

# Drug Adherence and Associated Factors in Patients with Systemic Sclerosis

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**Abstract:** ***Background:** Systemic sclerosis (SSc) is a rare, chronic and disabling autoimmune disease. Disease-modifying antirheumatic drugs are the cornerstone and initial therapy in SSc. Although drug adherence is crucial for successful therapy, non-adherence is a substantial problem in some patients. **Objectives:** to identify the determinants of adherence to medications among Iraqi patients with SSc. **Patients and Methods:** This cross-sectional study included a total of 143 consecutive patients diagnosed as having SSc. Disease severity was determined according to Arabic version of the eight-item Morisky Medication Adherence Scale (MMAS-8). The following data was collected through the questionnaire: age, gender, body mass index (BMI), residence, socioeconomic status (SES), marital status, education level, employment, duration of SSc, type of SSc, self-dependence, medications, chronic comorbidities, satisfaction with treatment and presence of side effects. **Results:** The adherence rate was 40%. In Multivariate analysis, high educational level (OR=6.56, 95%CI=1.18-72.32, p= 0.041), and high SES (OR=25.3, 95%CI= 2.3-27.36, p= 0.008) were significantly associated with increased drug adherence. On the other hand, unemployment (OR=0.25, 95%CI= 0.07-0.87, p= 0.039), the presence of side effects (OR= 0.19, 95%CI=0.04-0.98, p= 0.048), and patient treatment dissatisfaction (OR=0.31, 95%CI=0.7-0.77, p= 0.025) were independent risk factors for non-adherence. **Conclusions:** Sixty percent of studied patients with SSc attending Baghdad Teaching Hospital were of low medication adherence. High education level and higher socioeconomic status are significantly associated with increased treatment adherence in patients with SSc. Alternatively, unemployment, presence of drug side effects and treatment dissatisfaction were significantly associated with lower adherence rates in patients with SSc.*

**Keywords:** systemic sclerosis, drug adherence, multivariate analysis

## 1. Introduction

### Definition

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by small vessel vasculopathy, autoantibody production, and excessive collagen deposition in the skin and internal organs [1]. SSc may be triggered by environmental events in genetically susceptible individuals [2]. The disease can affect the lungs, heart, kidneys, gastrointestinal tract and musculoskeletal system with substantial impact on morbidity, mortality, and quality of life. Although it is a rare disease, SSc poses a substantial economic burden on the health care system and society [3].

### Epidemiology and risk factors

Globally, around one in 10,000 people are estimated to be affected by SSc [4]. This small number suggests that the causal factors are of uncommon occurrence, and these factors probably include several environmental elements alongside genetic susceptibility [5]. To the best of our knowledge no epidemiological study of SSc has been done among Iraqis.

### Classification

Patients with SSc can generally be classified into one of two major disease subsets based on the extent of skin involvement:

- Those with proximal involvement are classified as diffuse cutaneous SSc
- Those with restricted involvement affecting the limbs distal to the elbows or knees, with or without face and neck involvement, are classified as limited cutaneous

SSc [6].

### Clinical Features

Signs and symptoms of multiple organ-based manifestations are a hallmark of SSc and are important in the diagnosis and classification of the disease. In cases of diffuse disease, skin tightness and itching are early features [7]. Some patients present with musculoskeletal pain that might mimic inflammatory joint disease. Lower-limb swelling, and muscle weakness or fatigue might be reported, especially in early-stage diffuse cutaneous SSc [8]. Clinical examination allows major features of the external disease, as well as skin, vasculature, and musculoskeletal involvement, to be defined and assists in making a definite diagnosis. Organ-based complications require careful assessment [9].

### Diagnosis

There is no single diagnostic test for SSc. The diagnosis of SSc is usually based on the individual clinical features and from the results of targeted investigations such as SSc-associated autoantibodies and nail fold capillaroscopy [10]. For the general physician, the diagnosis of SSc is very unlikely in the absence of Raynaud's phenomenon and distal skin involvement (e.g. sclerodactyly). However, there are caveats to this generalization [11].

The 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) SSc classification criteria are a helpful reference tool for assessing patients with possible SSc [12]. Involvement of skin proximal to metacarpophalangeal joints is usually diagnostic of SSc. Furthermore, early diagnosis of SSc can be established in patients with Raynaud's phenomenon,

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puffy fingers, and positive antinuclear antibodies, and is confirmed by the presence of SSc-associated autoantibodies and/or capillaroscopic abnormalities<sup>[13]</sup>.

### Treatment

There are number of effective drug therapies used in the management of patients with SSc. Drug treatments can be generally divided into three groups: vascular acting<sup>[14]</sup>, immunosuppressive/ immunomodulatory<sup>[15]</sup>, and anti-fibrotic<sup>[16,17]</sup>. One or more group were used in the treatment of SSC patients, according to organ involvement.

### Adherence to therapy

Adherence or compliance is defined as “the extent to which person’s behavior (taking medication, following a diet program, or modifying her/his lifestyle), corresponds with agreed recommendations from a health care provider.<sup>[18]</sup>

### Adherence rates

These are typically lower among patients with chronic conditions, as compared to those with acute conditions. The persistence among patients with chronic conditions decreasing drastically after the first 6 months of therapy<sup>[18]</sup>.

### Consequences of non-adherence

In general, failure to adhere to regular treatment results in poor disease control, increasing morbidity and mortality and decreasing quality of life. Non-adherence also results in a significant economic burden, such as increased hospitalization and emergency department visits, resulting in unnecessarily high health care costs<sup>[18]</sup>.

### Determinants of non-adherence

Non-adherence to treatment is multifactorial for most patients and varies according to the unintentional or intentional pattern of non-adherence. The World Health Organization (WHO) has identified health-care systems, provider relationships, disease, treatment, patient characteristics and socioeconomic characteristics as factors affecting adherence<sup>[19]</sup>.

Polypharmacy appears to be an important predictor of non-adherence. Dosing can also have significant impact, with once a day dosing regimens being associated with the highest level of adherence<sup>[20]</sup>.

Low socioeconomic/educational status, depression, and other psychosocial characteristics have been associated with poor adherence. In contrast, social support may improve adherence. The relationship between disease severity, organ damage and poor adherence is likely to be bidirectional<sup>[21]</sup>.

In contrast to intentional non-adherence, unintentional non-adherence is thought to be the result of a passive process that is less strongly associated with individuals beliefs and perceptions. Unintentional non-adherence can be related to issues with the health system<sup>[22]</sup>.

### Aims of the Study

This study aimed to identify the determinants of adherence to medications among Iraqi patients with SSc.

## Patients and Methods

### Study design

This cross-sectional study was conducted at the Rheumatology Unit of Baghdad Teaching Hospital during the period 1<sup>st</sup> Feb 2023 - December 2023. The study was approved by the Iraqi Council for Medical Specializations.

### Sample Collection

A total of 143 consecutive patients diagnosed as having systemic sclerosis according to the 2013 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria, were enrolled in the study.

### Inclusion Criteria

- Patients were on treatment with one or more of the following three treatment group, at the time of enrolment:
- vascular acting, immunosuppressive/immunomodulatory and/or anti-fibrotic agents,
- Disease duration >3 months
- Have adequate cognitive status as determined by communicating with the patient

### Exclusion Criteria

- Patients with cognitive impairment
- Pregnancy
- Malignant diseases

### Ethical Considerations

The study protocol was approved by the Ethical committee of the Iraqi Board for Medical Specializations, with approval number 194 on the 16th of January 2023. Informed consent was obtained from each participant included in the study according to the declaration of Helsinki.

### Data collection and entry

Data entry of patients was done using paper clinical research form (CRF) through interview and questionnaires.

All participants completed three paper questionnaires: socio-demographic, clinical and treatment characteristics survey including the Arabic version of the eight-item. Morisky Medication Adherence Scale (MMAS-8).

The following data was collected through the questionnaire: age, gender, height (cm), weight (kg), BMI (calculated according to the equation  $BMI = \text{weight}/\text{height}^2$ ), residence, socioeconomic status, marital status, education level, employment, duration of SSc, type of SSc, self-dependence, medications, chronic comorbidities, satisfaction with treatment and presence of any drug side effects.

### Statistical analysis

Descriptive statistics were used to summarize the characteristics of participants. Factors associated with medication non-adherence were explored using logistic regression analysis and were shown as odds ratios (ORs) with 95% confidence interval (CI). All statistical analyses were performed using IBM SPSS version 25. A p-value of <0.05

was considered significant.

## 2. Results

All together 143 SSc patients were studied, their mean age was 40.23± 13.78 years (range 9-61 years), most of them (77.62%) were females. The male/female ratio was 1:4. About two-thirds of the patients (67.13%) were married. The mean BMI of the patients was 22.9± 4.26 kg/m<sup>2</sup> demographic data are shown in table 1.

**Table 1:** Description of demographic data among 143 SSC patients

Variables	Values
Age, years	
Mean±SD	40.23± 13.78
Range	9-67
Gender	
Male	32(22.38%)
Female	111(77.62%)
Marital status	
Married	96(67.13%)
Single	47(32.87%)
Body mass index, kg/m <sup>2</sup>	
Mean±SD	22.9± 4.26
Range	14.9-33.12
Education	
Primary or less	53(37.06%)
Secondary	71(49.65%)
Higher	19(13.27%)
Socioeconomic status	
Low	73(51.05%)
Intermediate	61(42.66%)
High	9(6.29%)
Residence	
Rural	31(21.68%)
Urban	112(78.32%)
Employment	
Yes	98(68.53%)
No	45(31.47%)
Self-dependent	
Yes	92(64.34%)
No	51(35.66%)

About half of the patients had secondary education, while higher education was found in 13.27%. Socio-economic status of 51% of the patents was low, while 6.29% of the patients are considered to have high socio-economic status. Most patients (78.53%) were urban residents, and 68% of them were employed. Most patients (64.34%) were self-dependent.

### Clinical and Therapeutic Characteristics of 143 SSc Patients

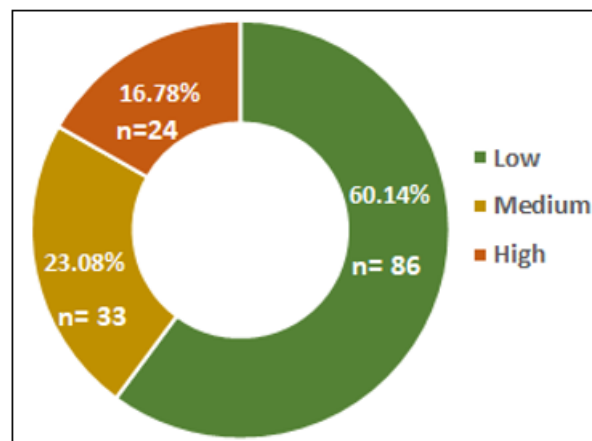
The mean disease duration was 7.22 ± 6.53 years (range 1-29 years). Slightly more than half of the patients had a limited type of SSc. Immuno-suppressants were used by 58% of patients, while antifibrotics were used by 10.5% of the patients, respectively. Drug side effects were reported in 26.57% of the patients. However, 45.45% of the patients were satisfied with their treatment. Systemic involvement of SSc and comorbidity were reported in 18.18% and 43.36% of the patients, respectively as shown in Table 2.

**Table 2:** Clinical and therapeutic characteristics among 143 SSc patients

Variables	Values
Disease duration, years	
Mean±SD	7.22± 6.53
Range	1.0-24
Medications	
Immunosuppressant	83(58.04%)
Vascular acting	28(19.58%)
Antifibrotic	15(10.49%)
Type	
Limited	74(51.75%)
Diffuse	69(48.25%)
Systemic involvement	
No	81(56.64%)
Interstitial lung disease	62(43.36%)
Comorbidity	
No	117(81.82%)
Yes	26(18.18%)
Drug side effects	
No	105(73.43%)
Yes	38(26.57%)
Patients satisfaction	
Yes	65(45.45%)
No	78(54.55%)

### Adherence Rate

According to Morisky scale, 24 patients (16.78%) had a high adherence rate, 33 patients (23.08%) had medium adherence, and 86 patients (60.14%) had a low adherence to their medications as shown in (Figure 1).



**Figure 1:** The adherence rate to the medications among 143 SSc patients

### Association of Patients' Characteristics with Adherence rate

Three demographic factors displayed a significant association with patients' adherence. More than 30% med-high adherent patients had higher education compared to only 2.33% of low adherent patients who had such level of education (with significant differences between them). Patients who were employed with high socioeconomic status, were more common amongst the adherent group (31.58% and 50.36%, respectively) than non-adherent group (3.49% and 19.77%, respectively) with significant differences as shown in Table 3.

**Table 3:** Association of patients' characteristics with adherence rate among 143 SSC patients

Variables	Low (<6) (n=84)	Med-high (≥6) (n=57)	p-value
Age, years	41.56±14.64	38.9±12.55	0.485
Gender			<b>0812</b>
Male	18(20.93%)	11(19.3%)	
Female	68(79.07%)	47(82.46%)	
Marital status			0.813
Married	59(68.6%)	40(70.81%)	
Single	27(31.4%)	17(29.82%)	
BMI, kg/m <sup>2</sup>	24.15±3.7	25.27±4.84	<b>0.609</b>
Education			<0.001
Primary or less	32(37.21%)	21(36.84%)	
Secondary	52(60.47%)	18(31.58%)	
Higher	2(2.33%)	18(31.58%)	
Socioeconomic status			<b>&lt;0.001</b>
Low	56(65.12%)	15(26.32%)	
Intermediate	27(31.4%)	24(42.11%)	
High	3(3.49%)	18(31.58%)	
Residence			0.360
Rural	73(84.88%)	45(78.95%)	
Urban	13(15.12%)	12(21.05%)	
Employment			<b>&lt;0.001</b>
Yes	69(80.23%)	27(47.37%)	
No	17(19.77%)	30(50.63%)	
Self-dependent			0.133
Yes	28(32.56%)	12(21.05%)	
No	58(67.44%)	45(78.95%)	

**Association of Clinical and Therapeutic Characteristics with Adherence Rate**

Only two clinical factors were significantly associated with drug adherence. The presence of side effects was significantly more common amongst the non-adherent group (36.05%) compared to the adherent group (10.53%). More than two thirds (70%) of non-adherent patients were unsatisfied with their medications compared to 33.33 % of adherent patients with significant differences between the two groups as shown in table 4.

**Table 4:** Association of clinical and therapeutic characteristics with adherence rate among 143 SSC patients

Variables	Low (<6) (n=86)	Med-high (≥6) (n=57)	p-value
Disease duration, years	9.2±6.84	6.75±5.89	0.282
Disease duration, years	8.8±6.84	6.9±5.89	0.282
Medications			0.751
Immunosuppressant	49(56.98%)	34(59.65%)	
Vascular acting	28(32.56%)	17(29.82%)	
Antifibrotic	9(10.47%)	6(10.53%)	0.739
Type			0.863
Limited	44(51.16%)	30(52.63%)	
Diffuse	42(48.84%)	27(47.37%)	
Systemic involvement			0.973
No	44(51.16%)	29(50.88%)	
Interstitial lung disease	42(48.84%)	28(49.12%)	
Comorbidity			0.291
No	75(87.21%)	46(80.7%)	
Yes	11(12.79%)	11(19.3%)	
Drug side effects			0.001
No	55(63.95%)	51(89.47%)	
Yes	31(36.05%)	6(10.53%)	
Patients satisfaction			<0.001
Yes	61(70.93%)	19(33.33%)	
No	25(29.07%)	36(63.16%)	

**Multivariate Analysis**

Multivariate logistic regression test was used to find out independent factors for drug adherence. All variables which had a significant association with adherence as well as those which had a p-value <0.15 were entered into the model. For this analysis, continuous variables (BMI) were categorized into categorical variables. The results are demonstrated in table 5. Each of high educational level (OR=6.56, 95%CI=1.18-72.32, p= 0.041), and high SES (OR=25.3, 95%CI= 2.3-27.36, p= 0.008) were significantly associated with increased drug adherence. On the other hand, unemployment (OR=0.25, 95%CI= 0.07-0.87, p= 0.039), the presence of drug side effects (OR= 0.19, 95%CI=0.04-0.98, p= 0.048), and patient's dissatisfaction (OR=0.31, 95%CI=0.7-0.77, p= 0.025) were independent risk factors for non-adherence as shown in Table 5.

**Table 5:** Multivariate Analysis among 143 SSC Patients

Variables	Low (<6) (n=86)	Med-high (≥6) (n=57)	p-value	OR (95%CI)
BMI, kg/m <sup>2</sup>			0.212	1.0 2.7(0.38-13.0)
≤25	57(66.28%)	25(43.86%)		
>25	29(33.72%)	32(56.14%)		
Education			0.140	1.0 0.62(0.17-2.33) 6.56(1.18-72.32)
Primary or less	32(37.21%)	21(36.84%)		
Secondary	52(60.47%)	18(31.58%)		
Higher	2(2.33%)	18(31.58%)	0.041	
SES			0.012	1.0 5.0(1.17-21.0) 25.3(2.3-27.36)
Low	56(65.12%)	15(26.32%)		
Intermediate	27(31.4%)	24(42.11%)		
High	3(3.49%)	18(31.58%)	0.008	
Employment			0.039	1.0 0.25(0.07-0.87)
Yes	69(80.23%)	27(47.37%)		
No	17(19.77%)	30(50.63%)		
Immunosuppressant			0.833	1.0 1.18(0.64-7.45)
No	37(43.02)	23(40.35%)		
Yes	49(56.98%)	34(59.65%)		
Side effects			0.048	1.0 0.19(0.04-0.98)
No	55(63.95%)	51(89.47%)		
Yes	31(36.05%)	6(10.53%)		
Satisfaction				

Yes	61(70.93%)	19(33.33%)	0.025	1.0
No	25(29.07%)	36(63.16%)		0.31(0.7-0.77)

### 3. Discussion

According to the present study, 23 patients (16%) had high adherence, 35 patients (24.5 %) had medium adherence, and 85 patients (59.4%) had low adherence rates to their medication. Different studies worldwide reported different adherence rates. In a cross-sectional study, Brijs et al [23] assessed treatment adherence in 66 Belgian patients with SSc using Compliance Questionnaire of Rheumatology (CQR). They recorded a higher adherence rate (56.1%) compared to the present study. In another study, Hromadkova et al [24] investigated 41 Czech SSc patients to evaluate their adherence to the drugs. The study also used CQR form for this purpose and revealed that 42% of patients as having good adherence. In Italy, Ludici et al [25], enrolled 98 patients with SSc to assess their adherence to glucocorticoids. The study used Morisky Medication Adherence Scale-4 (MMAS-4) for this assessment. The authors reported 64% of patients as having good adherence.

The relatively low adherence rate in the present study compared to the other studies is mainly related to the questionnaire. The present study utilized the MMAS-8 questionnaire. This involves 8 items with more rigorous and tenor compared to CQR (which contains 19 items with a more flexible tenor).

In Germany, Matrisch et al [26] conducted a monocentric, cross-sectional study on 85 patients with SSc to evaluate their adherence. Good medication adherence (MA) was seen in 51.8% of patients, using the Compliance Questionnaire of Rheumatology as the main measurement tool of medication adherence. They also used the Scleroderma Health Assessment Questionnaire, Illness Perception Questionnaire - Revised, Health Literacy Questionnaire, Lübeck Medication Satisfaction Questionnaire (a novel instrument created for this study), and patients' demographic and clinical data, to find factors contributing to MA.

On the other hand, the Italian study restricted only for glucocorticoid drug use which of course is one of many medications used for treatment of SSc and cannot reflect the real adherence rate. Other factors such as demographic and clinical characteristics, as well as patient follow up are factors that may influence the adherence rate.

In multivariate analysis, high educational level (OR=6.56, 95%CI=1.18-72.32, p= 0.041), and high SES (OR=25.3, 95%CI= 2.3-27.36, p= 0.008) were significantly associated with increased drug adherence in the present study. This implies that patients with high educational level or high SES will be 6.56-times or 25.3-times, respectively more adherent to his/her medication than those with primary education or low SES.

Global studies regarding the treatment adherence among SSc are scanty, and the four available studies [23-26] did not report any significant association of drug non-adherence with the included demographic or clinical factors. These

results could mainly be attributed to the high adherence rate in these studies.

Alternatively, studies conducted on rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) do reveal a significant association with several factors. Xia et al [27] found that monthly per capita income had significant correlation with adherence rates. Moreover, Sharma et al [28] found that low income was significantly responsible for the non-adherence to the treatment in those patients. Chambers et al [29], call attention to low SES in Jamaica, which the authors considered an important factor impacting adherence. Garcia Popa-Lisseanu et al [30] also highlight low income as a barrier to adherence among patients in North America. Furthermore, in a Thai study, Taibanguay et al [31] revealed that patient education significantly improved adherence. Also, a British randomized controlled study of RA patients revealed that patient education was correlated with adherence [32], which is in agreement with the present study.

Thus, it is evidenced that each population has their own characteristics that may interfere with the results of treatment adherence. A factor that has a significant association in one population may not have such an association in another population.

Some reports indicated that the extent of medication non-adherence in low and middle-income countries is greater than in developed countries because of a lack of health resources and unequal access to healthcare [33]. The healthcare system in Iraq provides free services to all Iraqi citizens, and most costs are covered by the government. This characteristic eliminates the impact of patients' income on adherence. However, most patients did not feel accommodated by the public health service owing to medications not being frequently available at the point of delivery (therefore, requiring the patient to purchase privately). Sometimes, the medication cost is out of reach for the patient, which is considered an important factor that prevented those patients from adhering to the treatment.

According to the results of the present study, unemployment (OR=0.25, 95%CI= 0.07-0.87, p= 0.039), the presence of side effects (OR= 0.19, 95%CI=0.04-0.98, p= 0.048), and patient's dissatisfaction (OR=0.31, 95%CI=0.7-0.77, p= 0.025) were independent risk factors for non-adherence. That means unemployed patients, a patient suffering from side effects, and a dissatisfied patient will be at 0.25-time, 0.19-time and 0.31-time respectively less adherent to the medication; compared to employed and satisfied patients that have no side effects.

These results are in line with many previous studies worldwide. In the USA, Gosh et al [34] demonstrated that 47.3% of unemployed and 21.8% employed were non-adherent to his/her medications, and there was a statistically significant difference in employed vs. unemployed (p<0.001).

In a Chinese study including 140 SLE patients, Xie et al [27] found that medication side effects were significantly associated with nonadherence. He also found that non-adherence was more common among participants who were not satisfied with treatment. Oliveira-Santos et al [35], have shown that 13.8% of SLE patients stopped taking their medication because it made them feel worse. In a German study of 579 patients, patient's satisfaction with their medication was significantly associated with their adherence [36].

In a study conducted on patients with RA and SLE, of all tested patient characteristics, only lower education and greater severity of side effects were associated with a lower CQR score [37].

Almost a quarter of patients experienced one or more side effects and that 15 % of patients were concerned about the information on side effects in the patient leaflet [24]. This explains the importance of side effects as risk factors for non-adherence. However, the presence of side effects is only mentioned by 5–10 % as a reason for noncompliance [38]. The unemployment is associated with SES, and unemployed patients cannot always afford the cost of their medications (which influences the adherence rate of those patients).

#### 4. Limitations

- 1) The sample size (143 patients) was relatively small, making it hard to generalize the results. Although SSc is an infrequent disease, a larger number of participating patients would be recommended for further research studies
- 2) There was no distinction between different medication groups. A drug-specific measurement of adherence could be applied in further research.
- 3) Finally, the Arabic version of the MMA was not validated in Iraq. Validation will be required before conducting further similar studies in Iraq

#### 5. Conclusions

- 1) More than half of our patients with SSc were non-adherent to their medications.
- 2) High education level and higher SES are significantly associated with increased treatment adherence in patients with SSc
- 3) Unemployment, the presence of drug side effects and treatment dissatisfaction were significantly associated with low adherence rates in SSc patients

**Conflict of interest:** The authors declare no conflict of interest.

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