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Original Research Article.

Hepatic Fibrosis in Rheumatoid Arthritis Patients on Methotrexate Therapy: A Cross-Sectional Study Using Transient Elastography, APRI and FIB-4 Score

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ABSTRACT

Introduction: Methotrexate (MTX) is the cornerstone therapy for rheumatoid arthritis (RA); however, long-term use has been associated with hepatic fibrosis, which may progress silently and is not reliably detected by conventional liver function tests. Non-invasive tools such as transient elastography (TE), AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) score provide useful alternatives for early fibrosis assessment.

Objectives: To determine the prevalence of hepatic fibrosis in rheumatoid arthritis patients receiving methotrexate therapy and to evaluate its association with cumulative MTX exposure and metabolic risk factors using non-invasive modalities.

Materials and Methods: This was an observational cross-sectional study conducted on 125 RA patients aged ≥18 years receiving MTX therapy who attended the OPD/IPD at Government Medical College and Rajindra Hospital, Patiala. Patients underwent detailed clinical evaluation including age, sex, disease duration, MTX dose, duration, cumulative exposure, metabolic comorbidities, and concomitant medications. Hepatic fibrosis was assessed using transient elastography, APRI, and FIB-4 score, and its association with clinical and biochemical parameters was analyzed.

Results: In our study, the mean age of patients was 46.41 ± 12.39 years, with 73.6% females and 26.4% males. Most patients belonged to the 41–50 years age group (32.0%). The mean MTX dose was 17.52 ± 7.58 mg/week, mean duration of therapy was 3.85 ± 2.95 years, and mean cumulative dose was 3.63 ± 2.35 g. Obesity was present in 33.6% of patients, diabetes mellitus in 27.2%, hypertension in 36.8%, and metabolic syndrome in 42.4%. On transient elastography, 73.6% of patients had no/minimal fibrosis (F0–F1), while significant fibrosis (F2–F4) was observed in 26.4% of patients, including advanced fibrosis/cirrhosis in 11.2%. APRI >0.50 and FIB-4 >1.45 were observed in 55.2% and 50.4% of patients respectively. Significant fibrosis showed a strong association with higher cumulative MTX dose (p=0.004) and longer duration of therapy (p=0.002). On multivariable analysis, cumulative MTX exposure, obesity, diabetes, hypertension, and sex were independent predictors of hepatic fibrosis.

Conclusion: In our study, 26.4% of RA patients receiving methotrexate therapy had significant hepatic fibrosis. Higher cumulative MTX exposure and metabolic comorbidities were associated with increased risk of hepatic fibrosis. Early identification using non-invasive tools like FIB 4, APRI and FibroScan is essential for risk stratification and to ensure safe continuation of methotrexate therapy.

Keywords: Rheumatoid arthritis, Methotrexate, Hepatic fibrosis, Transient elastography, APRI, FIB-4.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and various extra-articular manifestations. It is one of the most common inflammatory arthritis, affecting approximately 0.5–1% of the global population and is associated with significant morbidity and disability.[1,2]

Methotrexate (MTX) remains the cornerstone of disease-modifying therapy for RA due to its proven efficacy, safety profile, and cost-effectiveness.[3] However, long-term use of MTX has been associated with hepatic toxicity, ranging from asymptomatic elevation of liver enzymes to progressive hepatic fibrosis and cirrhosis.[4,5]

The pathogenesis of MTX-induced hepatotoxicity involves multiple mechanisms including disruption of folate metabolism, oxidative stress, mitochondrial dysfunction, and activation of hepatic stellate cells, leading to collagen deposition and fibrogenesis.[4] These changes often occur insidiously and may not be reflected by routine biochemical tests, making early detection challenging.[6]

The risk of hepatic fibrosis is further amplified in the presence of metabolic comorbidities such as obesity, diabetes mellitus, dyslipidaemia, and metabolic syndrome, which are frequently seen in patients with RA.[7] These factors may act synergistically with MTX exposure and contribute to the development and progression of hepatic fibrosis.

Traditionally, liver biopsy has been considered the gold standard for assessing hepatic fibrosis; however, it is invasive, associated with complications, and not suitable for routine monitoring.[8] Non-invasive modalities such as transient elastography (TE), AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) score have emerged as reliable alternatives for assessing liver fibrosis and are increasingly being used in clinical practice.[9-12]

Despite increasing use of these modalities, there is limited data regarding the prevalence of hepatic fibrosis and its association with cumulative MTX exposure in RA patients, particularly in the Indian population.

Hence, the present study was undertaken to assess the prevalence of hepatic fibrosis in rheumatoid arthritis patients receiving methotrexate therapy and to evaluate its association with cumulative MTX exposure and metabolic risk factors using non-invasive methods.

MATERIAL AND METHODS

This observational cross-sectional study was conducted in the Department of Medicine at Government Medical College and Rajindra Hospital, Patiala, a tertiary care centre, over a period of one year. A total of 125 adult patients aged ≥18 years diagnosed with rheumatoid arthritis and receiving methotrexate therapy were included in the study.

Patients were recruited from both outpatient and inpatient departments after obtaining informed consent. Rheumatoid arthritis was diagnosed based on the 2010 ACR/EULAR classification criteria.

Patients with viral hepatitis (Hepatitis B or C), HIV infection, other autoimmune or inflammatory diseases, malignancy, significant alcohol intake, and pregnant or lactating females were excluded from the study. Patients with pre-existing chronic liver disease unrelated to methotrexate were also excluded.

All patients underwent a detailed clinical evaluation including history of age, sex, duration of disease, duration of methotrexate therapy, weekly dose, cumulative dose, associated comorbidities such as diabetes mellitus, hypertension, dyslipidaemia, and metabolic syndrome, and use of concomitant medications including steroids, hydroxychloroquine, leflunomide, sulfasalazine, and NSAIDs. A thorough general and systemic examination was performed in all cases.

Relevant laboratory investigations including complete blood count, liver function tests, renal function tests, lipid profile, and blood glucose levels were performed.

Hepatic fibrosis was assessed using transient elastography (TE), AST-to-platelet ratio index (APRI), and fibrosis-4 (FIB-4) score. Significant fibrosis was defined as TE stage ≥F2.[12] APRI and FIB-4 scores were calculated using standard formulas.

Ethical Approval

The study was approved by the Institutional Ethics Committee, Government Medical College and Rajindra Hospital, Patiala. Written informed consent was obtained from all study participants prior to enrolment.

Statistical Analysis

The collected data was analyzed using appropriate statistical methods. Descriptive statistics such as mean and standard deviation were used for continuous variables, while frequency and percentage were used for categorical variables. The Chi-square test was used to assess association between categorical variables. Multivariable logistic regression analysis was performed to identify independent predictors of hepatic fibrosis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 125 patients with rheumatoid arthritis receiving methotrexate therapy were included in the study.

The mean age of the study population was 46.41 ± 12.39 years, with an age range of 19–72 years. Majority of the patients were females (73.6%), while males constituted 26.4% of the study population. Most patients belonged to the 41–50 years age group (32.0%), followed by 51–60 years (24.0%) and 31–40 years (22.4%). Regarding disease characteristics, 49.6% of patients had rheumatoid arthritis duration ≤5 years, while 32.8% had duration between >5–10 years and 17.6% had duration >10 years. Joint deformities were present in 33.6% of patients, and extra-articular manifestations were observed in 86.4% of cases.

The mean methotrexate dose was 17.52 ± 7.58 mg/week. The mean duration of methotrexate therapy was 3.85 ± 2.95 years, and the mean cumulative dose was 3.63 ± 2.35g. Most patients had methotrexate exposure of >2–5 years (39.2%), and 24.0% had therapy duration of more than 5 years. Similarly, 45.6% of patients had cumulative dose in the >2–5 g category, while 24.0% had cumulative exposure of >5 g.

The mean body mass index (BMI) was 28.28 ± 4.60 kg/m². Based on BMI classification, 39.2% of patients were overweight and 33.6% were obese. Among comorbidities, metabolic syndrome was present in 42.4% of patients, dyslipidaemia in 41.6%, hypertension in 36.8%, and diabetes mellitus in 27.2%.

Hydroxychloroquine was the most commonly used concomitant drug (56.8%), followed by steroids (46.4%), NSAIDs (38.4%), leflunomide (23.2%), and sulfasalazine (19.2%). (Table 1)

The laboratory profile of the study population showed mean AST and ALT levels of 73.24 ± 36.71 IU/L and 64.33 ± 50.79 IU/L respectively. The mean alkaline phosphatase was 121.34 ± 33.81 IU/L, and mean total bilirubin was 0.84 ± 0.23 mg/dL. The mean platelet count was 273.34 ± 78.50 ×10³/µL, and mean haemoglobin was 10.87 ± 1.25 g/dL.

On transient elastography, the majority of patients (73.6%) had no or minimal fibrosis (F0–F1). Significant fibrosis (F2) was present in 15.2% of patients, advanced fibrosis (F3) in 8.0%, and cirrhosis (F4) in 3.2%. Overall, significant fibrosis (F2–F4) was observed in 26.4% of patients.

Based on APRI categorization, 44.8% of patients were in the low-probability group, 43.2% in the indeterminate group, and 12.0% in the high-probability group. APRI positivity (>0.50) was observed in 55.2% of patients. Similarly, according to FIB-4 score, 49.6% of patients were in the low-risk category, 39.2% in the indeterminate group, and 11.2% in the high-risk group. FIB-4 positivity (>1.45) was observed in 50.4% of patients. (Table 2)

A statistically significant association was observed between cumulative methotrexate dose and significant hepatic fibrosis ($\chi^2 = 11.270$, $p = 0.004$). The prevalence of significant fibrosis

increased from 10.5% in patients with cumulative dose ≤2 g to 46.7% in those with dose >5g. Similarly, methotrexate duration was significantly associated with fibrosis ($\chi^2 = 12.915$, $p = 0.002$). The prevalence of fibrosis increased from 13.0% in patients receiving methotrexate for ≤2 years to 50.0% in those with duration >5 years. (Table 3).

On multivariable logistic regression analysis, cumulative methotrexate dose, duration of therapy, BMI category, diabetes mellitus, hypertension, and sex were identified as independent predictors of significant hepatic fibrosis.

Patients with cumulative MTX dose >5 g had markedly higher odds of fibrosis compared to those with ≤2 g (OR 22.106, p=0.001). Similarly, MTX duration >5 years (OR 37.688, p<0.001) and obesity (OR 33.563, p<0.001) were strongly associated with fibrosis. Diabetes mellitus and hypertension were also significant predictors. (Table 4)

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Table 1: Baseline, Clinical and Metabolic Characteristics of Study Participants

Variable	Category	Value
Age (years)	**Mean ± SD**	46.41 ± 12.39
	Range	19–72
Sex	**Male**	33 (26.4%)
	Female	92 (73.6%)
Age group	**18–30**	12 (9.6%)
	31–40	28 (22.4%)
	41–50	40 (32.0%)
	51–60	30 (24.0%)
	>60	15 (12.0%)
RA duration	**≤5 years**	62 (49.6%)
	>5–10 years	41 (32.8%)
	>10 years	22 (17.6%)
Joint deformities	**Yes**	42 (33.6%)
Extra-articular manifestations	**Yes**	108 (86.4%)
MTX dose	**Mean ± SD**	17.52 ± 7.58
MTX duration	**Mean ± SD**	3.85 ± 2.95
MTX cumulative dose	**Mean ± SD**	3.63 ± 2.35
MTX duration	**≤2 yrs**	46 (36.8%)
	>2–5 yrs	49 (39.2%)
	>5 yrs	30 (24.0%)
MTX cumulative dose	**≤2 g**	38 (30.4%)
	>2–5 g	57 (45.6%)
	>5 g	30 (24.0%)
BMI	**Mean ± SD**	28.28 ± 4.60
BMI category	**Normal**	34 (27.2%)
	Overweight	49 (39.2%)
	Obese	42 (33.6%)
Diabetes	**Yes**	34 (27.2%)
Hypertension	**Yes**	46 (36.8%)
Dyslipidemia	**Yes**	52 (41.6%)
Metabolic syndrome	**Yes**	53 (42.4%)
Steroids	**Yes**	58 (46.4%)
Hydroxychloroquine	**Yes**	71 (56.8%)
Leflunomide	**Yes**	29 (23.2%)
Sulfasalazine	**Yes**	24 (19.2%)
NSAIDs	**Yes**	48 (38.4%)

Table 2: Laboratory Profile and Non-Invasive Fibrosis Assessment

A. Laboratory Parameters			
Parameter	**Mean ± SD**	**Min**	**Max**
AST	73.24 ± 36.71	16	130
ALT	64.33 ± 50.79	14	160
ALP	121.34 ± 33.81	55	195
Bilirubin	0.84 ± 0.23	0.38	1.38
Platelets	273.34 ± 78.50	103	418
Haemoglobin	10.87 ± 1.25	7.8	13.9
B. Fibrosis Assessment			
Parameter	**Category**	**n (%)**	
TE stage	**F0–F1**	92 (73.6%)	
	F2	19 (15.2%)	
	F3	10 (8.0%)	
	F4	4 (3.2%)	
Significant fibrosis	**Yes**	33 (26.4%)	
APRI	**<0.5**	56 (44.8%)	
	0.5–1.5	54 (43.2%)	
	>1.5	15 (12.0%)	
APRI >0.5	**Yes**	69 (55.2%)	
FIB-4	**<1.45**	62 (49.6%)	
	1.45–3.25	49 (39.2%)	
	>3.25	14 (11.2%)	
FIB-4 >1.45	**Yes**	63 (50.4%)	

Table 3: Association of Methotrexate Exposure with Fibrosis

Variable	**Category**	**No fibrosis**	**Fibrosis**	**Total**	**p-value**
MTX dose	**≤2 g**	34 (89.5)	4 (10.5)	38	
	>2–5 g	42 (73.7)	15 (26.3)	57	
	>5 g	16 (53.3)	14 (46.7)	30	**0.004**
MTX duration	**≤2 yrs**	40 (87.0)	6 (13.0)	46	
	>2–5 yrs	37 (75.5)	12 (24.5)	49	
	>5 yrs	15 (50.0)	15 (50.0)	30	**0.002**

Table 4: Multivariable Logistic Regression Analysis for Predictors of Significant Hepatic Fibrosis

Predictor	**Comparison**	**OR**	**95% CI**	**p-value**
MTX dose	**>2–5 g**	5.375	1.047–27.596	0.044
	>5 g	22.106	3.706–131.860	0.001
MTX duration	**>2–5 yrs**	6.448	1.367–30.420	0.019
	>5 yrs	37.688	5.249–270.590	0.000
BMI	**Overweight**	9.185	1.487–56.714	0.017
	Obese	33.563	4.914–229.251	0.000
Diabetes	**Yes**	9.806	2.372–40.547	0.002
Hypertension	**Yes**	8.652	2.176–34.401	0.002
Sex	**Female**	0.148	0.036–0.608	0.008

DISCUSSION

Methotrexate (MTX) remains the cornerstone of therapy in rheumatoid arthritis; however, its long-term use has been associated with hepatotoxicity and development of hepatic fibrosis. In the present study, significant hepatic fibrosis (F2–F4) was observed in 26.4% of patients.

Similar findings have been reported in previous studies. Lertnawapan et al.[13] reported a comparable prevalence of hepatic fibrosis in RA patients receiving methotrexate therapy. However, lower prevalence has been reported in some studies, which may be due to differences in study population, duration of therapy, and presence of metabolic risk factors.[14,15]

In our study, a significant association was found between cumulative methotrexate dose and hepatic fibrosis (p=0.004). The prevalence of fibrosis increased progressively from 10.5% in patients with cumulative dose ≤2 g to 46.7% in those with dose >5 g. Similar dose-dependent association has been demonstrated by Miyata et al.[16] suggesting that cumulative exposure plays an important role in hepatic injury.

Duration of methotrexate therapy was also significantly associated with fibrosis (p=0.002). Patients receiving MTX for more than 5 years had a higher prevalence of fibrosis (50.0%) compared to those with shorter duration. These findings are consistent with previous studies, which have highlighted prolonged exposure as an important risk factor for hepatic fibrosis.[17]

In the present study, metabolic factors such as obesity, diabetes mellitus, and hypertension showed a significant association with hepatic fibrosis. On multivariable analysis, these factors emerged as independent predictors. Similar observations have been reported in earlier studies, which suggest that metabolic syndrome contributes significantly to liver fibrosis in patients on MTX therapy.[18,19] Non-invasive fibrosis markers such as APRI and FIB-4 identified a larger proportion of patients at risk compared to transient elastography. APRI positivity was seen in 55.2% and FIB-4 positivity in 50.4% of patients, whereas significant fibrosis on elastography was seen in 26.4% of patients. This indicates that serum-based markers may be useful screening tools, although their specificity is limited. Similar findings have been reported in previous studies evaluating non-invasive fibrosis assessment tools.[20]

In our study, majority of patients (73.6%) had no or minimal fibrosis (F0–F1), suggesting that clinically significant fibrosis is present only in a subset of patients. This supports the continued use of methotrexate with appropriate monitoring rather than routine discontinuation.

CONCLUSION

In the present study, 26.4% of rheumatoid arthritis patients receiving methotrexate therapy had significant hepatic fibrosis on transient elastography. Higher cumulative methotrexate dose and longer duration of therapy were significantly associated with increased risk of fibrosis. Metabolic factors such as obesity, diabetes mellitus, and hypertension were also found to be important independent predictors. Non-invasive markers such as APRI and FIB-4 identified a larger proportion of patients at risk; however, transient elastography remains a more reliable tool for assessment of hepatic fibrosis.

These findings suggest that while methotrexate can be safely continued in most patients, regular monitoring and risk stratification based on cumulative dose, duration of therapy, and metabolic factors are essential to prevent progression of hepatic fibrosis and prevent further complications.

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