







Original Research

Non-adherence to pharmacotherapy and its associated factors in outpatients with rheumatoid arthritis

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Received (first version): 23-Jan-2023

Accepted: 12-Feb-2023

Published online: 26-May-2023

Abstract

Background: Despite the availability of effective pharmacotherapy for the management of rheumatoid arthritis (RA), health outcomes are suboptimal due to poor adherence to the prescribed treatment. Limited research has been conducted to investigate medication non-adherence and its associated factors among patients with RA. **Objective:** This study aimed to assess medication adherence and to explore the factors associated with medication non-adherence among outpatients with RA in Jordan. **Methods:** The current cross-sectional study was conducted at outpatient rheumatology clinics at two teaching hospitals in Jordan. Variables including socio-demographics and biomedical variables, in addition to disease and medication characteristics, were collected using medical records and custom-designed questionnaire. Medication adherence was assessed using the validated 5-item Compliance Questionnaire for Rheumatology. Stepwise Logistic Regression analysis was performed to identify the factors that are independently and significantly associated with medication non-adherence. **Results:** A total of 261 patients participated in the study, from which, 43.3% were found non-adherent. Binary regression analysis results revealed that low monthly income (OR= 0.239, CI= 0.130-0.440, P<0.01), the presence of chronic respiratory disease (OR= 2.727, CI= 1.059-7.022, P<0.05), lower medication necessity scores (OR= 1.177, CI= 1.10-1.259, P<0.01) and higher concerns about RA medications (OR= 0.917, CI= 0.860-0.978, P<0.01) were significant and independent predictors of medication non-adherence in patients with RA. **Conclusion:** Future pharmaceutical care and clinical pharmacy service programs should emphasize medications benefits and minimizing medication-related concerns by selecting safe medications and providing guidance on mitigating side effects, particularly for RA patients who have low income and those who suffer from other comorbid diseases.

Keywords: medication adherence; medication beliefs; rheumatoid arthritis; pharmaceutical care; Jordan

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease characterized by persistent inflammation primarily in the joints.¹ The worldwide prevalence of RA has been estimated as 0.46%,² with around 25 to 50 new cases diagnosed in a population of 100,000 every year.³ RA has been found to increase the chance of early death by 50% and reduce life expectancy by 3 to 10 years.⁴ Uncontrolled RA can lead to joint damage, disability, poor quality of life and several other complications.⁵ To reduce the risk of joint damage and functional disability, the National Institute for Health and Clinical Excellence (NICE) has recommended the use of disease-modifying anti-rheumatic drugs (DMARDs), ideally in combination and within the first three months after symptoms onset.⁶ However, adherence to these medications is vital for achieving the optimal clinical outcomes.⁷

Adherence is defined as “the extent to which a person’s behavior regarding taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider”.⁸ Poor adherence to therapeutic drug regimens has been recognized as one of the most common barriers to achieving optimal clinical outcomes in RA.⁹ Several studies reported a significant relationship between medication non-adherence and higher disease activity among patients with RA.¹⁰⁻¹² Earlier studies reported inconsistent findings with regard to rate of medication adherence in patients with RA, ranging from 30-80%.^{9,10,12} These variations in medication adherence



rates may be attributed to the difference in the methods used for medication adherence assessment, the diversity of the studied population and the difference in the study design.

Literature also reported inconsistent findings regarding the variables associated with medication non-adherence among patients with RA. Advanced age, lower education level, and negative patients' beliefs regarding their medications were associated with non-adherence among RA patients in a British study.¹³ Another study conducted in the UK reported that younger age, decreased beliefs in medications necessity, higher medications concerns, and longer disease duration were significantly associated with lower adherence among patients with RA.¹⁴ A large cross-sectional study conducted across Europe, Canada, Latin America, the Asia-Pacific region and the Middle East reported that older age, lower beliefs in the necessity of RA medications, and higher concerns about medications side effects were associated with medication non adherence.¹⁵ RA patients who were taking a higher number of medications were found to be significantly non-adherent in studies conducted in USA,¹⁶ Canada,¹⁷ and China.¹⁸

Most of the earlier studies about medication non-adherence were conducted in USA and Europe.⁸ Investigating this issue in Jordan broadens the vision for more diverse social and cultural backgrounds because it has been found that socioeconomic and cultural differences could have the potential to impact medication adherence as much as the healthcare systems do.¹⁹ Furthermore, the variability in the rates of adherence to RA medications and the diversity of the factors that are associated with medication non-adherence in patients with RA requires the need for conducting more studies that would narrow down the variability in the medication adherence rate, and facilitate the revealing of the true predictors of medication non-adherence among patients with RA. The current study findings should provide insight for the upgrading of future pharmaceutical care interventions to improve medication adherence and health outcomes among patients with RA in Jordan. This study aimed to assess medication adherence and to explore the factors associated with medications non-adherence among outpatients with RA in Jordan.

METHODS

Study design and subjects

The current cross-sectional study was conducted on patients with RA attending the outpatients' rheumatology clinics at King Abdullah University Hospital (KAUH) and Prince Basma Teaching Hospital in Irbid/Jordan in the period from February through October 2021. The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. The study received ethical approval from the Institutional Review Board (IRB) of KAUH (Ref. # 58/132/2020), and patients who agreed to participate in the study were asked to sign an informed consent form.

Patients were included in the study if they were 18 years of age or older, had a confirmed diagnosis of RA for at least 4 months,

received at least one DMARD, and agreed to participate in the study. Patients who did not complete the study survey and those with cognitive impairment were excluded from the study. During the outpatient clinics visit, patients who met the inclusion criteria were informed by the research pharmacist that participation is voluntary and they have the right to withdraw from the study at any time. They were also informed that their medical care and treatment will not be affected by their participation. The researcher emphasized that the collected data will only be used for the research purposes and will be kept in the office of the Principal Investigator to ensure confidentiality. The interview took an average of 10-15 minutes to complete.

Study instruments

A custom-designed questionnaire was designed to collect information on socio-demographic variables including age, gender, marital status, smoking status, occupation, living conditions, income, education level, family history, insurance status, regular exercise, and healthy diet. Medical files and hospital data were used to obtain information about the disease, RA medications including biologic and non-biologic DMARDs, corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs), and other medications.

Beliefs about medicines questionnaire (BMQ) – Specific

The validated Arabic version of the specific part of the beliefs about medications questionnaire (BMQ-Specific) was used to evaluate the necessity of taking RA medications to control the disease (necessity scale) and concerns about the potential negative consequences of the prescribed medication (concerns scale).²⁰ The patients indicated their degree of agreement with each statement on a five-point Likert scale, ranging from 1 = strongly disagree to 5 = strongly agree. Scores obtained for individual items within each scale were summed. The score for each scale ranges from 5 to 25 with higher scores indicating stronger beliefs.²¹

The clinical disease activity index (CDAI)

The CDAI was used to measure disease activity in current study.²² According to the CDAI, participants were categorized as either having a low (3-10 points), moderate (>10-22 points), or high (>22 points) disease activity.

The Compliance Questionnaire for Rheumatology (CQR5)

This validated questionnaire is a short version of the 19-item Compliance Questionnaire for Rheumatology (CQR), which is the only self-report adherence measure specifically developed and validated for rheumatic diseases.²³ The CQR-5 has been used in previous studies to assess medication non-adherence in patients with RA.^{12,24} The validated Arabic version of the questionnaire used in the present study was adapted after permission from the corresponding author of an earlier study.²⁵ The participants indicated their level of agreement regarding certain statements on a 4-point Likert answering scale ranges from; "Definitely don't agree" (scored 1) to "Definitely agree" (scored 4), with lower scores indicating lower levels of adherence. The questions were as follows: 1. I take my anti-rheumatic medicines because I then have fewer



problems, 2. I definitely don't dare to miss my anti-rheumatic medications, 3. My medicines are always stored in the same place and that's why I don't forget them. 4. I take my medicines because I have complete confidence in rheumatologist. 5. What the doctor tells me, I hang on to. The participants were categorized into low or high adherents based on two formulas, one for high adherence (D1) and one for low adherence (D0). If D0 is greater than D1 then the participant was classified as low adherent. Conversely, if D1 is larger than D0, then the participant was classified as highly adherent. The formulas are presented as the following: $D0 = -27.611 + (4.407 * Q2) + (0.939 * Q3) + (6.101 * Q5) + (2.366 * Q6) + (2.531 * Q17)$, $D1 = -33.304 + (2.801 * Q2) + (5.008 * Q3) + (6.471 * Q5) + (1.215 * Q6) + (3.252 * Q17)$.²³

Data analysis

The Statistical Package for the Social Sciences (SPSS version 27 from IBM) was used to run descriptive and analytical statistics. Descriptive analysis was used to describe continuous variables in terms of the mean (standard deviations) or median (25th-75th quartiles) depending on the normality of data tests using the Kolmogorov–Smirnov and the Shapiro–Wilk statistical tests, and the categorical variables in term of frequencies (percentages). Participants' differences with regard to medication non-adherence were tested using the independent sample t-test and the Mann–Whitney U-test for normally and non-normally distributed continuous variables respectively. The Pearson chi-square test was conducted to investigate the association between the categorical variables and medication non-adherence among the study participants. Variables with a P value < 0.05 at the univariate analysis were included in the stepwise binary logistic regression to explore significant and independent predictors of medication non-adherence.

Sample size calculations

Binary logistic regression was applied to identify variables association with adherence level. The rule of Events Per Variable criterion (EPV) ≥ 10 was utilized to estimate the minimal required sample size.²⁶ The current regression model included 11 independent variables, therefore, 110 patients in the smaller group is sufficient.

RESULTS

A total of 313 patients were invited to participate in the study. Of those, 32 patients refused to participate, 4 patients didn't complete the questionnaire, 16 were excluded from the study because they did not receive a DMARD, and the remaining 261 patients completed the survey, with a response rate of 83.4%. The majority of the study participants were females (86.6%), married (77.0%), unemployed (83.1%), insured (78.5%), living with their families (96.6%), had low education level (63.6%), nonsmokers (80.1%), with monthly income of less than 500JD (64.0%), did not eat a healthy diet (63.6%), had not practiced in a regular physical activity (78.5%), and have negative family history of RA (73.2%). The study population age ranged from 19 to 83 years with a mean of 48.7 (SD= 12.57). Demographic characteristics of the participants are presented in Table 1.

Characteristics	N (%)	Mean (SD)
Age		48.7 (12.57)
Body mass index (BMI)		30.04 (6.52)
Gender		
Male	35 (13.4)	
Female	226 (86.6)	
Education level ^a		
Low	166 (63.6)	
High	95 (36.4)	
Occupation		
Employed	44 (16.9)	
Unemployed	217 (83.1)	
Living condition		
Alone	9 (3.4)	
Not alone	252 (96.6)	
Insurance		
Yes	205 (78.5)	
No	56 (21.5)	
Marital status		
Married	201 (77.0)	
Single ^b	60 (23.0)	
Income		
Less than 500 JD	167 (64.0)	
500 JD or more	94 (36.0)	
Smoking status		
Smoker	52 (19.9)	
Non-smoker	209 (80.1)	
Healthy diet		
Yes	95 (36.4)	
No	166 (63.6)	
Regular exercise		
Yes	56 (21.5)	
No	205 (78.5)	
Family history		
Yes	70 (26.8)	
No	191 (73.2)	

JD: Jordanian Dinar, SD: standard deviation

^aHigh educational level includes diploma degree or higher, Low educational level includes illiterate, primary, secondary, and high school.

^bSingle includes unmarried, divorced, and widow.

As shown in Table 2, the most prescribed conventional DMARD was methotrexate (67.8%), followed by sulfasalazine (28.0%), while the least prescribed was leflunomide (0.4%). About one third of the study participants were treated with biologic DMARDs either as monotherapy or in combination with other medications (36.8%), and more than half of them were receiving a single DMARD (51.7%). The study results revealed that the majority of the participants were using corticosteroids or NSAIDs to reduce the inflammation and to relief their pain (75.1%). Around 37.5% of the participants had high disease activity, with a median CDAI score of 19 (11-26). Other disease and medication characteristics are presented in Table 2.



Table 2. Disease and medication characteristics of the study participants (n=261)				
Variable		N (%)	Variable	Median (25th-75th quartiles)
Medications for RA	Methotrexate	177 (67.8)	Duration since RA diagnosis (years)	10.0 (4.0-16.5)
	Sulfasalazine	73 (28.0)	Number of comorbidities other than RA	2.0 (1.0-3.0)
	Hydroxychloroquine	32 (12.3)	Number of RA medications	2.0 (2.0-3.0)
	Azathioprine	14 (5.4)	Number of total medications	6.0 (4.0-8.0)
	Leflunomide	1 (0.4)	Duration of medications intake (years)	8.0 (2.0-14.0)
	Biologic DMARDs	96 (36.8)	ESR (mm/hour)	44.0 (30.0-65.0)
	Corticosteroids/NSAIDs	196 (75.1)	CDAI score	19.0 (11.0-26.0)
Number of DMARDs	Single DMARD	135 (51.7)		
	Double DMARDs	96 (36.8)		
	Triple DMARDs	27 (10.3)		
	Quadruple DMARDs	3 (1.2)		
Frequency of medication administration	Monthly	1 (0.4)		
	Biweekly	7 (2.7)		
	Once weekly	115 (44.1)		
	Once daily	48 (18.4)		
	Twice daily	90 (34.5)		
Presence of chronic disease other than RA		177 (67.8)		
Type of comorbidities	Hypertension	77 (29.5)		
	Diabetes mellitus	53 (20.3)		
	Chronic respiratory disease	24 (9.2)		
	Hypothyroidism	20 (7.7)		
	Atherosclerotic disease	15 (5.7)		
	Herniated disc	15 (5.7)		
Presence of any complications of RA		243 (93.1)		
Type of complications	Joint deformity	55 (21.1)		
	Arthroplasty	36 (13.8)		
	Peripheral neuropathy	202 (77.4)		
	Osteoporosis	98 (37.5)		
	Eye problems	122 (46.7)		
	Cardiovascular disease	13 (5.0)		
Positive RF		81 (31.0)		
Disease activity estimated by CDAI	Low	53 (20.3)		
	Moderate	88 (33.7)		
	High	98 (37.5)		
	Missing	22 (8.5)		

RA: rheumatoid arthritis, DMARD: disease-modifying anti-rheumatic drug, RF: rheumatoid factor, NSAIDs: non-steroidal anti-inflammatory drugs, ESR: erythrocyte sedimentation rate, CDAI: clinical disease activity index.

According to the CQR-5, 43.3% of the study participants were found non-adherent. Factors that were significantly associated with medication non-adherence in the univariate analysis including low income, having a chronic respiratory disease, receiving three or more DMARDs, higher disease activity, higher ESR levels, lower beliefs in medication necessity, and higher concerns about medications side effects were entered into the multivariate analysis model. Stepwise Logistic Regression was performed with final model of factors which are significantly

and independently associated with medication adherence as shown in Table 3. Results revealed that the odds of being adherent in participants with high income (>500JD) was 4.184 times the odds of being adherent in participants with low income (OR=4.184, 95%CI 2.273:7.692, P<0.01). The odds of being adherent in participants who suffered from a chronic respiratory disease was 0.367 times the odds of being adherent in the participants who did not have a chronic respiratory disease (OR=0.367, 95%CI 0.142:0.944, P<0.05). With regard to



Table 3. Multivariate analysis of variables associated with medication non-adherence			
Variable		OR (95% CI)	P-value
Monthly income ^c			
	Low	Reference	<0.0001 ^a
	High	4.184 (2.273-7.692)	
Having chronic respiratory disease			
	No	Reference	0.038 ^b
	Yes	0.367 (0.142-0.944)	
Necessity score			
		1.177 (1.10-1.259)	<0.0001 ^a
Concerns score			
		0.917 (0.860-0.978)	0.008 ^a

^aSignificant at 0.01 level.

^bSignificant at 0.05 level.

^cLow income is <500 JD, High income= 500JD or more.

patients' beliefs about medications, each unit increase in the medication necessity score was associated with an increase in the odds of being adherent (OR=1.177, 95%CI 1.10:1.259, P<0.01). In addition, each unit increase in the concerns score was associated with a decrease in the odds of being adherent (OR=0.917, 95%CI 0.860:0.978, P<0.01).

DISCUSSION

The study participants reported low adherence. Factors including negative medication beliefs which are demonstrated by decreased medication necessity and increased medication-related concerns, having a comorbid respiratory disease and low income were significantly associated with medication non-adherence in the present study.

Several studies were conducted to investigate the rate of adherence among patients with different chronic diseases in Jordan including hypertension,²⁷ diabetes,²⁸ and cardiovascular diseases.²⁹ However, medication adherence among patients with RA and its associated factors has not been evaluated in Jordan. Investigating this issue in Jordan broadens the vision for more diverse social and cultural backgrounds which have been reported to impact medication adherence. Identifying the factors associated with medication non-adherence represents a preliminary step for the development of future pharmaceutical care intervention programs in order to improve health outcomes among patients with RA.

The current study showed that 43.3% of the participants were non-adherent. Consistent with the current findings, an earlier Nigerian study reported 48.5% rate of non-adherence among patients with RA.¹² A UK study found that 41% of the patients reported low adherence at least one time point from baseline to follow up using Compliance Questionnaire for Rheumatology (CQR).¹⁴ Another cross-sectional study reported

that 42% of the 501 RA patients were not taking methotrexate as prescribed.³⁰ Furthermore, other studies reported higher rates of non-adherence. A study conducted in Egypt showed that the majority of the patients with RA (90.6%) were found non-adherent using the 8-item Morisky adherence scale.³¹ Despite the similarity between the Egyptian and the Jordanian community, the difference in rates of adherence between the two studies could be attributed to the difference in the tool used to assess medication adherence and the variables that were evaluated in each study. For example, the current study evaluated patients' beliefs about medications which were not considered in the Egyptian study. A Chinese study reported that more than half of the patients (62%) reported low adherence to their DMARDs medications.¹⁸

Consistent with the results found in a Chinese study,¹⁸ findings of the present study showed that low income level was significantly and independently associated with medication non-adherence; this could be attributed to the fact that not having enough money is a crucial issue when it comes to buying medications or dealing with healthcare costs. Patients who were treated for chronic respiratory diseases such as asthma, COPD, and allergic rhinitis in addition to RA were significantly less adherent to their medications than patients with a healthy respiratory system in the present study. Methotrexate is one of the most commonly used medications for the treatment of RA. The potential side effects of Methotrexate include pulmonary toxicity such as pneumonitis, shortness of breath, bronchial asthma, and, in rare cases, it could result in pulmonary fibrosis,³² which could justify the prevalence of medication non-adherence among patients with respiratory disease as shown in the present study.

Beliefs about medications were also significantly associated with non-adherence. In the present study, patients who had positive beliefs manifested by higher medication necessity scores had significantly higher medication adherence than those who had negative beliefs manifested by lower medication necessity scores. In contrast, patients who had negative beliefs manifested by greater medication-related concerns score had significantly lower medication adherence. In a study conducted to investigate the impact of beliefs about medications on adherence, results showed that patients who had more negative beliefs about DMARDs were significantly non-adherent to the prescribed treatment.¹³ In a large cross-sectional study, which recruited a large number of patients with different rheumatic diseases from multiple countries, results showed that concerns about medication harms were significantly higher in the RA group. The study also showed that higher medication -related concerns score was associated with significantly less medication adherence among the study participants, while higher medication necessity scores were associated with higher medication adherence.¹⁵ The influence of patients' beliefs on medication adherence is not exclusive only for RA; it was also reported in other chronic diseases including asthma, hypertension, and chronic pain.³³ Therefore, in addition to emphasizing on medication role in improving clinical outcomes, clinical pharmacists should select medications with the best safety profile and educate the



patients on the potential side effects and how to mitigate them.

The current study has some limitations, the self-report method used to assess medication adherence may have overestimated patients' adherence due to social desirability bias. Although the target sample size was achieved, a larger sample size would help to draw more robust conclusions from the present study.

CONCLUSIONS

The current study clearly demonstrates a low level of medication adherence among the study participants. Empathizing on medication benefits and minimizing medication related concerns by choosing safe medications and offering guidance on mitigating side effects should be considered in future clinical pharmacy service programs, particularly for patients who have low income and those who suffer from other comorbid diseases.

ACKNOWLEDGEMENTS

The authors would like to express their sincere thanks to Dr. Hani Shatnawi for his grateful cooperation in the recruitment of the study participants. The contribution of the participants, participating hospitals and the research team is also acknowledged.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to declare.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTION

ASJ conceived and designed the study, supervised the project, conducted research, provided research materials, and wrote initial and final draft of article. SRA designed the study, collected, organized, analyzed and interpreted data, and wrote initial and final draft of article. WAA validated instruments, organized, analyzed and interpreted data and reviewed the manuscript. TLM conceived the study, provided research material and reviewed the final draft of article. RB validated instruments, organized, analyzed and interpreted data and reviewed the manuscript. SA conceived the study, supervised the project, reviewed the final draft of article and provided logistic support. All authors have critically reviewed and approved the final draft of the study and agreed to be accountable for all aspects of the work.

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