

THE IMPACT OF DISEASE ACTIVITY ON QUALITY OF LIFE, FATIGUE, FUNCTIONAL STATUS AND PHYSICAL ACTIVITY IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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SUMMARY

Background: Inflammatory back pain and stiffness are the leading symptoms of ankylosing spondylitis (AS). AS progression leads to substantial functional impairment and can reduce quality of life (QoL). The aim of this study was to determine the impact of disease activity on QoL, fatigue, functional status and physical activity.

Subjects and methods: One hundred and fifty AS patients were included in the study, their body mass index (BMI) was calculated and they completed questionnaires regarding disease activity (The Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) functional status (The Bath Ankylosing Spondylitis Functional Index, BASFI) spinal mobility (The Bath Ankylosing Spondylitis Metrology Index, BASMI), physical activity (the International Physical Activity Questionnaire, IPAQ), functional disability (The Health Assessment Questionnaire Disability Index, HAQ-DI), fatigue (The Functional Assessment of Chronic Illness Therapy – fatigue, FACIT-F) and QoL (The Short Form Survey -36, SF-36).

Results: Patients with inactive disease (BASDAI <4) had significantly better HAQ scores ($p=0.001$), SF-36 mental component scores - MCS (65.68±19.54 inactive vs. 46.89±21.78 active disease, $p=0.001$), SF-36 physical component scores - PCS (median score 56.25 inactive vs. 30.00 active disease, $p=0.001$) and FACIT-F scores (38.49±10.62 inactive vs. 26.21±10.81 active disease, $p=0.001$). There was no significant difference in patient's physical activity or BMI regarding disease activity ($p=0.564$ and $p=0.162$ respectively). Also, there was no significant difference in BASDAI, BASMI or BASFI scores regarding different BMI categories ($p=0.818$, $p=0.474$, $p=0.436$, respectively).

Conclusion: AS activity increased fatigue, impaired functional ability and QoL, especially the physical component. Although more than half (61.4%) of our patients were categorized as pre-obese or obese according to BMI, this was not related to disease activity, spinal mobility or daily functioning scores. Reported physical activity level had no effect on disease activity. Disease activity influences the course of AS and QoL assessment should be implemented into regular AS evaluation in order to improve treatment outcome.

Key words: ankylosing spondylitis - quality of life – fatigue - physical activity - body mass index

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that belongs to the spondyloarthritis (SpA) group and is considered as its main prototype (Dougados & Baeten 2011). It primarily affects sacroiliac joints, axial spine and the entheses at an early stage, with inflammatory back pain and stiffness as the leading symptoms (Braun & Sieper 2007). AS is a progressive disease, in which the pathological process leads to the development of syndesmophytes and spine ankylosis, irreversible structural changes, that have substantial impact on patient's daily functioning and quality of life (QoL) (Kotsis et al. 2014). According to the World Health Organization, QoL is defined as 'an individual's perception of their position in life in the context of culture and value systems in which they live and concerning their goals, expectations, standards and concerns' (Öncülokur et al. 2018, WHOQoL Group 1993). Even though the Ankylosing Spondylitis Assessment Study (ASAS) group currently does not recom-

mend QoL as a core assessment domain in AS patients due to uncertainty in the selection of the best measure, the interest in the research of the QoL among patients with inflammatory rheumatic diseases has increased over the last years (Öncülokur et al. 2018, Packham et al. 2011). Patient reported outcome (PRO) measures are used to provide information on treatment effectiveness, functioning and overall well-being (van der Heijde 2009). A widely used PRO instrument in the evaluation of health related QoL in AS is the 36-Item Short Form Survey (SF-36) (Medical Outcomes Trust, Boston, MA) (van der Heijde et al. 2009, Boonen et al. 2007, Braun et al. 2005, 2007, Davis et al. 2007, Revicki et al. 2008). Other useful tools that comprise patient's wellbeing are the Health Assessment Questionnaire Disability Index (HAQ-DI), as one of the most cited and employed PRO instruments to assess functionality, although it has some limitations regarding assessing disability associated with sensory organ or psychiatric dysfunction, and The Functional Assessment of Chronic Illness Therapy - fatigue (FACIT-F) scale, designed to assess tiredness

and its impact on daily activities and functioning in many chronic diseases (Kirwan & Reeback 1986, Bruce & Fries 2005, Cella et al. 2005, Singh et al. 2014). For the assessment of the level of physical activity an International Physical Activity Questionnaire (IPAQ) was developed in 1999, in both short and long versions. These questionnaires provide comprehensive information on patients' physical and functional status, emotions, work ability and social activity in the context of disease activity. Regardless, there is still no consensus on their use, or the consequently intervention strategies which would improve overall patient health.

The aim of this study was to determine the impact of disease activity on QoL, fatigue, functional status and physical activity, as well as the role of BMI in disease activity.

SUBJECTS AND METHODS

This cross-sectional study was conducted from June 2015 to April 2016 at the Clinic for Rheumatic Diseases and Rehabilitation at the University Hospital Centre Zagreb, Zagreb, Croatia. Patients diagnosed with AS according to the ASAS 2009 criteria were enrolled and assessed for disease activity, QoL and functional status. The patient sample was the same as in the previous study of Žagar et al. (Žagar et al. 2019). Each patient signed written informed consent and the study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study has been approved by the Ethical Committees of the University Hospital Centre Zagreb and the University of Zagreb, School of Medicine.

A total of 150 patients, 105 (70%) male and 45 (30%) female were included in the study, with age median of 46 years (range 23-74 years). The subjects did not differ significantly in age distribution ($p=0.765$). The median of disease duration was 6 years (range 2-9 years). All patients completed specific questionnaires regarding basic anthropometric data (sex, age, height, weight and BMI), disease activity, functional status and disability, spinal mobility, physical activity, fatigue and QoL. Demographic and basic anthropometric data are shown in Table 1. Three basic questionnaires were used for the assessment of the clinical impact of the disease: The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), The Bath Ankylosing Spondylitis Functional Activity Index (BASFI), and The Bath Ankylosing Spondylitis Measurement Index (BASMI) (Calin et al. 1994, Zochling 2011, Garrett et al. 1994, Calin et al. 1999). BASDAI measures patient reported disease activity by assessing severity of fatigue, back pain, peripheral joint pain and swelling, localized tenderness, and the duration and severity of morning stiffness. The score ranges from 0 (no disease activity) to 10 (maximal disease activity), with a cut-off of 4

which indicates active disease (Garrett et al. 1994, Calin et al. 1999). BASFI assesses physical functioning through specific questions regarding different daily activities, such as standing, turning, bending, reaching, changing position, climbing steps and patient's ability to cope with everyday life. The score ranges from 0 (no functional impairment) to 10 (maximal impairment) (Calin et al. 1994, Zochling 2011). BASMI assesses the mobility of the axial skeleton. The score ranges from 0 to 10, with higher score indicating more severe impairment (Zochling 2011). IPAQ short form was used to measure health-related physical activity and to obtain comparable estimates of patient's activity during leisure time, domestic and gardening tasks, at work and transportation. Subsequently patients were scored as having low, moderate or high level of physical activity (Hagströmer et al. 2006, Craig et al. 2003). HAQ-DI was used to assess the functional ability, with score 0 considered as mild, score 1 as moderate and score 2 as severe disability (Kirwan & Reeback 1986, Bruce & Fries 2005). FACIT-F questionnaire was used for the assessment of patient's fatigue and consists of 13 questions, scores range from 0-52, with higher score indicating better quality of life, i.e. less fatigue (Cella et al. 2005, Singh et al. 2014). The SF-36 was used to measure patient-reported health status and QoL, consisting of two summary scores – Physical Component Score (PCS) and Mental Component Score (MCS), scores range in each of the eight subscale form 0-100, with higher score indicating better health status (Ware Jr 2000).

Statistical analysis

Descriptive statistics were used to describe continuous and categorical variables. Kolmogorov-Smirnoff test was run to determine the normality of data distribution. Independent samples t test or Mann Whitney U test, where applicable, were run for the analysis of the numerical values in two groups. Chi square test was run for comparing three or more independent groups. Spearman's test was used to determine the correlation between specific variables. A value of $p<0.05$ was deemed statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.

RESULTS

A total of 94 (62.7%) patients had active disease with mean BASDAI score of 4.69 ± 2.38 . Mean scores for spinal mobility (BASMI) and daily functioning (BASFI) were 4.41 ± 1.96 and 4.06 ± 2.66 respectively. According to HAQ-DI questionnaire, most of the patients, 79 (52.7%), had mild disability, 65 (43.3%) had moderate and 6 (4%) had severe disability. The mean fatigue score (FACIT-F) was 30.91 ± 12.26 . Median patient reported health status from SF-36 PCS was 36.25 (range

7.5-93), while MCS was normally distributed with a mean score of 54.21±22.81. According to IPAQ categories, 45 (30%) patients had low, 63 (42%) moderate and 42 (28%) high physical activity level (Table 1).

Table 1. Patient demographic and anthropometric data

Patient characteristics	Number of patients
Sex	
male	105 (70%)
female	45 (30%)
BMI categories	
normal range	57 (38%)
pre-obese	55 (36.7%)
class I obese	28 (18.7%)
class II obese	6 (4%)
class III obese	1 (0.7%)
	median (range)
Age (years)	46 (23-74)
Disease duration (years)	6 (2-9)
	mean±SD
Height (cm)	172.57±9.19
Weight (kg)	79.77±17.12
BMI	26.75±5.44

*BMI – body mass index

Disease activity and patient's physical functioning and QoL

Patients with inactive disease (BASDAI<4) had significantly better HAQ scores (p=0.001), SF-36 MCS scores (65.68±19.54 inactive vs. 46.89±21.78 active disease, p=0.001), SF-36 PCS scores (median score 56.25 inactive vs. 30.00 active disease, p=0.001) and FACIT-F scores (38.49±10.62 inactive vs. 26.21±10.81 active disease, p=0.001). Both SF-36 MCS and PCS scores correlated positively with FACIT-F score and negatively with BASMI and BASFI scores (Table 2).

FACIT-F score correlated negatively with BASFI and BASMI scores (r=-0.552, p=0.001 and r=-0.288, p=0.001 respectively). Regarding the disease activity, we found no significant difference in patient's physical activity (IPAQ categories) or BMI (p=0.564 and p=0.162 respectively). Also, there was no significant difference in BASDAI, BASMI or BASFI scores regarding different BMI categories (p=0.818, p=0.474, p=0.436, respectively).

DISCUSSION

This research showed that disease activity significantly affects patient's functional ability, fatigue and QoL, in terms that patients with inactive disease had better scores in all mentioned domains. Similar results were confirmed in other studies, where AS patients had significantly lower health related QoL measured with SF-36 compared to the general population (Law et al. 2018, Yang et al. 2016, Kotsis et al. 2014, Salaffi et al. 2009, Wafa et al. 2012, Ovayolu et al. 2011, Dagfinrud et al. 2004, Singh & Strand 2009, Davis et al. 2005). Also, Bodur et al. showed on a large sample of 962 patients that patients with high disease activity (BASDAI≥4) had significantly worse QoL scores compared to those with low disease activity (Bodur et al. 2011). Disease activity is considered as a powerful predictor of QoL (Kotsis et al. 2014). Studies that investigated the change in QoL during the course of AS reported no significant changes in QoL, but attributed those findings mainly to the lack of major clinical deterioration (Kotsis et al. 2014, Martindale et al. 2006, Healey et al. 2013). On the other hand, Younes et al. showed significant worsening of QoL in a sample of AS patients followed for 6 months, with a wide range of disease duration (Younes et al. 2011). Similarly, van der Heijde et al. showed significant improvement in disease activity, patient reported physical function and health related QoL physical component in adalimumab-treated patients during the early phase of double-blind placebo controlled ATLAS study, but the same was not observed for mental component (van der Heijde et al. 2009). In our study, the physical component of SF-36 was more affected than the mental component (PCS median score 36.25 vs. MCS mean score 54.21), showing even greater difference regarding PCS in active vs. inactive disease (median score 30.00 vs. 56.25). Study of Law et al. investigated only SF-36 summary scores on the whole sample, without considering disease activity, but also observed the same trend of lower PCS scores (mean PCS score of 41.3±10.1 vs. mean MCS score of 44.6±12.7) (Law et al. 2018). Yang et al. also showed that pooled mean PCS scores were lower than MCS scores (45.93-58.28 vs. 47.49-62.52), with subgroup analysis based on disease severity showing deteriorated health related QoL with increase of disease activity (Yang et al. 2016).

Table 2. Correlation of SF-36 summary scores with fatigue and physical functioning

SF-36 summary scores		FACIT-F	BASMI	BASFI
SF-36 MCS	Correlation Coefficient	0.566	-0.512	-0.268
	p value	0.001	0.001	0.001
SF-36 PCS	Correlation Coefficient	0.548	-0.634	-0.364
	p value	0.001	0.001	0.001

FACIT-F-Functional Assessment of Chronic Illness Therapy-Fatigue, BASFI-Bath Ankylosing Spondylitis Functional Activity Index, BASMI-Bath Ankylosing Spondylitis Measurement Index, SF-36 MCS-Short Form 36-mental component score, SF-36 PCS-Short Form 36-physical component score

These findings can be explained regarding disease progression, which causes more pronounced pain, impaired spinal mobility and daily functioning, causing primarily physical disability. Also, patients report that the most commonly affected aspects of QoL are stiffness, pain, fatigue, poor sleep, appearance, worries about future and medication side effects, while mental health aspects such as coping, depression and anxiety are regarded as not very important (Kotsis et al. 2014, Ward 1999). Expectedly, better MCS and PCS scores were associated with less fatigue, better spinal mobility (BASMI) and physical functioning in daily activities (BASFI) (Table 1), while fatigue was worse in patients with impaired spinal mobility and daily functioning. Similarly, meta-analysis of Yang et al. showed that lower BASFI was associated with higher physical function, PCS and MCS scores (Yang et al. 2016). As well, Bodur et al. showed that patients with worse functional status (BASFI \geq 5) had significantly poorer QoL scores compared to patients with better functional status (Bodur et al. 2011). Fatigue is present in up to 60% of AS patients, being the third most common AS complaint, after pain and morning stiffness (Kotsis et al. 2014, Aissaoui et al. 2012, Alkan et al. 2013, Günaydin et al. 2009, Missaoui & Revel 2006). Besides disease activity, fatigue is affected by functional status, duration of morning stiffness and pain at rest, as well as depression and sleep disturbance (Günaydin et al. 2009). More than half (61.4%) of examined patients were categorized as pre-obese or obese according to BMI. There has been extensive research on the effect of the adipose tissue, i.e. serum levels of leptin and adiponectin and their involvement in different inflammatory processes (Fantuzzi 2005). The potential role of leptin as a biomarker for the development of syndesmophytes in patients with AS was investigated and higher leptin concentrations were shown to be associated with radiographic progression (Gonzalez-Lopez et al. 2017, Kim et al. 2012). Moreover, Park et al. showed that concentrations of leptin and the proinflammatory cytokine interleukin-6 were associated with disease activity in AS patients (Park et al. 2007). Also, pre-obesity was reported to led to increase in disease activity of AS patients, as well as deterioration of functional condition, and significant decline in QoL (Toy et al. 2017). Durcan et al. reported that most patients with AS in their cohort were overweight and that patients with higher BMI had higher disease activity (Durcan et al. 2012). Similar results were obtained in a study by Vargas et al., where ASDAS score was slightly increased in the overweight SpA patients, although not reaching statistical significance (Vargas et al. 2016). However, we found that disease activity (BASDAI), spinal mobility (BASMI) or daily functioning (BASFI) were not in any way dependent of patient's BMI. Although we would expect the excess adipose tissue to produce greater proinflammatory activity, some of the research shows that serum adipokines and ghrelin in patients with AS failed to prove clear

relationship between circulating adipokines and clinical or laboratory markers of disease activity (Toussirot et al. 2007). Hartl et al. also indicated the controversial effects of leptin on radiographic progression in AS and showed its protective role in terms of progression (Hartl et al. 2017). Most of our patients (42%) reported moderate physical activity level according to IPAQ categories, with physical activity having no effect on disease activity. Regular physical activity especially in terms of physical therapy has proven to have a positive effect on disease activity and QoL (Kotsis et al. 2014, van den Berg et al. 2012, Durmus et al. 2009, Altan et al. 2012, Karapolat et al. 2008). That was not the case in our study, possibly because the IPAQ score was a result of patients' subjective evaluation of his/her physical activity and not an interventional study where we could observe an objective effect.

CONCLUSION

The most significantly affected QoL components by AS activity in this study were overall health, with dominantly physical component, functional disability and fatigue. Intriguingly, BMI did not affect any of the AS outcome measures; disease activity, spinal mobility or daily functioning. Disease activity and symptom severity influence the course of AS which in turn affects QoL. Further longitudinal studies are warranted to investigate possible predictors for impaired QoL over the course of the disease in order to plan appropriate intervention strategies, considering that QoL assessment should become a standard part of AS patient evaluation for developing personalized care and overall outcome improvement.

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Contribution of individual authors:

Iva Žagar & Valentina Delimar: study design, data collection, first draft, statistical analysis, approval of the final version.

Stjepan Čota & Sanda Špoljarić Carević: data collection, first draft, approval of the final version.

Kristina Kovač Durmiš & Nadica Laktašić Žerjavić: study design, first draft, approval of the final version.

Porin Perić: study design, first draft, approval of the final version.

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