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Adherence to folic acid among methotrexate-treated patients with rheumatologic diseases: a cross-sectional study

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ABSTRACT

Background. Methotrexate (MTX), a fundamental drug used in treating various rheumatologic diseases such as rheumatoid arthritis (RA), is often associated with side effects due to its interference with folate metabolism. Folic acid (FA) is routinely prescribed to counteract these adverse effects. However, adherence to FA among MTX users remains an important but underexplored issue.

Objectives. This study aimed to assess adherence to folic acid among patients using methotrexate for rheumatologic diseases and to identify factors contributing to non-adherence.

Materials and methods. A cross-sectional study was conducted between August and December 2024 at outpatient clinics in Al-Basrah and Al-Sayyab Teaching Hospitals, including private rheumatology clinics. Data were collected from 73 patients receiving medical care, using structured interviews and medical records. Adherence was evaluated using the medication adherence rating scale (MARS) and the medication adherence reasons scale (MAR-Scale). Demographic, clinical, and treatment-related characteristics were analyzed. Statistical analysis was performed using SPSS version 27.

Results. Among the 73 patients (91.8% female; mean age: 48.25 ± 14.79 years), 79.5% were non-adherent to folic acid. The only factor significantly associated with non-adherence was the duration of folic acid use ($p < 0.05$). According to the MAR-Scale, the primary reasons for non-adherence were the burden of multiple medications (31.5%), concerns about long-term effects (27.4%), and fear of side effects (21.9%).

Conclusions. This study highlights a high rate of folic acid non-adherence among methotrexate-treated patients. The duration of supplementation was the only significant correlate. These findings emphasize the need for targeted adherence interventions and enhanced patient counseling in rheumatology clinics.

Keywords: folic acid, adherence, methotrexate, rheumatologic diseases, medication adherence rating scale (MARS), medication adherence reasons scale (MAR-Scale)

Abbreviations (in alphabetical order):

BMI	– body mass index
DAS28	– disease activity score 28
DMARDs	– disease-modifying anti-rheumatic drugs
EULAR	– European Alliance of Associations for Rheumatology
FDA	– Food and Drug Administration
ID	– Iraqi dinar
MAR-scale	– medication adherence reasons scale
MARS	– medication adherence rating scale
MTX	– methotrexate
RA	– rheumatoid arthritis
SPSS	– Statistical Package for the Social Sciences

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INTRODUCTION

Folic acid and methotrexate

Folic acid, a synthetic form of folate, contributes to various vital phases of nucleic acid (DNA and RNA) synthesis and to the maturation and development of red blood cells [1]. Methotrexate is a cornerstone medication frequently used in managing many rheumatologic diseases, such as rheumatoid arthritis. As a folate antagonist, methotrexate interferes with folate metabolism, resulting in a well-known spectrum of side effects, including oral ulcers, elevated liver enzymes, and toxic effects on red cell precursors, often leading to premature discontinuation of the medication. Traditionally, folic acid is prescribed alongside methotrexate to reduce these adverse effects [2].

On the other hand, the capacity of the enzyme dihydrofolate reductase to metabolize folic acid is limited to approximately 1 mg daily. Any additional unmetabolized fraction of folic acid might contribute to a variety of detrimental effects at the cellular level [3].

In rheumatoid arthritis, folic acid doses of 5 mg per week are effective in reducing methotrexate-related side effects without impairing its efficacy [4]. In practice, most clinicians avoid prescribing methotrexate and folic acid on the same day. However, because they act through different pathways and have relatively simple regimens, concurrent use does not reduce methotrexate efficacy [5,6]. Daily folic acid instead of weekly dosing may reduce gastrointestinal side effects associated with methotrexate [7].

Methotrexate use in rheumatologic diseases: doses and routes of administration

Since its approval in 1988 by the FDA for the treatment of rheumatoid arthritis, methotrexate has remained the benchmark standard medication for this prototypical rheumatologic disease, as well as for arthritis related to other autoimmune connective tissue disorders. Methotrexate exerts both anti-inflammatory and immunomodulatory effects [8].

In rheumatology, methotrexate is typically used in low weekly doses (mini-pulses between 7.5–25 mg/week), unlike the much higher doses (up to 1000–5000 mg/week) used in oncology. This difference reflects distinct pharmacologic properties and mechanisms of action, effectively making small and large doses behave as separate agents [9].

After polyglutamation, methotrexate acts chiefly by competitively inhibiting dihydrofolate reductase, reducing the availability of tetrahydrofolate and thereby impairing cell replication and DNA synthesis – mechanisms that are central to its role in cancer therapy. In rheumatologic diseases, methotrexate also increases extracellular adenosine concentrations, activating adenosine receptors and suppressing inflammation and immune responses [10].

Additional anti-inflammatory mechanisms are proposed, such as inhibition of nuclear factor κB activation and attenuation of inflammatory cell signaling pathways relevant to rheumatologic disease. However, these mechanisms remain incompletely understood [11].

The initial dose of methotrexate in rheumatoid arthritis varies based on clinical context, patient tolerability, and disease severity. A common approach is to start with 10 mg or more per week orally, with gradual dose escalation depending on treatment response [12–14].

Side effects of methotrexate and strategies for reduction

The most common gastrointestinal adverse effect of methotrexate is mucositis, which can affect the entire gastrointestinal mucosa. Hepatotoxicity is another well-known side effect and may occasionally be severe or even fatal. Methotrexate can also cause myelosuppression and macrocytic anemia. Rare but serious complications include pneumonitis. The primary strategy to counteract these side effects is folic acid supplementation. In severe cases, folinic acid may be used to reverse bone marrow toxicity [15].

Other strategies include dividing oral methotrexate doses (administering two or three doses 12 hours apart over one to two days) or switching to intramuscular or subcutaneous administration, which may reduce gastrointestinal side effects [16–18].

Drug non-adherence

Drug non-adherence can involve misunderstanding instructions, using medications incorrectly, or failing to take them as prescribed. Contributing factors include medication cost, psychosocial issues, complex regimens, and patient-related barriers [19]. Non-adherence is commonly observed in chronic diseases after the initial treatment period (beyond six months) [20]. It can be classified into three categories: primary non-adherence, non-persistence, and non-compliance (or poor execution) [21].

Consequences of drug non-adherence

Medication non-adherence is a significant global health concern. It impairs disease control and increases mortality risk [19,22]. In musculoskeletal disorders, non-adherence contributes substantially to outpatient healthcare costs [23].

This study aimed to evaluate adherence to folic acid in methotrexate-treated patients with rheumatologic diseases and to identify key factors contributing to non-adherence using validated adherence scales.

METHOD

This cross-sectional study was conducted to assess adherence to supplemental folic acid among patients using methotrexate (MTX) for various rheumatologic diseases. The study took place from August 2024 to December 2024 in the outpatient clinics of Al-Basrah Teaching Hospital, Al-Sayyab Teaching Hospital, and selected private rheumatology clinics in Basrah, Iraq.

The study included adult patients (≥18 years) with a confirmed diagnosis of a rheumatologic disease (e.g., rheumatoid arthritis, psoriatic arthritis) who were prescribed MTX along with supplemental folic acid. Patients were recruited through non-probability convenience sampling during routine visits to rheumatology clinics. A total of 73 patients participated in the study, including 67 females (91.8%) and 6 males (8.2%).

Patients were excluded if they were under the age of 18, refused to participate, or had incomplete clinical or interview data.

Data were collected using a structured, interviewer-administered questionnaire and a review of medical records. The questionnaire consisted of six sections:

1. **Demographic and socioeconomic data:** Included age, sex, marital status, education level, occupation, and place of residency (urban/rural). Physical measurements of height and weight were recorded to calculate body mass index (BMI).
2. **Methotrexate treatment profile:** Included route of administration (oral, subcutaneous, or intramuscular), weekly dosage and duration of methotrexate use, underlying diagnosis (e.g., rheumatoid arthritis, psoriatic arthritis), disease duration, documented side effects, and the estimated monthly cost of methotrexate therapy.
3. **Folic acid use:** Patients were asked about weekly folic acid dosage and number of tablets taken, estimated monthly cost of folic acid, and their subjective assessment of disease control (good, moderate, or poor).
4. **Laboratory investigations:** Recent results were recorded, including complete blood count (Hb%, MCV, WBC, platelet count), liver function tests (AST, ALT), and renal function (serum creatinine).
5. **Medication adherence rating scale (MARS-10):** Adherence to folic acid was assessed using the 10-item MARS-10, a self-reported questionnaire in which each item is answered with "yes" or "no". A total score of 10 indicated full adherence, while a score of less than 6 was considered non-adherence. The tool evaluates behavioral patterns (e.g., forgetfulness, intentional discontinuation) and beliefs about medication use. The Arabic version of MARS-10 was used [24,25].
6. **Medication adherence reasons scale (MAR-scale):** Patients identified barriers to adherence using the MAR-scale, a validated Likert-type tool that assesses five domains:
   1. **Management issues** (e.g., difficulty opening containers, embarrassment),
   2. **Multiple medications** (e.g., polypharmacy, difficulty swallowing),
   3. **Beliefs about medications** (e.g., fear of long-term effects, perception of unnecessary medication),
   4. **Availability issues** (e.g., pharmacy stock, affordability),
   5. **Forgetfulness and inconvenience** (e.g., busy schedules, difficulty maintaining routine).

Each item was answered with "yes" or "no". Higher total scores in a domain indicated greater barriers to adherence [26].

For patients with rheumatoid arthritis, disease activity was assessed using the Disease Activity Score 28 (DAS28); for psoriatic arthritis, the Disease Activity in Psoriatic Arthritis (DAPSA) score was used. For other rheumatologic diseases, disease activity was evaluated clinically and supplemented with laboratory indices according to standard rheumatology practice, to assess any association with drug non-adherence.

Informed consent was obtained from each patient, and they were assured that their information would remain confidential and be used solely for research purposes. **Ethical approval** was granted by the ethical committee at Al-Zahraa College of Medicine, Basrah University (ET/52).

Data were analyzed using IBM SPSS Statistics version 27. Continuous variables were expressed as means, standard deviations, and ranges, while categorical variables were summarized using frequencies and percentages. The chi-square test was used to assess associations between categorical variables. The independent samples t-test was applied to compare the means of continuous variables between adherent and non-adherent groups. A p-value <0.05 was considered statistically significant.

RESULTS

Responses regarding folic acid adherence in patients using methotrexate were collected from 73 patients, of whom 67 were female (91.8%). The majority of participants were married, unemployed, and only 19.2% were university graduates. Most patients (86.3%) were diagnosed with rheumatoid arthritis.

TABLE 1. Sociodemographic and disease characteristics of the patients

Variables		No.	%
Age	Mean ± SD	48.25 ± 14.79	
Sex	Male	6	8.2
	Female	67	91.8
Marital status	Single	13	17.8
	Married	46	63
	Divorced	2	2.7
	Widow	12	16.4
Education	Illiterate	16	21.9
	Primary	19	26.0
	Secondary	24	32.9
	University	14	19.2
Occupation	Employed	15	20.5
		58	79.5
Residence	Rural	46	63.0
	Urban	27	37.0
BMI	Mean ± SD	29.6 ± 6.44	
	Underweight	2	2.7
	Normal	15	20.5
	Overweight	22	30.1
	Obesity	30	41.1
	Morbidly obese	4	5.5
Diseases variables			
Diagnosis	RA	63	86.3
	Psoriasis arthritis	3	4.1
	Reactive arthritis	3	4.1
	Others	4	5.5
Duration of disease	Mean ± SD	83.82 ± 10.1	
Duration of treatment with folic acid	Mean ± SD	60.62 ± 9.2	

Other sociodemographic and disease characteristics are presented in Table 1.

The study found that most participants were non-adherent to folic acid while using methotrexate. Non-adherence was evaluated using the medication adherence rating scale (MARS), as illustrated in Figure 1.

When assessing the associations of non-adherence, none of the sociodemographic factors were found to be significantly associated with adherence status. Similarly, no statistically significant associations were found between diagnosis, disease duration, or disease activity. Detailed results are systematically presented in Table 2.

Further analysis explored the potential effect of frequency, cost, and duration of folic acid use on adherence. Among these variables, only the duration of folic acid use was significantly associated with adherence. Although a lower cost of folic acid appeared to be associated with better adherence, the finding was not statistically significant. These associations are shown in Table 3.

The medication adherence reasons scale (MAR-scale) was used to identify the main reasons for non-adherence. The top three reasons reported were: use of too many medications (31.5%), concerns about long-term effects (27.4%), and fear of side effects (21.9%). These results are presented in Table 4.

Based on these observations, more than two-thirds of the reported reasons for folic acid non-adherence in patients taking methotrexate fell into the category of multiple medication issues. Additionally, over 70% of participants expressed false beliefs or concerns about folic acid.

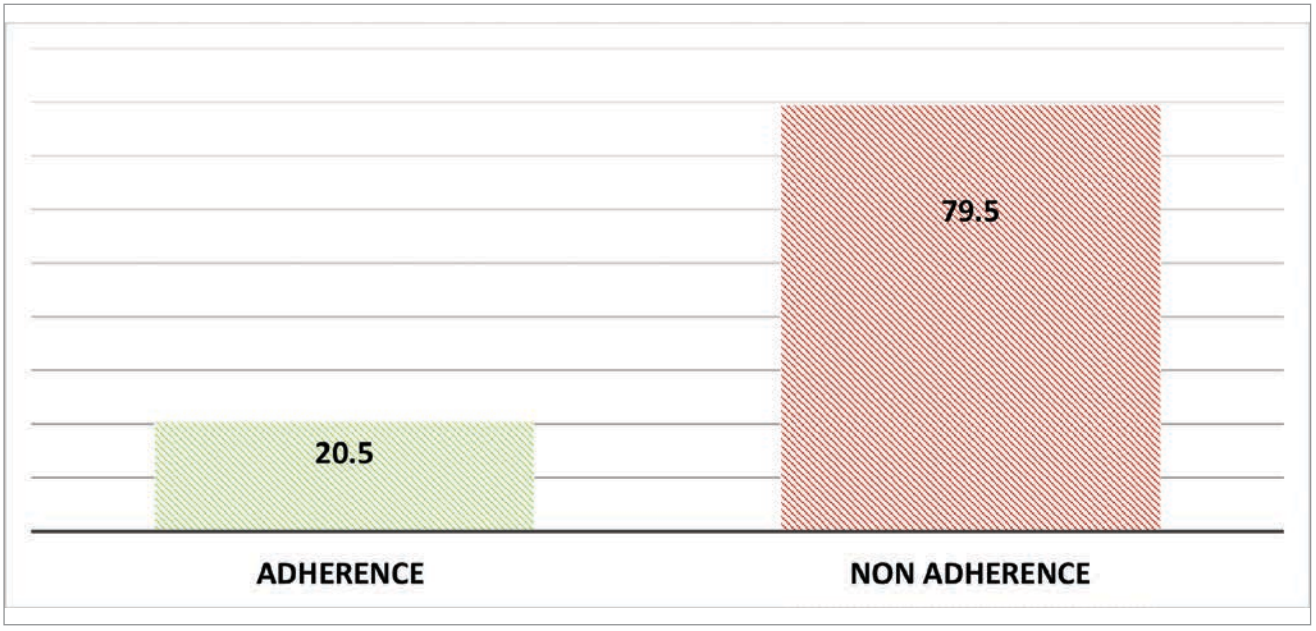

FIGURE 1. Patients' adherence to folic acid while using methotrexate (MTX)

TABLE 2. The association of sociodemographic and clinical characteristics of the patients with folic acid non-adherence while using methotrexate (MTX)

Variables		Adherence	Non-adherence	p-value
Age	Mean ± SD	47.48 ± 14.8	51.2 ± 14.73	0.389
Sex	Male	2 (13.3)	4(6.9)	0.418
	Female	13 (86.7)	54 (93.1)	
Marital status	Single	1 (6.7)	12(20.7)	0.513
	Married	11 (73.3)	35 (60.3)	
	Divorced	0 (0.0)	2 (3.4)	
	Widow	3 (20.0)	9 (15.5)	
Education	Illiterate	3 (20.0)	13 (22.8)	0.505
	Primary	2 (13.3)	17 (29.8)	
	Secondary	6 (40.0)	18 (31.6)	
	University	4 (26.7)	10 (15.8)	
Occupation	Employed	4 (26.7)	11 (19.0)	0.721
	Unemployed	11 (73.3)	47 (81.0)	
Residence	Rural	5 (33.3)	22 (37.9)	0.742
	Urban	10 (66.7)	36 (62.1)	
BMI	Mean ± SD	29.44 ± 6.69	30.22 ± 5.52	0.573
	Underweight	0 (0.0)	2 (3.4)	
	Normal	2 (13.3)	13 (22.4)	
	Overweight	7 (46.7)	15 (25.9)	
	Obesity	5 (33.3)	25 (43.1)	
	Morbidly obese	1 (6.7)	3 (5.2)	
Clinical variables				
Diagnosis	RA	14 (93.3)	49 (84.5)	0.697
	Psoriasis arthritis	0	3 (5.2)	
	Reactive arthritis	0	3 (5.2)	
	Others	1 (6.7)	3 (5.2)	
Duration of disease	Mean ± SD	85.15 ± 27.6	83.52 ± 9.5	0.946
DAS 28 (for RA patients)	Mean ± SD	4.10 1.94	4.74 1.5	0.231

TABLE 3. Folic acid characteristics and their association with non-adherence

Variables		Adherence	Non-adherence	p-value
Frequency of treatment	Daily	4 (26.7)	21 (36.2)	0.488
	Weekly	11 (73.3)	37 (63.8)	
Cost of folic acid (ID)	Mean ± SD	2833.3 ± 130.2	3301.72 ± 170.4	0.327
Duration of treatment with folic acid	Mean ± SD	51.8 ± 16.94	62.90 ± 8.29	0.05

TABLE 4. Medication adherence reasons scale response results

Category	Question	No.	%
1. Management issues	Problems opening medication containers	7	9.6
	Embarrassment in taking medications	0	0.0
	Difficulty swallowing medications	8	11.0
	Uncertainty about proper medication administration	14	19.2
2. Multiple medication issues	Concerns about the long-term effects of medications	20	27.4
	Consumption of too many medications	23	31.5
	Cost of medications	6	8.2
3. Belief issues with medications	Ineffective medications	14	19.2
	Side effects/fear of side effects	16	21.9
	Unnecessary medications	9	12.3
	Medication cessation to see if it is still needed	13	17.8
4. Availability issues	Medications are unavailable in the pharmacy	3	4.1
	End of medication supply due to a busy schedule	10	13.7
5. Forgetfulness and inconvenience issues	Forgetfulness in taking medications due to a busy schedule	10	13.7
	Inconvenience in taking medications as prescribed	6	8.2

DISCUSSION

To the best of our knowledge, this is the first study to describe adherence to folic acid, which is prescribed concurrently to counteract methotrexate (MTX) side effects in various rheumatologic diseases, especially rheumatoid arthritis.

Unfortunately, but not unexpectedly, the study found that folic acid non-adherence in the studied population was high (79.5%), and significantly related only to the duration of folic acid usage. The main reasons for this non-adherence were pill burden, concerns about long-term effects of medications, and fear of side effects.

All comparative studies addressed MTX and other disease-modifying anti-rheumatic drugs (DMARDs) non-adherence, due to the paucity of data regarding folic acid adherence in these diseases. Our findings align with previous observations from broad reviews such as Osterberg et al. Generally, non-adherence has been associated with adverse outcomes, increased healthcare costs, and higher mortality [27].

In our study, attempts to associate non-adherence with sociodemographic characteristics were unsuccessful, consistent to some extent with Van den Bemt et al. Nonetheless, these associations are likely more complex and influenced by heterogeneous methods for assessing adherence (no gold standard exists), differences in rheumatology infrastructure, availability of trained personnel, patient comorbidities, and implementation of adherence-promoting strategies [28,29].

We also attempted to correlate non-adherence with clinical factors such as diagnosis, disease activity (using DAS28 for RA), and disease duration, but no significant associations were found. Elliott suggests that patients with longstanding disease may develop tolerance to symptoms and deprioritize treatment adherence. Conversely, newly diagnosed patients may focus on symptom relief and undervalue long-term treatment goals, including the importance of folic acid [30].

These results were also in line with Contreras-Yáñez et al., who found that high disease activity was associated with non-adherence, potentially due to cultural or logistical barriers and misconceptions about treatment efficacy [31].

As folic acid supplementation is mandatory alongside MTX – as cited by guidelines such as EULAR and other rheumatology authorities – this study focused on its use in this population [32,33].

Fautrel et al. found no effect of dose or frequency on medication adherence in RA, whereas our findings revealed that among all characteristics of folic acid use (frequency, duration, and cost), only duration significantly correlated with adherence ($p < 0.05$) [34]. The reasons for non-adherence were further explored using the validated medication adherence reasons scale (MAR-Scale) [24,25].

Polypharmacy was the most reported barrier. This is consistent with Pardo et al., who found that multi-drug regimens in RA reduce adherence [35], and with Balsa et al., who emphasized the impact of treatment complexity on adherence [36]. However, Mohamadzadeh et al. did not find such an association, possibly due to simplified regimens or sociocultural factors [37].

Concerns about long-term effects and side effects were the second and third leading causes of non-adherence in this study. Neame et al. found that, although most UK patients trusted their treatment efficacy, many feared long-term side effects – especially those with prior negative DMARD experiences – suggesting this issue is multifaceted [38].

These findings support the need for healthcare administrators to address adherence barriers through structured education, even in brief follow-up visits. Discussions about pill burden and safety concerns are both essential and modifiable.

Community pharmacists can also play a key role in improving adherence and achieving better clinical outcomes in rheumatologic conditions [39].

Additionally, public education via media and targeted brochures has been shown to improve disease-related knowledge and adherence [40].

In the future, fixed-dose combination packaging of MTX and folic acid may offer a cost-effective, practical solution, as concurrent administration has not been shown to reduce MTX's anti-inflammatory effects [5,6,14].

CONCLUSION

This study highlights a high rate of folic acid non-adherence among methotrexate-treated patients. Duration of supplementation was the only significant correlate. These findings support the need for targeted adherence interventions and patient counseling in rheumatology clinics.

Recommendations

1. The rheumatology field in Iraq should undergo significant enhancement through the establishment of specialized tertiary outpatient clinics operated with an effective referral system and plans to strengthen the patient–physician relationship.
2. Implement medication adherence supervision programs, including pharmacist-led clinics, to address non-adherence and improve clinical outcomes.
3. Conduct a larger, expanded study to include patient comorbidities and concomitant medications, with a focus on methotrexate–folic acid coadministration.

Limitations

This study includes several limitations, the most important of which are:

- **Clinical infrastructure limitations.** The absence of specialized rheumatology clinics in the Basrah governorate complicated data collection. This may be a key contributor to folic acid non-adherence, due to the significant communication gap between patients and treating physicians.
- **Unaccounted comorbidities.** Concomitant medications for other health conditions were not recorded, limiting the understanding of polypharmacy's role in adherence.
- **Methodological limitations.** The study relies on self-reported data from a small, region-specific sample, which may introduce selection bias. In addition, disease activity for rheuma-

tological conditions other than rheumatoid arthritis was not calculated due to logistical constraints.

- **Verification gaps.** Pharmacy dispensing data were not obtained for most patients, due to the lack of a formal medication-tracking system.

Preliminary study statement:

This study represents an initial exploration into folic acid adherence among methotrexate-treated patients in the Iraqi rheumatology setting. While the findings offer important insights into patient behavior and treatment challenges, the results should be interpreted with caution due to the study's limited sample size and regional scope. Further large-scale, multicenter research is warranted to confirm these findings and develop targeted interventions to improve folic acid adherence and optimize clinical outcomes in diverse patient populations.

Conflict of interest:

The authors declare no competing interests.

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