

## Use of Transient Elastography in Detection of Liver Fibrosis in Psoriasis Patients – A Cross- Sectional Study

### Abstract

**Background and Aims:** The risk of liver damage in psoriasis increases with increase in cumulative dose of methotrexate and guidelines suggest use of liver biopsy for risk mitigation. Recently, transient elastography (TE) has been used for detection of liver fibrosis. Most studies for TE are in hepatitis B and C patients. However, psoriasis patients have risk factors like metabolic syndrome which predisposes them to increased risk of liver damage due to methotrexate. This underlying liver disease may change the TE values in patients with psoriasis. The aim of this study is to determine utility of transient elastography in detection of liver fibrosis in patients with psoriasis. **Methods:** 82 patients with chronic plaque psoriasis requiring systemic therapy or already on methotrexate were included in the study. Clinical examination and biochemical investigations were conducted. Data were analysed using STATA 12.1 (Texas, USA). Univariate analysis using Chi-square and independent 't-test' was carried out to evaluate the association between categorical variables and outcomes. **Results:** Patients consists of 62 males and 20 females. TE value  $>7$  kPa (kilopascal) were seen in 23 patients and  $<7$  kPa were seen in 59 patients. Value of  $>7$  kPa was significantly associated with age, waist circumference, diastolic blood pressure, fasting and post prandial blood sugar, AST, PASI and presence of metabolic syndrome. Cumulative methotrexate dose was not significantly associated with high TE value. Mean TE value in patients with metabolic syndrome was significantly higher. **Limitations:** Small sample size and inability to confirm TE findings on liver biopsy. **Conclusion:** TE is a non-invasive tool for detection of liver fibrosis. Value of  $>7$  kPa correlates with liver fibrosis in most chronic liver diseases. However, high prevalence of metabolic syndrome in psoriasis patients may confound utility of TE for monitoring of methotrexate toxicity.

**Keywords:** Liver fibrosis, metabolic syndrome, methotrexate, psoriasis, transient elastography

### Introduction

Psoriasis is a chronic, idiopathic, T cell mediated autoimmune disorder. It typically involves skin, nails and joints. Methotrexate is the most commonly used systemic agent for the management of psoriasis. Other options are narrow band ultraviolet B (NB-UVB), cyclosporine, acitretin and biologics. Due to its effectiveness, easy availability, oral route of administration and economic factors, methotrexate remains the first choice for systemic treatment of psoriasis in the absence of contraindications. Hepatotoxicity is the one of the most common adverse effects of long term use of methotrexate. Liver biopsy is the gold standard for detection of liver fibrosis. However, it is an invasive procedure with significant morbidity; like bleeding, pneumothorax and rarely even mortality.<sup>[1]</sup> American guidelines advise

liver biopsy in patient after cumulative dose of 3.5-4 gm in low risk patients and delayed baseline biopsy in high risk patients (metabolic syndrome, alcohol consumption and pre-existing liver disease). The 2016 British guidelines advise use of procollagen type III N-terminal peptide (PIIINP) with routine liver biochemistry for methotrexate monitoring. The 2017 Australasian guidelines advise use of transient elastography (TE) for monitoring.<sup>[2-4]</sup> Transient elastography is a relatively new tool for monitoring of liver fibrosis. It has been studied in hepatitis B and C induced liver fibrosis. TE values correlates with histologic scoring (METAVIR) for hepatitis C. There are not many studies utilising TE for monitoring methotrexate-induced liver fibrosis, especially in psoriasis patients. Psoriasis is associated with obesity, metabolic syndrome and non-alcoholic

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fatty liver disease in significant number of patients. These co-morbid conditions can affect the liver health and TE value in psoriasis patients.

## Methods

This study was cross-sectional in nature. The study was conducted in a tertiary care centre of eastern India between Jan 2017-Dec 2017. Institutional ethical committee clearance was obtained. Patients with chronic plaque psoriasis who were candidates for systemic therapy (psoriasis area severity index (PASI)>10, body surface area (BSA)>10%) or who were already on systemic therapy with methotrexate and willing to be part of study were included in study. Exclusion criteria of the study were hepatitis B, hepatitis C, excessive alcohol intake (>20 gm/day in males, >10 gm/day in females), concomitant systemic medication for psoriasis other than methotrexate, any other hepatotoxic medication.

Demographic data, PASI, BSA, physician global assessment (PGA) score, body mass index (BMI), waist circumference in cm, blood pressure and cumulative dose of methotrexate were recorded for all patients. Blood sugar fasting and post prandial, lipid profile, serum uric acid, liver biochemistry and transient elastography were done for all patients and recorded in the proforma.

Data was analysed using STATA 12.1 (Texas, USA). All continuous variables except gender were expressed as mean  $\pm$  standard deviation (SD). Univariate analysis using Chi-square and independent 't-test' was carried out to evaluate the association between categorical variables and outcomes. A *P* value of < 0.05 was considered statistically significant.

### Technique: Transient elastography

TE unit consists of probe, electronic system and control unit. The probe contains a low frequency (50 MHz) vibrator and 5 MHz transducer. The transducer acts as

emitter and receiver. The vibrator sends low frequency elastic waves through the medium examined. With the help of an automated processor, elasticity value of the liver is calculated. These measurements are done on the right lobe of liver in intercostal spaces. A minimum of 10 readings are taken to obtain the median value by an experienced operator. Obesity can lead to failure to obtain correct TE value and obese people require separate probe. Results are expressed in kilopascals (kPa). It ranges from 1.5 to 75 kPa and normal values are around 5 kPa. Values of >7 kPa are considered as indicative of fibrosis, while diagnosis of cirrhosis has different threshold for different diseases.<sup>[5]</sup>

## Results

A total of 94 patients of chronic plaque psoriasis were assessed for inclusion. 82 patients were included in the study, out of which 62 were males and 20 were females. 12 patients were excluded (6 - excessive alcohol intake, 2 - hepatitis C positive, 1 - hepatitis B positive, in 3 patients, TE could not be performed due to obesity). Mean age of the patients and mean duration of disease were 47 years and 10 years, respectively. 32 patients (39%) had metabolic syndrome.

Depending on TE value, the patients were divided in two groups [Table 1]. 59 patients had TE value of 7 Kpa or less and 23 patients had TE value of more than 7 kPa. Age of the patient, higher waist circumference, diastolic blood pressure, fasting and post prandial blood sugar, aspartate aminotransferase (AST), presence of metabolic syndrome, severe psoriasis were associated with higher TE value. In subgroup with metabolic syndrome (*n* = 32), TE value was higher and statistically significant. There was no significant difference in cumulative methotrexate intake in patients with either lower or higher (>7 kPa) TE value.

In the group with cumulative methotrexate intake of less than 1.5 gms (*n* = 60), TE value was found to be

**Table 1: Demographic data based on the TE value (kPa)**

Variable	All patients (n=82) (Mean $\pm$ SD)	TE $\leq$ 7 kPa (n=59) (Mean $\pm$ SD)	TE >7 kPa (n=23) (Mean $\pm$ SD)	<i>P</i>
Age	47.04 $\pm$ 12.45	44.29 $\pm$ 12.02	53.13 $\pm$ 11.53	0.02
Male	62	44 (73.3)	16 (26.6)	0.42
Duration	10.01 $\pm$ 8.68	8.39 $\pm$ 7.20	13.09 $\pm$ 10.55	0.21
BMI	25.16 $\pm$ 3.95	24.65 $\pm$ 3.64	26.70 $\pm$ 4.37	0.07
Waist	93.03 $\pm$ 9.28	90.87 $\pm$ 8.52	99.23 $\pm$ 8.21	0.01
DBP	81.16 $\pm$ 7.19	79.96 $\pm$ 6.65	85.18 $\pm$ 6.86	0.03
Sugar (F)	94.66 $\pm$ 29.56	92.90 $\pm$ 32.26	99.79 $\pm$ 22.81	0.05
Sugar (PP)	129.51 $\pm$ 47.48	122.10 $\pm$ 44.52	148.42 $\pm$ 52.91	0.04
AST	29.93 $\pm$ 18.36	28.14 $\pm$ 20.11	34.61 $\pm$ 12.60	0.03
PASI	16.26 $\pm$ 7.99	15.48 $\pm$ 7.29	17.64 $\pm$ 9.24	0.04
PGA	3.76 $\pm$ 1.05	3.60 $\pm$ 0.93	4.09 $\pm$ 1.23	0.003
Metabolic syndrome	32	18 (30.5)	14 (60.86)	0.01
Methotrexate				
<1.5	60	45	15	0.063
>1.5	22	12	10	

5.31 ( $\pm 1.21$ ) kPa in absence of metabolic syndrome and 7.03 ( $\pm 1.84$ ) kPa in presence of metabolic syndrome. This difference was also statistically significant. In second group ( $n = 22$ ), TE value was 13.11 ( $\pm 11.97$ ) kPa in presence of metabolic syndrome and 8.87 ( $\pm 5.87$ ) kPa in the absence of metabolic syndrome. However, this difference was statistically not significant [Table 2].

## Discussion

TE is a relatively new, non-invasive method for detection of liver fibrosis. The prevalence of hepatic fibrosis in patients taking methotrexate is approximately 5%.<sup>[6]</sup> Psoriasis patients, unlike patients with rheumatoid arthritis or inflammatory bowel disease, have higher risk of development of liver injury due to risk factors like metabolic syndrome, obesity and alcohol intake. Prevalence of advanced liver fibrosis in severe psoriasis as detected by TE in recent study was found to be 14.1%.<sup>[7]</sup> Monitoring of methotrexate toxicity in patients with psoriasis is more stringent as compared to other subset of patients. Due to morbidity associated with liver biopsy, newer guidelines emphasise on non-invasive modalities as the first line of assessment for methotrexate toxicity.<sup>[8]</sup> Australasian guidelines advocates baseline TE, if TE value is  $< 7.5$  kPa repeated every 1-3 years. If value is between 7.5-9.5 kPa, repeat after 1 year and consider referral to hepatologist. If value is more than 9.5 kPa, liver biopsy or other specific investigations are indicated.<sup>[4]</sup>

A meta-analysis conducted in 2007 concluded that TE has sensitivity and specificity of 87% and 91%, respectively, for diagnosis of liver cirrhosis arising from various causes (predominantly HCV infection).<sup>[9]</sup> TE has a high negative predictive value ( $> 90\%$ ) and positive predictive value of 75% in diagnosis of cirrhosis. Use of TE in psoriasis has shown a good negative predictive value and identified 88% patients without fibrosis in study of 24 patients.<sup>[10]</sup> In a recent study, cut-off TE of 7.1 kPa had sensitivity of 50% and specificity of 76.9% for detection of methotrexate associated liver injury in patients with psoriasis.<sup>[11]</sup> In this study, 23 patients (28%) had TE value of  $> 7$  kPa. High prevalence of metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) in psoriasis may influence TE

measurement.<sup>[11]</sup> Our study showed metabolic syndrome in 39% of patients. High TE score ( $> 7$  kPa) in our study was significantly associated with age, waist circumference, AST level, diastolic blood pressure, fasting and post prandial blood sugar levels, PASI score, PGA and presence of metabolic syndrome. The total cumulative dose of methotrexate was not found to be significantly associated with high TE value in our study. This finding is similar to studies published by Laharie *et al.* on 111 patients of psoriasis and Pongpit *et al.* on 168 patients, where they found metabolic factors and not methotrexate dose or duration to be significantly associated with high TE value.<sup>[11,12]</sup> This study also showed inability of TE to be performed in obese patients, seen in 3% patients. However, failure rate of TE due to obesity varies from 1.8% to 52% in previous studies.<sup>[13,14]</sup> This wide variation in failure rate may be due to unavailability of XL probe required for obese patients in previous studies.

## Conclusion

TE is a non-invasive method for detection of liver fibrosis. However, its role in detection of liver fibrosis due to methotrexate toxicity in psoriasis patients is not yet established. Unlike other diseases, high prevalence of metabolic syndrome and NAFLD in psoriasis confounds the TE measurements in this subset of patients. It is important to perform baseline TE in psoriasis, especially in the presence of high-risk factors, as these patients have high risk of development of liver damage due to hepatotoxic drugs and progression of liver disease from NAFLD to non-alcoholic steatohepatitis (NASH) due to metabolic factors. Baseline TE measurement in presence of metabolic factors can make physicians aware about potential risk of using hepatotoxic drugs and help in closer monitoring and making patients aware about lifestyle changes to improve liver morbidity. TE has a high negative predictive value and is an important tool for holistic management of psoriasis patients, including early referral to hepatologist for better care of liver. This study throw light on other risk factors associated with liver disease in psoriasis other than methotrexate use. However, the exact role of TE in detection of liver fibrosis in psoriasis patients will require prospective studies with larger sample size.

**Table 2: Comparison of TE value and PASI in presence of metabolic syndrome at various methotrexate dose**

	With metabolic syndrome (mean $\pm$ SD) ( $n=32$ )	Without metabolic syndrome (mean $\pm$ SD) ( $n=50$ )	P
All patients ( $n=82$ )			
TE (kPa)	8.99 $\pm$ 7.32	5.63 $\pm$ 1.51	0.007
PASI	15.74 $\pm$ 8.27	16.42 $\pm$ 6.89	0.70
Methotrexate $< 1.5$ gm ( $n=60$ )			
TE (kPa)	7.03 $\pm$ 1.84	5.31 $\pm$ 1.21	0.0006
PASI	12.6 $\pm$ 1.22	14.4 $\pm$ 1.20	0.32
Methotrexate $> 1.5$ gm ( $n=22$ )			
Fibro scan	13.11 $\pm$ 11.97	8.87 $\pm$ 5.87	0.40
PASI	21.84 $\pm$ 10.08	17.12 $\pm$ 10.77	0.13

Unpaired *t*-test was applied

### Limitations of study

Small sample size and inability to confirm TE findings on liver biopsy were the main limitations of study. We counselled patients with high TE values for liver biopsy. However, due to associated morbidity and availability of other treatment options, none of our patients agreed for liver biopsy.

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### Conflicts of interest

There are no conflicts of interest.

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