Accepted manuscript

Increased Proportion of Comorbidities but no Deterioration of sexual QOL during a 5-year follow-up in Patients with ax-SpA in the biologic Treatment Era

Kari. Hansen. Berg[1] Gudrun Rohde,[1,2] Are Pripp,[5] Anne. Prøven,[3] Esben. Ester. Pirelli. Benestad[1],

Monika. Østensen[2], Glenn. Haugeberg[2,4]

[1] Faculty of Health and Sport, University of Agder, Norway. [2] Division of Rheumatology, Department of Medicine, Sørlandet Hospital HF, Kristiansand, [3] Department of Rheumatology, Martina Hansens Hospital, Bærum, [4] Department of Neuroscience, Division of Rheumatology, Norwegian University of Science and Technology, Trondheim, Norway, [5] Oslo Centre of Biostatistics and Epidemiology, Research Support Services, Oslo, Norway

Kari Hansen Berg (Corresponding Author),

PhD-student and Assistant Professor

Faculty of Health and Sport, University of Agder, Norway

Mailbox 422,

4604 Kristiansand

Phone: 0047 93037669

E-mail: kari.h.berg@uia.no

Gudrun Rohde

Professor

Faculty of Health and Sport, University of Agder, Norway and Department of Clinical

Reserach, Sorlandet Hospital HF, Kristiansand

E-mail: Gudrun.e.rohde@uia.no

Are Pripp

Oslo Centre of Biostatistics and Epidemiology

Research Support Services

Oslo University Hospital

E-Mail: apripp@ous-hf.no

Anne Prøven

MD

Department of Rheumatology, Martina Hansens Hospital, Bærum; Norway

E-mail: anne.proven@mhh.no

Esben Ester Pirelli Benestad

MD, Professor

Department of Psychosocial Health, Faculty of Health and Sport, University of Agder,

Norway

E-mail: esben.esther@uia.no

Monika Østensen

Professor Emeritus, Division of Rheumatology, Medicine department, Sorlandet Hospital

E-mail: monika.ostensen@gmail.com

Glenn Haugeberg

MD, PhD and Professor

Division of Rheumatology, Department of Medicine, Sorlandet Hospital HF and Department of Neuroscience, Division of Rheumatology, Norwegian University of Science and Technology, Trondheim, Norway

E-mail: glenn.haugeberg@sshf.no

Keywords:

Axial spondyloarthritis

bDMARD

SQOL (Sexual Quality of Life)

Follow-up

Disease control

Lifestyle

KEY MESSAGES

- Significant increase in comorbidities, but no significant changes in Sexual Quality of Life (SQOL) over a 5-year period

- Exercise less than 1 h/week was associated with deterioration in total SQOL score over the 5-year period

- SQOL in patients with axSpA benefits from good disease control and a healthy lifestyle

ABSTRACT

Objective. To explore patient perception of sexual quality of life (SQOL), an important category of quality of life, in male and female patients with axial spondyloarthritis (axSpA) after a five-year follow-up.

Methods. A broad spectrum of demographic, disease-related, treatment and SQOL data was collected at baseline and at 5-year follow-up. SQOL was assessed by the SQOL-Female (SQOL-F) questionnaire. For statistical analysis, McNemar's tests, paired *t* tests and multiple regression analyses were applied.

Results. A total of 245 axSpA patients (168 men and 77 women) from outpatient clinics were examined, mean age was 46 years and mean disease duration was 11.9 years at baseline. Compared with baseline, the patients had lower C-reactive protein (CRP), lower Maastricht Ankylosing Spondylitis Enthesitis score (MASES), lower Bath Ankylosing Spondylitis Functional Index (BAS-G), less use of smoking, and significantly more patients were treated with biologic DMARDs at 5-year follow-up. Patient perception of SQOL was basically unchanged at the 5-year follow-up despite a significantly increased Proportion of comorbidities including cardiovascular, endocrine, and gastrointestinal disease. A decrease in SQOL after 5 years was observed only in patients exercising <1 h/week at baseline (p = 0.048) and in patients >65 years old.

Conclusion. In our axSpA patients, no statistically significant changes in SQOL were observed over 5 years, despite a significant increase in comorbidities. Overall disease symptoms decreased indicating better disease control. Increased use of biologic drugs at 5 years follow-up may have contributed to this favorable outcome.

Introduction

Axial spondyloarthritis (axSpA) is a chronic, systemic inflammatory rheumatic disease affecting the axial skeleton (1),. AxSpA can be divided into two subgroups radiographic ax-SpA (r-axSpA) and non-radiographic axSpA (nr-axSpA). which also may cause peripheral arthritis and increase the risk of comorbidities (2). Onset of axSpA is predominantly in early adulthood, which is an important time in life when most people start relationships and prepare for or start their career (3). In recent years, major improvement in clinical outcome has been achieved in patients with axSpA attributed to biologic disease-modifying anti-rheumatic drugs (bDMARDs) and the treat-to-target (T2T) treatment strategy (4).

Despite improvements in clinical outcome, the physical and psychological consequences of axSpA may still influence all dimensions of quality of life (QOL), including sexual function and sexual perception in a lifelong perspective. The understanding of sexual QOL (SQOL) includes the relationship between sexual function, intimate relationship and QOL (5, 6). In general, limited data are available on sexuality and SQOL in patients with rheumatic diseases, including axSpA (7).

In previous studies, the impact of axSpA on sexuality has mainly explored sexual dysfunction or sexual problems in cross-sectional studies (8-11) whereas axSpA patients' perception of SQOL has rarely been investigated. In a recent cross-sectional study from the present cohort, we found female sex, increased body mass index (BMI), measures reflecting disease activity and current use of bDMARDs to be independently associated with an impaired SQOL (12).

To our knowledge, long-term changes of SQOL in axSpA patients have not been examined previously. Thus, the aim of this study was to explore whether a follow-up after 5 years would reveal long-term changes in perception of SQOL in male and female axSpA

patients. Furthermore, we wanted to explore which baseline demographics, disease-related or lifestyle variables, were associated with changes in SQOL.

METHODS

Patient recruitment. At baseline, 379 adult axSpA patients were consecutively recruited and included in the study when visiting the outpatient rheumatology clinics at Martina Hansens Hospital (MHH, n = 252) and Sørlandet Hospital (SSHF, n = 127). Among these 360 had responded to SQOL. All included patients were 18 years or older and fulfilled the Assessment of Spondyloarthritis Society (ASAS) criteria for axSpA (13). The study patients included at baseline have previously been described in detail (11, 12).

Data collection. The same data collection performed at baseline was also performed at the 5-year follow-up. Demographic, disease- and treatment-related as well as lifestyle variables were the time between the date fulfilling the ASAS criteria for axSpA and the date for inclusion in collected using questionnaires, laboratory tests, direct interviews, and physical examinations both at baseline and at 5-year follow-up. Demographic data included age, gender, BMI (kg/m^2), current smoker status, alcohol consumption, work status and education. Education is presented as <10 years, 11–13 years and >13 years, this corresponds with the Norwegian education system were < 10 year corresponds to lowest level of education, 11 – 13 years to high school and >13 years to college/university. Physical exercise was classified as >3 hours/week, 1-3 hour /week, < 1 hour/week and seldom or never. The three response categories were dichotomized. The response ">3 hours/week and 1-3 hour /week" were defined as >1 h/week and "< 1 hour/week and seldom or never" were defined as < 1 h/week. Disease duration was calculated from date of diagnosis and the date of entry into the study. HLA-B27 status was registered. Data on comorbidities (cardio-

vascular diseases [CVD], pulmonary diseases, neurological disorders, endocrine disorders, haematological disorders, gastro-intestinal disorders, urogenital disorders, peripheral arthritis, cancer, and mental disorders) were collected. We also computed a summed score to reflect comorbidity (range, 0–10). This score has also been used in other studies (11, 12, 14).

Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), 68 tender and 66 swollen joint counts, the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and C-reactive protein (CRP). Physical function was assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) and the Health Assessment Questionnaires (HAQ) (15). Data on the Bath Ankylosing Spondylitis Patient Global Score (BAS-G) and morning stiffness were also collected. Current medication including non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs) and bDMARDs was also recorded.

SQOL was assessed by the Sexual Quality of Life-Female (SQOL-F) questionnaire. The SQOL-F is a generic self-reported questionnaire and is used to assess the relationship between female sexual dysfunction and QOL (5). The SQOL-F questionnaire was developed by Symonds et al (16) based on Spitzer's Quality of Life measure. The questionnaire can also be used on partners and on male partners with minor modifications. In our study, we changed Question 4 to "When I think about my sexual life, I feel less of a woman/man" (16). This is also supported in an article from Abraham et al. 2008 , " Discussion with experts, a review of the literature and interviews with men with either ED or PE suggested that the items of the SQOL-F were also applicable to men, with only small change needed to question -QU 4: When I think about my sexual life I feel less of a man" (17). The questionnaire was translated into Norwegian by MAPI Research Institute in 2006. SQOL consists of 18 items, rated on a six-point response: completely agree, moderately agree, slightly agree, slightly disagree, moderately disagree, completely disagree. A total sum score for SQOL and for the SQOL

subcategories of Psychosexual Feelings, Sexual and Relationship Satisfaction, Self-worthlessness and Sexual Repression was calculated (18). A higher score indicates better SQOL, except for Sexual and Relationship Satisfaction, where a low score indicates better SQOL (12). For the entire study population, Cronbach's alphas in the study were 0.77 for total SQOL, 0.91 for Psychosexual feelings, 0.81 for Sexual and Relationship Satisfaction, 0.84 for Self-worthlessness and 0.87 for Sexual Repression. The same pattern persisted analysing women and men separately.

Statistical analyses. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean with standard deviation (SD) and categorical variables as numbers and percentages (%). To compare data between baseline and 5-year follow-up, we used McNemar's tests for categorical data and paired samples t tests for continuous data. To calculate the SQOL change scores, we subtracted the baseline scores from the 5-year follow-up scores. We also calculated effect size by subtracting the mean SQOL score (and its sub scores) at baseline from the mean score at 5-year follow-up and then divided by the SD at baseline, within the groups (19). The effect size estimate was interpreted according to Cohen's effect size index: 0.2 as a small difference, 0.5 as moderate and ≥0.8 as large (19). To estimate the proportion of patients with clinically significant changes in SQOL over the period, we identified patients with modest changes (5–9.99%), moderate changes (10–19.99%) and substantial changes (≥20%) (19).

Univariable and multivariable linear regression analyses (GLM) in SPSS were used to identify associations between demographic, clinical and treatment variables and 5-year changes in SQOL sum score and its subcategories; demographic, comorbidity, measures of disease activity, damage, health status, and treatment variables listed in Table 1 with $p < 0.1$

tested in univariate analysis were included in the linear multiple regression analysis. These factors also resonate with the wider theory within the field and clinical experience (20, 21).

Ethical and legal aspects. The study was approved by the Regional Committee for Medical Research Ethics in Norway (REK #: 4.2007.2152). All patients gave written informed consent before inclusion.

Patient involvement. After informed consent were obtained, the patients participated in the study by being interviewed and filling out questionnaires. There was no further patients' involvement. The findings are given in this publication.

RESULTS

Of the 360 axSpA patients (MHH, 246 and SSHF, 114) assessed at baseline with SQOL-F data available (12), 245 patients (MHH, 138 and SSHF, 107) were assessed at the 5-year follow-up. Among the 245 patients assessed at 5-year follow-up, 24 (MHH, 12 and SSHF, 12) did not respond to the SQOL-F questionnaire, leaving 221 patients for the final analysis. Because of funding restrictions at MHH, not all included patients at baseline were invited for the 5-year assessment. This is reflected by the lower percentage of patients with follow-up data at MHH (56%) compared with SSHF (94%). Only minor differences in baseline characteristics were seen between patients with and without 5-year follow-up data. More patients without 5-year data were not cohabitant (32% vs. 25%, $p = 0.023$), were not current users of bDMARDs (76% vs. 64%, $p = 0.038$) and exercised <1 h/week (17% vs. 7%, $p = 0.019$).

When comparing demographic and clinical characteristics between responders and non-responders to SQOL, responders were significantly younger (M = 45.4 vs. M = 50.9 years, p

= 0.025), more were married and cohabitant (81% vs. 42%, p < 0.001), fewer were smokers (26% vs. 46%, p = 0.037) and more exercised longer (89% vs. 75%, p = 0.046). For the other variables listed in Table 1, no significant differences were found.

Table 1. about here

Demographic data, disease activity measures, damage, health status and comorbidity at both baseline and 5-year follow-up for the 221 patients are shown in Table 1. At the 5-year follow-up, the patients had more comorbidities (0.95 vs. 0.58, p ≤ 0.001), lower CRP (5.34 vs. 8.25, p < 0.001), lower MASES score (1.30 vs. 3.19, p < 0.001), lower BAS-G score (3.03 vs. 3.67, p = 0.003), fewer were smokers (17% vs. 26%, p < 0.001) and more were using bDMARDs (40% vs. 23%, p < 0.001). We also compared baseline and 5-year follow-up data for each gender separately. In men, a significant change at 5-year follow-up was found for the same variables as shown for the whole group. However, in women, the change between baseline and 5-year follow-up was not found to be statistically significant for current smoking (28% vs. 22%, p = 0.180), CRP (7.04 mg/dl [13.6] vs. 4.90 mg/dl [9.56], p = 0.147) and BAS-G score (4.05 [2.57] vs. 3.41 [2.59], p = 0.139).

Table 2 about here

SQOL in patients with axSpA at baseline and 5-year follow-up.
As shown in Table 3, no statistically significant changes in SQOL sum score and its sub score were found between baseline and 5-year follow-up for all patients, as well as for men and women examined separately. The smallest change of SQOL was seen in Self-worthlessness

(−0.16, SD 3.2) and the largest in Sexual and Relationship Satisfaction (0.51, SD 5.2). The effect sizes for all were <0.2.

Table 3. about here

Although we did not find significant mean changes for SQOL in the whole cohort, over the 5-year period, we identified some patients with clinically significant changes. Moderate/substantial improvement in SQOL was identified in 33 patients, and deterioration in 33 patients. For Psychosexual Feelings, moderate/substantial improvement was identified in 55 patients, and deterioration in 45 patients. Moderate/substantial improvement for Sexual and Relationship Satisfaction was identified in 62 patients, and deterioration in 47 patients. For Self-worthlessness, moderate/substantial improvement was identified in 43 patients, and deterioration in 50 patients. Finally, for Sexual Repression, moderate/substantial improvement was identified in 50 patients, and deterioration in 43 patients. When comparing demographic and clinical data for patients with moderate/substantial deterioration with those patients with deterioration, we did not identify significant differences between the groups.

Baseline characteristics associated with 5-year changes in SQOL. Using multivariate analysis to identify baseline characteristics associated with 5-year changes in SQOL, we identified few significant associations. Exercise <1 h/week was associated with deterioration in total SQOL score (B = −4.29 [−8.55 to −0.04], p = 0.048), and age >65 years (B = −0.12 [−0.22 to −0.01], p = 0.028) was associated with deterioration in the SQOL sub score of Psychosexual Feelings (Table 4).

Table 4. about here

Changes in comorbidity in patients with axSpA between baseline and 5-year follow-up.

The number of comorbidities increased significantly between 5-year follow-up and baseline, with a total score of 0.95 (1.13) vs. 0.58 (0.82), p < 0.001. Within the type of comorbidity, significant deterioration at 5-year follow-up was observed for gastro-intestinal disorders (reflux and ulcus ventriculi) (18% vs. 11%, p < 0.001), hypertension and hypercholesterolaemia 34% vs. 21%, p < 0.001, and for endocrine disease (diabetes) 9% vs. 5%, p < 0.001. As shown in figure 1, these differences were more prominent in men than in women.
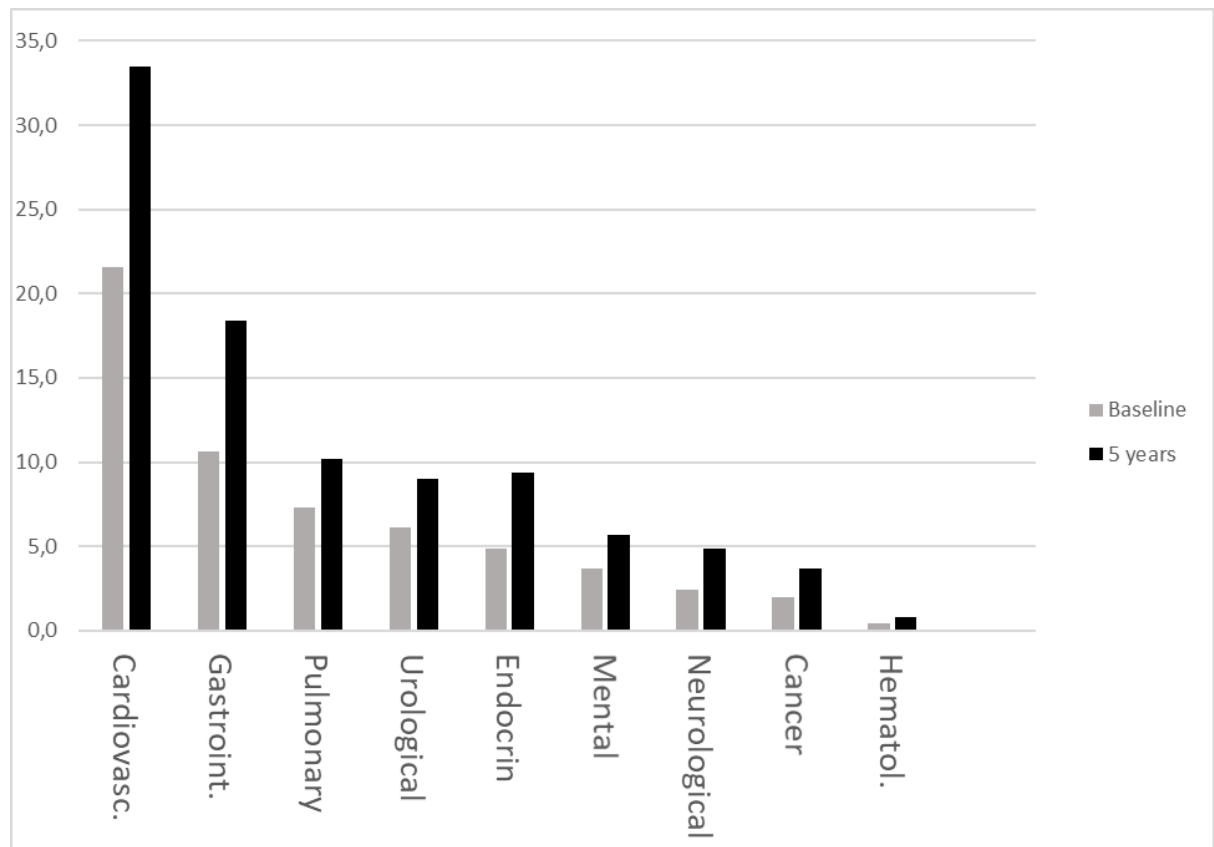

Figure 1. Comorbidities in % at baseline and 5-year follow-up in 221 axial spondylarthritis patients.

DISCUSSION

The main finding in this 5-year prospective study exploring axSpA patients recruited from two ordinary outpatient clinics revealed no deterioration in SQOL total score or its sub scores during follow-up, although the number of comorbidities increased significantly.

At the same time, bDMARDs were used of a larger proportion of patients and a trend emerged towards better disease control as reflected by reduced markers of disease activity, CRP, MASES and BASDAI, less pain and better functioning. Previous studies on Health-related quality of life has shown significantly clinical improvement using patient reported outcomes as HAQ, SF36 and BASDAI and measurements on disease activity in both RA and AS (22-24). The increased use of bDMARD in our study may have contributed to lower disease activity, better functioning and less pain thereby exerting a beneficial effect on SQOL.

Previous studies have shown that axSpA patients are at a higher risk of comorbidities than the general population (25, 26), which was also the case in our study. In general comorbidities develop during the disease course, particularly CVD and depression (26-29) but they are often underdiagnosed in patients with ankylosing spondylitis (AS) (25). From baseline to 5-year follow-up, we found a significant increase in endocrine disease (predominantly diabetes), CVD and gastro-intestinal symptoms, which was more marked in men than in women, in line with previous findings (2). The increase in gastro-intestinal symptoms included reflux and ulcers, possible related to therapy with NSAIDs, which were used by 30–45% of our patients. Increase in cardio-vascular comorbidities comprised mainly hypertension and hypercholesterolaemia. In a study using the same patient cohort, we found no increase in depression as assessed by either the SF-36 mental component score or self-reported depression (Question 15 in 15D) (14).

The lack of the expected deterioration in SQOL over a 5-year period despite the increased number of comorbidities might partly be explained by the psychology of QOL, whereby patients adjust and cope with their chronic illness (30). Using various strategies, they tend to adjust their life goals, expectations and the way they want to live their life in accordance with the actual situation (31, 32). Response shift is one such strategy and is defined as a change in internal standards and values, and a redefinition of what is important in the patient's life (31, 32). These findings are in line with a recent study from our group exploring HRQOL in the same cohort of axSpA patients (14). In that study no deterioration in HRQOL over the 5-year period occurred and the physical dimension in HRQOL (SF-36) improved (14).

There were few significant baseline characteristics associated with significant changes in SQOL. Exercise <1 h/week was associated with a decrease in SQOL. Other studies support the notion that exercise is positive, both in patient-reported and physical outcomes in axSpA (33). Exercise also helps prevent CVD and endocrine disease (34). In addition to medical treatment, regular exercise is one of the core elements in the standard treatment of axSpA and has been shown to be important both for disease control and for general well-being (35). At both hospitals, disease-specific courses for patients with axSpA were routinely offered and information on lifestyle changes, such as quitting smoking and increasing regular exercise, was given.

Our study population had a considerable age range, from 18 to 81 years at baseline and at the 5-year follow-up. Older age at baseline was associated with deterioration in the SQOL sub score of Psychosexual Feelings, but not with the total SQOL score. Increased age has been reported to reduce SQOL in healthy individuals (30), however, better disease control in our axSpA patients at 5 years compared with baseline might have compensated for the expected decrease in SQOL with increased age reported by others (36). Ageing does not

necessarily cause a lack of sexual desire but may have a strong influence on the quality of relationships and sexual functioning. The subcategory Psychosexual Feelings includes items such as frustration, depression, anxiety, anger, worrying about a partner's hurt or rejection, feeling like something is lost and becoming more aware of this as one gets older. Other studies suggest that quality of sexuality is more important than quantity (30, 36). Ageing may be associated with learned skills and strategies throughout a long life that can buffer age-related declines in SQOL, particularly in the context of a positive relationship; this is also called sexual wisdom (30). Furthermore, with respect to the effect of age, younger patients have had their disease for a shorter time and are thus likely to be less affected by disease duration and resulting structural damage.

Strengths and limitations. A clear strength of our study is the long-term prospective follow-up of axSpA patients over a period of 5 years. Furthermore, the study comprised a relatively high number of patients followed during this period, and many variables (objective measures and generic and disease-specific patient-reported outcome measures) were included both at baseline and 5-year follow-up. In Norway, Rheumatology is a speciality on its own and rheumatologists follow the T2T strategy to achieve optimal disease control in patients with axSpA. We believe that selection bias is probably limited because patients were consecutively collected from the daily outpatient clinic at the two hospitals. We also previously reported that patients recruited from SSHF reflected the entire axSpA outpatient clinic cohort (11). Thus, the internal validity of the study is most likely good.

Some limitations of the study should be noted. Our patient population included patients from 18 – 81 years and comprised all patients attending the outpatient clinic during a defined period. The age distribution of the patient population showed that only four patients were in the group 66-81 years and 23 patients were 30 years or younger. The main proportion of the

patients were aged between 31 and 65 year. The group of patients aged <30 in our cohort is small. Younger patients with early and active disease may indeed suffer more impairment of sexual function resulting in less SQOL but we have no sub analysis of the 23 patients aged <30 years.

Furthermore, data collection using SQOL-F in both genders was taken with support in the literature, but may be a limitation (17, 37).

Data were collected only twice over the 5 years. Thus, although we identified changes, it is unknown when the changes occurred, and another two or three time points for data collection would have been advantageous. In addition, there were some minor differences between patients who attended the follow-up and those who were lost to follow-up. From the data collected we were not able to distinguish between radiographic axSpA and non-radiographic axSpA. Finally, interviewing the participants using qualitative methods could also have given us more in-depth information.

CONCLUSION

In our study over a 5-year period, we observed no deterioration in SQOL, despite an increase in age and numbers of comorbidities. This finding is most likely explained by better disease control at 5 years compared with baseline due to more patients being treated with bDMARDs. Our findings add evidence to the importance of suppressing inflammation in axSpA patients to maintain and improve HRQOL including SQOL.

Competing interests

Non, of the authors has competing interests.

Contributor ship

All authors have contributed to the paper.

REFERENCES

1.   Bal S, Bal K, Turan Y, Deniz G, Gürgan A, Berkit IK, et al. Sexual functions in ankylosing spondylitis. Rheumatol Int. 2011;31(7):889-94.
2.   Terenzi R, Monti S, Tesei G, Carli L. One year in review 2017: spondyloarthritis. Clin Exp Rheumatol. 2018;36(1):1-14.
3.   Ostensen M. New insights into sexual functioning and fertility in rheumatic diseases. 2004.
4.   Smolen JS, Braun J, Dougados M, Emery P, FitzGerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. Ann Rheum Dis. 2014;73(1):6-16.
5.   Quirk F, Haughie S, Symonds T. The use of the sexual function questionnaire as a screening tool for women with sexual dysfunction. J Sex Med. 2005;2(4):469-77.
6.   Maasoumi R, Lamyian M, Montazeri A, Azin SA, Aguilar-Vafaie ME, Hajizadeh E. The sexual quality of life-female (SQOL-F) questionnaire: translation and psychometric properties of the Iranian version. Reproductive Health. 2013;10(1):25.
7.   Tristano AG. The impact of rheumatic diseases on sexual function. Rheumatol Int. 2009;29(8):853-60.
8.   Akkurt HE, Yilmaz H, Yilmaz S, Parlak L, Ordahan B, Salli A. Evaluation of Sexual Dysfunction in Females With Ankylosing Spondylitis. Archives of Rheumatology. 2016;31(1):41-7.
9.   Shen B, Zhang A, Liu J, Da Z, Xu X, Gu Z. A primary analysis of sexual problems in Chinese patients with ankylosing spondylitis. Rheumatol Int. 2013;33(6):1429-35.
10.   Christensen BS, Grønbæk M, Osler M, Pedersen BV, Graugaard C, Frisch M. Sexual Dysfunctions and Difficulties in Denmark: Prevalence and Associated Sociodemographic Factors. Arch Sex Behav. 2011;40(1):121-32.
11.   Berg KH, Rohde G, Prøven A, Almås E, Benestad E, Østensen M, et al. Exploring the relationship between demographic and disease-related variables and perceived effect of health status on sexual activity in patients with axial spondyloarthritis: associations found only with non-disease variables. Scand J Rheumatol. 2017;46(6):461-7.
12.   Berg KH, Rohde GE, Prøven A, Benestad EEP, Østensen M, Haugeberg G. Sexual Quality of Life in Patients with Axial Spondyloarthritis in the Biologic Treatment Era. The Journal Of Rheumatology. 2019.
13.   Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-83.
14.   Rohde G, Berg KH, Pripp AH, Prøven A, Haugeberg G. No deterioration in health-related quality of life in patients with axial spondyloarthritis followed for 5 years in ordinary outpatient clinics in the biological treatment era. Qual Life Res. 2019.
15.   Pincus T, Callahan LF, Brooks RH, Fuchs HA, Olsen NJ, Kaye JJ. Self-Report Questionnaire Scores in Rheumatoid Arthritis Compared with Traditional Physical, Radiographic, and Laboratory Measures. Ann Intern Med. 1989;110(4):259.
16.   Symonds T, Boolell M, Quirk F. Development of a Questionnaire on Sexual Quality of Life in Women. J Sex Marital Ther. 2005;31(5):385-97.

17.   Abraham L, Symonds T, Morris MF. Psychometric Validation of a Sexual Quality of Life Questionnaire for Use in Men with Premature Ejaculation or Erectile Dysfunction. The Journal of Sexual Medicine. 2008;5(3):595-601.
18.   Symonds T, Abraham L, Bushmakin AG, Williams K, Martin M, Cappelleri JC. Sexual function questionnaire: further refinement and validation. J Sex Med. 2012;9.
19.   Fayers PMM, D. Quality of life: The assessment, analysis and interpretation of patient-reported outcomes. Chichester: John Wiley; 2007.
20.   Law L, Beckman Rehnman J, Deminger A, Klingberg E, Jacobsson LTH, Forsblad-d'Elia H. Factors related to health-related quality of life in ankylosing spondylitis, overall and stratified by sex. Arthritis Res Ther. 2018;20(1):284.
21.   Lie E, Fagerli KM, Mikkelsen K, Rødevand E, Lexberg Å, Kalstad S, et al. First-time prescriptions of biological disease-modifying antirheumatic drugs in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis 2002–2011: data from the NOR-DMARD register. Ann Rheum Dis. 2014;73(10):1905.
22.   Tumkur A, Foong K, Chuah S, Chow C, Ng L, Low YO. Impact of Biological DMARDS on Quality of Life of Rheumatoid Arthritis Patients-A Narrative Review. 2019:1.
23.   Chen M-H, Lee M-H, Liao H-T, Chen W-S, Lai C-C, Tsai C-Y. Health-related quality of life outcomes in patients with rheumatoid arthritis and ankylosing spondylitis after tapering biologic treatment. Clin Rheumatol. 2018;37(2):429-38.
24.   Strand V, Singh JA. Patient Burden of Axial Spondyloarthritis. J Clin Rheumatol. 2017;23(7):383-91.
25.   Walsh JA, Song X, Kim G, Park Y. Evaluation of the comorbidity burden in patients with ankylosing spondylitis using a large US administrative claims data set. Clin Rheumatol. 2018;37(7):1869-78.
26.   Meesters JJ, Bremander A, Bergman S, Petersson IF, Turkiewicz A, Englund M. The risk for depression in patients with ankylosing spondylitis: a population-based cohort study. Arthritis Res Ther. 2014;16(4):418.
27.   Keller JJ, Hsu J-L, Lin S-M, Chou C-C, Wang L-H, Wang J, et al. Increased risk of stroke among patients with ankylosing spondylitis: a population-based matched-cohort study. Rheumatol Int. 2014;34(2):255-63.
28.   Bengtsson K, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, et al. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. Arthritis Res Ther. 2017;19(1):102.
29.   Essers I, Stolwijk C, Boonen A, De Bruin ML, Bazelier MT, de Vries F, et al. Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study. Ann Rheum Dis. 2016;75(1):203.
30.   Forbes MK, Eaton NR, Krueger RF. Sexual Quality of Life and Aging: A Prospective Study of a Nationally Representative Sample. The Journal of Sex Research. 2017;54(2):137-48.
31.   Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MAG, Fayers PM. The clinical significance of adaptation to changing health: A meta-analysis of response shift. Qual Life Res. 2006;15(9):1533-50.
32.   Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med. 1999;48(11):1507-15.
33.   Rausch Osthoff A-K, Niedermann K, Braun J, Adams J, Brodin N, Dagfinrud H, et al. 2018 EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. Ann Rheum Dis. 2018;77(9):1251.

34. Nilsen V, Bakke PS, Rohde G, Gallefoss F. Predictors of health-related quality of life changes after lifestyle intervention in persons at risk of type 2 diabetes mellitus. Qual Life Res. 2014;23(9):2585-93.

35. Wang C-Y, Chiang P-Y, Lee H-S, Wei JC-C. The effectiveness of exercise therapy for ankylosing spondylitis: a review. Int J Rheum Dis. 2009;12(3):207-10.

36. Cybulski M, Cybulski L, Krajewska-Kulak E, Orzechowska M, Cwalina U, Jasinski M. Sexual Quality of Life, Sexual Knowledge, and Attitudes of Older Adults on the Example of Inhabitants Over 60s of Bialystok, Poland. Front Psychol. 2018;9(483).

37. Symonds T, Boolell M, Quirk F. Development of a questionnaire on sexual quality of life in women. J Sex Marital Ther. 2005;31(5):385-97.

Table 1. Demographic data, disease markers, disease activity measures, damage, health status and comorbidity, in 221 patients with axial spondyloarthritis at baseline and 5-year follow-up

	All Baseline (SD)	All 5-year (SD)	P value
Demographic			
Age, years	46.0 (10.94)		
Married\cohabiting	179 (81%)	185 (77%)	0.405
Current smoker	57 (25.8%)	38 (17%)	< 0.001
Employed	162 (75.3)	153 (70.2)	0.073
Exercise >1 h/week	214 (87%)	218 (89%)	0.618
BMI (kg/m^2)	27.08 (4.4)	27.18 (4.5)	0.576
Education			0.370
<10 years	25 (11%)	20 (9%)	
11–13 years	73 (33%)	74 (34%)	
>13 years	122 (56%)	125 (57%)	
Comorbidity			

Mean total score for comorbidity (range 0–10)	0.58 (0.82)	0.95 (1.13)	< 0.001
Disease activity measures			
CRP (mg/dl)	8.25 (12.13)	5.34 (10.59)	< 0.001
BASDAI	3.02 (2.05)	2.82 (2.16)	0.209
MASES	3.19 (3.81)	1.30 (2.21)	< 0.001
Damage			

BASMI	2.29 (1.92)	2.33 (2.07)	0.682
Health status			
BASFI	2.50 (2.09)	2.31 (2.12)	0.196
BAS-G	3.67 (2.52)	3.03 (2.59)	0.003
HAQ (range 0–3)	0.51 (0.45)	0.45 (0.44)	0.075
Current treatment			
NSAIDs	93 (43%)	84 (39%)	0.358
Synthetic conventional DMARDs	14 (7%)	14 (7%)	0.688
Biologic DMARDs	51 (23%)	86 (40%)	< 0.001

McNemar's tests were used to compare categorical data and paired sample t tests for continuous variables. BMI = body mass index, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index (range 1–10), MASES = the Maastricht Ankylosing Spondylitis Enthesitis Score (range 1–13), CRP = C-reactive protein, BASFI = Bath Ankylosing Spondylitis Functional Index (range 0–10), HAQ = Health Assessment Questionnaires (range 0–3), BAS-G = Bath Ankylosing Spondylitis Patient Global Score (range 0–10), NSAIDs = non-steroidal anti-inflammatory drugs), DMARDs = disease-modifying anti-rheumatic drugs.

Table 2. Comorbidities in patients with axial spondyloarthritis at baseline and 5-year follow-up for all patients and for men and women separately

	Baseline	5-year	P	Baseline N=77	5-year N = 77	P	Baseline N = 168	5-year N = 168	P
Comorbidities	Number (%)	Number (%)		Women	Women		Men	Men	
Neurologic events/disease	6 (2%)	12 (12%)	0.031	2 (3%)	3 (4%)	1.000	4 (2%)	9 (5%)	0.063
Psychiatric diseases	9 (4%)	14 (6%)	0.063	2 (3%)	4 (5%)	0.500	7 (4%)	10 (6%)	0.250
Cancer	5 (2%)	9 (4%)	0.125	0	2 (3%)		5 (3%)	7 (4%)	0.500
Endocrine disease	12 (5%)	23 (9%)	0.001	7 (9%)	10 (13%)	0.250	5 (3%)	13 (8%)	0.008
Haematological disease	1 (0.4%)	2 (1%)	1.000	0	1 (1%)	1.000	1 (0.6%)	1 (0.6)	1.000
Lung disease	18 (7%)	25 (10%)	0.039	4 (5%)	6 (8%)	0.500	14 (8%)	19 (11%)	0.125

Coronary heart diseases	53 (21%)	82 (34%)	< 0.001	19 (25%)	30 (39%)	0.001	34 (20%)	52 (31%)	< 0.001
Gastro-intestinal disease	26 (11%)	45 (18%)	< 0.001	10 (13%)	14 (18%)	0.125	6 (10%)	31 (19%)	< 0.001
Urogenital disease	15 (6%)	22 (9%)	0.016	4 (5%)	5 (6%)	1.000	11 (6%)	17 (10%)	0.031

McNemar's tests were used to compare differences in categorical variables between baseline and 5-year follow-up.

Table 3. Sexual quality of life in patients with axial spondyloarthritis with total score and subscores at baseline and 5-year follow-up, for all and for men and women separately

	Baseline	5-year	P	Mean change (SD)	Baseline women	5-year women	p	Mean change (SD)	Baseline men	5-year men	P	Mean change (SD)
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
SQOL	76.5 (11.3)	79.0 (11.2)	0.633	0.32 (9.7)	73.4 (12.9)	75.3 (11.5)	0.194	1.9 (11.3)	77.8 (10.4)	77.5 (11.0)	0.647	−0.3 (8.9)
Psychosexual Feelings	33.6 (8.3)	33.9 (8.3)	0.694	0.20 (7.4)	32.0 (9.7)	33.6 (7.9)	0.161	1.6 (8.7)	34.3 (7.6)	34.0 (8.5)	0.500	−0.4 (6.7)
Sexual and Relationship Satisfaction	11.8 (5.1)	12.3 (5.8)	0.161	0.5 (5.2)	12.1 (5.8)	12.6 (6.1)	0.555	0.4 (5.7)	11.7 (4.9)	12.1	0.193	0.5 (5.0)
Self-worthlessness	15.5 (3.5)	15.3 (3.2)	0.462	−0.16 (3.2)	14.8 (3.8)	14.8 (3.5)	0.961	−0.02 (3.7)	15.8 (3.3)	15.6 (3.2)	0.361	−0.2 (2.9)
Sexual Repression range	15.3 (3.6)	15.3 (3.5)	0.720	−0.08 (3.2)	14.3 (4.0)	14.4 (3.8)	0.898	0.1 (3.8)	15.8 (3.3)	15.6 (3.3)	0.557	−0.1 (2.8)

Paired sample *t* tests were used when comparing the groups Psychosexual Feelings (range, 7–42), Sexual and Relationship Satisfaction (range, 5–30), Self-worthlessness (range, 3–18), Sexual Repression (range, 3–18) and SQOL-F sum (range, 18–108).

Table 4. P Baseline predictors associated with 5-year changes in SQOL-F (delta SQOL) Sum score and the SQOL sub scores Psychosexual Feelings, Sexual and Relationship Satisfaction, Self-worthlessness and Sexual Repression in 221 patients with axial spondyloarthritis in outpatient clinics; the final model used linear regression analysis (GLM)

	SQOL-F Sum (range, 18–108)		Psychosexual Feelings (range, 7–42)		Sexual and Relationship Satisfaction (range, 5–30)		Self-worthlessness (range, 3–18)		Sexual Repression (range, 3–18)	
	Adj. B (95% CI)	P	Adj. B (95% CI)	P	Adj. B (95% CI)	P	Adj. B (95% CI)	P	Adj. B (95% CI)	P
Demographic factors										
Age (years)	−0.11 (−0.25 to 0.02)	0.104	−0.12 (−0.22 to −0.01)	0.028	0.07 (−0.01 to 0.16)	0.087	−0.01 (−0.06 to 0.03)	0.588	−0.45 (−0.10 to 0.002)	0.059
Male	−0.37 (−4.29 to 5.55)	0.357	−1.34 (−3.61 to 0.94)	0.247	−0.69 (−2.43 to 1.06)	0.437	0.46 (−0.48 to 1.41)	0.337	0.33 (−0.67 to 1.33)	0.511
Living alone	−3.02 (−6.88 to 0.83)	0.123	−2.21 (−5.24 to 0.82)	0.152	−0.87 (−3.24 to 1.50)	0.471	−0.01 (−1.15 to 0.56)	0.986	0.35 (−0.83 to 1.54)	0.558
Education										
<10 years	4.20 (−0.23 to 8.63)	0.063	3.26 (−0.24 to 6.75)	0.067	−0.66 (−3.33 to 2.02)	0.629	1.18 (−0.24 to 2.60)	0.102	0.62 (0.88 to 2.12)	0.415
11–13 years	2.27 (−0.58 to 5.12)	0.118	1.08 (−1.14 to 3.36)	0.332	−0.09 (−1.84 to 1.67)	0.923	0.52 (−0.41 to 1.44)	0.271	0.61 (−0.36 to 1.58)	0.218
>13 years	Ref.		Ref.		Ref.		Ref.		Ref.	
Exercise <1 h/week	−4.29 (−8.55 to −0.04)	0.048	−3.29 (−6.64 to 0.06)	0.054	0.62 (−1.95 to 3.19)	0.634	0.78 (−2.1 to 0.56)	0.249	−0.66 (−2.08 to 0.75)	0.356
Exercise >1 h/week	Ref.		Ref.		Ref.		Ref.		Ref.	
BMI (kg/m^2)	−0.18 (−0.49 to 0.13)	0.245	−0.00 (−0.25 to 0.24)	0.986	−0.03 (−0.22 to 0.16)	0.724	−0.07 (−0.17 to 0.03)	0.182	−0.04 (−1.15 to 0.06)	0.432

Disease activity Measures

BASDAI (range, 0–10)	−0.29 (−1.17 to 0.59)	0.517	−0.20 (−0.89 to 0.50)	0.623	0.03 (−0.49 to 0.56)	0.898	0.02 (−031 to 0.27)	0.895	−0.19 (0.50 to 0.11)	0.213
CRP (mg/dl)	0.09 (−0.03 to 0.22)	0.125	0.01 (−0.09 to 0.10)	0.846	0.04 (−0.03 to 0.11)	0.283	0.02 (−0.2 to 0.06)	0.265	0.04 (−0.00 to 0.08)	0.055

Health status

HAQ (range, 0–3)	−1.59 (−5.46 to 2.27)	0.417	−0.83 (−3.87 to 2.22)	0.593	−0.73 (−3.09 to 1.64)	0.544	0.02 (−1.25 to 1.30)	0.970	0.25 (−1.09 to 1.59)	0.712

Damage

BASMI (range, 0–10)	−0.19 (−0.90 to 0.53)	0.611	−0.14 (−0.71 to 0.42)	0.623	−0.01 (−0.45 to 0.43)	0.967	−0.10 (−0.33 to 0.14)	0.418	−0.01 (−0.25 to 0.24)	0.961
Comorbidity Mean total score for comorbidity (range, 0–10)	−0.20 (−2.01 to 1.62)	0.832	0.04 (−1.39 to 1.47)	0.594	−0.32 (−1.43 to 0.78)	0.564	0.20 (−0.39 to 0.80)	0.500	−0.07 (−0.70 to 0.56)	0.836

Current treatment

NSAIDs	−0.84 (−1.87 to 3.54)	0.541	−0.20 (−2.33 to 1.94)	0.854	−0.51 (−2.17 to 1.1)	0.544	−0.17 (−1.06 to 0.72)	0.701	0.20 (−0.73 to 1.14)	0.668
Synthetic DMARDs	1.62 (−7.13 to 3.89)	0.562	0.08 (−4.28 to 4.44)	0.972	0.00 (−3.39 to 3.40)	0.998	0.78 (−1.06 to 2.62)	0.403	0.56 (−1.39 to 2.50)	0.571
Biologic DMARDs	1.14 (−4.28 to 2.00)	0.474	0.46 (−2.00 to 2.92)	0.711	0.03 (−1.86 to 1.93)	0.972	−0.21 (−1.25 to 0.82)	0.688	0.59 (−0.49 to 1.67)	0.285

Sexual Quality of life at baseline

	Adj. (95% CI)	P	Adj. (95% CI)	P	Adj. (95% CI)	P	Adj. (95% CI)	P	Adj. (95% CI)	P
SQOL baseline	−0.35 (−0.47 to −0.24)	<0.001								
Psychosexual Feelings			0.35 (−0.48 to 0.22)	<0.001						
Sexual and Relationship Satisfaction					−0.32 (−0.47 to −0.16)	<0.001				
Self-worthlessness							−0.42 (−0.53 to 0.029)	<0.001		
Sexual Repression									−0.37 (−0.50 to −0.024)	<0.001
R²	23.2%		18%		4.8%		20.9%		19.5%	

Key: Adj., adjusted unstandardized regression coefficients with 95% confidence interval (CI) and P values; SQOL-F Sum range 18–108; BMI, body mass index; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; BASFI, Bath Ankylosing Spondylitis Functional Index; BAS-G, Bath Ankylosing Spondylitis Patient Global Score; BASMI = Bath Ankylosing Spondylitis Metrology Index; HAQ, Health Assessment Questionnaires; NSAIDs = non-steroidal anti-inflammatory drugs; DMARDs = disease-modifying anti-rheumatic drugs; reference values for statistical comparison.