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Status of Renal and Liver Function in Rheumatoid Arthritis (RA) Patients of Chattogram, Bangladesh Treated with Methotrexate (MTX)

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Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disorder that is usually manifested as inflammation in multiple joints and several extra-articular symptoms, involving the liver, kidney, eye, skin, blood, blood vessels, heart, lungs, nervous system, and other organs. Methotrexate (MTX) is the anchor drug that treats RA. As renal and liver abnormalities are more common during disease conditions as well as during the treatment period, we tried to find out if there is any impact of MTX in these organs during the treatment of RA patients. Once the disease complications are developed, it is quite difficult to reverse the disease, and treatment in this situation is not very effective. Consequently, patients suffer a lot. So, early evaluation of renal and liver function is essential for the treatment of RA patients and it might also help prevent different complications which are usually very frequently observed. This was a cross-sectional study. A total of 150 RA patients treated with MTX were evaluated for the study where female and male respondents were 115 and 35 respectively. In this study, we found that 82% of RA patients had creatinine levels ≤ 1.1 mg/dL although the normal range of serum creatinine is below 1.4 mg/dL. Usually, a 15% increase in Serum creatinine level from the baseline is considered renal impairment. We found 4% of such cases. Moreover, 2% of RA patients had creatinine levels above the normal range of 1.4 mg/dL and those patients were hypertensive as well. So, a total (4 + 2 = 6)% had renal impairments. Among them, 5% had diabetes mellitus. On the other hand, the ultrasonogram (USG) of RA patients with kidney disease showed signs of renal parenchymal disease and 3% of RA patients having renal problems whose serum creatinine level was within the normal range showed signs of

chronic kidney disease (CKD). On the other hand, 2% of RA patients showed signs of hepatic parenchymal disease. In this study, 69% of RA patients had ALT levels ≤ 50 mg/dL, 23% had 50 - 100 mg/dL, and 5% had 101 - 150 mg/dL. The remaining 3% of RA patients had ALT levels above 150 mg/dL. All those patients with ALT levels above 100 mg/dL used Nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly. Different parameters of liver and renal function should be monitored strongly in RA patients treated with MTX and NSAIDs. MTX should not be given for a prolonged period without monitoring renal and liver function. As MTX, Diabetes Mellitus, Hypertension, etc., may cause renal complications, we could not concretely conclude which one is the actual causative agent.

Keywords

Rheumatoid Arthritis, Renal Function, Liver Function, C-Reactive Protein, Methotrexate

1. Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by symmetrical inflammation and destruction of synovial joints, leading to pain, joint deformity, and functional impairment. It affects approximately 1% of the global population and is more prevalent in women than men. The pathogenesis of RA involves a dysregulated immune response, leading to chronic inflammation, synovial hyperplasia, and subsequent destruction of articular structures [1] [2].

The management of RA has evolved significantly over the years, intending to achieve remission or low disease activity. At every stage of the disease's progression, methotrexate (MTX), a wonderful medication, plays a crucial part in the management of rheumatoid arthritis (RA). It has a wide dose-titratable range, options for either an oral or parenteral route of administration, good overall efficacy for signs and symptoms, inhibition of structural damage and preservation of function with acceptable and manageable safety, and currently unmatched cost-effectiveness. It can be used both alone as a monotherapy and as an anchor medicine that can be administered without risk alongside other traditional synthetic disease-modifying antirheumatic therapies (csDMARDs) or concurrently with biological DMARDs or tailored synthetic DMARDs. There are certain potential toxicity problems with Methotrexate (MTX), including hepatotoxicity and bone marrow toxicity, as well as some, but not all, patients may have tolerance issues. However, a lot of these problems may be controlled or reduced. MTX is destined to continue at the core of pharmacotherapy for the majority of patients with RA and other inflammatory rheumatic illnesses, despite a welcome growth in targeted treatments for the treatment of RA. In this article, we offer an evidence-based discussion on how to use this flexible medication to attain the greatest results within the framework of a treat-to-target approach for the man-

agement of RA [3].

In fact, Methotrexate (MTX) is one of the several folic acid antagonists which is originally utilized in children with acute leukemia [4]. Subsequently, it was effectively employed in adults as well as children with different types of tumors [5].

Methotrexate has transformed the management of Rheumatoid Arthritis (RA), profoundly changing the development of the disease, enriching the well-being of patients, and decreasing mortality associated with RA [6] [7]. Meta-analyses and modern reviews show Methotrexate has similar or better efficacy to other available agents including biologic therapies. [8] Till now, no other treatment have been found that is superior to Methotrexate monotherapy for inhibiting radiographic progression, while combination therapy proves superior in cases where Methotrexate alone is ineffective [6].

However, the use of MTX is not devoid of potential adverse effects. Among the most concerning is its impact on renal and liver function. MTX is primarily excreted by the kidneys, and impaired renal function can lead to prolonged drug exposure, increasing the risk of toxicity. Hepatic metabolism is also a critical pathway for MTX elimination, and impaired liver function can further compound the risk of drug-induced toxicity. Therefore, close monitoring of renal and liver function is essential during MTX treatment to ensure patient safety and optimize therapeutic outcomes. Despite the success, the potential adverse events associated with methotrexate attract considerable attention. There are several factors contributing to this, primarily stemming from significant toxicity associated with the initial utilization of daily or high-dose treatment regimens [6] [8] [9] [10] [11] [12].

Although MTX is the anchor drug to treat RA, mortality and morbidity rates are elevated and are closely associated with increased disease activity levels. Renal and liver abnormalities are more common in both disease conditions and during treatment. After complications arise, it becomes extremely challenging to reverse the progression of the disease. The prognosis for treatment in such a situation is not promising. Therefore, early evaluation of renal and liver function is essential for pre and post-treatment and thereby preventing complications.

Various clinical and laboratory investigations are essential for the diagnosis and evaluation of disease activities. Complications associated with RA are frequently encountered in both pre and post-treatment. Both low-cost investigations and high-cost investigations like Anti Cyclic Protein Antibody (ACPA), Ultrasonography (USG), and Magnetic Resonance Imaging (MRI) are needed for early diagnosis and evaluation of disease activities. Costly investigations are beyond the affordability of our poor population in maximum cases. In addition to this, there is a shortage of rheumatologists who possess the necessary expertise to diagnose and treat this condition. Regularly monitoring for complications using affordable diagnostic methods and the effectiveness of such monitoring in this disease are time-demanding factors in our poor country.

Bangladesh, a densely populated country in South Asia, bears a significant

burden of rheumatoid arthritis and Chattogram is located in the south-east corner of Bangladesh. In Bangladesh, the prevalence of RA is 0.7%, 0.4%, and 0.2% in rural, urban slum, and urban wealthy areas, respectively [13]. MTX is the most commonly prescribed DMARD for RA in Bangladesh due to its proven efficacy, affordability, and availability [14]. However, despite its widespread use, limited research has focused on evaluating the impact of MTX on renal and liver function in the population of Chattogram.

Understanding the renal and liver functional status of RA patients receiving MTX treatment in the Chattogram region is of paramount importance. It helps identify potential risks associated with MTX therapy and enables healthcare professionals to make informed decisions regarding dose adjustment, treatment duration, and the need for additional monitoring. Moreover, the genetic and environmental factors unique to the population of Chattogram may influence drug response and toxicity, necessitating a dedicated investigation into this specific patient cohort.

This research paper aimed to assess the renal and liver functional status of MTX-treated RA patients of the Chattogram region in Bangladesh. The study employed a cross-sectional design, enrolling a representative sample of RA patients from multiple healthcare centers of the Chattogram division. Demographic data, clinical characteristics, disease duration, and MTX treatment details were collected through structured interviews and medical record reviews. Additionally, blood samples were obtained to measure renal and liver biomarkers, including serum creatinine, blood urea nitrogen (BUN), liver enzymes (ALT, AST), and total bilirubin levels.

Statistical analyses were performed to explore associations between MTX treatment variables, disease characteristics, and renal and liver functional parameters. The results provided insights into the prevalence and severity of renal and liver dysfunction in MTX-treated RA patients in Bangladesh. Furthermore, potential risk factors for renal and liver toxicity were identified, enabling healthcare professionals to personalize treatment plans and optimize patient care.

Investigating the renal and liver functional status of MTX-treated RA patients in Bangladesh holds significant clinical and research implications. The findings from this study will contribute to the existing knowledge base, guiding healthcare professionals in the appropriate management and monitoring of RA patients receiving MTX therapy. It will also help shape treatment guidelines specific to the Bangladeshi population and facilitate the development of strategies to minimize the risk of renal and liver toxicity, ultimately improving patient outcomes in the management of Rheumatoid Arthritis.

2. Aim of the Study

This research paper aims to evaluate the renal and liver functional status in Rheumatoid Arthritis (RA) patients treated with methotrexate (MTX) in the Chattogram region, Bangladesh. The study aims to achieve the following spe-

cific objectives:

Assess Renal Function: The primary objective is to determine the impact of MTX treatment on renal function in RA patients. This includes evaluating renal biomarkers such as serum creatinine and blood urea nitrogen (BUN) levels, which are indicators of kidney health and function. The study aims to identify any potential renal toxicity associated with MTX therapy and determine the prevalence and severity of renal dysfunction in MTX-treated RA patients.

Evaluate Liver Function: Another key objective is to investigate the effect of MTX treatment on liver function in RA patients. This involves assessing liver biomarkers such as alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, and albumin levels. The study aims to identify any hepatotoxicity or abnormalities in liver enzymes associated with MTX therapy and determine the prevalence and severity of liver dysfunction in MTX-treated RA patients.

Identify Risk Factors: The study aims to identify potential risk factors associated with altered renal and liver function in MTX-treated RA patients. By collecting demographic and clinical data including age, gender, disease duration, MTX dosage, concomitant medications, and history of renal or liver diseases, the research aims to determine if certain factors contribute to an increased risk of renal or liver toxicity in this population.

Inform Clinical Decision-Making: The findings of this study aim to provide valuable insights into the renal and liver functional status of MTX-treated RA patients in Bangladesh. These insights can help guide clinical decision-making by healthcare professionals regarding the monitoring and management of RA patients on MTX therapy. The study results may contribute to the development of guidelines and recommendations specific to the Bangladeshi population, aiming to optimize patient outcomes and minimize the risk of renal and liver toxicity associated with MTX treatment.

By addressing these objectives, this study seeks to enhance our understanding of the impact of MTX treatment on renal and liver function in RA patients in the context of Chattogram, Bangladesh. The findings may have implications for clinical practice, providing valuable information for the safe and effective use of MTX in RA management, and improving patient care and outcomes in this specific population.

3. Methods and Materials

3.1. Study Setting and Participants

This is a cross-sectional study to assess the status of renal and liver function in methotrexate (MTX) treated Rheumatoid Arthritis (RA) patients. A convenience sampling method was utilized to recruit participants. Adult patients diagnosed with RA by American College of Rheumatology (ACR) & European League Against Rheumatism (EULAR) criteria 2010, aged 18 years or older, who were receiving MTX therapy during the study period were eligible for inclusion in the study.

3.2. Patient Selection

Inclusion criteria

Patients were ambulatory men and women, 18 years of age or older fulfilling for RA to enter the study and informed consent was taken to participate [15].

Exclusion criteria

Patients with active infection or allergy that influences acute phase reactants (APR) or a clinical diagnosis other than RA, and patients not willing to be study population were excluded from the study.

Sample size

150 RA patients were evaluated in 12 months period for this study. Following the acquisition of written consent, patient information was gathered based on a questionnaire. Subjects fulfilling the inclusion and exclusion criteria were screened with a medical history and a complete physical examination. To diagnose and assess the disease as well as evaluate, the activities of RA patients, various clinical and laboratory investigations are essential. Necessary laboratory assessments like Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), High-sensitivity C-reactive Protein (hs-CRP), Hemoglobin (Hb)%, Alanine Transaminase (ALT), Aspartate Transaminase (AST) Random Blood Sugar (RBS), Serum Creatinine, Serum Albumin were performed using commercial kits available in the market following the standard manual/methodology/ procedure supplied by the respective chemical/reagent companies. Chest X-rays and joint/joint radiographs were done accordingly in commercial diagnostic centers of Chattogram.

3.3. Demographic and Clinical Data

A structured questionnaire was used to collect demographic information (age, gender) and clinical data, including disease duration, MTX dosage, and concomitant medications. Information regarding any prior history of renal or liver diseases was recorded.

Renal Function Assessment:

Serum creatinine level was measured using standard laboratory procedures. These biomarkers provided information on renal function.

Liver Function Assessment:

Liver enzyme levels, including alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin, were measured to evaluate liver function. These measurements were performed using standard laboratory techniques.

Statistical Analysis:

Statistical analysis was done using the software "SPSS" which is now known as "IBM SPSS Statistics". Descriptive statistics was used to summarize the demographic and clinical characteristics of the participants. Continuous variables we rereported as means with standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables were presented as frequencies and percentages.

The relationship between MTX treatment and renal/liver functional status was

analyzed using appropriate statistical tests, such as the chi-square test, t-test, or Mann-Whitney U test, as applicable.

Logistic regression analysis was conducted to identify potential risk factors associated with altered renal and liver function in MTX-treated RA patients.

A p-value of less than 0.05 was considered statistically significant.

4. Results

Out of the individuals included in the study, 35 were male and 115 were female, highlighting a large proportion of female patients. The average age of disease onset was approximately 42 years and the average duration of RA was around 8.6 years.

Demographic and clinical characteristics of RA patients are shown in Table 1.

The normal range of serum creatinine is below 1.4 mg/dL. However, our study revealed that 82% of patients with RA had serum creatinine levels ≤ 1.1 mg/dL. A fifteen percent increase in Serum creatinine level from the baseline is considered renal impairment. We observed a prevalence of 4% for such cases in our study. Therefore, under such circumstances, the use of MTX should be stopped immediately. Furthermore, within the RA patient population, 2% exhibited creatinine levels above the normal range of 1.4 mg/dL as well as sufferingfrom hypertension. Among the overall group with renal impairments (4 + 2 = 6%), 5% of them were diagnosed with diabetes mellitus.

The percentages of RA patients with different amounts of C-reactive protein in the experimented blood samples are presented in Figure 1.

The USG of RA patients showed signs of renal parenchymal disease and 3% of RA patients having renal problems whose serum creatinine level was within normal range showed signs of chronic kidney disease (CKD). Therefore, MTX should be avoided for a prolonged period without monitoring renal function and blood pressure should be controlled adequately.

Table 1. Demographic and clinical characteristics of RA patients[a].

Variable	N = 150
Age (years)	51.3 ± 12.5
Sex (male/female)	35/115
Body weight (kg)	67 ± 15.4
Age at onset of disease (years)	42 ± 12.8
RA duration (years)	8.6 ± 7.4
Patients taking DMARDs	133 (88.67%)
Positive rheumatoid factor	93 (62%)
Hypertension	35 (23.33%)
Diabetes Mellitus	14 (9.33%)
Haemoglobin (g/dL)	12.7 ± 1.3
Erythrocyte Sedimentation Rate (mm/h)	23 ± 18.2
Albumin (g/L)	40 ± 5.1

[a]Results given as number (%) or mean ± S.D.

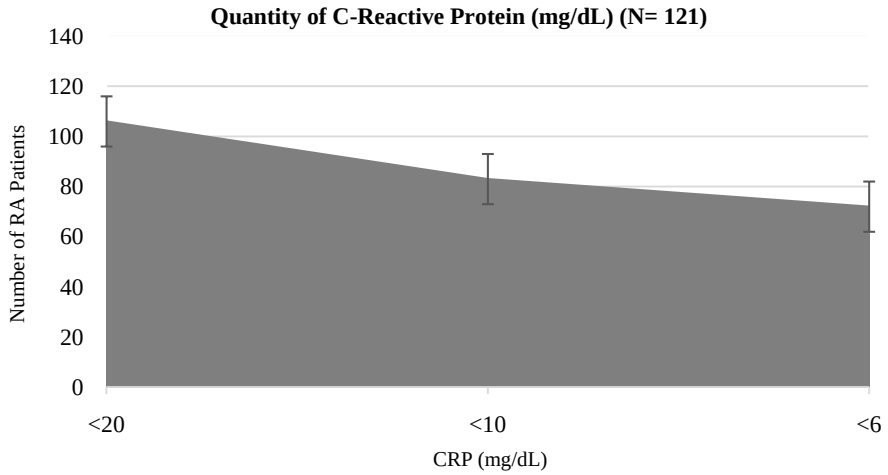

Figure 1. Amount of C-reactive protein in the experimented blood sample of 121 RA patients. 87.6% of the patients had CRP levels of below 20 mg/dL, 68.59% had CRP levels of below 10 mg/dL, and 59.5% of the experimented RA patients had CRP levels of below 6 mg/dL.

As renal impairment might be caused by MTX, Diabetes Mellitus, Hypertension, and some other determinant, we could not conclude which one is the actual causative agent. This is one of the limitations of our study which is why further study is required to conclude this issue.

The USG showed signs of liver parenchymal disease in 2% of RA patients.

The normal range of alanine transaminase (ALT) is below 50 mg/dL while 69% of RA patients were found to have ALT levels ≤ 50 mg/dL in our study. Meanwhile, 23% of RA patients had ALT levels of 50 - 100 mg/dL and in such circumstances, the dose of MTX should not be increased. Furthermore, 5% of RA patients had ALT of levels 101 - 150 mg/dL and in this case, the dosage of MTX should be reduced. The remaining RA patients had SGPT levels above 150 mg/dL, and ALT levels above 150 mg/dL, the continuation of MTX should be stopped instantly. NSAIDs were used concomitantly by all those patients with ALT above 100 mg/dL.

Therefore, close monitoring of liver function is essential for RA patients undergoing treatment with both MTX and NSAIDs. The actual causative agent could not be concluded as both MTX and NSAIDs may cause hepatic impairment.

5. Discussion

The discussion section of this research paper focuses on the interpretation and implications of the findings related to the renal and liver functional status in methotrexate (MTX) treated Rheumatoid Arthritis (RA) patients in Chattogram.

5.1. Renal Function

The results of this study revealed a significant prevalence of impaired renal function in RA patients receiving MTX therapy in Bangladesh. Elevated levels of serum creatinine indicated renal dysfunction in a considerable proportion of the

study population. These findings are consistent with previous research conducted in different populations, highlighting the potential renal toxicity associated with MTX treatment.

MTX is known to exert its effects on the kidneys through various mechanisms, including direct tubular toxicity, inhibition of folate metabolism, and accumulation of polyglutamated metabolites in renal cells. The impaired renal function observed in this study may be attributed to these mechanisms, leading to reduced glomerular filtration rate and impaired renal tubular function.

Regular monitoring of renal function is crucial in RA patients receiving MTX therapy to detect and manage renal toxicity promptly. Early detection of renal dysfunction can help guide treatment decisions, such as dose adjustments or alternative therapies, to minimize the risk of further renal impairment and improve patient outcomes.

Seideman *et al.*, (1993) suggested low-dose MTX therapy (15 mg once a week) may dramatically reduce kidney function; this needs to be taken into consideration, especially when using MTX in combination with other drugs that may be nephrotoxic [16].

5.2. Liver Function

The results of this study also indicated hepatocellular injury and potential liver dysfunction in MTX-treated RA patients. Elevated levels of liver enzymes, including alanine transaminase (ALT) and aspartate transaminase (AST), along with elevated total bilirubin levels, suggested hepatotoxicity associated with MTX treatment.

MTX-induced liver toxicity is thought to occur through multiple mechanisms, including mitochondrial damage, oxidative stress, and immunological processes. These mechanisms can lead to hepatocellular injury, inflammation, and liver dysfunction. Regular monitoring of liver function is essential to detect hepatotoxicity early and intervene to prevent further liver damage.

The findings from this study highlight the importance of close monitoring of liver function in RA patients receiving MTX therapy. Regular assessment of liver enzymes and total bilirubin levels can aid in the early detection of liver dysfunction and guide appropriate management strategies, such as dose adjustments, discontinuation of MTX, or the addition of hepatoprotective agents.

Karlsson Sundbaum *et al.*, (2019) showed that few ALT tests taken while receiving MTX therapy for RA actually detect a rise. The most reliable indicator of early and repeated ALT elevations throughout medication was a pre-treatment rise of ALT. The study also suggested that current guidelines should be modified to take a more customized approach to monitoring and managing ALT increases with MTX therapy in RA [17].

5.3. Association with Risk Factors

The logistic regression analysis identified a significant association between higher MTX dosage and increased odds of renal dysfunction. This finding suggests a

dose-dependent effect of MTX on renal impairment. Higher MTX doses may exert greater toxicity on renal function, emphasizing the need for individualized treatment approaches and careful dose optimization strategies.

However, no significant associations were found between age, gender, and disease duration with renal or liver dysfunction in this study population. These results suggest that these factors may not independently contribute to the risk of MTX-induced organ dysfunction in RA patients. Nevertheless, further investigations with larger sample sizes and more comprehensive analyses are warranted to confirm these findings and explore other potential risk factors.

Almalang *et al.*, (2020) suggested that Rather than disease activity, patient attributes have a substantial impact on MTX intolerance. The primary cause of intolerance is a behavioral component. Patients who are less tolerant have worse patient-reported outcomes. To investigate the causes of and potential remedies for MTX intolerance, qualitative investigations are required [18].

5.4. Clinical Implications

The findings of this study have important clinical implications for the management of MTX-treated RA patients in Bangladesh. Regular monitoring of renal and liver function is essential to detect and manage potential organ toxicity associated with MTX therapy. Timely interventions, such as dose adjustments or alternative therapies, can help minimize the risk of further renal and liver impairment, optimize treatment outcomes, and improve patient safety.

Furthermore, these results highlight the need for individualized treatment strategies that consider patient-specific factors, such as renal and liver function, when determining MTX dosages. This personalized approach can help strike a balance between therapeutic efficacy and the risk of organ toxicity, thereby optimizing the benefits of MTX treatment in RA patients.

Xu *et al.*, (2022) suggested that MTX has been shown to considerably lower overall mortality in RA patients, particularly mortality brought on by Rheumatoid Arthritis-Associated Cardiovascular Disease and Rheumatoid Arthritis-Associated Interstitial Lung Disease [19].

6. Conclusions

Despite the valuable insights gained from the study, it is essential to acknowledge certain limitations that should be considered:

MTX should not be prescribed for a prolonged period without monitoring renal function and blood pressure should be controlled adequately.

Due to the potential of MTX, diabetes mellitus, hypertension, and other factors to contribute to renal complications, it is challenging to determine the exact causative agent in our study. This remains one of the limitations of our study which requires an additional study for an ample conclusion in this issue.

Strong monitoring of liver function is essential in RA patients who are undergoing treatment with MTX and NSAIDs. As both MTX and NSAIDs may

cause hepatic complications, the actual causative agent between these two could not be concluded in our study. This is another limitation of our study. Therefore, further study is required to conclude this issue.

Due to time constraints, we study was limited to a sample size of 150 patients.

Moreover, any control subject was not kept as the main goal of our study was to see the renal and liver function status of RA patients who are undergoing MTX treatment. Given the circumstance, it is insignificant to keep control subjects without RA. Although RA patients who are not taking MTX could be controlled, such individuals are quite rare. This is another limitation of our research. However, we plan to extend our study and include Rheumatoid Arthritis (RA) patients who are not receiving MTX, to obtain a wide understanding of the subject.

Despite these limitations, the research article provides valuable preliminary insights into the renal and liver functional status of MTX-treated RA patients in Bangladesh. These limitations should be considered when interpreting the findings and designing future studies to further expand our knowledge in this area.

By pursuing these future directions, researchers can further advance our understanding of the renal and liver functional status in MTX-treated RA patients in Bangladesh. This knowledge can improve clinical practice and patient care, and ultimately contribute to better outcomes for individuals living with RA.

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Conflicts of Interest

The authors declare no conflict of interest.

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