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Erectile dysfunction in ankylosing spondylitis – associations with disease-related parameters

Параметри болести удружени са еректилном дисфункцијом код болесника са анкилозирајућим спондилитисом

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SUMMARY

Introduction/Objective Patients with AS often experience chronic musculoskeletal pain, fatigue and stiffness, which may contribute to psychological distress and sexual dysfunction. This study aims to assess prevalence of ED in patients with AS and identify potential associations between clinical parameters related to AS with the presence of ED.

Methods Forty consecutive male patients with the AS (mean age 42.8 ± 8.9 years) and 60 healthy men (mean age 38.9 ± 10.9 years) were included. All subjects filled-in the International Index of Erectile Function (IIEF) questionnaire, as well as the Beck anxiety inventory (BAI) and the Beck depression inventory (BDI). In patients with AS disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functionality using the Bath Ankylosing Spondylitis Functional Index (BASFI), and quality of life using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire.

Results ED was significantly more frequent in patients with AS compared to controls (52.5%: 25%, p = 0.049). AS patients with ED had more severe symptoms of depression, than AS patients without ED (p = 0.034). According to ASQoL scores, patients with AS and ED had a worse quality of life, compared to patients with AS without ED (p = 0.022). The increase in one unit of ASQoL increased the odds of having ED for 17.5% (p = 0.035).

Conclusion ASQoL score, as a measure of quality of life, was the only independently associated parameter with the presence of ED. It is necessary to raise awareness of ED in patients with AS.

Keywords: ankylosing spondylitis; erectile dysfunction; ASQoL; depression; IIEF

САЖЕТАК

Увод/Циљ Болесници са анкилозирајућим спондилитисом (АС) често имају укоченост и болове у мишићноскелетном систему што је праћено хроничним умором. Ове тегобе доприносе настанку психолошких сметњи и сексуалној дискфункцији. Циљ ове студије је био да испита учесталост еректилне дисфункције (ЕД) код оболелих од АС и да идентификује потенцијалну удруженост клиничких параметара који се односе на АС са присуством ЕД.

Методе У студију је било укључено четрдесет мушкараца оболелих од АС (просечне старости 42,8 ± 8,9 година) и 60 здравих мушкараца (просечне старости 38,9 ± 10,9 година). Сви учесници студије су попунили Интернационални упитник за процену еректилне функције, Бекову скалу за процену анксиозности и Бекову скалу за процену депресивности. За процену активности АС код оболелих су коришћени скорови *ASDAS* и *BASDAI*. Функцијска способност је процењивана употребом индекса *BASFI*, док је квалитет живота евалуиран употребом упитника *ASQoL* (енгл. *Ankylosing Spondylitis Quality of Life*).

Резултати ЕД је значајно више присутна код оболелих од АС у поређењу са контролном групом (52.5%: 25%, p = 0.049). Болесници са АС и ЕД имају озбиљније симптоме депресивности у односу на болеснике са АС који немају ЕД ($p = 0.034$). Према скору *ASQoL*, оболели од АС са ЕД имају лошији квалитет живота у поређењу са оболелим од АС који немају ЕД ($p = 0.022$). Пораст скора *ASQoL* за јединичну вредност повећава шансу за присуство ЕД за 17,5% ($p = 0.035$).

Zaključak Скор *ASQoL*, као мера процене квалитета живота оболелих од АС, се показо као једини параметар независно удружен са присуством ЕД. Потребно је подићи свест о присуству ЕД код оболелих од АС.

Кључне речи: анкилозирајући спондулитис; еректилна дисфункција ; *ASQoL*; депресија; *IIEF*

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, inflammatory, autoimmune disease that dominantly affects younger men [1]. AS belongs to the group of spondyloarthropathies (SpA). Prevalence of the disease is believed to be between 0.1% and 1.4% [2]. There is a strong association between human leukocyte antigen (HLA) B27 and AS. The onset of the disease is insidious and usually presented with bilateral sacroiliitis and inflammatory low back pain (improved by

exercise and not relieved by rest). Progressively, inflammation and ankylosis of the axial joints may result in dorsal kyphosis. Patients with AS may also have enthesitis (inflammation of insertions of tendons and ligaments to the bone and an asymmetrical oligoarthritis (especially on lower extremities). Extra-articular manifestations (EAM) of AS include iridocyclitis, inflammatory bowel disease (IBD) and psoriasis [3]. The Assessment of SpondyloArthritis International Society (ASAS) criteria are widely used for the classification of AS. When a patient with at least 3 months back pain and age less than 45 years at disease onset has verified sacroiliitis on X-ray or MRI, one of the following criteria is necessary for classifying the patient as having axial spondylarthritis: inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, IBD, good response to non-steroidal anti-inflammatory drugs (NSAID), family history for SpA, HLA-B27 or elevated CRP. Additionally, if patient is HLA-B27 positive and has not verified sacroiliitis on X-ray or MRI, it is necessary to have two of the features listed above in order to be classified as AxSpA (non-radiographic AS) [4]. Management of AS includes combination of non-pharmacological and pharmacological treatment. The non-pharmacological treatment includes physical therapy, regular exercises, education and lifestyle modification. Pharmacological treatment of AS with axial predominance includes NSAID, biologic agents such as tumor necrosis factor-alpha (anti-TNFα) inhibitors and anti-interleukin 17a (anti-IL17a) antibodies and recently added Janus kinase inhibitors (JAKi). When patient has peripheral joints affected sulfasalazine, methotrexate and leflunomide may be used [1].

Patients with AS often experience musculoskeletal pain, fatigue, stiffness and low self-confidence. The chronicity of the disease may lead to psychological disturbances as well as sexual dysfunction (SD). Beside the effort to combat AS by treating physical symptoms of the disease, it is important not to overlook other associated conditions, like depression, anxiety or erectile dysfunction (ED) [5]. ED is a sexual dysfunction characterized by the inability to develop or maintain an erection of the penis sufficient for satisfactory sexual performance. It has a negative impact both on the patient`s quality of life (QoL) and his relation with the sexual partner [6].

Some studies have shown that the prevalence of ED is higher among male patients with AS than in healthy males [7, 8]. According to the literature, morning stiffness, disease activity and depression are associated with ED [9]. But some studies did not find a clear association between AS and ED [10]. There are laboratory and imaging-based methods used for assessment of ED. However, self-reported questionnaires are important tools in diagnosing and classifying ED in the clinical practice. The aim of this study was to determine prevalence of ED in patients with

AS and to find potential association between clinical parameters related to AS and the presence of ED.

METHODS

This observational cross-sectional study was approved by the institutional Ethics Committee. The study included 40 consecutive male patients with AS (mean age 42.8 ± 8.9 years) and 60 healthy men (mean age 38.9 ± 10.9 years), who signed inform consent to participate in the study. Patients with the AS were recruited during their regular visit at the hospital. They were matched with healthy controls by age, education and socioeconomic status. Excluding criteria were previous pelvic radiation or surgeries of the pelvis, penile deformities as well as unregulated cardiovascular and endocrine diseases such as hypertension and diabetes mellitus.

All of the subjects enrolled in the study filled-in the International Index of Erectile Function (IIEF-15), the Beck's anxiety inventory (BAI) and the Beck's depression inventory (BDI) questionnaires. IIEF-15 is a multidimensional self-assessment questionnaire with 15 questions, divided into five domains of sexual function (erectile and orgasmic functions, sexual desire, satisfaction with intercourse and overall sexual satisfaction). There are six questions in the domain related to erectile function [11]. The answers were scored from 0 to 5. IIEF score between 0 and 10 is categorized as severe ED, 11-16 as moderate, 17-21 as mild to moderate, and 22-25 as mild ED. Subject with IIEF score above 25 is considered as having normal erectile function. BDI is an useful tool for the assessment of depressive symptoms in everyday practice. The inventory consists of 21 questions. Answers to each question are scored from 0 to 3, with overall score ranged from 0 to 63. The cut-off value for clinically significant symptoms of depression is 17. BAI is self-reported questionnaire with 21 questions related to anxiety symptoms. The answers are scored on a 4-point scale from 0 (not at all) to 4 (severely). Total BAI scores are classified as follows: minimal anxiety (0 to 7), mild anxiety (8 to 15), moderate anxiety (16 to 25) and severe anxiety (30 to 63) [12].

Disease activity was evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS). This score includes patient estimation of morning stiffness, back pain, global disease activity, number of swollen and painful joints, as well as biohumoral markers of inflammation (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)). The 3 cut-offs for staging the activity of the AS were: <1.3 between "inactive disease" and "low disease activity", <2.1

between "low to moderate disease activity" and "high disease activity", and >3.5 between "high disease activity" and "very high disease activity" [13]. In addition, patients answered six questions for calculating Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). These questions were related to major symptoms of the AS: fatigue, spinal pain, arthralgia or arthritis, enthesitis, morning stiffness duration and morning stiffness severity. Scores of 4 and greater suggested active disease [14]. To assess the functional status of the AS patients, the Bath Ankylosing Spondylitis Functional Index (BASFI) questionnaire was used. The BASFI scores ranges between 0 and 10 points. Higher score indicates a higher degree of functional limitations [15]. Ankylosing Spondylitis Quality of Life (ASQoL) is disease-specific questionnaire used to evaluate QoL in patients with AS. It consists of 18 questions with dichotomous answers (yes or no). The questionnaire is related to the impact of disease on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life with a total score of 0-18. Lower ASQoL scores represent a better QoL [16]. Numerical rating scale (NRS) was used for the assessment of the back pain (BP) and back pain at night (BP night). The 11-point numeric scale ranges from 0 representing one pain extreme (e.g. no pain) to 10 representing the other pain extreme (e.g. pain as bad as you can imagine or worst pain imaginable) [17]. Other relevant clinical and demographic data (duration of the disease, CRP, medication) about the patients with the AS were obtained from medical records.

The Statistical Package of Social Sciences for Windows (SPSS) version 23 was used for statistical analysis. Categorical variables were presented as numbers or percentages and compared using Chi-squared test. Continuous variables were expressed as mean with the standard deviation (SD) and depending on the normality of the distribution, independent t-test or Mann Whitney test was performed. The univariate and multiple logistic regression model were used to predict statistically significant and independent parameters of the AS associated with the presence of the ED. Statistical significance was considered when $p < 0.05$.

RESULTS

This study included 40 male patients with AS and 60 healthy males in the control group. The age of the patients with AS varied from 21 to 64 years and 18 to 68 years in the control group. There was no statistically significant difference in the mean age between these two observed groups (Table 1). ED of any degree was significantly more present in patients with AS (21/40, 52.5%) comparing with the control group (15/60, 25%) ($p = 0.049$). The mean value of IIEF

score in the group with AS was significantly lower than in the control group (p = 0.035). BAI and BDI scores were higher in the group with the AS but without statistical significance. The mean duration of the disease was 10 ± 7.5 years. Anti-TNFα antibodies were used as part of the treatment in 77.5% patients with the AS (Table 1).

The mean age of group with AS and ED was 42.8 ± 9.2 years and 39.4 ± 11.9 years in the control group with ED. There was no significant difference in IIEF scores between these groups. BAI and BDI scores were higher in the control group with no statistical significance (Table 2).

Patients with AS were divided into two groups based on the presence of ED and comparisons were made between those groups. There was no statistically significant difference in terms of age and duration of the disease among groups (Table 3). According to the BDI, the group with the AS and ED was likely to be more depressed than the group with AS without ED (p = 0.034). The same observation was made about anxiety symptoms and BAI in the groups with and without ED in patients with AS but this observation was not statistically significant. Parameters reflecting disease activity (ASDAS, BASDAI, CRP), patient functionality (BASFI) as well as values of the NRS for back pain (BP, BP night) were higher in the patients with AS and ED (Table 3). However, these findings were not statistically significant. The QoL of the group with AS and ED seemed worse than the QoL of the group with AS and without ED according to ASQoL scores (p = 0.022) (Table 3). The biologics were used in 76.2% of patients with AS and ED and 78.9% of patients with AS and without ED respectively (p = 1).

The scores for anxiety and depression assessment (BAI, BDI) as well as score for quality of life (ASQoL) showed negative correlation with the IIEF score (Table 4). Univariate logistic regression showed that BDI and ASQoL scores were associated with the presence of ED in patients with AS. However, in multivariate logistic regression analysis only ASQoL sustained itself as independent parameter associated with the presence in patients with AS (Table 5). The increase in one unit of ASQoL score increased the odds of having ED for 17.5% (p = 0.035).

DISCUSSION

This study found that more than half of included patients with AS had some grade of ED (52.5%). The inflammation as underlying pathological mechanism in AS may contribute to the

atherosclerosis which is strongly associated with the risk of ED [18]. In addition, there were studies about the role of high levels of proinflammatory cytokine TNFα in the upregulation of phosphodiesterase type 5, which resulted in decreased levels of pro-erectile mediators and potential onset of ED [19, 20]. However, most of the patients with AS and ED in this study were treated with anti-TNFα therapy implicating the possible significance of other risk factors for the development of ED. The mean CRP levels were higher in the group of patients with AS and ED, but without significant difference. Although the CRP and ESR are serological markers widely used to estimate the degree of inflammation, it is hard to judge inflammation over using them in spondyloarthropathies [21]. The inflammatory process could disturb the balance of male sexual hormones and perhaps could lead to the low testosterone level which could possibly lead to ED. In one study on 35 patients with AS and 104 healthy controls, Nisihara et al. showed no difference in free and bioavailable testosterone in patients with AS comparing to healthy controls [22].

The chronic inflammation as well as anatomical and physiologic impairments in patients with AS have great impact on QoL. In our study, there was no statistically significant difference between parameters related to disease activity (ASDAS, BASDAI) and functionality (BASFI) among patients with and without ED. Despite that, mean ASDAS and BASFI scores were higher in the group with ED. The negative correlation between BASDAI and BASFI with the IIEF score was found in the meta-analysis of 39 studies [23]. However, Pirildar et al. reported that only morning stiffness is associated with the ED [24]. In our study, patients with AS and ED had higher scores on NRS for daily back pain as well as for back pain at night than patients without ED. The patients with AS may have limited mobility of the intervertebral joints of the lower back and combined with back pain could experience discomfort during the sexual intercourse which may contribute to the ED.

The age of the patients and the duration of the disease were similar among groups with and without ED. Santana et al. as well as several other authors did not find correlation between age of patients and the duration of the disease with the ED [21, 25]. However, Dhakad et al. in their study reported that the patients with the AS and ED had a longer duration of the disease comparing to those without ED. Also in the same study, the older age was a risk factor for ED [26]. Even though our study had not reported the association between the age of the patients with AS and ED, knowing that the AS is the disease of the predominantly younger males, the impact of the age on the ED may be neglected.

The anxiety and depression were shown to be associated with ED. Chronic inflammation, pain, fatigue and stiffness contribute to the onset of these conditions. Furthermore, disabilities and deformities in patients with AS may lead to state of being handicapped. Altogether, psychic status of patients with AS could be altered and lead to onset of ED [25]. BAI, BDI and ASQoL scores showed negative correlation with IIEF score in our study which was also shown in the study by Santana et al. [21]. That study reported that problems with emotional health were present in 20% of patients with AS. One study which included 117 patients with AS and mean duration of the disease of 10 years showed that the symptoms of clinical depression were present in 49.5% [27]. The mean BDI and ASQoL scores in our study in patients with AS and ED were higher than in group without ED. The symptoms of depression might be associated with the sexual dysfunction due to low QoL patients reported. However, in our study BDI did not sustain itself as statistically independent parameter associated with ED.

While the previous parameters about disease activity (ASDAS, BASDAI) and functionality (BASFI) provide important information about the degree of disabilities and impairment experienced by patients, they do not inform us clearly about the impact of the condition on QoL [28]. ASQoL is made to concern the impact of the disease from the patient's perspective (rather than a clinical) [29]. Sexual function is recognized as important part of QoL. In our study, ASQoL was shown to be the independent parameter associated with the presence of ED. Patients with AS and ED had reported lower QoL than patients without ED. Similar results in ASQoL in patients with AS and ED were reported by Erdem et al. [25]. Van der Meer and al. showed that the presence of EAM is associated with worse QoL and reduced spinal mobility [30]. Our results suggested that patients with ASQoL score five or more points should be encouraged to talk about this segment of life because the odds of having ED are higher than 50%.

The study lacked data on lipid status and history of smoking of the patients and healthy controls.

CONCLUSION

In our study, the prevalence of ED in patients with AS was higher than in the healthy controls as reported in the literature. It is well known that patients with chronic rheumatic inflammatory diseases have more chance of developing ED, but the direct connection between AS and ED is

still being researched. Rheumatologists should be aware of ED in patients with AS and accordingly to values of the associated parameters should make referral to urologist if appropriated.

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Table 1. Clinical and demographic data on patients with ankylosing spondylitis and healthy controls

Parametrs	AS (n = 40, 100%)	Control (n = 60, 100%)	p
Age (years)	42.8 ± 8.9	38.9 ±10.9	0.065
ED	21 (52.5%)	15 (25%)	0.049
IIEF	22.3 ± 8.9	25.7 ± 7.5	0.035
IIEF grade			0.016
none	19 (47.5%)	45 (75%)	
mild	13 (32.5%)	10 (16.7%)	
moderate	3 (7.5%)	0 (0%)	
severe	5 (12.5%)	5 (8.3%)	
BAI	10.3+12.5	9.2+10.1	1
BDI	7.6 ± 7.4	6 ± 6.1	0.289
Duration of the disease (years)	10 ± 7.5	-	NA
CRP (mg/L)	6.8 ±10.3	-	NA
ASDAS	2.26 ± 1.2	-	NA
BASDAI	3.2 ± 2	-	NA
BASFI	3.43 ± 2.2	-	NA
ASQoL	5.9 ± 5.2	-	NA
BP	3.8 ± 2.7	-	NA
BP night	3.5 ± 2.7	-	NA
anti-TNFα	31 (77.5%)	-	NA

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck anxiety inventory; BDI – Beck depression inventory; CRP – C reactive protein; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain; TNFα – tumor necrosis factor alpha

Table 2. Erectile dysfunction in patients with ankylosing spondylitis and control group with erectile dysfunction

Parameters	AS (n = 21, 100%)	Control (n = 15, 100%)	p
Age (years)	42.8 ± 9.2	39.4 ± 11.9	0.338
IIEF score	16.1 ± 8.2	16.4 ± 10.3	0.357
IIEF grade			0.292
mild	13 (61.9%)	10 (66.7%)	
moderate	3 (14.3%)	0 (0%)	
severe	5 (23.8%)	5 (33.3%)	
BAI	14.2 ± 15.6	17.9 ± 14.2	0.119
BDI	10 ± 8.1	11.9 ± 6	0.327

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck anxiety inventory; BDI – Beck depression inventory

Table 3. Erectile dysfunction *vs.* without erectile dysfunction in patients with ankylosing spondylitis

Parameters	AS with ED (n = 21)	AS without ED (n = 19)	p
Age (years)	42.8 ± 9.2	42.7 ± 9	0.980
IIEF score	16.1 ± 8.2	29.1 ± 1.3	0
BAI	14.2 ± 15.6	6 ± 5.9	0.117
BDI	10 ± 8.1	5 ± 5.7	0.034
Duration of the disease (years)	9.21 ± 6.9	10.9 ± 8.2	0.714
CRP (mg/l)	7.4 ± 12	6.1 ± 8.3	0.714
ASDAS	2.4 ± 1.2	2.1 ± 1.17	0.578
BASDAI	3.1 ± 2	3.3 ± 2.2	0.763
BASFI	3.8 ± 2.3	3 ± 2	0.286
ASQoL	7.7 ± 5.4	4 ± 4.2	0.022
BP	4.1 ± 2.75	3.5 ± 2.6	0.470
BP night	3.7 ± 2.8	3.2 ± 2.8	0.576
anti-TNFα	16 (76.2%)	15 (78.9%)	1

AS – ankylosing spondylitis; ED – erectile dysfunction; IIEF – International Index of Erectile Function; BAI – Beck anxiety inventory; BDI – Beck depression inventory; CRP – C-reactive protein; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain; TNFα – tumor necrosis factor alpha

Table 4. Correlation of the clinical and demographic data of patients with the ankylosing spondylitis and erectile dysfunction with the International Index of Erectile Function

Parameters	AS (n = 40, 100%)	Spearman's ρ	p
Age (years)	42.8 ± 8.9	-0.47	0.773
BAI	10.3 ± 12.6 (0–54, med = 6)	-0.324	0.042
BDI	7.6 ± 7.4 (0-30, med = 6)	-0.430	0.006
Duration of the disease (years)	10 ± 7.5	0.061	0.707
CRP	6.8 ±10.3	-0.035	0.832
ASDAS	2.26 ± 1.2	-0.132	0.416
BASDAI	3.2 ± 2	-0.008	0.961
BASFI	3.43 ± 2.2	-0.310	0.051
ASQoL	5.9 ± 5.2	-0.428	0.006
BP	3.8 ± 2.7	-0.124	0.447
BP night	3.5 ± 2.7	-0.160	0.323

AS – ankylosing spondylitis; ED – erectile dysfunction; BAI – Beck anxiety inventory; BDI – Beck depression inventory; ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; ASQoL – Ankylosing Spondylitis Quality of Life; BP – back pain

Table 5. Univariate and multivariate logistic regression of correlated parameters of ankylosing spondylitis and erectile dysfunction

Parameters	B	Wald	p	B (exp)
Univariate				
ASQoL	0.161	4.437	0.035	1.175
BAI	0.073	3.370	0.066	1.076
BDI	0.113	3.869	0.049	1.120
Multivariate				
ASQoL	0.161	4.437	0.035	1.175

ASQoL – Ankylosing spondylitis quality of life; BAI – Beck anxiety inventory; BDI – Beck depression inventory

