Monitoring Methotrexate-Induced Hepatotoxicity in Patients With Psoriasis: Utility Of Serum Wingless Integration 5a Protein Level And Transient Elastography

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ABSTRACT

Introduction: Liver fibrosis is a side effect of methotrexate (MTX) that develops with prolonged use in psoriasis patients. Currently, patients are followed up for MTX-induced hepatic fibrosis either through liver biopsy, which carries danger and burden for the patient, or with the non-conclusive measurement of plasma procollagen type III amino peptide (PIIINP). Transient elastography (TE) has recently been utilized to identify liver fibrosis. **Aim of the study** is to determine the effectiveness of transient elastography for monitoring psoriasis patients for MTX-induced hepatic fibrosis and to identify Serum Wingless Integration 5a Protein (Wnt5a) as a novel predictive and preferably non-invasive biomarker. **Subjects and methods:** The study comprised 59 individuals with methotrexate-treated persistent psoriasis who were divided into two groups (I, II): Psoriasis patients who take MTX at a low dose (0.2mg/kg/week) and a high dose (0.4mg/kg/week) for longer than three months. Both a clinical examination and biochemical workup were done. **Results:** There are 19 women and 40 men among the patients. Wnt5a, which is linked to hepatic fibrosis and considerably more prevalent in group II, was found in the sera of psoriasis patients receiving high MTX doses. Group II showed TE values >7 kPa while group I showed values <7 kPa. High TE value and Wnt5a level were both substantially correlated with high methotrexate dose. **Conclusion:** In psoriasis patients receiving high doses of MTX, Wnt5a Protein was found as a potentially predictive biomarker for MTX-induced hepatic fibrosis. A non-invasive method for detecting liver fibrosis is TE. In most chronic liver diseases, a value of >7 kPa is associated with liver fibrosis.

Keywords: liver fibrosis, Methotrexate, Psoriasis, Toxicity, Transient Elastography, Wingless Integration 5a.

1. INTRODUCTION

As a folic acid antagonist, methotrexate (MTX) has mostly been used to treat psoriasis and rheumatoid arthritis (RA) **[1].** MTX has been prescribed for years and decades due to its potent antiproliferative and anti-inflammatory characteristics, despite the fact that it has a number of adverse pharmacological reactions, such as

hepatotoxicity **[2].** Hepatic fibrosis, which is more commonly shown in psoriasis patients than RA patients, is a sign of the hepatotoxic effects of MTX **[3].** In 33% of psoriasis patients receiving long-term MTX treatment, liver toxic effects developed **[4].**

The likelihood of MTX-induced hepatic fibrosis increases with longer MTX treatment periods, especially when the total MTX dose is between 1500 and 6000 mg **[5].** Risk factors for MTX-induced hepatic fibrosis include patients with type 2 diabetes and obesity **[6].** A novel biomarker with sensitive correlation to hepatic status is required to identify patients who will develop hepatic fibrosis at an early stage. The standard indicators for liver function impairment, including plasma alanine aminotransferase (ALT), couldn't predict liver fibrosis, making it difficult to identify MTX-induced hepatic fibrosis in psoriasis patients **[7].**

The gold standard for monitoring MTX-induced hepatic fibrosis is a liver biopsy, which is invasive, hazardous, and burdensome for the patient **[8].** Measuring plasma procollagen type III aminopeptide (PIIINP), a less dangerous and frequently used approach, is not a reliable indicator of hepatic fibrosis in psoriasis patients **[9].** As the previous result, research has concentrated on finding new plasma biomarkers for MTX-induced hepatic fibrosis, such as laminin, matrix metalloproteinase-1 (MMP-1), and tissue-inhibitor of metalloprotease-1 (TIMP-1). Additionally, transient elastography (Fibroscan) and fibrotest have been used to track MTX-induced hepatic fibrosis **[10].**

Transient elastography and serum PIIINP are outperformed as biomarkers for hepatic fibrosis measured in accordance with liver status within various MTX treatment groups, according to Chládek et al.'s findings **[11].**

We currently lack adequate biomarkers to early predict MTX-induced hepatic fibrosis in psoriasis patients, and non-invasive sensitive biomarkers are still required. The serum wingless integration 5a protein (Wnt5a) level has been suggested as a possible tool for the ELISA-based detection of liver fibrosis **[12].**

We are aware of only a few number of prior research examining the efficacy of serum Wnt5a in comparison to transient elastography to evaluate MTX-induced hepatotoxicity in those have psoriasis. The aim of this study is to determine the effectiveness of transient elastography for monitoring psoriasis patients for MTX-induced hepatic fibrosis and to identify Serum Wingless Integration 5a Protein (Wnt5a) as a novel predictive and preferably non-invasive biomarker.

Ethical approval:

A letter of approval was acquired from the Faculty of Medicine at Zagazig University's Ethical Committee for Research Institutional Review Board ‘IRB’(ZU-IRB # 10555/8-3-2023). Each patient signed a written informed consent form to agree to participate in the study. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

2. SUBJECTS AND METHODS

Study population

Patients who were admitted to the dermatology department at Zagazig University Hospital in Egypt were the subjects of this cross-sectional study. Patients with psoriasis who had received methotrexate for longer than three months between March 2023 and May 2023 provided a history of treatment divided into two patient groups group I who received low dose MTX (0.2mg/kg/week) and group II who received a higher dose of MTX (0.4mg/kg/week).

Inclusion Criteria:

Patients with a psoriasis area severity index (PASI) >10 who were male or female and older than 18 years were included in our study. Patients with hepatitis B or C, concurrent systemic psoriasis therapy other than methotrexate, or any other hepatotoxic medication were excluded from the study.

Exclusion criteria:

Patients having a history of chronic renal illness and obesity, defined as a BMI of 30 or above were excluded from our study. Additionally, patients with anemia, leucopenia, thrombocytopenia, or pancytopenia as well as those with lung fibrosis or a history of pulmonary illness were excluded. Women who were nursing or pregnant were also excluded. Only 59 patients were included in this study due to these exclusion criteria.

Study design

Before sample collection, a written informed consent detailing the purpose of the study and the right to withdraw at any time without affecting the health care offered was signed. Patient anonymity is protected through the gathering of anonymous data, and the data will only be utilized for research.

Questionnaire includes: Age, sex, BMI, PASI, dose of methotrexate, and medical history of comorbidities were all collected as sociodemographic information for each patient.

Biochemical tests:

All patients had biochemical tests, including fasting blood sugar and liver aminotransaminase values, which were documented.

Serum wingless integration 5a protein (Wnt5a) level: Using an enzyme-linked immunosorbent assay (ELISA) calibrated in accordance with the manufacturer's instructions (SunRed, Shanghi), the serum Wnt5a levels of each subject were measured.

Transient elastography:

Transient elastography (TE) is a type of shear wave ultrasonic elastography that gauges shear wave velocity to determine the stiffness of hepatic tissue. An elastic shear wave is produced in the tissue via an ultrasonic transducer attached on a vibrator that delivers a low-frequency (50 Hz) vibration. The transducer monitors the shear wave's velocity, which is used to determine the stiffness of the tissue. With typical values, the result ranges from 1.5 to 75 kPa and is stated in kPa. In the majority of chronic liver diseases, a TE measurement of >7 kPa is symptomatic of severe fibrosis; Various thresholds can be used to diagnose cirrhosis, with nonalcoholic fatty liver disease having ideal thresholds of >10 kPa.To assess the elasticity of the right lobe of the liver, the transducer is positioned over the right 9th, 10th, or 11th intercostal space.

Statistical analysis

With the exception of gender, all continuous variables were presented as mean± standard deviation (SD). A Chi square and independent 't test' analysis was used to assess the relationship between categorical variables and outcomes, a non-parametric one-way ANOVA Kruskal-Wallis test was used for the ELISA data. A *P* value of < 0.05 was regarded as statistically significant.

3. RESULTS

Table 1 displays the demographic characteristics of all patients who subjected at the study, excluding MTX dose. A total of 59 chronic psoriasis patients on methotrexate were evaluated for inclusion; 40 (67.8%) of them were men, and 19 (32.2%) were women. The patients' mean age was 40.04±12.45 years; their disease had been present for 2.01±8.68 years; their BMI was 25.16±3.95; their FBS was 94.66±29.56, their DBP was 81.16±7.19; and their AST was 29.93±18.36; and their PASI was 16.26±7.99 (Table 1).

Based on the dose of MTX, two groups of psoriasis patients were collected. Group I, n = 20, methotrexate intake of 0.2mg/kg/week. Group II, total methotrexate consumption of 0.4mg/kg/week (n = 39).

Table 2 listed the patients' demographic, laboratory, and clinical information including: age, sex, DBP, FBS, AST, BMI, and disease duration. A non-significant difference existed between the two groups. Wnt5a protein serum levels, TE values, and PASI were extremely statistically different across the groups examined, as shown in Table 3. Wnt5a protein levels, TE readings, and PASI were all noticeably elevated in the group receiving high dose MTX. Patients receiving high doses of MTX compared to the low dose MTX group appeared to have greater serum concentrations of Wnt5a, TE values, and PASI (<0.001**).

Table (1): Demographic ,clinical, and laboratory data of all studied patients:

Variable	Studied patients (n=59)
Age	40.04±12.45
Sex • **Male** • **Female**	 40(67.8%) 19(32.2%)
Duration	2.01±8.68
BMI	25.16±3.95
BP	81.16±7.19
FBS	94.66±29.56
AST	29.93±18.36
PASI	16.26±7.99

Table (2): Demographic, clinical, and laboratordy data of the studied groups:

Variable	Group I MTX 02mg/kg/week (*n*=20)	Group II MTX 04mg/kg/week (*n*=39)	*P* value
Age	40.35±6.91	39.65± 4.25	0.702
Sex • **Male** • **Female**	 19 (95%) 1 (5%)	 16 (80%) 4 (20%)	0.342
Disease Duration	2.39±7.20	3.09±10.55	0.21
BMI	24.65±3.64	26.70±4.37	0.17
DBP	79.96±6.65	85.18±6.86	0.23
FBS	92.90±32.26	99.79±22.81	0.65
AST	28.14±20.11	34.61±12.60	0.33

Twenty patients had Wnt5a protein levels of 1.2 ng/ml or less, and 39 patients had levels greater than 3.4 ng/ml. Wnt5a was discovered to be 1.2±0.11ng/ml in the group (n = 20) with methotrexate intake of 0.2mg/kg/week. The TE value was 3.4±0.543ng/ml in the second group (n = 39) with methotrexate intake of 0.4mg/kg/week. Wnt5a level showed a statistically

significant difference between the two MTX groups under study (Table 3).

Twenty patients had TE values of 7 Kpa or less and 39 patients had TE values of more than 7 kPa. The TE value was 7.16±1.91 kPa in the group with methotrexate intake of 0.2mg/kg/week. The TE value was 12.98 ±10.69 kPa in the second group with methotrexate intake of 0.4mg/kg/week. The TE value was statistically different between the two MTX groups under study (Table 3).

Table (4) showed a substantial positive association between the serum level of Wnt5a protein and the dose of MTX, TE values, disease duration, and PASI.Wnt5a protein levels in the serum did not correlate with age, sex, blood pressure, AST, or FBS.

Table (3): Comparison of Wnt5a level, TE value and PASI in the studied groups.

Variable	Group I MTX 0.mg/kg/week (*n*=20)	Group II MTX 0.4mg/g/week gm (*n*=39)	*P* value
WI5a (ng/mL):	1.2±0.11	3.4±0.543	<0.001**
TE (kPa)	7.16±1.91	12.98 ±10.69	<0.001**
PASI	12.6±1.22	21.84±10.08	<0.001**

Table (4): Correlation of Serum levels of WI5a protein with other variables in psoriasis patients:

Variable	r	*P*
Dose of MTX	0.539	<0.001**
TE	0.604	<0.001**
Disease duration	0.473	<0.001**
PASI	0.53	<0.001**
Age	0.19	0.146
Sex	0.26	0.56
BMI	0.14	0.41
DBP	0.136	0.36
AST	0.28	0.53

Table (5) demonstrated a substantial positive correlation between the TE value and MTX dose, the duration of the sickness, and the PASI. The TE value was unrelated to age, sex, blood pressure, AST, or FBS.

Table (6) demonstrated that the optimal (p<0.001) cutoff for serum Wnt5a protein and TE in the diagnosis of MTX-induced hepatic fibrosis is equal to or higher than (2.06ng/ml, 12 pka), with a specificity of (75%,76.9%), sensitivity of (80%,90.1%), NPV of (65.2%,88.8%), and PPV of (86.5%,71.9). Higher TE value was correlated with higher Wnt5a.

Table (5): Correlation TE value with other variables in psoriasis patients using methotrexate:

Variable	r	*P*
Dose of MTX	0.619	<0.001**
Disease duration	0.611	<0.001**
PASI	0.49	<0.001**
Age	0.119	0.16
Sex	0.201	0.43
BMI	0.104	0.39
DBP	0.139	0.25
AST	0.279	0.72

Table (6): Performance of serum level of WI5a protein and TE values in diagnosis of methotrexate induced hepatic fibrosis across the studied groups:

		AUC					*P* value
WI5a (ng/ml)	≥2.06	0.891	80%	75%	86.5%	65.2%	<0.001**
TE (kPa)	≥12 kPa	0.975	90.1%	76.9%	71.9%	88.8%	<0.001**

4. DISCUSSION

It is challenging to monitor hepatic fibrosis caused by long-term MTX usage, particularly in psoriasis patients [13-14]**.** In people receiving methotrexate, hepatic fibrosis occurs in about 5% of cases. Individuals with psoriasis have a higher chance of developing liver damage than individuals with rheumatoid arthritis or inflammatory bowel disease because of risk factors such metabolic syndrome, obesity, and alcohol consumption. A liver biopsy, testing plasma liver enzymes, and taking folic acid supplements are all recommended as part of the current guidelines for baseline assessments, monitoring, and prevention of MTX-induced hepatotoxicity [15]**.**

These recommendations highlight the need for more accurate, ideally noninvasive biomarkers to track MTX-induced hepatic fibrosis. The goal of this study was to evaluate transient elastography and serum Wnt5a as prospective biomarkers for early and non-invasive detection of MTX-induced hepatic fibrosis in psoriasis patients. We classified psoriasis patients into a low MTX dose group (0.2mg/kg/week) and a high dose group (0.2mg/kg/week) because MTX often causes hepatic fibrosis above a dose of 1500 mg/week according to Wollina et al. **[16].**

In this manner, we were able to connect the dose of MTX that is most likely to cause hepatic fibrosis with Wnt5a levels and ET values. The Wnt5a protein serum levels in our study showed highly statistically significant difference between the tested groups. The high dosage MTX group II had significantly greater serum Wnt5a protein levels.

These findings are in accordance with **Pashirzad et al. [17] who reported that** Wnt5a was high and would be a special diagnostic component and a post-treatment marker for RA, atherosclerosis, psoriasis, and sepsis. Systemic lupus

erythematosus(SLE) has been linked to Wnt5a, and suggested using it as a biomarker to gauge the severity of SLE reported by **Shuhong et al. [18].**

Another study supported our results that Wnt5a has a high level the sera of in psoriatic arthritis (PsA) patients, as **Lin et al. [19]** discovered that PsA patients had higher levels of Wnt5a mRNA and protein in MDOC (monocyte-derived osteoclasts) than did healthy controls. Wnt5a, a ligand that encourages non-canonical Wnt signaling in the control of cell migration and polarity, causes inflammation during embryonic morphogenesis by activating macrophages. Evidence for the expression of Wnt5a protein and mRNA has been described in a range of inflammatory illnesses and disorders, including psoriasis, rheumatoid arthritis, atherosclerosis, and TB [20]. Recent research has shown that a key activation mechanism for Wnt5a expression is the JAKSTAT3/NF-kB/TLR signaling cascade [21].

Wnt5a serum levels positively correlated with MTX doses, disease duration, and PASI in a statistically significant way. This may suggest that Wnt5a is a biomarker for MTX-induced hepatic fibrosis in psoriasis. These results were confirmed by **Yu et al. [23]** who discovered a strong positive correlation between plasma Wnt5a protein, and CRP indicating activity of the psoriatic disease.

In our investigation, there were highly statistically significant TE differences between the examined groups. The high dose MTX group II had significantly higher TE values.

These findings are in line with those of **Neema et al. [24],** who reported that the TE value was 5.31 kPa in the group with low dose methotrexate intake of and increased to 13.11 kPa in the group with high dose methotrexate especially in prescence of metabolic syndrome.

These findings are consistent with **Zaiton et al. [25],** who found that TE showed a significant positive connection with fibrosis stage ($P = 0.005$). In hepatitis C patients, there was a significant connection between TE, hepatic fibrosis's stage $P < 0.001$.

Our investigation demonstrated a statistically significant positive association between TE value and MTX dose, disease duration, and PASI. This may suggest that TE value is an indicator of MTX-induced hepatic fibrosis in psoriasis.

Contrary to our findings, studies by **Laharie et al. [26]** on 111 psoriasis patients and **Pongpit et al. [27]** on 168 patients found methotrexate dose or duration, were not significantly associated with high TE value.

The non-invasive TE approach is a relatively recent one for detecting liver fibrosis. This in accordance with a recent study indicated that 14.1% of patients with severe psoriasis had advanced liver fibrosis determined by TE **[28].**

Australasian recommendations recommend baseline TE, if the TE value is less than 7.5 kPa repeated every one to three years. If the value is between 7.5-9.5 kPa, repeat the test after a year and think about referring the patient to a hepatologist. If the value is greater than 9.5 kPa, a liver biopsy or other specialized examinations are recommended **[29].**

Our research revealed that the best cutoff for the diagnosis of MTX-induced hepatic fibrosis is equal to or higher than (12 pka) ($p<0.001$), with a specificity of TE (76.9%), sensitivity of (90.1%), NPV of (88.8%), PPV of (71.9).

According to a meta analysis done in 2007, TE has a sensitivity and specificity of 87% and 91%, respectively, for the diagnosis of liver fibrosis due to a variety of reasons (most commonly HCV infection) **[30].**

When used to diagnose fibrosis, TE has a strong negative predictive value (>90%) and a 75% positive predictive value. These results are in accordance with a study of 24 patients, the use of TE in psoriasis had a good negative predictive value and successfully identified 88% of individuals without fibrosis **[31].** In a recent investigation, a cutoff TE of 7.1 kPa showed a sensitivity of 50% and a specificity of 76.9% for detecting liver impairment caused by methotrexate in psoriasis patients **[32].**

Limitations of the study:

In order to establish the clinical reason for routine serum Wnt5a level and TE in psoriatic illness, the current results give the justification for beginning a larger prospective, randomized trial as the current study is a cross-sectional study. Consequently, the sample size has a built-in constraint. Additionally, consent was necessary because this was a prospective study, this might have caused some patients who were rejected sampling and examination to self-select against enrolment.

Conclusions:

For the non-invasive detection of liver fibrosis, Wtn5a and TE are used. Their utility in identifying methotrexate-induced liver fibrosis in psoriasis patients has not yet been established. Physicians might become aware of the potential danger of taking hepatotoxic medications through baseline Wtn5a and TE measurement, which can aid in closer monitoring and decision-making. Wtn5a and TE is a crucial tool for the comprehensive management of psoriasis patients, including the early referral to a hepatologist for better liver care.

5. RECOMMENDATIONS:

This study sheds information on methotrexate use that is a risk factor for liver damage in psoriasis disease. However, prospective studies with a larger sample size will be necessary to determine the precise significance of Wnt5a level and TE value in detecting hepatic fibrosis in psoriasis patients.

6. ACKNOWLEDGEMENT

Thank you so much for helping to make the clinical portion of the study possible, Zagazig University Hospitals' medical staff in the Dermatology department.

7. CONFLICT OF INTERESTS STATEMENT

Conflicts of interest were not disclosed by the author(s).

8. FUNDING

The author (s) received no funding for the investigation into, or publishing of, this article.

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