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Research Article

The Relation Between Functional Parameters, C-Reactive Protein and Erythrocyte Sedimentation Rate in Ankylosing Spondylitis: A Cross-Sectional Study

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Abstract

Introduction: Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterised by inflammation of the spine and the sacroiliac joints and stiffness, which leads to a progressive decline in the quality of life of individuals. Bath indices are considered the principal functional outcome measure and Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) are the most widely used biomarkers in AS to assess disease activity.

Objective: To characterise individuals with AS and to examine the association between functional parameters and biomarkers.

Methods: Thirty-one patients were recruited from the National Association of Ankylosing Spondylitis (ANEA) – Centre of northern region of Portugal, between February 2014 and June 2015, to be included in the present study. The Bath indices [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI)], the Neck Disability Index (NDI), the Oswestry Disability Index (ODI) and laboratory parameters such as ESR and CRP were analysed.

Results: The participants' mean age was 42.77 (±14.37) years, with 18 (58.1%) women and 13 (41.9%) men. The mean scores were 3.55 (BASDAI), 2.78 (BASFI) and 2.58 (BASMI). The final mean scores were 25.81± 18.36 (NDI) and 23.29±15.32 (ODI). We found a negative association between ESR and BASDAI (β=-0.038, p=0.025), and between ESR and BASFI (β=-0.044, p=0.013). As to CRP, there was no statistically significant association between Bath indices.

Conclusion: This cross-sectional study in AS patients demonstrated that, on the one hand, this sample had a high education level, having been diagnosed with AS for more than 15 years, with a moderate disability and, on the other hand, with the adjustment of education level and years since diagnosis, there was an association between ESR and BASDAI and BASFI scores.

Keywords: Ankylosing spondylitis; Functionality; Biomarkers; Inflammation; pain

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease, characterised by inflammation of the spine, the sacroiliac joints and stiffness, which can lead to a progressive decrease in the quality of life [1,2]. Disease activity, functionality and symptoms are great impact areas in AS [3]. Pain, stiffness, fatigue and spinal mobility are symptoms which reflect the disease's inflammatory effect [3]. As a consequence, the irreversible changes that accompany AS, the decreased functionality in activities of daily living, the direct and indirect costs associated with the disease and its effect on patients' quality of life are important parameters to take into account in

the clinical practice to achieve a good diagnosis and an adequate intervention [2]. The socioeconomic impact of AS is substantial, considering the reduced working hours, occasional work changes/adaptations, missed professional opportunities and early retirement. On the other hand, it has been reported that a higher educational level is associated with maintenance in the labour force, decreased years since AS diagnosis, a higher socioeconomic level and a better understanding of the disease [4,5].

The most commonly used biomarkers to monitor AS activity are Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) [6]. These parameters are usually high in AS, in association with lumbar and cervical pain, as inflammation and entheses in these regions are the first symptoms of the disease [7]. However, there is some issue as to the sensitivity of these inflammatory biomarkers in AS activity and their correlation with functional parameters [6,8]. The basis for this controversy is the assessment of their specificity regarding AS, as these biomarkers are specific to assess the inflammation in structures affected by the disease, such as tendons, bone, ligaments, cartilage, among others, but are also influenced by non-inflammatory aspects, such as age, gender, anaemia and renal failure, which can influence these laboratory parameters [6,9]. Their correlation with functional parameters has been more evident in the assessment of disease activity (BASDAI) [8]. However, to achieve a deeper and more specific understanding of the disease it is necessary to include functional (BASFI), metric (BASMI) and disease activity (BASDAI) parameters in the assessment of an individual with AS, as these are the preferred methods to evaluate individuals with AS [2,6,10,11].

Equally important, given the complexity of this chronic disease, in particular the ankylosis of some segments of the spine, is to explore the assessment of more specific parameters associated with the impact of spinal mobility (cervical and lumbar regions) on activities of daily living [12]. The characterisation of AS individuals in the literature is still scarce. For this reason, it is important to enhance knowledge regarding functional and biomarker parameters, improving the orientation of health professionals in the management of this disease and in providing patient advice. The aims of this study were: (1) to characterise individuals with AS and (2) to verify the association between functional joint and biomarker parameters.

Methods

Study design and participants

A cross-sectional study with a convenience sample of patients with AS was conducted in the northern region of Portugal. The study received approval from the Ethics Committee of the School of Health Allied Sciences of the Polytechnic Institute of Porto. Potential candidates were identified by physiotherapists from the institution and from the National Association of Ankylosing Spondylitis (ANEA) – Centre of northern region of Portugal, and the recruitment occurred between February 2014 and June 2015.

Subjects were eligible to participate in the study if they: (1) were diagnosed with AS according to the modified New York criteria [10]; (2) were aged 18 years or older and [10]; (3) voluntarily consented to participate. The study excluded all patients presenting any other clinically diagnosed spondyloarthropathy, neurological or cardiorespiratory pathologies [10].

Instruments

All patients completed the Portuguese version of the Bath Spondylitis Functional Index (BASFI) [13], a characterisation questionnaire which measures the functional status of patients with AS through ten questions regarding daily activities, with the mean score (range, 0–10) being obtained from the sum of all values. The Portuguese version of the Bath Spondylitis Metrics Index (BASMI) [13] was used to determine the participants' physical mobility, with the Shober's test, lateral spine flexion, tragus to wall distance, cervical rotation and intermalleolar distance, with a final score ranging from 0 to 2 in each one of the five parameters (0 – mild disease involvement, 1 – moderate disease involvement, 2 – severe disease involvement).

The Portuguese version of the Bath Spondylitis Disease Activity Index (BASDAI) [13] was used to measure the disease activity status through six questions with a score ranging from 0 to 10, regarding fatigue, spinal pain, peripheral joint, entheses and morning stiffness, to determine a final mean score. A mean of the two scores relating to morning stiffness was calculated before averaging all the answers [13,14].

The Portuguese version of the Oswestry Disability Index (ODI) was used in each of its ten items, each of them including 6 statements, and patients were requested to select only one, obtaining a score from 0 to 5. The Portuguese version of the Neck Disability Index (NDI) also includes 6 statements and the score 0-5. ODI and NDI total scores were converted into a percentage score with 0-20% indicating minimal disability, 21-40% moderate disability, 41-60% severe disability, 61-80% crippled and 81-100% total incapacitation [15-17]. Disease activity variables used included both C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR).

Data collection procedures

Aspects such as age, gender, level of education and employment situation were identified as sociodemographic and anthropometric. Physical examination of patients by a blind trained observer included the assessment of BASMI. Patients have completed two self-administered questionnaires – the NDI and the ODI.

As laboratory assessments of patients' ESR and CRP were determined, overnight fasting blood samples from all subjects were collected through standard antecubital forearm venepuncture to 8 ml serum-separator and 3.5 ml K2-EDTA tubes (BD Vacutainer® System, BD Diagnostics, Franklin Lakes, NJ). After room temperature clotting, serum was separated by low-speed centrifugation (4500 rpm, 10 min, 22°C) (Sigma ® 3k15, SIGMA Laborzentrifugen GmbH, Osterode am Harz, Germany), transferred into aliquots, and stored at -80°C until analysis [18] and latex immunoturbidimetry (CRP) [19] techniques.

For ESR estimation, K2-EDTA anticoagulated blood samples were mixed for 10 minutes before the test. Samples were aspirated into a Westergren pipette and the distance that the column of blood

fell in 1h was recorded according to the International Council for Standardisation in Haematology (ICSH) standardised method [20].

Data analysis

Sample characteristics are presented as counts and proportions for categorical variables and as mean ± standard deviation (SD) for biomarkers and functional parameters. The association between biomarkers and functional parameters was estimated through crude regression coefficients and years since diagnosis and education level-adjusted regression coefficients (β and adjβ). Since the regression prerequisites were not achieved when analysing the ODI and NDI functional parameters, Spearman's correlation coefficients were calculated. A p-value ≤ 0,005 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 23.0 (Chicago, IL).

Results

Table 1 summarises the characteristics of the 31 participants in this study. The patients' mean age was 42.77 ±14.37 years. Most subjects were female (58.1%), and 45.2% had between 13 and 16 years of education (45.2). 38.7% were diagnosed with AS for more than 15 years. 38.7% of participants had a salary lower than 500€ and 35.5% had a salary higher than 1000€. All participants were taking non-steroidal anti-inflammatory drugs (NSAID).

Table 1: Sample characteristics: socio-demographic information and history of AS.

N (%)	
Gender	
Female	18 (58.1)
Male	13 (41.9)
Education level (years)	
<=9	9 (29.0)
<=12	7 (22.6)
>12	14 (45.2)
<=17	1 (3.2)
Diagnosis (years)	
<=4	8 (25.8)
>5	5 (16.1)
<=10	6 (19.4)
>15	12 (38.7)
Salary (month)	
<=500 euros	12 (38.7)
<=1000 euros	6 (19.4)
>1000 euros	11 (35.5)
>2000 euros	2 (6.5)
Medication	
NSAID	31 (100)

Patients' clinical parameters are shown in Table 2. The mean scores were 3.55 ± 1.94 BASDAI), 2.78 ± 2.12 (BASFI) and 2.58 ± 1.86 (BASMI), with a minimum of zero and a maximum of ten. On average, the NDI score was 25.81 ± 18.36 and the ODI score was 23.29 ± 15.32, which indicates a moderate disability in both cases.

Table 2: Clinical parameters of patients with ankylosing spondylitis.

	Mean (SD)	Min.	Max.
Biomarkers			
ESR (mm/h)	14.19 ± 14.40	1	74
CRP (mg/dl)	0.56 ± 0.76	0.01	4.08
Functional parameters			
ODI	23.29 ± 15.32	4	64
NDI	25.81 ± 18.36	2	66
BASDAI	3.55 ± 1.94	0.37	7.25
BASFI	2.78 ± 2.12	0	7.94

BASMI	2.58 ± 1.86	0	7

SD: Standard Deviation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Spondylitis Metrics Index; ODI: Oswestry Disability Index; NDI: Neck Disability Index; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein.

The correlation values between biomarkers and ODI and NDI scores are shown in Table 3. No statistically significant association between biomarkers and ODI or NDI scores was found.

When considering the crude effect, no statistically significant association was found between biomarkers and functional parameters. After adjustment to years since diagnosis and education level, used here as a proxy of professional group, we found a negative association between ESR and BASDAI (β=-0.038, p=0.025) and between ESR and BASFI (β=-0.044, p=0.013), but not between ESR and BASMI (β=0.010, p=0.615). No statistically significant association was found between CRP and functional parameters in BASDAI, BASFI and BASMI (Table 4).

Table 3: Spearman's correlations between functional and biomarker parameters.

	ESR	CRP
	Coef. (P- Value)	Coef. (P- Value)
ODI	0.072 (0.701)	0.276 (0.132)
NDI	-0.029 (0.877)	0.181 (0.330)

ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; ODI: Oswestry Disability Index; NDI: Neck Disability Index.

Table 4: Association between biomarkers and functional parameters.

	ESR		**CRP**	
	Crude β (P- Value)	**Adjusted* β (P- Value)**	**Crude β (P- Value)**	**Adjusted* β (P- Value)**
BASDAI	-0.025 (0.296)	**-0.038 (0.025)**	0.475 (0.290)	0.123 (0.722)
BASFI	-0.025 (0.337)	**-0.044 (0.013)**	0.095 (0.849)	-0.219 (0.549)
BASMI	0.017 (0.452)	0.010 (0.615)	-0.236 (0.587)	-0.561 (0.129)

ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index. *Adjusted to years since diagnosis and education level.

Discussion

The aims of this study were to characterise individuals with AS and to verify the association between functional and biomarker parameters in these patients. The sample of this cross-sectional study included more female than male subjects (58.1% women versus 41.9% men), contrarily to a recent study conducted in Portugal [10] and to the described in the literature regarding other European populations with AS [21]. This difference can result from women's increased interest in obtaining health-related information when compared to men, showing more interest in participating in this type of programmes [22,23] and volunteering more than men.

Individuals in this sample have an education level of more than 12 years (45.2%), which suggests that they are more demanding when searching for information regarding the disease, an important factor contributing for recognition and control of the associated symptoms [23]. 38.7% of the individuals included in this study have been diagnosed with AS for more than 15 years, as in another study recently conducted in Portugal, in which most subjects were diagnosed with AS for more than 10 years [10]. The therapeutic strategies existing at that time were clearly different from those that are available today, either due to the insufficient knowledge of the disease or to the individual variation during the disease and to the understanding of pathophysiological and biomechanical principles combined with the pharmacological therapy [10,24].

The mean age was 42.77 years, with the younger subject aged 18. This reveals that AS is being diagnosed earlier, which provides for a more adequate monitoring of patients. This is coincident with more modern diagnosis approaches, increased accessibility and availability of assessment instruments and the more comprehensive information available to healthcare professionals and patients [10].

As to monthly income, 58% of the individuals have a salary lower than or equal to 1000€, while 42% earn more than 1000€. These values are in accordance with the sample's education level and another recent Portuguese study [23].

The sample's mean BASDAI (3.55±1.94), BASFI (2.78±2.12) and BASMI (2.58±1.86) scores show that these individuals are between percentiles 25 and 50 for the Portuguese population, taking the disease's evolution in years into account [10]. These values are similar to those obtained in previous cross-sectional studies, with similar values as to the education level, years since diagnosis and medication intake, although with a higher sample [25-27]. It should be noted that NDI mean scores in this sample were higher (25.8 ±18.36) than ODI scores (23.29±15.32), although all of them are in the same interval, revealing an increased mean score of cervical disability compared to lumbar disability, as opposed to the described in the literature, which reports that the latter is the most affected segment [28]. This evidence can be due to the female predominance of the sample, as women are more commonly affected at the cervical segment than at the lumbar segment, as opposed to men [29,30]. On the other hand, our results show that both segments have mean scores situated in the interval 21-40, which means a moderate disability, in accordance with the Bath indices' scores (BASDAI, BASMI and BASFI), taking into account the percentiles for the Portuguese population with AS [10]. As to ESR

and CRP parameters, several studies have been reporting that these biomarkers have no predictive value to determine disease activity in individuals with AS [2,6,7,9]. Our results show low ESR and CRP values, suggesting that individuals in our sample have low disease activity. This can be due to the fact that all individuals take anti-inflammatory medication, which can influence these biomarkers [31], or to the fact that most subjects were diagnosed with AS for more than 12 years, having an increased knowledge and control of the disease. Patients who have been diagnosed for more years have an increased need of information than recently diagnosed individuals, which provides a safer management of the disease [22].

It has been verified that when values were adjusted for years since diagnosis and education levels, there was an association between ESR and BASDAI and BASFI scores. As ESR levels increase, BASDAI scores also increase, deteriorating these individuals' functionality; in the same way, when ESR values increase, BASFI scores also increase, which translates into higher disease activity. This can be explained by disease duration/evolution because of the progressive activation of bone reparative/remodelling pathways that are likely to affect these biomarkers [32,33]. As concerns the education level, it influences functionality and disease activity by the knowledge these individuals have regarding the disease [34], although there is no association between this parameter and BASMI scores. As to CRP, there was no association between Bath indices, possibly because this biomarker is more sensitive in inflammation detection and is not increased by the influence of age, sex or anaemia. As this biomarker values were low in individuals of this sample, no association was found with the Bath indices [35].

Both cervical and lumbar vertebral mobility and the inflammation of these segments are dynamic processes which vary in time and with time. This inflammation is a non-linear process, which improves, deteriorates and even disappears throughout time, which makes that its assessment using biomarker parameters is a point estimation, as they are sensitive to changes [6].

Our results also show that the NDI and ODI present a low association with the biomarker parameters. These findings may be explained by the number of years of disease evolution of patients participating in this study, which has somehow provided for adaptations to perform activities of daily living, decreasing the impact of chronic pain in the cervical and lumbar segments. These results have implications for healthcare professionals dealing directly with patients with AS, as they would allow to better understand and monitor these individuals.

Our study has some limitations, such as the reduced number of individuals who constitute our sample and the fact that it is a convenience sample. A second limitation in result analysis was that it was not possible to adjust the years since diagnosis and the education level for NDI and ODI scores, as these parameters do not meet the requirements for that analysis. For these reasons, additional studies with a bigger sample using these two instruments (NDI and ODI), together with additional objective parameters such as imaging examinations, for their sensitivity to detect active inflammation, are required for correlation with biomarkers.

Conclusion

Individuals with AS included in this study have a high education level, an aspect which is in accordance with their monthly income, a disease evolution of at least 15 years and a moderate functional disability.

Our results show a negative association between ESR and BASDAI and BASFI scores.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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