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Original article

Sexual dysfunction in male patients treated with methorexate for arthritis: Analysis of the IIEF5 questionnaire and hormonal status

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ABSTRACT

Objective: The aim of this study is to evaluate the impact of methotrexate (MTX) on erectile function in male patients through the International Index of Erectile Function (IIEF5) questionnaire and hormonal dosage.
Methods: Male patients affected by inflammatory arthritis (rheumatoid arthritis [RA] or psoriatic arthritis [PsA]) with good disease control and treated with chronic MTX were enrolled. Age-matched patients affected by chronic arthritis not treated with MTX were enrolled as controls. Each patient had a complete sexual hormone evaluation. IIEF5 questionnaire was administered to each patient.
Results: One hundred and nine patients were included, 77 in the MTX group and 32 as controls. The median weekly MTX dose was 10 mg (IQR 7.5) with a median MTX duration therapy of 8 years (IQR 17). The total IIEF5 score was lower in patients MTX exposed compared to the control group without a significant result. The total IIEF5 score of patients treated with MTX $\geq$ 5 years was statistically significantly lower when compared to those non-MTX exposed patients (17 [IQR 15] versus 20 [IQR 7.7]; $P = 0.04$) and compared to those treated for < 5 years (17 [IQR 15] versus 20 [IQR 7]; $P = 0.01$). A negative correlation was identified between the total IIEF5 score and MTX time exposure ($r = -0.20$ CI [−0.38 to −0.04]; $P = 0.039$). MTX exposure was still associated with a lower IIEF5 score when adjusted for age (β Estimate = −2.63; CI [−5.13 to −0.13]; $P = 0.039$). Hormonal dosage was similar in both groups for all hormones evaluated.
Conclusion: MTX exposure was associated with a lower IIEF5 score in male patients adjusted for age. The preliminary results need to be confirmed in larger prospective studies.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint destruction and systemic manifestations, possibly leading to disability, fatigue, and diminished quality of life. Among these manifestations, RA-associated sexual dysfunction (SD) may affect both males and females with a reported prevalence ranging from 30 to 70% [1]. Male SD encompasses erectile dysfunction (ED) and reduced libido, both contributing to a decline in the frequency and/or quality of sexual activity. SD is a complex condition influenced by several cofactors [2] such as endocrine, neurological, or vascular pathologies, medications, diabetes, hypertension, and disturbances in hormone levels. Inflammatory arthritis, including both RA and psoriatic arthritis (PsA), has been identified as a potential determinant of male SD. RA itself may contribute to SD through chronic pain and physical disability, while medication side effects can further negatively impact patients' sexual function [3]. Although fewer reports have focused on this topic in PsA, especially in men, individuals with PsA are at a higher risk of developing ED compared to an age-matched population [4]. Older age and comorbidities increase the likelihood of sexual dysfunction [5]. MTX is the anchor drug of RA treatment and inflammatory arthritis. While considered a safe and convenient drug, MTX does have well-known side effects, predominantly mild, such as nausea, fatigue, alopecia, or elevated transaminases. Sexual dysfunction has been reported as a rare adverse effect of MTX

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therapy [6]. Even though reduced libido is reported as a "very rare" side effect, the exact prevalence is still unknown and only clinically severe cases emerged, while the pathogenic mechanism remains unclear. The International Index of Erectile Function (IIEF5) questionnaire is a self-administered tool that is used to diagnose the presence and severity of ED [7]. In light of the above, this study aims to evaluate the impact of MTX on male sexual function patients through the application of the IIEF5 questionnaire and hormonal evaluation.

2. Methods

We performed a cross-sectional analysis of our UCLouvain Brussels cohort. Male patients affected by inflammatory arthritis (RA or PsA) according to the 2010 EULAR/ACR diagnostic criteria for RA [8] and the 2006 CASPAR criteria for PsA [9] and treated with chronic MTX were enrolled. Only patients reaching the Clinical Disease Activity Index (CDAI) remission criteria for RA [10] and Minimal Disease Activity (MDA) for PsA [11] were enrolled. Age-matched patients affected by rheumatological inflammatory diseases not treated with MTX were enrolled as the control group. Each patient underwent blood collection for a complete serum sexual hormone evaluation: sex hormone binding protein (SHBG), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), prolactin (PRL), dehydroepiandrosterone-sulfate (DHEA-S). IIEF5 questionnaire was administered to the enrolled patients. Briefly, it consists of 5 items with a maximum score of 25; a lower score corresponds to a lower sexual function. Erection dysfunction (ED) was classified into the following categories: 5–10 severe ED; 11–15 mild ED; 16–20 moderate ED; 21–25 no ED. All the patients gave signed consent. The study was performed according to the protocol and good clinical practice principles and Declaration of Helsinki statements and was approved by the Ethics Committee of the UCLouvain, Brussels, Belgium.

3. Statistical analysis

The statistical evaluation was performed using GraphPad 9.0 (GraphPad Software, La Jolla, CA, USA). Variables were summarized using the median and range. Frequencies were expressed by percentage. Wilcoxon's matched pairs test and paired *t*-test were performed accordingly. Univariate comparisons between nominal variables were calculated using a Chi-square test or Fisher's exact test where appropriate. Spearman's test was used to assess the correlations. To test the differences among the groups, we performed an ANOVA analysis for non-parametric data and applied the Kruskal-Wallis test and correction for multiple comparisons by controlling the False Discovering Rate (Benjiamini, Krieger and Yekuteli method). Two-tailed *P* values were reported, and *P* values less than 0.05 were considered significant. A multivariate linear regression analysis was performed to analyze the contribution of the main confounding factor.

4. Results

One hundred and nine patients were included, 77 in the MTX group (Group A) and 32 in the control group (Group B). The clinical and demographic features of both groups are reported in Table 1. Among the MTX group, 61 have an RA diagnosis, while the remaining 16 were affected by PsA. Group B included 4 RA patients (12.5%) and 28 patients (87.5%) affected by seronegative spondyloarthropathy. The median disease duration of RA and PsA patients was respectively 108 months (IQR 138) and 66 months (IQR 114). The median MTX dose was 10 mg (IQR 7.5) with a median MTX duration therapy of 8 years (IQR 17). Eighty-three percent of RA patients were Anti-citrullinated protein antibodies (ACPA) positive, and 73.1% were Rheumatoid Factor (RF) positive. Bone erosions were detected in 71.7% of patients. The total IIEF5 score was lower in patients treated with MTX compared to the control group without reaching a statistically significant result (19 [IQR 11] versus 20 [IQR 7.7]; *P* = ns, Fig. 1A). However, when comparing the IIEF5 score between MTX exposed versus non-exposed patients stratifying by years of treatment, the total IIEF5 score of patients treated with MTX ≥ 5 years was statistically significantly lower when compared to those non-MTX exposed patients (17 [IQR 15] versus 20 [IQR 7.7]; $P < 0.05$) and those treated for < 5 years (17 [IQR 15] versus 20 [IQR 7]; $P < 0.05$) (Fig. 1B).

Table 1
Clinical, demographic features and serum sexual hormones evaluations of the two groups.

	Group A	Group B
Median (IQR)		
Age (years)	54 (28)	53.5 (20.5)
BMI	25.4 (3.85)	25.6 (5.8)
IIEF5 score		
Severe ED	13 (16.4)	1 (3.1)
Moderate ED	10 (12.6)	5 (15.6)
Mild ED	24 (30.3)	13 (40.6)
No ED	28 (25.4)	13 (40.6)
Not evaluable	2 (2.5)	0 (0)
n (%)		
Arterial hypertension	23 (29.1)	17 (53.2)[a]
Hypercholesterolemia	18 (33)	11 (34.3)
Type 2 diabetes	3 (3.8)	6 (18.7)[b]
Prostatic hyperplasia	2 (2.5)	0 (0)
Depression/Psychotropic therapy	8 (10.1)	5 (15.6)
Abdominal surgery	2 (2.6)	0 (0)
Hypertension therapy	6 (7.8)	5 (15.6)
Diuretics	1 (1.3)	1 (3.2)
Beta blocker	9 (11.6)	0 (0)
Marriage	53 (67)	23 (71.8)
Alcohol (NO units/day, IQR)	1 (2.5)	1 (2)
Children (NO, IQR)	1 (2)	2 (2)
Cigarette (NO/day, IQR)	5.6 (12.6)	5.2 (2.1)
Drugs (yes/no)	4 (5.2)	2 (6.4)
Married (yes/no)	53 (73.6)	23 (74.2)
Median (IQR)		
Free testosterone (nmol/L)	0.24 (0.13)	0.25 (0.14)
Total testosterone (nmol/L)	16.3 (8.2)	14.8 (7.7)[a]
SHBG (nmol/L)	53.9 (29.1)	47.6 (25.1)
LH (UI/L)	5.6 (4.1)	5.3 (2.4)
FSH (UI/L)	5.2 (5.3)	6.6 (3.82)
E2 (ng/mL)	24 (13.2)	20 (11.5)[a]
PRL (µg/mL)	7 (3.5)	8 (4.1)
DHEA-S (nmol/L)	4.7 (4.1)	3.8 (4.7)

BMI: body mass index; SHBG: sex hormone binding protein; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; PRL: prolactin; DHEA: dehydroepiandrosterone; GH: growth hormone; IIEF5: International Index of Erectile Function; ED: erectile dysfunction; NO: nitric oxidase.
[a] $P < 0.05$.
[b] $P < 0.01$.

In the univariate analysis (Table 2) a negative correlation between the total IIEF5 score and MTX exposure (expressed in years) has been identified ($r = -0.20$ CI [−0.38 to −0.04]; $P < 0.05$). To test the differences among the groups, we performed an ANOVA analysis with correction for multiple comparisons, with a $P < 0.05$. Specific comparisons for each pares and corresponding *q*-value and *P*-value are reported in Table 3.

MTX exposure was still associated with a lower IIEF5 score when adjusted for age (β Estimate = −2,63; CI [−5,13 to −0,13]; $P < 0.05$). As expected, age was the variable with the strongest negative association with the IIEF5 score ($r = -0,42$ CI [−0.57 to −0.25]; $P < 0.001$). Among the other variables, LH ($r = -0,24$; CI [−0,42 to −0,04]; $P < 0.01$), FSH ($r = -0,21$; CI [−0,39 to −0,006]; $P < 0.05$) and E2 ($r = -0,21$; CI [−0,40 to −0,009]; $P < 0.05$) negatively correlated whit IIEF5 score while DHEA-S, was the only parameter with a weak positive association ($r = 0.22$; CI [0,02 to 0,40]; $P < 0.05$). Patients affected

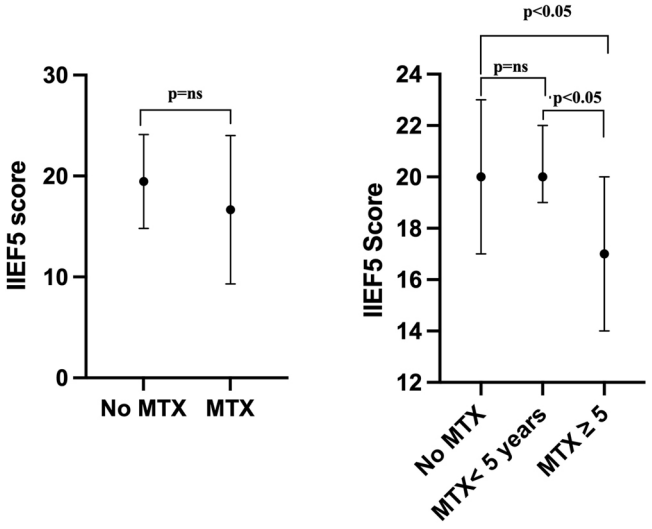

Fig. 1. A. Comparison of IIEF5 score in MTX exposed versus non-exposed patients. B. Comparison of IIEF5 score in MTX exposed versus non-exposed patients stratified by age (< 5 years and ≥ years).

Table 2
Univariate analysis: A. Correlation between continuous variables and IIEF5 score. B. Univariate comparisons between nominal variables.

A	*r*	CI
Age	−0.42	−0.57 to −0.25[b]
BMI	−0.11	−0.30 to 0.08
MTX (years of therapy)	−0.20	−0.38 to −0.004[a]
Total testosterone	0.00	−0.20 to 0.19
Free testosterone	0.18	−0.04 to 0.38
SHBG	−0.03	−0.25 to 0.18
LH	−0.24	−0.42 to −0.04[a]
FSH	−0.21	−0.39 to −0.006[a]
E2	−0.21	−0.40 to −0.009[a]
TSH	−0.09	−0.28 to 0.11
T4 libre	−0.07	−0.26 to 0.14
PRL	−0.02	−0.22 to 0.18
DHEA-S	0.22	0.02 to 0.40[a]
Alcoholic unit per day	−0.01	−0.20 to 0.19
Sport (hours/weekly)	0.14	−0.06 to 0.33
Number of children	−0.16	−0.34 to 0.039

B	Median IIEF5 score (IQR)	
	Yes	No
Arterial hypertension	16 (9)	20 (8.25)[a]
Hypercholesterolemia	16 (9)	20 (8.5)[a]
Abdominal surgery	18 (9)	19 (3.5)
Antihypertensive therapy	17 (5)	20 (9)
Beta-blocking therapy	17 (17)	19 (8.25)
Psychotropic therapy	16.5 (9.5)	20 (8.25)

BMI: body mass index; SHBG: sex hormone binding protein; LH: luteinizing hormone; FSH: follicle-stimulating hormone; E2: estradiol; PRL: prolactin; DHEA: dehydroepiandrosterone; GH: growth hormone; IIEF5: International Index of Erectile Function; ED: erectile disfunction.

[a] $P < 0.05$.

[b] $P < 0.001$.

Table 3
Multiple *t*-test comparison (ANOVA).

	Mean rank difference	*q* value
No MTX versus MTX < 5	−2.5	0.81
No MTX versus MTX ≥ 5[a]	14.2	0.06
MTX < 5 versus MTX ≥ 5[a]	16.8	0.06

[a] $P < 0.05$.

by arterial hypertension and hypercholesterolemia showed lower scores compared to non-affected patients ($P < 0.05$ for each comparison). No other significant associations were identified for both continuous and dichotomic variables analyzed. Variables with a prevalence too low to allow reliable statistical evaluation were excluded from the analysis, including prostatic hyperplasia, depression, diuretics therapy, diabetes, pituitary adenoma, and hepatopathies.

In the multivariate analysis, the variables significantly influencing the IIEF5 score in the univariate analysis were included in the model. The age was the only factor associated with a decrement of IIEF5 score (β −0.21 [−0.32 to −0.094]; $P < 0.001$), while MTX exposure (expressed as years of treatment) was not confirmed as an independent factor for a lower score (β −0,17 [−0.39 to −0.05]; P = ns). Moreover, we performed a logistic regression analysis with an IIEF5 score < 12 as the dependent variable, according to the score distribution (19 [IQR 11], 25% Percentile 12, 75% Percentile 23). Age was confirmed as associated with a lower IIEF5 Score ≤ 12 (OR 1.1 [CI 1.04–1.2]; $P < 0.001$), while none of the other variables was identified as an independent predictor, including the MTX-time exposure (OR 1.02 [CI 0.89–1.17]; P = ns). Considering the IIEF5 definition for moderate-erectile dysfunction, we also performed the analysis using an IIEF5 15 points as the threshold. Age was confirmed as associated with a IIEF5 Score ≤ 15 (OR 1.08 [CI 1.02–1.15]; $P < 0.01$), while none of the other variables was identified as an independent predictor, including the MTX-time exposure (OR 1.05 [CI 0.93–1.18], P = ns).

5. Discussion

Our results suggest that MTX treatment could be associated with a decrease in men's sexual function with a time-exposure relationship. The first description of the association between MTX and ED dates back to 1988 when MTX was found as the only medication associated with erectile disturbance [12] even when the result was adjusted for comorbidities. Subsequently, a few cases reported reduced libido and ED as rare adverse events in men [13–16]. ED typically manifested within a range of 2 weeks to 2 years and showed complete regression upon MTX withdrawal. However, most of the described cases are patient-reported and thus emerged only once significantly impairing sexual performances. Notably, sexual dysfunction is not commonly mentioned as a potential side effect when MTX treatment is proposed, suggesting a potential underestimation of mild and moderate sexual impairments. Furthermore, considering the chronic nature of RA and the older age of patients, particularly in long-standing diseases, age emerges as a primary factor associated with ED. Utilizing the IIEF5 score, a reliable questionnaire for assessing male sexual capacity, we observed a time-exposure effect of MTX on males sexual function. Its effect persisted even after adjusting for age, which remained the most significant factor associated with a low IIEF5 score and sexual function impairment. In our limited cohort, factors such as hypertension and diabetes, more prevalent in the control group, were not linked to ED.

The mechanisms through which MTX may induce ED and libido reduction remain unclear. However, two main hypotheses are proposed. The first one suggests an MTX influence on sex hormone balance, influencing prolactin secretions by the pituitary gland through blocking IL-1. Our analysis revealed a correlation with sex hormone state, with LH, FSH, and E2 negatively influencing sexual function, while DHEA-S levels showed a positive correlation. However, age must be considered in interpreting these results. On the other side, the prolactin and the free testosterone levels were similar in MTX-treated and non-treated patients, excluding possible iatrogenic hypogonadism. The second hypothesis binds to the

MTX-dependent reduced production of nitric oxidase (NO), a central molecule for smooth muscle relaxation in *corpora cavernosa* [17,18] and in the physiological erection process [19]. Besides its classic mechanism of action, MTX is responsible for the reduction of dihydrobiopterin (BH2) to tetrahydrobiopterin (BH4). This last is a necessary cofactor for NO production without which the synthesis is unbalanced towards reactive oxygen species (ROS). Thus, it may be speculated that MTX reduces the capacity of NO production in the corpora cavernosa of the penis with a negative effect on erectile function. This hypothesis is more coherent with our results, suggesting a time-dose effect evident after at least 5 years of treatment.

Our study has some strengths and some limitations. Foremost, all the enrolled patients in the MTX-treated group were in remission or at least low disease activity status; thus, we excluded a possible influence of active disease on sexual function. On the other side, the cohort was well characterized from an anamnestic perspective, including pharmacological history and comorbidities although a vascular evaluation to rule out one of the main determinants of ED was not performed.

The main limitation is certainly represented by the small number of patients and the cross-sectional design of the study. Further studies are needed with wider cohorts and a prospective design.

In conclusion, we identified an association between MTX exposure and a lower IIEF5 score in male patients. These preliminary results, suggesting a possible iatrogenic effect of MTX need to be confirmed in larger randomized prospective studies.

Statement of ethics and consent

The study was performed according to the protocol and good clinical practice principles and Declaration of Helsinki statements and was approved by the Ethics committee of the UCLouvain, Brussels, Belgium.

Disclosure of interest

The authors declare that they have no competing interest.

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