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# Utility of Transient elastography of liver in patients with Rheumatoid arthritis on methotrexate

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**Abstract**

**Background:** *Methotrexate is an anchor drug in the treatment of Rheumatoid arthritis. But it can cause liver toxicity on long term treatment. Liver enzymes are conventionally monitored to detect the liver toxicity. Transient elastography (TE) is a novel tool to detect the fibrosis of the liver.*

**Aim:** *To find out the utility of Transient elastography of liver in patients with Rheumatoid arthritis on methotrexate*

**Materials and Methods:** *50 patients with Rheumatoid arthritis (RA) on methotrexate for more than 2 years were subjected to Transient elastography evaluation. The resistance or stiffness offered by the liver was measured in kilopascals. According to the stiffness of the liver, the amount of fibrosis was graded from F0 to F4 using colour codes. Stiffness of < 6 kilopascals (kpa) is graded under F0; 6-7.2 kpa = grade F1; 7.3 -8.1 KPA = grade F2; 8.2 – 8.8 kpa = grade F2-F3; 8.9 – 10.5 kpa = grade F3; 10.6 – 11.8 kpa = grade F3-F4; > 11.8 kpa = grade F4. Serum Alanine transaminase (ALT) was measured in all patients.*

**Results:** *50 patients with RA on methotrexate for more than 2 years were enrolled. The duration of treatment with methotrexate ranged from 2- 6.5 years. The stiffness of liver ranged from 2.7 to 8.6kpa. Grade 0 fibrosis (F0) = 40 patients; Grade 1 fibrosis (F1) = 7 patients; Grade 2 fibrosis (F2) = 2 patients; Grade 2-3 fibrosis (F2-F3) = 1; No patients were in grade 3 fibrosis or more.10 patients had elevated ALT above upper limit of normal (40 U/L). No patients had elevated serum ALT of more than two times of normal. Nine patients with normal ALT had evidence for fibrosis in TE. One patient in F2 grade and one patient in F2-F3 grade had normal ALT.*

**Conclusion:** *Transient elastography of liver is more useful than liver enzymes in monitoring the liver toxicity in RA patients on long term methotrexate.*

**Keywords:** *methotrexate, liver toxicity, alanine transaminase, Transient elastography.*

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology characterised by symmetric peripheral polyarthritis.[1] Even though the treatment armamentarium for RA is wide, methotrexate is still considered as the anchor drug which can be used as monotherapy or in combination with other conventional (cDMARDs) or biologic (bDMARDs) disease modifying anti rheumatic

drugs. Since RA can only be controlled by drugs, patients may need long term treatment to prevent joint damage and further deformities. Exposure to methotrexate for prolonged period may induce liver toxicity ranging from transaminitis to cirrhosis of liver.[2] So monitoring for liver damage is mandatory to prevent further progression of hepatotoxicity. Conventionally liver enzymes and serum albumin are monitored to detect early liver involvement. Alanine aminotransferase may be ineffective in monitoring drug induced liver injury.[3,4] Serum albumin may be normal until decompensation of the liver occurs. Transient elastography is a novel technique to detect early fibrosis of the liver.[5]This study is aimed to find out the utility of Transient elastography in patients with RA on long term methotrexate.

**Materials and Methods**

50 patients with Rheumatoid arthritis on methotrexate, attending Rheumatology outpatient department of our tertiary care centre for more than two years were enrolled consecutively in this study. Those patients with positive hepatitis B and C infection, diabetes mellitus, metabolic syndrome and history of alcoholism were excluded. All patients underwent Transient elastography study of liver along with serum alanine transaminase (ALT) estimation. Transient elastography (TE) measures the stiffness of the liver in kilopascals (kpa). According to the stiffness of the liver, the amount of fibrosis is graded from F0 to F4 using colour codes. Since there is no separate colour code for methotrexate induced liver fibrosis, the colour code for Non Alcoholic Fatty Liver Disease (NAFLD) was taken for the reference value. Stiffness of < 6 kilopascals (kpa) is graded under F0; 6-7.2 kpa = grade F1; 7.3 -8.1 KPA = grade F2; 8.2 – 8.8 kpa = grade F2-F3; 8.9 – 10.5 kpa = grade F3; 10.6 – 11.8 kpa = grade F3-F4; > 11.8 kpa = grade F4 (Table 1). This is an observational study to analyse the level of liver injury using TE in RA patients.

**Results**

Of the 50 patients enrolled for the study, 11 were males and 39 were females. The age group ranged from 27 to 58 years with a mean of 43.5 years. The duration of the illness ranged from 3.25 to 7.5 years with a mean of 5.3 years. The duration of treatment on methotrexate ranged from 2 to 6.5 years with a mean of 4.45 years. The dose of methotrexate ranged from 10 to 20 mg/week with a mean of 16.5mg/week.

Of the 50 patients underwent Transient Elastography, (Table 2), 40 patients had no evidence for liver fibrosis (F0 < 6 kpa). 7 patients had grade F1 fibrosis (6 – 7.2 kpa). 2 patients had grade F2 fibrosis (7.3 – 8.1 kpa). One patient had grade F2-F3 fibrosis (8.2-8.8 kpa). No patient had grade F3 fibrosis or above. Total of 10 patients out of 50 had evidence for fibrosis in Transient Elastography with the prevalence of 20% of liver fibrosis in patients with Rheumatoid arthritis on long term methotrexate of more than 2 years. Of the 50 patients alanine amino transaminase was elevated in 10 patients in the range of 41 – 60 U/Lwith the prevalence of 20%. No patient had elevated ALT of more than two times of upper limit of normal.

Out of 10 patients with elevated ALT, (Table 3) only one patient had evidence for fibrosis (F2=8kpa) in TE. Among the other9 patients with elevated ALT, no one had evidence for fibrosis (F0) in TE. Out of 10 patients with evidence for fibrosis, (Table 4) only one patient had elevated ALT (45 U/L). Other nine patients with evidence for fibrosis in TE had normal ALT (<40 U/L). The liver fibrosis in TE was not correlating with serum ALT level.

**Table 1** Grading of liver fibrosis in Transient Elastography

| Stiffness in Kpa | Fibrosis grade(F) |
|---|---|
| < 6 | F0 |
| 6-7.2 | F1 |
| 7.3-8.1 | F2 |
| 8.2-8.8 | F2-F3 |
| 8.9-10.5 | F3 |
| 10.6-11.8 | F3-F4 |
| >11.8 | F4 |

**Table 2** Grading of liver fibrosis in patient population

| No. of patients ( N=50) | Liver fibrosis (F) |
|---|---|
| 40 | F0 |
| 7 | F1 |
| 2 | F2 |
| 1 | F2-F3 |
| 0 | F3 |
| 0 | F3-F3 |
| 0 | F4 |

**Table 3** Liver fibrosis in patients with elevated ALT

| ALT level (U/L) | Liver fibrosis (kpa) | Fibrosis grade (F) |
|---|---|---|
| 41 | 4.5 | F0 |
| 41 | 5.1 | F0 |
| 43 | 3.3 | F0 |
| 44 | 4.1 | F0 |
| 44 | 4.8 | F0 |
| 45 | 8 | F2 |
| 46 | 4 | F0 |
| 49 | 4 | F0 |
| 52 | 5.3 | F0 |
| 60 | 3.5 | F0 |

**Table 4** ALT level in the presence of liver fibrosis in TE

| Liver fibrosis (kpa>6) | Fibrosis grade (F) | ALT level (U/L) |
|---|---|---|
| 6.1 | F1 | 19 |
| 6.1 | F1 | 21 |
| 6.1 | F1 | 27 |
| 6.4 | F1 | 21 |
| 6.4 | F1 | 25 |
| 6.6 | F1 | 16 |
| 6.8 | F1 | 21 |
| 7.8 | F2 | 21 |
| 8 | F2 | 45 |
| 8.6 | F2-F3 | 26 |

## Discussion

Rheumatoid arthritis is one of the common rheumatic diseases with a prevalence of around 1% in the general population. Even though so many conventional andbiologic DMARDs are used for the treatment, methotrexate is the anchor drug in all patients unless contraindicated. Since the patients will need long term treatment with methotrexate, one has to monitor for serious adverse effects like cytopenias, interstitial lung disease and indeed methotrexate related liver disease.[2] The methotrexate related liver diseases include transient elevation of liver enzymes, fatty liver, liver fibrosis, cirrhosis of liver and liver failure. It may be due to reduction in hepatic folate stores, but is not confirmed in research studies even though folic acid supplementation is associated with lower incidence of elevated transaminases.[6] Increased extracellular adenosine due to inhibition of 5-aminoimidazole 4-carboxamide ribonucleotide formyltransferase by methotrexate may lead to up regulation of collagen production and suppression of metalloproteinases resulting in fibrosis.[7] So regular monitoring for liver adverse effects is mandatory in all patients on methotrexate.

Monitoring of liver toxicity involves both invasive and non-invasive methods. Liver biopsy is considered as a gold standard for liver diseases. But it is an invasive procedure requiring hospital admission. It is costly and associated with significant morbidity (1%) and mortality (0.01 – 0.1%).[8] About 20%-30% of cases of liver biopsy may have sampling errors and inter pathologist variation.[9] These limitations favour non-invasive methods which include biochemical markers and imaging. Biochemical modalities include ALT to platelet ratio, Fibro Test, Fibro Spect, European liver fibrosis panel, Hepascore and procollagen type III N-terminal peptide.[10] Imaging techniques include MRI elastography and ultrasound scan based elastography like Strain elastography, Transient elastography, point shear wave elastography and two dimensional shear wave elastography.[5]

In this study we used Transient Elastography (TE) and Alanine transaminase (ALT) for monitoring methotrexate related liver disease. The prevalence of liver fibrosis in our study is 20% in patients on long term methotrexate of more than 2 years. In Visser K et al reported a prevalence of 16.3% liver fibrosis by liver biopsyin patients on methotrexate.[11] Robinson et al found a prevalence of 25.6% liver fibrosis in 43 patients of psoriasis on methotrexate by liver biopsy.[12] The prevalence of liver fibrosis was 22% in 49 patients with

psoriasis on methotrexate studied by Boffa et al by liver biopsy.[13] A study of 104 psoriatic patients on methotrexate by Malatjalian et al revealed 20% having liver fibrosis by liver biopsy.[14] In Rosenberg et al study, they reported a prevalence of liver fibrosis in 20% of patients by liver biopsy in 71 psoriatic patients.[15] These studies are consistent with our study revealing a prevalence of liver fibrosis in 20% of our patients on long term methotrexate by using a non- invasive technique of TE. In a meta–analysis the sensitivity and specificity of TE was 87% and 91% respectively for hepatic cirrhosis compared with liver biopsy.[16]

The prevalence of ALT elevation in our study is 20% in patients on long term methotrexate. A systematic review found that 20% of patients on methotrexate for 1 year had elevated transaminases.[17] Two recent studies reported a prevalence of elevated transaminases in 22% of patients on methotrexate.[18,19] These studies are consistent with our study. But we observed no patients with elevated ALT of more than two times of upper limit of normal. Salliot C et al reported 13% of their patients on methotrexate with elevated transaminase level greater than twice the upper limit of normal.[17] Studies by Curtis JR et al[18] and Dirven et al[19] revealed 1% of patients on methotrexate having elevated transaminases more than twice the upper limit of normal. Surprisingly, out of 10 patients with liver fibrosis by TE, only one patient had elevated ALT in our study not correlating with each other. Again of the 10 patients with elevated ALT, only one had liver fibrosis by TE not correlating with each other. Lewis JH et al[3] and Senior R[4] have observed that transaminase levels are ineffective in liver fibrosis. The explanation may be that the liver fibrosis due to methotrexate may be preceded by more of apoptotic liver injury rather than necrosis. Only in liver cell necrosis the transaminases will be released into the circulation raising their level. The elevated ALT with absent fibrosis may be explained by earlier stages of liver injury before the formation of fibrosis.

In summary the prevalence of liver fibrosis is 20% in patients with Rheumatoid arthritis on long term methotrexate using TE. Serum ALT is not useful in detecting early liver fibrosis in patients on methotrexate. TE is far superior to serum transaminases in monitoring for liver fibrosis in patients with Rheumatoid arthritis on methotrexate. Harriet S Sheng[5] recommend that TE should be considered within 6 months of starting methotrexate and if TE < 7.5 kpa, it should be repeated every 3 years; If the stiffness by TE is 7.5-9.5, the test should be repeated in 1 year with a referral to a hepatologist; If the TE is > 9.5 kpa, liver biopsy and other liver related investigations should be considered. Further studies with large study population may be needed to establish the utility of TE in patients on methotrexate.

**Disclosure**

The authors report no conflicts of interest in this study.

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