ORIGINAL RESEARCH

Morning Stiffness Correlates with Disease Activity, Blood Pressure and Cholesterol Levels in Patients with Seropositive Rheumatoid Arthritis

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Abstract

Introduction. Morning stiffness (MS) is the hallmark of rheumatoid arthritis (RA) and it has important implications on daily life of the patients. There are conflicting reports of its association with disease activity.

Methods. This observational study included 125 patients with seropositive RA from Health Care Center, Visoko. We obtained data on patient's gender and age, duration of RA, pain in hands and feet, MS and its duration, hospital admission, blood pressure, laboratory values and treatment modalities.

Results. MS lasted up to 30 minutes in 71 (56.8%) patients, 30 to 60 minutes in 40 (32%) patients, and more than 60 minutes in 14 (11.2%) patients. There was no difference in the duration of MS between genders. Patients with longer MS were younger and had a longer duration of illness. Patients with MS longer than 30 minutes had higher blood pressure and cholesterol levels. ESR in the second hour and CRP correlated with a duration of MS. Patients on methotrexate had a longer duration of MS. No significant differences in the duration of MS were observed for leflunomide, corticosteroids and supportive treatment modalities.

Conclusion. Duration of MS correlates with RA disease activity and remains an important burden for patients. Usage of newer treatment options, such as biologic disease-modifying antirheumatic drugs (DMARDs), may be required.

Keywords: biomarkers, disease activity, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting around 1% of the world population. It is more common in women than men, with peak incidence around 50 years of age. It is assumed that RA develops in genetically predisposed

individuals exposed to an external factor that triggers an autoimmune reaction (1, 2).

Clinical features of RA include constitutional symptoms, joint pain and swelling predominantly and symmetrically affecting the small joints of the hands and feet, although other joints lined by a synovial membrane may be affected (1, 3). The hallmark of RA is morning joint stiffness lasting longer than an hour, which is described as a limitation of motion after a period of rest (1, 4). However, this is not specific to RA, and this finding can be present in other inflammatory joint disorders (3). It can be explained by the circadian rhythm of pro-inflammatory cytokines like the tumor necrosis factor (TNF) and interleukin-6 (IL-6) (5). Morning stiffness (MS) may temporarily improve with active exercise and heat application (1).

MS is no longer included in classification criteria for RA, last published by the American College of Rheumatology (ARC) and the European Alliance of Associations for Rheumatology (EULAR) in 2010, but physicians still use it to help differentiate inflammatory arthritis from degenerative arthritis (6). There are conflicting reports of its association with disease activity, but there is evidence that MS is associated with local joint inflammation and elevated markers of systemic inflammation (7-9). It has an important impact on everyday activities and the well-being of patients with RA. It is the most common reason for early retirement of patients with RA (10). Previous studies showed that in the arthralgia preceding clinical arthritis, MS already reflects systemic and subclinical joint inflammation (11).

The aim of this study was to determine the significance of MS in patients with RA, especially its association with disease activity.

METHODS

Patients and study design

This observational study included 125 patients from the Public Institution "Health Care Center" Visoko. We collected data from the medical records of the patients with seropositive RA in the year 2022.

Methods

We obtained data on the following: patient's gender, age, duration of RA, pain in hands and feet, morning stiffness and its duration, hospital admission, systolic and diastolic blood pressure. We obtained data on laboratory values: erythrocyte sedimentation rate (ESR) in the 1st hour, ESR in the 2nd hour, white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets, fasting blood glucose, urea, creatinine, cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP). We collected data on the following treatment modalities: methotrexate, leflunomide, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs, protein pump inhibitors (PPIs), vitamin D, glucosamine chondroitin, pomegranate extract supplement, omega-3 fish oil, calcium, herbal gel.

Statistical Methods

Data analysis was performed using the SPSS Windows software package (version 25, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 2311 of Microsoft Corporation, Redmond, WA, USA). Mann-Whitney U test was used to assess differences in the duration of MS based on gender, hospital admission and treatment modalities. The effect size was small for r=0.10-0.29, moderate for r=0.30-0.49, large for r=0.5-1.0. To assess differences in the duration of MS based on laboratory values, patient's age, duration of illness and blood pressure, we used the Kruskal Wallis test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Basic patient information

Most patients were female, 91 (72.8%). There were 34 (27.2%) male patients. The mean age was 62.3±11.4 years (range 43-100 years). The mean duration of RA was 5.3±1.8 years (range 1-10 years).

Regarding symptoms, all patients reported pain in hands and feet and MS. MS lasted up to 30 minutes in 71 (56.8%) patients, 30 to 60 minutes in 40 (32%) patients, and more than 60 minutes in 14 (11.2%) patients. 124 (99.2%) patients had swollen joints. 44 (35.2%) patients were admitted to the hospital due to rheumatoid arthritis.

There was no difference in the duration of MS between genders (U=1514, z=-0.20, p=0.83, r=0.01). Patients with MS longer than 30 minutes were younger (Median (Mdn) of 67 years for patients with MS<30min vs Mdn of 55 years for patients with MS 30-60min), χ^2=30.39, p<0.001. Patients with longer MS had a longer duration of illness (χ^2=54.67, p<0.001).

Patients with MS > 30 min had higher systolic BP (Mdn=140mmHg) and diastolic BP (Mdn=90mmHg), χ^2=36.70, p<0.001 and χ^2=22.50, p<0.001, respectively.

Hospitalized patients had a longer duration of MS (U=1035, z=-4.36, p<0.001, r=0.38).

Laboratory values and duration of morning stiffness

Comparations of laboratory values based on the duration of MS are presented in Table 1. Patients with longer MS had higher ESR in the second hour (χ^2=7.73, p=0.02). Patients with MS> 30 min had higher CRP (Mdn=11 mg/L vs 9mg/L; χ^2=6.16, p=0.04) and higher cholesterol (Mdn=6 vs 5.5 mmol/L; χ^2=6.44, p=0.04).

Patients with MS > 60 min had higher urea blood nitrogen (Mdn=6.05 vs 5.65 mmol/L; χ^2=6.62, p=0.03). ALT was significantly higher in patients with MS 30-60 minutes compared to patients with shorter or longer duration of MS (Mdn=22 U/L vs 19 U/L), χ^2=6.57, p=0.03.

Table 1. Comparing laboratory values between patients based on duration of their morning stiffness.

	Mdn for patients with morning stiffness <30 min (n=71)	Mdn for patients with morning stiffness 30-60 min (n=40)	Mdn for patients with morning stiffness >60min (n=14)	χ^2	Df	P
ESR in the 1st hour	27 mm	30.5 mm	34.5 mm	4.30	2	0.11
ESR in the 2nd hour	55 mm	62 mm	70.5 mm	7.73	2	0.02
WBC count	7×10^{12}/L	7.05×10^{12}/L	5.95×10^{12}/L	3.71	2	0.15
RBC count	4.5×10^{12}/L	4.55×10^{12}/L	4.4×10^{12}/L	0.97	2	0.61
Hemoglobin	136 g/L	137 g/L	133.5 g/L	2.20	2	0.33
Hematocrit %	0.41 L/L	0.40 L/L	0.39 L/L	2.31	2	0.31
MCV	88.5 fL	88.8 fL	89.15 fL	1.77	2	0.41
MCH	29.8 pg	29.9 pg	29.8 pg	0.28	2	0.86
MCHC	336 g/L	340 g/L	341 g/L	0.63	2	0.72
Platelets	277×10^{9}/L	293×10^{9}/L	299×10^{9}/L	2.32	2	0.31
Fasting blood glucose	5.5mmol/L	6.05mmol/L	6.35mmol/L	2.98	2	0.22
Urea	5.4mmol/L	5.65mmol/L	6.05mmol/L	6.62	2	0.03
Creatinine	72 µmol/L	74.5µmol/L	73 µmol/L	0.33	2	0.84
Cholesterol	5.5mmol/L	6 mmol/L	6 mmol/L	6.44	2	0.04
Triglycerides	2.3mmol/L	2.85mmol/L	2.8mmol/L	1.90	2	0.38
AST	20 U/L	25 U/L	22 U/L	4.80	2	0.09
ALT	19 U/L	22 U/L	19 U/L	6.57	2	0.03
CRP	9 mg/L	11 mg/L	11.5 mg/L	6.16	2	0.04

Mdn-median; ESR-erythrocyte sedimentation rate; WBC-white blood cell; RBC-red blood cell; MCV-mean corpuscular volume; MCH-mean corpuscular hemoglobin; MCHC-mean corpuscular hemoglobin concentration; AST-aspartate aminotransferase; ALT-alanine aminotransferase; CRP- C-reactive proteine; χ2 Chi-Square; Df - Degree of freedom; p -level of significance.

Treatment and duration of morning stiffness

Patients on methotrexate had longer duration of MS (U=1449, z=-2.74, p=0.006, r=0.24). No significant differences in the duration of MS were observed for leflunomide, corticosteroids, and supportive pharmacological and non-pharmacological treatment (Table 2).

Table 2. Duration of morning stiffness based on treatment modalities.

	Mann-Whitney U	z	P	R
Methotrexate	1449	-2.74	0.006	0.24
Leflunomide	1421	-0.23	0.81	0.02
Corticosteroids	879	-0.31	0.75	0.02
NSAID	626	-0.93	0.35	0.08
Topical NSAID	1207	-1.22	0.22	0.10
PPI	787	-0.32	0.74	0.02
Vitamin D	1710	-0.30	0.75	0.02
GC	1075	-0.70	0.48	0.06
Pomegranate extract supplement	1065	-0.49	0.62	0.04
Omega-3 fish oil	607	-0.19	0.84	0.01
Calcium	1276	-0.31	0.75	0.02
Herbal gel	780	-0.38	0.69	0.03

NSAID-non-steroidal anti-inflammatory drug; PPI-proton pump inhibitor; GC-glucosamine chondroitin

DISCUSSION

Higher ESR and CRP were found in patients with longer duration of MS, which goes in favor that MS is correlated with RA disease activity. Correlation between ESR and MS was also confirmed in the QUEST-RA study (12).

As previously reported, we confirmed no significant difference in MS duration between genders (12, 13). Large QUEST-RA database suggested no correlation between MS duration and duration of illness, while we found longer MS in patients with a longer duration of RA. On the contrary, the Japanese study reported that MS duration was higher in patients with a shorter duration of illness (14). Patients in our study were not treated with the biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs); rather, they were treated with conventional DMARDs. Since evidence confirms that biologic DMARDs markedly improve MS, this could be one of the reasons why there is a higher burden of MS in patients with a longer duration of illness in our study (15). These drugs should be more accessible in Bosnia and Herzegovina to improve RA disease activity and symptom control (16).

We identified an inverse correlation between age and duration of MS, with younger patients having longer MS. Higher burden of MS in younger patients was previously reported (13). MS may be more noticeable in younger patients, as it may impact their daily activities more (13).

Previous reports suggest that patients with RA have higher average blood pressure compared to patients without RA, and our results indicated that patients with MS longer than 30 minutes have higher blood pressure, with its median in values diagnostic for hypertension (17, 18). Inflammation has its role in the pathogenesis of hypertension, including pro-inflammatory cytokines like TNF-α and IL-6, whose circadian elevation is also considered responsible for MS, which may explain this correlation (19). A similar concept can be applied to explain why patients with MS longer than 30 minutes had higher cholesterol levels, since cholesterol is linked to chronic inflammation (20). Patients with MS longer than 60 minutes had higher urea levels, and previous studies have shown that uremic toxins increase the levels of TNF-α and IL-6 and cause an exacerbation of the inflammatory state, but it should be noted that urea levels were still in the reference range in patients with longer MS duration in our study (21).

Since patients on methotrexate had a longer duration of MS, the question remains as to why methotrexate, being a standard of care for patients with RA, is not sufficient for symptom control and if other treatment modalities should be tried. One of the possible explanations may be poor patient compliance. CAPRA-1 and CAPRA-2 studies showed that the evening administration of modified-

release prednisone alleviates MS, by reducing the nocturnal levels of pro-inflammatory cytokines (22, 23). We did not confirm the difference in MS duration for patients on glucocorticoid treatment, however, our patients were prescribed standard methylprednisolone or prednisone to be taken in the morning.

It is difficult to alleviate stiffness with standard treatment, and usage of newer treatment options, such as biologic DMARDs, may be required. Reducing both systemic and local inflammation should be the focus.

Our study has several limitations. First, our sample size is small, and conducting more detailed research, especially randomized controlled studies, is necessary. It is not specified how long the patients were on a particular treatment before data collection, and whether they were taking treatment regularly. We did not report MS severity, which can be assessed using a numerical rating scale or the visual analogue scale (VAS). MS severity showed a stronger correlation with measures of disease activity than a duration of MS, although its assessment can be more subjective and it can overestimate the actual data (8, 24, 25). Also, we did not correlate the duration of MS with other patient-reported outcomes, such as physical function and pain. It was previously found that the duration of MS correlated better with functional disability than with ESR and swollen and tender joint counts (12, 26).

CONCLUSION

Duration of MS correlates with RA disease activity, systolic and diastolic blood pressure and cholesterol levels. Shorter MS duration was not associated with observed treatment modalities. MS in RA remains an important burden for patients, and its monitoring should be continued in clinical practice and research studies.

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