

# Determine the Prevalence of Methotrexate Induced Hepatotoxicity in Rheumatoid Arthritis Patients whom Treated with Low Dose Methotrexate

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## ABSTRACT

**Aim:** To examine the prevalence of methotrexate affected hepatotoxicity in rheumatoid arthritis patients whom were treated with low dose of methotrexate.

**Methods:** This cross-sectional/observational study was carried out at Department of Medicine, Islam Teaching Hospital, Sialkot from 1<sup>st</sup> July 2017 to 31<sup>st</sup> December 2017. One hundred and thirty eight patients of both genders having rheumatoid arthritis were included. Patient's ages were ranging from 20 to 60 years. Patients detailed history including, age, sex, socio-economic status was examined after taking informed consent from all the patients. All patients were treated with low dose 7.5mg methotrexate weekly and proper and regular follow up was taken for six months.

**Results:** Forty eight (34.78%) patients were males while rest 65.22% patients were females. 53 (38.41%) patients were ages between 20 to 34 years, 59(42.75%) patients had ages 35 to 49 years and 26 (18.64%) patients were ages >49 years. One hundred (72.46%) patients had rural residency. Mean hemoglobin, bilirubin, alkaline ph, ALT and weight were noted as 11.97±2.12, 0.96, 22.84±1.42 and 44.34±3.6, 64.97±5.32 respectively. Fifteen (10.87%) patients had found with raised serum ALT. Hepatotoxicity was defined as serum ALT of above than two time of reference range. In 48 males' patient, hepatotoxicity was found in 7 patients and in females it was observed in 11 patients.

**Conclusion:** Hepatotoxicity is commonly observed side effect in patients treated with methotrexate. Regular monitoring with serum ALT of these patients necessitate early and proper treatment.

**Keywords:** Rheumatoid arthritis, Hepatotoxicity, Methotrexate

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## INTRODUCTION

Worldwide, rheumatoid arthritis is commonly found in medical department of health care centers. It is a chronic multisystem autoimmune disease with several pathogenesises. Rheumatoid arthritis may lead to several morbidities if it not treated proper and regularly<sup>1,2</sup>. Globally, the frequency of rheumatoid arthritis estimated 1 to 3% of the general population. In Asian countries the prevalence of this disorder is reported as 0.37%<sup>3</sup>. For initial treatment of rheumatoid arthritis antirheumatic drug methotrexate is commonly used in weekly doses in medical centers and it considered as the main and effective drug for rheumatoid arthritis affected patients<sup>4,5</sup>. Because of MTX best results and lower cost it has been using frequently for the treatment of rheumatoid arthritis<sup>6</sup>. Despite being well tolerated, long-term use of MTX in recommend dose regimens might be associated with toxic effects especially on bone marrow, liver and gastrointestinal system.<sup>7-9</sup> Methotrexate helps to increase the adenosine concentration and to decrease the cytokine.<sup>10</sup> Hepatotoxicity followed by methotrexate in rheumatoid arthritis patients is well recognized and it can lead to hepatic fibroses and cirrhosis<sup>11</sup>. Supplementation of oral folic acid in doses of 1 mg/day or 2.5 mg of folic acid/week is associated with reduced incidence of hepatotoxicity<sup>12,13</sup>.

The effects of methotrexate can increased the risk

factors associated with liver fibrosis and cirrhosis is reported such as age, Alcohol consumption, diabetes, obesity, chronic viral hepatitis and medications such as arsenic and vitamin A have been reported to be significant risk factors of MTX associated liver fibrosis<sup>14,15</sup>.

In Pakistan, rheumatoid arthritis is commonly found in hospital and most of the population has rural residency. This study may helps to reduce the morbidity and to provide the better treatment.

## MATERIALA AND METHODS

This cross-sectional/observational study was carried out at Department of Medicine, Islam Teaching Hospital, Sialkot from 1<sup>st</sup> July 2017 to 31<sup>st</sup> December 2017. One hundred and thirty eight patients of both genders having rheumatoid arthritis were included. Patient's ages were ranging from 20 to 60 years. Patients having history of chronic liver disease, thrombocytopenia, renal insufficiency, leucopenia and those who were not interested to participate were excluded in this study. Patients detailed history including, age, sex, socio-economic status, medical history and physical status was examined after taking informed consent from all the patients. All patients were treated with low dose 7.5mg methotrexate weekly and proper and regular follow up was taken for six months. All statistical data was analyzed by statistical software SPSS-20. P-value <0.05 was considered as significant.

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## RESULTS

There were 48 (34.78%) males while rest 65.22% patients were females. Fifty three (38.41%) patients were ages between 20 to 34 years, 59(42.75%) patients had ages 35 to 49 years and 26(18.64%) patients were ages > 49 years. One hundred (72.46%) patients had rural residency (Table 1). Mean hemoglobin, bilirubin, alkaline ph, ALT and weight was noted as 11.97±2.12, 0.96, 22.84±1.42 and 44.34±3.6, 64.97±5.32 respectively. 15(10.87%) patients had found with raised serum ALT. Hepatotoxicity was defined as serum ALT of above than two time of upper limit of reference range. In 48 males' patient, hepatotoxicity was found in 4 patients and in females it was observed in 11 patients (Tables 2-4).

Table 1: Demographical details of all patients

Variable	No.	%
<b>Gender</b>		
Male	48	34.78
Female	90	65.22
<b>Age (years)</b>		
20 – 34	53	38.41
35 – 49	59	42.75
>49	26	18.64
<b>Residency</b>		
Rural	100	72.46
Urban	38	27.54

Table 2: Variables findings of all the patients

Characteristics	Mean±SD	P-Value
Hemoglobin	11.97±2.12	0.01
Bilirubin	0.96	0.231
AlkinePh	223.84±7.42	0.231
Alanine aminotranferase	44.34±3.6	0.172
Weight	64.97±5.32	0.582

Table 3: Cross-sectional observation between hepatitis and non-hepatitis groups

Characteristics	Hepatitis Group (n=15)	Non-Hepatitis (n=123)	P-value
Patients age	36.72±6.23	39.87±10.72	0.736
Hemoglobin	12	13.23±1.03	0.001
Bilirubin	0.96	0.91	0.254
AlkinePh	223.02±5.88	218.02±10.76	0.175
Weight	72.9	66.86	0.585

Table 4: Gender wise hepatotoxicity

Characteristics	No.	%
Males (n=48)	4	8.33
Females (n=90)	11	12.22

## DISCUSSION

Methotrexate is a well known cause of the hepatic enzymes elevation.<sup>16</sup> Many of studies reported that the low dose of methotrexate 7.5mg per week resulted better outcomes as compared to high dose.<sup>17-19</sup> In this study, out of 138 patients we found 34.78% patients were males while 65.22% patients were females. The rate of females patients population is too high as compared to males. A study conducted by Abbas et al<sup>20</sup> regarding methotrexate reported that females population rate was high as compared to males. Many of other studies illustrated that

the females patients population rate is high in rheumatoid arthritis patients<sup>21,22</sup>.

In our study we treated rheumatoid arthritis patients with low dose of 7.5mg methotrexate on weekly basis and monitor all the patients or strong follow up on six months. We found that 15(10.87%) patients had hepatotoxicity associated with methotrexate. These results shows similarity to the study conducted regarding MTX.<sup>23</sup> Another study conducted regarding MTX affected hepatotoxicity in rheumatoid patients resulted 23.7%.<sup>24</sup> Other studies has reported that chronic low to moderate dose of MTX can cause hepatic enzyme elevation in 15% to 50% of cases<sup>25</sup>, which is usually reversible on stopping the drug or reducing its dose.<sup>26</sup>

In this study, Mean hemoglobin, bilirubin, alkaline ph, ALT and weight was noted as 11.97±2.12, 0.96, 22.84±1.42 and 44.34±3.6, 64.97±5.32 respectively. 15(10.87%) patients had found with raised serum ALT. Hepatotoxicity was defined as serum ALT of above than two time of upper limit of reference range, these results shows similarity to the other studies<sup>27</sup>. In our study, we found 2 patient out of 4 hepatotoxic males were smoker and it may be the main cause of affecting with this malignant disorder. We found that 123(89.13) patients had no hepatotoxicity associated with Methotrexate. These results shows similarity to the other studies.<sup>20</sup> These results was much better for the treatment of rheumatoid arthritis and this was due to strong follow up and proper regular monitoring.

## CONCLUSION

Hepatotoxicity is commonly observed side effect in patients treated with methotrexate, while low dose of methotrexate can reduce the rate of liver enzymes. Moreover, regular monitoring with serum ALT of these patients necessitates early and proper treatment.

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