        | 23 (44)                | 22 (18)                 |         |
| Eczema                    | 5 (10)                 | 5 (4)                   |         |
| Lupus                     | 8 (15)                 | 20 (17)                 |         |
| Past HBV/HCV, no. (%)†    | 19 (36.5)              | 29 (24.1)               | >0.05   |
| AST, U/L, mean (SD)       | 27.4 (3.5)             | 34.3 (4.5)              | <0.05*  |
| ALT, U/L, mean (SD)       | 26.7 (2.8)             | 37.8 (4.2)              | <0.05*  |
| Platelets per mm³, mean (SD) | 270 (12.5)           | 274 (13.7)              | >0.05   |
| Albumin, g/L, mean (SD)   | 43.6 (3.6)             | 43.4 (4.2)              | >0.05   |
| Cumulative methotrexate dose, g, mean (SD) | 3.2 (1.4)              | 5.6 (2.1)               | <0.05*  |
| Diabetes mellitus, no. (%)| 2 (4)                  | 42 (35)                 | <0.05*  |
| Hypertension, no. (%)     | 4 (7.6)                | 55 (46)                 | <0.05*  |
| Dyslipidemia, no. (%)     | 4 (7.6)                | 46 (38)                 | <0.05*  |
| Moderate alcohol use, no. (%) | 13 (25)               | 77 (64)                 | <0.05*  |
| TE, kPa, mean (SD)        | 4.6 (2.2)              | 7.67 (2.8)              | <0.05*  |
| BMI, kg/m², mean (SD)     | 24.1 (3.4)             | 28.9 (6.2)              | <0.05*  |
| APRI, mean (SD)           | 0.32 (0.25)            | 0.45 (0.58)             | >0.05   |
| FIB-4, mean (SD)          | 1.28 (0.74)            | 1.47 (1.49)             | >0.05   |

* Statistically significant  
† Hepatitis C post sustained virologic response or past hepatitis B infection (surface antigen negative and core antibody positive) 
CAP = Computed attenuation parameter; PsA = Psoriatic arthritis; PsO = Psoriasis; RA = Rheumatoid arthritis; HBV = Hepatitis B virus; HCV = Hepatitis C virus; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; TE = Transient elastography; APRI = Aspartate aminotransferase to platelet ratio index; FIB-4 = Fibrosis-4 index

Pearson correlation analysis determined no correlation between TE and cumulative MTX dose (r = 0.12, p = 0.21).

**DISCUSSION**

Our study highlights the importance of metabolic syndrome and hepatic steatosis in the development of hepatic fibrosis. Steatosis was present in a large proportion of patients with rheumatologic and dermatologic diseases on MTX. Population estimates reveal a 5%–30% prevalence of steatosis.
Table 2: Demographic parameters of patients on methotrexate with CAP evidence of moderate to severe steatosis (N = 172)

| Variable                          | CAP ≤270 dB/m (n = 83) | CAP ≥270 dB/m (n = 89) | p-value |
|-----------------------------------|------------------------|------------------------|---------|
| Age, y, mean (SD)                 | 60.6 (13.3)            | 60.4 (13.2)            | >0.05   |
| Sex (male/female)                 | 33/50                  | 38/51                  | >0.05   |
| Diagnosis no. (%)                 |                        |                        |         |
| PsA                               | 12 (14)                | 25 (28)                | <0.05*  |
| PsO                               | 18 (22)                | 35 (40)                |         |
| RA                                | 33 (40)                | 12 (13)                |         |
| Eczema                            | 8 (10)                 | 4 (4)                  |         |
| Lupus                             | 12 (14)                | 13 (15)                |         |
| Past HBV/HCV, no. (%)†            | 25 (30)                | 23 (25)                | >0.05   |
| AST, U/L, mean (SD)               | 26.5 (4.2)             | 37.6 (5.5)             | <0.05*  |
| ALT, U/L, mean (SD)               | 26.3 (3.6)             | 38.5 (5.3)             | <0.05*  |
| Platelets per mm³, mean (SD)      | 275 (13.6)             | 276 (15.5)             | >0.05   |
| Albumin, g/L, mean (SD)           | 43.3 (4.4)             | 43.2 (3.8)             | >0.05   |
| Cumulative methotrexate dose, g, mean (SD) | 2.8 (1.6) | 6.4 (2.7) | <0.05*  |
| Diabetes mellitus, no. (%)        | 8 (9)                  | 35 (40)                | <0.05*  |
| Hypertension, no. (%)             | 15 (18)                | 44 (50)                | <0.05*  |
| Dyslipidemia, no. (%)             | 11 (13)                | 39 (44)                | <0.05*  |
| Moderate alcohol use, no. (%)     | 30 (36)                | 60 (68)                | <0.05*  |
| TE, kPa, mean (SD)                | 4.6 (1.9)              | 8.3 (2.9)              | <0.05*  |
| BMI, kg/m², mean (SD)             | 24.7 (3.8)             | 29.8 (6.7)             | <0.05*  |
| APRI, mean (SD)                   | 0.68 (0.24)            | 0.65 (0.28)            | >0.05   |
| FIB-4, mean (SD)                  | 1.3 (0.75)             | 1.5 (1.7)              | >0.05   |

* Statistically significant
† Hepatitis C post sustained virologic response or past hepatitis B infection (surface antigen negative and core antibody positive)
CAP: Computed attenuation parameter; PsA = Psoriatic arthritis; PsO = Psoriasis; RA = Rheumatoid arthritis; HBV = Hepatitis B virus; HCV = Hepatitis C virus; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; TE = Transient elastography; APRI = Aspartate aminotransferase to platelet ratio index; FIB-4 = Fibrosis-4 index

worldwide with locoregional variation (22,23). Previous studies have noted an increased prevalence of NAFLD in patients with PsO, as high as 59% (7,24). In our study, 80% of patients with PsO had evidence of steatosis. The risk of NAFLD appears to be even higher in patients with PsA and moderate to severe PsO compared with mild PsO (5). In our study, 85% of patients with PsA had evidence of steatosis. Chronic low-grade inflammation is postulated to play a role in the development of NAFLD in these patients (25). Conversely, NAFLD could be a driver for inflammation in keratinocytes and joints in PsO and PsA (8). Primary care data from the United Kingdom assessed the role of treatment of PsO, PsA and RA on the risk of NAFLD. When compared with the general population, treated and untreated patients with PsO had a higher risk of NAFLD. Patients treated for PsA had a higher risk for NAFLD, whereas those who were untreated did not. However, previous studies have not detected increased rates of NAFLD in RA patients regardless of treatment...
Steatosis measured by CAP predicts fibrosis in long-term methotrexate use

Table 3: Predictors of steatosis (CAP ≥245 dB/m) by multivariate logistic regression analysis

| Variable                  | Odds ratio (95% CI) | p-value |
|---------------------------|---------------------|---------|
| Moderate alcohol use      | 1.36 (0.65–2.89)    | >0.05   |
| Past HBV/HCV†             | 0.78 (0.58–1.29)    | >0.05   |
| Dyslipidemia              | 2.25 (0.70–6.65)    | >0.05   |
| Diabetes mellitus         | 10.47 (1.42–75.35)  | <0.05†  |
| Hypertension              | 5.15 (1.75–15.38)   | <0.05†  |
| BMI ≥30, kg/m²            | 7.75 (4.43–10.87)   | <0.05†  |
| BMI ≥25, kg/m²            | 1.98 (1.45–3.22)    | <0.05†  |
| Male                      | 1.02 (0.54–1.92)    | >0.05   |

* Statistically significant
† Hepatitis C post sustained virologic response or past hepatitis B infection (surface antigen negative and core antibody positive)
CAP = Computed attenuation parameter; HBV = Hepatitis B virus; HCV = Hepatitis C virus

Table 4: Predictors of moderate to severe steatosis (CAP ≥270 dB/m) by multivariate logistic regression analysis

| Variable                  | Odds ratio (95% CI) | p-value |
|---------------------------|---------------------|---------|
| Moderate alcohol use      | 1.41 (0.54–2.4)     | >0.05   |
| Past HBV/HCV†             | 0.19 (0.19–0.79)    | <0.05†  |
| Dyslipidemia              | 3.75 (1.48–9.5)     | <0.05†  |
| Diabetes mellitus         | 4.6 (1.47–14.49)    | <0.05†  |
| Hypertension              | 4.40 (1.94–9.97)    | <0.05†  |
| BMI ≥30, kg/m²            | 7.75 (4.43–10.87)   | <0.05†  |
| BMI ≥25, kg/m²            | 1.98 (1.45–3.22)    | <0.05†  |
| Male                      | 1.02 (0.54–1.92)    | >0.05   |

* Statistically significant
† Hepatitis C post sustained virologic response or past hepatitis B infection (surface antigen negative and core antibody positive)
CAP = Computed attenuation parameter; HBV = Hepatitis B virus; HCV = Hepatitis C virus

In our study, the mean BMI, rates of diabetes mellitus, hypertension and dyslipidemia were significantly higher among patients with steatosis. These observations could be related to the metabolic syndrome, the underlying inflammatory condition, MTX use or a combination of these. PsA is associated with a metabolic phenotype including dyslipidemia, hypertension, impaired fasting glucose, diabetes mellitus, and obesity (26). PsA patients have increased triglyceride levels and decreased high-density lipoprotein, which is consistent with dyslipidemia. Unexpectedly, their low-density lipoprotein-C levels are lower, but this is likely a result of systemic inflammation (27). Obesity is associated with a higher risk of developing PsA. Weight loss improved disease activity in patients with PsA and obesity (28). An increased risk of diabetes mellitus was noted in patients with PsO and PsA (29). Hypertension is more prevalent among patients with PsO and PsA (30). It is less certain whether there is a link between metabolic syndrome and RA. The data supporting a link between obesity and RA are mixed (26,31). Increased abdominal girth, independent of BMI, has been associated with RA (32). It remains unclear whether patients with RA are at increased risk of diabetes mellitus (29). RA patients, however, have a higher baseline blood pressure compared with the general population (33). Previous studies have...
Table 5: Predictors of moderate to severe fibrosis (Metavir ≥F2) by multivariate logistic regression analysis

| Variable                                      | Odds ratio (95% CI)   | p-value |
|----------------------------------------------|----------------------|---------|
| Moderate alcohol use                         | 3.06 (1.2–7.49)      | <0.05†  |
| Past HBV/HCV                                 | 0.36 (0.12–1.05)     | >0.05   |
| Dyslipidemia                                 | 3.71 (1.50–9.18)     | <0.05†  |
| Diabetes mellitus                            | 2.85 (1.09–7.48)     | <0.05†  |
| Hypertension                                 | 5.40 (2.23–13.0)     | <0.05†  |
| BMI ≥30, kg/m²                               | 3.38 (1.86–6.65)     | <0.05†  |
| BMI ≥25, kg/m²                               | 2.50 (1.58–4.51)     | <0.05†  |
| Steatosis (CAP ≥245 dB/m)                   | 4.94 (0.63–38.76)    | >0.05   |
| Moderate to severe steatosis (CAP ≥270 dB/m) | 8.36 (1.88–37.14)    | <0.05†  |
| APRI >0.7                                    | 2.27 (1.32–4.74)     | <0.05†  |
| FIB-4 >1.45                                  | 2.68 (1.49–5.33)     | <0.05†  |

* Meta-analysis of histological data in viral hepatitis
† Statistically significant
‡ Hepatitis C post sustained virologic response or past hepatitis B infection (surface antigen negative and core antibody positive)
CAP = Computed attenuation parameter; HBV = Hepatitis B virus; HCV = Hepatitis C virus; APRI = Aspartate aminotransferase to platelet ratio index; FIB-4 = Fibrosis-4 index

We demonstrated that patients with PsO on MTX develop more hepatic fibrosis than patients with RA (34). Concordantly, patients with PsO have higher rates of NAFLD than patients with RA. This observation has generated the hypothesis of the importance of metabolic syndrome and steatosis in the pathogenesis of hepatic fibrosis.

Our study noted a correlation between an increased total lifetime dose of MTX and increased steatosis by CAP score, which highlights the potential role of MTX in the development of steatosis. Liver biopsy has previously identified a non-alcoholic steatohepatitis (NASH)-like pattern of injury in 17 of 24 patients treated with MTX at a total cumulative dose of 5 g. Most of the patients who developed NASH-like changes had a feature of the metabolic syndrome. A positive correlation between MTX dose and NASH stage on biopsy was also noted (35). Our study provides further evidence supporting MTX’s potential role in the pathogenesis of steatosis in a dose-dependent fashion. Further studies should attempt to determine whether withdrawing MTX plays a role in reversing steatosis as measured by CAP.

We did not note a correlation between cumulative MTX dose and fibrosis as measured by TE. This is consistent with another study that has shown that cumulative MTX dose is not a predictor of fibrosis in the context of PsO (36). However, two further studies have identified that the duration of MTX exposure and higher cumulative MTX dose were correlated with fibrosis (37,38). High-quality prospective studies with sequential TE measurements are still lacking and would help determine whether cumulative MTX dose is associated with fibrosis.

We demonstrated that patients on MTX have significantly higher rates of fibrosis if they are known to have metabolic syndrome and moderate to severe steatosis. Understanding that MTX cumulative dose was not associated with increased fibrosis suggests that patient and disease factors may have a more significant role than MTX exposure alone in causing fibrosis. Fibrosis surveillance should be intensified in patients on MTX with known diabetes mellitus, hypertension, dyslipidemia, obesity, or hepatic steatosis.

We present further convincing data supporting the use of non-invasive markers of fibrosis and steatosis to guide the treatment of rheumatologic and dermatologic diseases. TE has been used to advise which patients on MTX have already developed fibrosis (12–14). However, our study shows that an increased CAP score can advise which patients are at increased risk of fibrosis. Moderate and severe steatosis were predictors of moderate and severe fibrosis. This is in support of steatosis playing a role in the development of fibrosis. Previous studies have identified that co-existent risk factors such as diabetes mellitus and obesity decrease the threshold at which patients on MTX develop severe fibrosis (39).

TE is thought to be limited by the presence of obesity. This is relevant to our study with high rates of metabolic syndrome and obesity. The XL probe can be used in the obese patient population and provides more reliable results than the standard M probe (40). The optimal CAP and histopathologic cut-offs for grading steatosis require further study and have not been fully validated (41,42). As a result, the optimal CAP cut-offs for steatosis grading provided in this study may change with further research. More importantly, the absolute CAP values ≥270 dB/m seen here have been shown to be a predictor of moderate to severe fibrosis. The CAP measurement can be easily obtained at the time of TE measurement and...
Steatosis measured by CAP predicts fibrosis in long-term methotrexate use

should be used to determine which patients on MTX are at increased risk of developing fibrosis.

The limitations of our study include its retrospective nature, which relies on the accuracy of medical records documentation. Patients had been referred to an academic tertiary care hepatology centre, and selection bias may have occurred for patients more likely to have hepatotoxicity. It was not possible to account for the use of corticosteroid medication which has previously been associated with NAFLD.

In summary, moderate to severe steatosis as measured by CAP (≥270 dB/m) and metabolic syndrome are predictors of moderate to severe fibrosis in patients on MTX. Patients known for the metabolic syndrome would likely benefit from a more intensive evaluation for fibrosis. Future studies should determine the optimal role of other non-invasive markers of fibrosis in screening patients prior to initiating MTX therapy as well as in surveillance.

ACKNOWLEDGEMENTS: The authors wish to thank Miroslaw Tomaszewski for his contribution in proofreading the manuscript.

CONTRIBUTIONS: Conceptualization, M Tomaszewski, SA Mohajerani, A Ramji; Methodology, M Tomaszewski, SA Mohajerani, HH Ko, A Ramji; Investigation, M Tomaszewski, M Dahiya, SA Mohajerani, H Punja, HH Ko, M Sun, A Ramji; Writing – Original Draft, M Tomaszewski, SA Mohajerani; Writing – Review & Editing, M Tomaszewski, M Dahiya, SA Mohajerani, H Punja, HH Ko, M Sun, A Ramji; Supervision, HH Ko, M Sun, A Ramji.

ETHICS APPROVAL: The study was approved by the University of British Columbia Providence Health Care Research Institute Research Ethics Boards (H19–02689).

INFORMED CONSENT: N/A

REGISTRY AND REGISTRATION NO. OF THE STUDY/TRIAL: N/A

FUNDING: No funding was received for this work.

DISCLOSURES: The authors have nothing to disclose.

PEER REVIEW: This article has been peer reviewed.

REFERENCES

1. Rohekar S, Chan J, Tse SM, et al. 2014 update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada treatment recommendations for the management of spondyloarthritis. Part II: Specific management recommendations. J Rheumatol. 2015;42(4):665–81. https://doi.org/10.3899/jrheum.141001. Medline: 25684768.

2. Bykerk VP, Akhavan P, Hazlewood GS, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559–82. https://doi.org/10.3899/jrheum.110207. Medline:21921096

3. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Risk of liver injury among methotrexate users: a meta-analysis of randomised controlled trials. Semin Arthritis Rheum. 2015;45(2):156–62. https://doi.org/10.1016/j.semarthrit.2015.05.003. Medline:26088004

4. Lertnawapan R, Chonprasertsuk S, Siramolpiwat S. Association between cumulative methotrexate dose, non-invasive scoring system and hepatic fibrosis detected by FibroScan in rheumatoid arthritis patients receiving methotrexate. Int J Rheum Dis. 2019;22(2):214–21. https://doi.org/10.1111/1756-185X.13442. Medline: 30565876

5. Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2015;29(4):656–62. https://doi.org/10.1111/jdv.12847. Medline:25418531

6. Haroon M, Rafiq Chaudhry AB, Fitzgerald O. Higher prevalence of metabolic syndrome in patients with psoriatic arthritis: a comparison with a control group of noninflammatory rheumatologic conditions. J Rheumatol. 2016;43(2):463–4. https://doi.org/10.3899/jrheum.150757. Medline:26834258

7. Carrascosa JM, Bonanad C, Dauden E, Botella R, Olveira-Martín A. Psoriasis and nonalcoholic fatty liver disease. Actas Dermosifiliogr. 2017;108(6):506–14. https://doi.org/10.1016/j.ad.2016.12.017. Medline:28318525

8. Ogdie A, Grewal SK, Noe MH, et al. Risk of incident liver disease in patients with psoriasis, psoriatic arthritis, and
rheumatoid arthritis: a population-based study. J Invest Dermatol. 2018;138(4):760–7. https://doi.org/10.1016/j.jid.2017.10.024. Medline:29104161

9. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents. J Am Acad Dermatol. 2009;61(3):451–85. https://doi.org/10.1016/j.jaad.2009.03.027. Medline:19493586

10. Bombardier C, Hazlewood GS, Akhavan P, et al. Canadian rheumatology association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: Part ii safety. J Rheumatol. 2012;39(8):1583–602. https://doi.org/10.1001/jrheum.120165. Medline:22707613

11. Shetty A, Cho W, Alazawi W, Syn WK. Methotrexate hepatotoxicity and the impact of nonalcoholic fatty liver disease. Am J Med Sci. 2017;354(2):172–81. https://doi.org/10.1016/j.amjms.2017.03.014. Medline:28864376

12. Iliescu M, Craciun RL, Stavar AN. The role of FibroScan in detecting hepatic fibrosis induced by methotrexate. ARS Med Tomitana. 2017;23(1):17–20. https://doi.org/10.1515/arsm-2017-0004.

13. Lynch M, Higgins E, McCormick PA, et al. The use of transient elastography and FibroTest for monitoring hepatoxicity in patients receiving methotrexate for psoriasis. JAMA Dermatol. 2014;150(8):856–62. https://doi.org/10.1001/jamadermatol.2013.9336. Medline:24964792

14. Mansour-Ghanaei F, Erfani A, Shafaghi A, et al. Transient elastography in methotrexate administered patients. Hepatitis Monthly 2017;17(8):e57917. https://doi.org/10.5812/hepatmon.57917.

15. Baranova A, Lal P, Birerdinc A, Younossi ZM. Non-invasive markers for hepatic fibrosis. BMC Gastroenterol. 2011;11:91. https://doi.org/10.1186/1471-230X-11-91. Medline:21849046

16. Rademaker M, Gupta M, Andrews M, et al. The Australasian Psoriasis Collaboration view on methotrexate for psoriasis in the Australasian setting. Australas J Dermatol. 2017;58(3):166–70. https://doi.org/10.1111/ajd.12521. Medline:27402434

17. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dermatol. 2020;82(6):1445–86. https://doi.org/10.1016/j.jaad.2020.02.044. Medline:32119894

18. Karlas T, Petroff D, Sasso M, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66(5):1022–30. https://doi.org/10.1016/j.jhep.2016.12.022. Medline:28039099

19. Lee JI, Lee HW, Lee KS. Value of controlled attenuation parameter in fibrosis prediction in nonalcoholic steatohepatitis. World J Gastroenterol. 2019;25(33):4959–69. https://doi.org/10.3748/wjg.v25.i33.4959. Medline:31543686

20. Petta S, Wong VW, Cammà C, et al. Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. Hepatol. 2017;65(4):1145–55. https://doi.org/10.1002/hep.28843. Medline:27639088

21. Iluz-Freundlich D, Uhanova J, Grubert Van Iderstine M, Minuk GY. The impact of primary biliary cholangitis on non-alcoholic fatty liver disease. Eur J Gastroenterol Hepatol. 2021;33(4):565–70. https://doi.org/10.1097/MEG.0000000000001782. Medline:32541239

22. Ruhl CE, Everhart JE. Fatty liver indices in the multiethnic united states national health and nutrition examination survey. Aliment Pharmacol Ther. 2015;41(1):65–76. https://doi.org/10.1111/apt.13012. Medline:25376360

23. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology. 2004;40(6):1387–95. https://doi.org/10.1002/hep.20466. Medline:15565570
24. Carrascosa JM, Bonanad C, Dauden E, Botella R, Olveira-Martín A; en nombre del Grupo de Trabajo en Enftramacion Sistema en P. Psoriasis and nonalcoholic fatty liver disease. Actas Dermosifiliogr. 2017;108(6):506–14. https://doi.org/10.1016/j.ad.2016.12.017. Medline:28318525. English, Spanish.

25. Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? Br J Dermatol. 2018;179(1):16–29. https://doi.org/10.1111/bjd.16239. Medline:29235656

26. Ferguson LD, Siebert S, McInnes IB, Sattar N. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. Nat Rev Rheumatol. 2019;15(8):461–74. https://doi.org/10.1038/s41584-019-0256-0. Medline:31292564

27. Mok CC, Ko GT, Ho LY, Yu KL, Chan PT, To CH. Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. Arthritis Care Res (Hoboken). 2011;63(2):195–202. https://doi.org/10.1002/acr.20363. Medline:20890981

28. Klingberg E, Bilberg A, Björkman S, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. Arthritis Res Ther. 2019;21(1):17. https://doi.org/10.1186/s13075-019-1810-5. Medline:30635024

29. Dubreuil M, Rho YH, Man A, et al. Diabetes incidence in psoriatic arthritis, psoriasis and rheumatoid arthritis: a UK population-based cohort study. Rheumatology (Oxford).2014;53(2):346–52. https://doi.org/10.1093/rheumatology/ket343. Medline:24185762

30. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens. 2013;31(3):433–42; discussion 442-3. https://doi.org/10.1097/HJH.0b013e32835bcce1. Medline:23249828

31. Rodríguez LA, Tolosa LB, Ruigomez A, Johansson S, Wallander MA. Rheumatoid arthritis in UK primary care: incidence and prior morbidity. Scand J Rheumatol. 2009;38(3):173–7. https://doi.org/10.1080/0300974082448825. Medline:19117247

32. Symmons DP, Bankhead CR, Harrison BJ, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum. 1997;40(11):1955–61. https://doi.org/10.1002/art.1780401106. Medline:9365083

33. Baker JF, Sauer B, Teng CC, et al. Initiation of disease-modifying therapies in rheumatoid arthritis is associated with changes in blood pressure. J Clin Rheumatol. 2018;24(4):203–9. https://doi.org/10.1097/RHU.0000000000000736. Medline:29664818

34. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009;68(7):1100–4. https://doi.org/10.1136/ard.2008.093690. Medline:19060002

35. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol. 2001;16(12):1395–401. https://doi.org/10.1046/j.1440-1746.2001.02644.x. Medline:11851839

36. Laharie D, Seneschal J, Schaeverbeke T, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. J Hepatol. 2010;53(6):1035–40. https://doi.org/10.1016/j.jhep.2010.04.043. Medline:20801541

37. Lynch M, Higgins E, McCormick PA, et al. The use of transient elastography and FibroTest for monitoring hepatotoxicity in patients receiving methotrexate for psoriasis. JAMA Dermatol. 2014;150(8):856–62. https://doi.org/10.1001/jamadermatol.2013.9336. Medline:24964792

38. Lertnawapan R, Chonprasertsuk S, Siramolpiwat S. Association between cumulative methotrexate dose, non-invasive scoring system and hepatic fibrosis detected by FibroScan in rheumatoid arthritis patients receiving methotrexate. Int J Rheum Dis. 2019;22(2):214–21. https://doi.org/10.1111/1756-185X.13442. Medline:30565876
39. Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. J Hepatol. 2007;46(6):1111–8. https://doi.org/10.1016/j.jhep.2007.01.024. Medline:17399848

40. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63(1):237–64. https://doi.org/10.1016/j.jhep.2015.04.006. Medline:25911335

41. Thiele M, Rausch V, Fluhr G, et al. Controlled attenuation parameter and alcoholic hepatic steatosis: diagnostic accuracy and role of alcohol detoxification. J Hepatol. 2018;68(5):1025–32. https://doi.org/10.1016/j.jhep.2017.12.029. Medline:29343427

42. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with non-alcoholic fatty liver disease. Gastroenterology. 2019;156(6):1717–30. https://doi.org/10.1053/j.gastro.2019.01.042. Medline:30689971