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BRIEF REPORT

Changes of patient-reported outcomes and protein fingerprint biomarkers after exercise therapy for axial spondyloarthritis

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Abstract The objective of this study was to investigate the patient-reported outcomes (PROs) and matrix metalloproteinase (MMP) derived extracellular matrix (ECM) biomarkers in non-radiographic (nr)-axial spondyloarthritis (axSpA) and radiographic (r)-axSpA after exercise intervention. Forty-six axSpA patients with stable disease and treatment underwent 24 weeks long exercise intervention. The clinical and laboratory assessments were performed at baseline and at follow-up. The PROs included evaluation of patient's global disease activity (PGDA), disease activity (DA7), pain (PAIN7) and fatigue during last week and quality of life questionnaires. ELISAs for MMP-degraded collagen type II, C-reactive protein (CRPM) and citrullinated vimentin were used. The data of 23 r-axSpA and 19 nr-axSpA were analysed. The PDGA was similar for nr-axSpA (35.2 ± 18.9) and r-axSpA (33.4 ± 22.3) at baseline, improved significantly after intervention ($p < 0.01$) and the change of PDGA was almost identical for nr-axSpA (− 10.0 ± 15.4) and r-axSpA (− 9.8 ± 11.9). Evaluations of DA7 and PAIN7 were significantly improved only in nr-axSpA (3.5 ± 2.3 and 34.7 ± 25.6 at baseline vs. 2.1 ± 1.9 and 21.0 ± 20.5, respectively, $p < 0.01$). The decline of DA7 and PAIN7 was more profound, but not significantly in nr-axSpA than in r-axSpA (− 1.4 ± 1.6 and − 13.7 ± 17.4 vs. − 0.5 ± 3.1 and − 3.7 ± 3.3, respectively). The quality of life was not changed. At baseline, increased levels of CRPM were found in r-axSpA (14.85 ± 4.10) compared to nr-axSpA (11.83 ± 3.20), $p < 0.05$, but all three biomarkers were not influenced by exercise therapy. We found that exercise therapy mainly in the nr-axSpA improves PROs, but not ECM turnover biomarkers. This indicates that exercise therapy is important for patients' health but does not affect ECM turnover.

Keywords axial spondyloarthritis · exercise therapy · extracellular matrix · matrix metalloproteinase

Introduction

Axial spondyloarthritis (axSpA) comprises two variants of the disease—radiographic axSpA (r-axSpA, or ankylosing spondylitis (AS)), characterised by modified New York criteria [1], and the non-radiographic (nr-axSpA) form, which has been suggested as the early stage of the disease [2]. Although not all nr-axSpA patients progress to the structural changes typical of r-axSpA, clinical features occur analogously in both cases [2, 3]. However, the long-term AS disease duration may result in impaired function and reduced quality of life [3–5]. Additionally, poorer outcomes of the Bath AS Functional Index (BASFI) have been found in AS individuals than in nr-axSpA [5, 6]. On the other hand, patient experiences with pain, stiffness and fatigue included in questionnaires of

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patient-reported outcomes (PROs) were similar for both axSpA forms [3–6]. The main goals of management for both axSpA subtypes are improvement in the disease activity and quality of life [7]. Exercise programmes are important treatment strategies [8], and beneficial effects of exercise therapy on disease activity and the lowering of biomarkers associated with severe disease has been documented [9, 10].

AxSpA is associated with changes in the extracellular matrix (ECM) of the affected tissues, and a successful treatment should halt and ultimately inhibit accelerated ECM turnover. Matrix metalloproteinase (MMP) mediated degradation of type II collagen (C2M), the main ECM protein in cartilage, has been shown to be elevated in AS [11, 12] to be modulated with biological treatment [13] and have diagnostic and prognostic capacities [12]. The disease activity in axSpA may be accompanied by the increased serum C-reactive protein (CRP) levels [10, 13], and tissue inflammation may be reflected by the MMP-degraded CRP (CRPM). Macrophages activation that could be assessed by citrullinated and MMP-degraded vimentin (VICM) has been found to be prognostic for radiographic progression [14]. This finding indicates that serological biomarkers of tissue turnover may be biomarkers of disease activity and effective treatment in axSpA. As disease activity and mobility were improved with exercise therapy, biomarkers of tissue turnover may be modulated by this intervention. However, how levels of the biomarkers C2M, CRPM and VICM are affected by exercise therapy is still unknown.

In this study, we investigated the PROs of axSpA patients who followed an exercise intervention. Moreover, we investigated whether the levels of selected ECM turnover markers (C2M, CRPM and VICM) were affected by the exercise programme.

Participants and methods

Nr-axSpA (n = 23) and r-axSpA (n = 23) patients characterised according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria [2] participated in a 6-month long intervention consisting of twice weekly group supervised physiotherapy [10]. The exercise unit consisted of three sections: warm-up with cardiorespiratory fitness, the main session focused on the practice of correct activation of deep core stabilisation and involvement muscles in motion, spinal traction and balance training, and cool-down with relaxation [10].

The inclusion criteria were stable disease and long-term therapy for at least 6 months prior to baseline and ability to attend exercise lessons. Main exclusion criteria were concomitant cardiac disorders, previous vertebral fractures and epilepsy. Participants missing two or more consecutive lessons and with medication changes were not included into final analysis.

All patients signed informed consent (approved by the Ethics Committee of the Institute of Rheumatology) and have all data and biomarkers analysed after study conclusion. Principles of Good Clinical Practice and the Declaration of Helsinki were reflected in this study.

Clinical analysis

Clinical data were obtained at baseline and at study conclusion. The PROs included morning stiffness (MS) (yes/no), duration of MS (minutes), patient's global disease activity (PGDA), evaluation of disease activity on the previous 7 days (DA7) (characterised by visual numeric scale (VNS) 0–10), experience with pain during the previous 7 days (PAIN7), experience of unusual fatigue during the previous 7 days (Fatigue7) and evaluation of the daily health status (DHS) (the latter three on VNS 0–100). The quality of life was assessed by the following: AS Quality of Life (ASQoL) and European Quality of Life (EuroQoL) questionnaires [15, 16]. The AS Disease Activity Score with CRP (ASDAS-CRP) was evaluated as well as the Bath AS Disease Activity Index (BASDAI) and BASFI [10].

Biomarker analysis

Biomarker ELISAs based on neoepitopes were used to quantify extracellular matrix turnover in serum. A neoepitope is an amino acid sequence that is specific to cleavage of a protein by a certain protease. We quantified C2M, CRPM and VICM. All these neoepitope ELISAs are based on monoclonal antibodies and are competitive ELISAs produced at Nordic Bioscience.

Statistical analysis

The variables are shown as the mean ± standard deviation. The Wilcoxon paired test and Mann-Whitney U tests were used for intra- and intergroup differences at baseline and after the exercise programme. Qualitative variables were tested using chi-square or Fisher's exact tests and correlation analyses by Spearman correlation. P values of < 0.05 were considered statistically significant. The SPSS (version 22) and GraphPad Prism 7 programmes were used for all analyses.

Results

Clinical data of axSpA patients

Data from 23 r-axSpA and 19 nr-axSpA patients were analysed and compared to the results of our previous work [10]; 1 nr-axSpA patient with current Crohn's disease and 1

r-axSpA patient with disease exacerbation were also included. The demographic data are in Table 1.

Similar to our previous study [10], we found a significant reduction of ASDAS-CRP in nr-axSpA after the exercise intervention (2.0 ± 0.8 at baseline to 1.7 ± 0.7 $p < 0.05$) and a trend towards ASDAS-CRP improvement in r-axSpA (2.2 ± 0.8 at baseline to 2.0 ± 0.7, $p = 0.05$). In both groups, the change (Δ) of ASDAS-CRP was not dependent on disease duration or smoking history and was not correlated with either the ASQoL or the EuroQoL (data not shown). Both the BASDAI and BASFI decreased after the intervention but not significantly (data not shown).

Patient-reported outcomes

Both axSpA groups reported significant improvement in the PGDA after the exercise intervention (both $p < 0.01$; Fig. 1). The ΔPGDA correlated significantly with ASDAS-CRP at baseline and at study end ($\rho = -0.53$ and $\rho = -0.47$, both $p < 0.05$, respectively) in r-axSpA (data not shown) and with ΔASDAS-CRP ($p = 0.02$) in nr-axSpA (Table 2). On the other hand, no correlations among ΔPGDA, smoking history, disease duration or ASQoL and EuroQoL were found in either group (data not shown).

In contrast to r-axSpA, patients with nr-axSpA demonstrated significant improvements in the DA7 and PAIN7 (both $p < 0.01$, Fig. 1). The ΔPAIN7 correlated significantly with ΔDA7 in r-axSpA ($\rho = 0.93$, $p < 0.01$) and nr-axSpA ($\rho = 0.81$, $p < 0.01$) and with ΔPGDA in both r-axSpA and nr-axSpA groups ($\rho = 0.51$ and $\rho = 0.50$, both $p < 0.05$; data not shown). The improvement of PAIN7 and DA7 correlated significantly with ΔBASFI, ΔBASDAI and ΔASDAS-CRP in both axSpA forms ($p < 0.01$), see Table 2. The evaluation of the DHS improved only in the nr-axSpA patients ($p < 0.05$, Fig. 1), not in the r-axSpA counterparts.

The experiences with fatigue and the evaluations of quality of life (ASQoL and EuroQoL) were improved but not significantly in either axSpA group after the exercise programme (Suppl. 1 A, B, C). However, ΔASQoL significantly correlated with the improvement in PAIN7 in r-axSpA ($p < 0.05$), Table 2. The experiences with MS were similar at baseline in r-axSpA and nr-axSpA (91.3 and 73.7%, respectively), and were not changed after the intervention, r-axSpA (86.9%) and nr-axSpA (78.9%) (data not shown). Duration of MS was not affected by the intervention (Suppl. 1 D).

Furthermore, in all axSpA, we analysed whether the changes in the PROs after the intervention were influenced by the regular vs. on-demand therapy by non-steroidal antirheumatic drugs (NSAIDs), or the therapy by disease-modifying drugs (DMARDs)—both biologic (bDMARDs) and synthetic (sDMARDs). Only ΔDA7 was more pronounced in axSpA with regular NSAIDs and ΔPGDA in axSpA without DMARDs (Suppl. 1E). However, the limited number of patients in each group may affect these findings, and the subanalysis results of each axSpA subgroup did not show any significant differences (data not shown).

Biomarker study

Only the levels of CRPM were significantly higher in patients with r-axSpA compared to nr-axSpA at baseline and after the intervention (both $p < 0.05$, Fig. 2). The exercise intervention

Table 1 Clinical characteristics of axSpA patients with completed exercise intervention at baseline

Age	r-axSpA ($n = 23$)	nr-axSpA ($n = 19$)	p
	36.4 ± 5.9	35.7 ± 9.2	ns
Gender (female/male)	4/19	9/10	0.05
Disease duration since first symptoms (years)	12.9 ± 6.7	6.3 ± 8.4	< 0.001
Disease duration since diagnosis (years)	6.2 ± 6.5	1.5 ± 2.3	< 0.001
HLA B27 positivity (%)	91.3	89.5	ns
Extra-articular manifestation (%)[a]	26.1	47.4	ns
Therapy—NSAIDs (daily use/on demand) (%)	100 (21.8/78.2)	100 (36.8/63.2)	ns
Therapy—sulfasalazine/bDMARDs (TNFi) (%)	4.3/8.7	15.8/5.3	ns, ns
ASDAS-CRP	2.2 ± 0.8	2.0 ± 0.8	ns
BASDAI	2.7 ± 1.7	2.9 ± 2.2	ns
BASFI	1.0 ± 0.9	1.2 ± 1.1	ns

Statistical analysis—p value was calculated between r-axSpA and nr-axSpA groups using either the Mann-Whitney test or chi-square/Fisher's exact test. Data are characterised as the mean ± standard deviation

Abbreviations: *r-axSpA* radiographic axSpA, *nr-axSpA* non-radiographic axSpA, *NSAIDs* non-steroidal antirheumatic drugs, *ns* not significant, *p p* value (statistical significance), *bDMARDs* biological disease-modifying drugs, *TNFi* tumour necrosis factor alpha inhibitors, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score-C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index

[a] Only uveitis and Crohn's disease were manifested

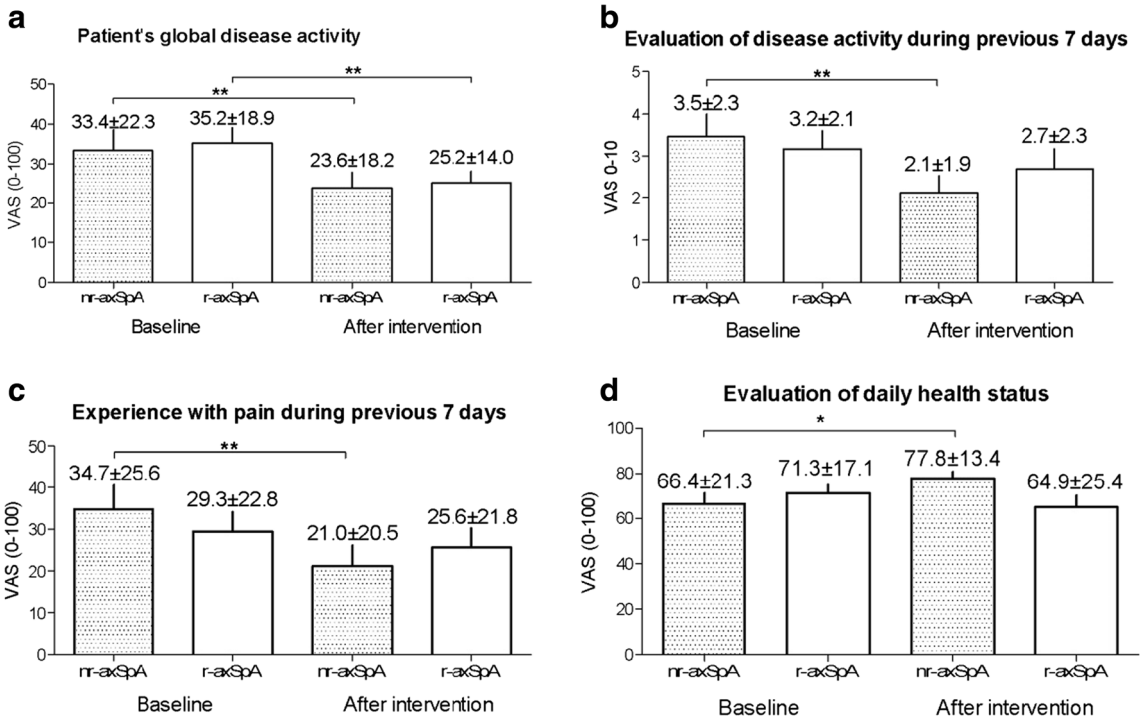

Fig. 1 The improvement of patient-reported outcomes after the exercise intervention. Explanation—on the top of bars are data characterised as the mean ± standard deviation, only significant differences are marked, the ** means $p < 0.01$, *$p < 0.05$. Statistical analysis—p value was calculated for r-axSpA and nr-axSpA groups between baseline and after intervention using the Wilcoxon matched pairs test. The Mann-Whitney unpaired test was used for calculating intergroup differences at baseline. r-axSpA radiographic axial spondyloarthritis, nr-axSpA non-radiographic axial spondyloarthritis, VAS visual analogue scale

did not influence the levels of any of the three biomarkers (Fig. 2 and Suppl. 1E). At baseline, we found no relationship of VICM, CRPM and C2M with disease duration, medication, disease activity (ASDAS-CRP, BASDAI and BASFI), all tested PROs or quality of life questionnaires (data not shown). However, in the nr-axSpA group, ΔVICM was correlated with ΔPGDA ($\rho = 0.52$, $p < 0.05$), (Table 2). In r-axSpA, on the other hand, ΔCRPM was negatively correlated with ΔPGDA ($\rho = -0.49$, $p < 0.05$) and ΔVICM with ΔBASFI, ΔDA7 and ΔASQoL ($\rho = -0.49$, $\rho = -0.46$, both $p < 0.05$ and $\rho = -0.64$ $p < 0.01$, respectively) (Table 2).

Discussion

Our study demonstrates reduction of the patient's global disease activity in both axSpA forms, whereas improvement in disease activity, pain and daily health status were found only in the non-radiographic patients after the exercise intervention.

With respect to the chronic course of axSpA, complex therapeutic programmes should be required for the best possible clinical outcomes. The optimal strategy of exercise therapy should maintain the patient's motivation for adherence [8, 17]. Our findings of the positive effect of exercise on disease activity and PROs such as of pain, disease activity and daily health status support the suitability for the early initiation of exercise therapy, particularly in nr-axSpA. Similarly to Karapolat et al., we did not notice the significant improvement of BASFI after the exercise programme [9], but our data suggest that exercise therapy is beneficial in axSpA patients with regular NSAIDs therapy. The positive synergistic effect on disease activity and quality of life in axSpA patients treated with bDMARDs together with physiotherapy has been suggested [18, 19], but our study could not confirm this superiority, because of the small number of patients treated with DMARDs included. The outcomes of our study may be biased by the following limitations: Firstly, this is a single-centre study, and the results, may be affected by the limited number of participants, particularly the subanalysis targeted on some patient characteristics. Furthermore, no control group without exercise and PROs evaluation was included. However, in r-axSpA, after the exercise therapy, the improvement of disease activity, quality of life and mobility was found [9, 10, 20, 21], even compared to controls without exercise [10, 22]. Next, all axSpA patients had better clinical outcomes (such as ASDAS-CRP and BASFI) at baseline than those usually found in axSpA cohorts [6, 23], so the improvement after the intervention may not be noticeable. It is necessary to keep in mind that the study group consisted of only patients who were able to attend such a time-dependent and intensive exercise programme. Further studies to evaluate the exercise benefits for

Table 2 The relationship between the change of the clinical and biomarker variables in r-axSpA and nr-axSpA due to exercise intervention

			ΔVICM	ΔCRPM	ΔC2M	ΔBASDAI	ΔASDAS	ΔBASFI	ΔASQoL	ΔEuroQoL
ΔBASDAI	r-axSpA	ρ	− 0.37	− 0.22	− 0.35					
	nr-axSpA	ρ	0.01	− 0.10	− 0.24					
ΔASDAS	r-axSpA	ρ	− 0.06	− 0.28	− 0.06	0.58**				
	nr-axSpA	ρ	0.25	0.22	− 0.11	0.77**				
ΔBASFI	r-axSpA	ρ	− 0.49*	− 0.41	− 0.59**	0.34	0.26			
	nr-axSpA	ρ	0.13	0.13	0.05	0.32	0.55*			
ΔASQoL	r-axSpA	ρ	− 0.64**	0.06	− 0.31	0.35	0.21	0.19		
	nr-axSpA	ρ	0.25	0.18	0.04	− 0.05	0.23	0.31		
ΔEuroQoL	r-axSpA	ρ	0.13	− 0.19	− 0.01	− 0.05	− 0.13	− 0.29	0.12	
	nr-axSpA	ρ	− 0.07	− 0.13	− 0.12	− 0.43	− 0.21	0.13	0.08	
ΔPatient's global disease activity	r-axSpA	ρ	0.04	− 0.49*	− 0.18	0.36	0.31	0.35	− 0.07	− 0.02
	nr-axSpA	ρ	0.52*	0.17	0.15	0.44	0.53*	0.09	0.05	− 0.16
ΔEvaluation of disease activity in previous 7 days	r-axSpA	ρ	− 0.46*	− 0.26	− 0.53*	0.79**	0.68**	0.53**	0.35	− 0.30
	nr-axSpA	ρ	0.11	0.02	− 0.19	0.65**	0.78**	0.48*	0.29	− 0.12
ΔExperience with pain in previous 7 days	r-axSpA	ρ	− 0.41	− 0.04	− 0.47*	0.73**	0.60**	0.36	0.42*	− 0.19
	nr-axSpA	ρ	0.09	0.16	− 0.14	0.63**	0.82**	0.54*	0.29	− 0.05
ΔExperience with unusual fatigue in previous 7 days	r-axSpA	ρ	− 0.29	− 0.09	− 0.22	0.53**	0.25	0.17	0.37	0.25
	nr-axSpA	ρ	0.21	0.13	0.15	0.40	0.46*	0.55*	0.15	− 0.13

Statistical analysis—the Spearman correlation coefficient (ρ) was used for relation analyses

Abbreviations: *r-axSpA* radiographic axial spondyloarthritis, *nr-axSpA* non-radiographic axial spondyloarthritis, *VICM* citrullinated and metalloproteinase-degraded vimentin, *CRPM* metalloproteinase-degraded C-reactive protein, *C2M* metalloproteinase-degraded collagen type 2, *ASDAS-CRP* Ankylosing Spondylitis Disease Activity Score-C-reactive protein, *BASDAI* Bath Ankylosing Spondylitis disease activity index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *ASQoL* Ankylosing Spondylitis Quality of Life, *EuroQoL* European Quality of life, Δ changes of the score/biomarker values

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)

patients with severely impaired function and higher disease activity are essential. The final limitation involves the absence of psychological questionnaires, because personal characteristics may influence the comprehension of quality of life [24].

Although research found that therapy of bDMARDs modulates serological MMP-derived ECM biomarker to significantly lower levels after only 2 weeks [13], we found no connection between their levels and the decline in disease activity caused by exercise intervention in our study. However, CRPM levels were higher in r-axSpA than nr-axSpA although both groups had the same disease activity; this likely reflects severe local inflammation in the radiographic variant. We previously confirmed the increased serum CRP levels in r-axSpA compared to nr-axSpA [6, 10, 23] and found reduction in serum calprotectin but not pro-inflammatory cytokines, IL-6 and TNF-α, by exercise therapy

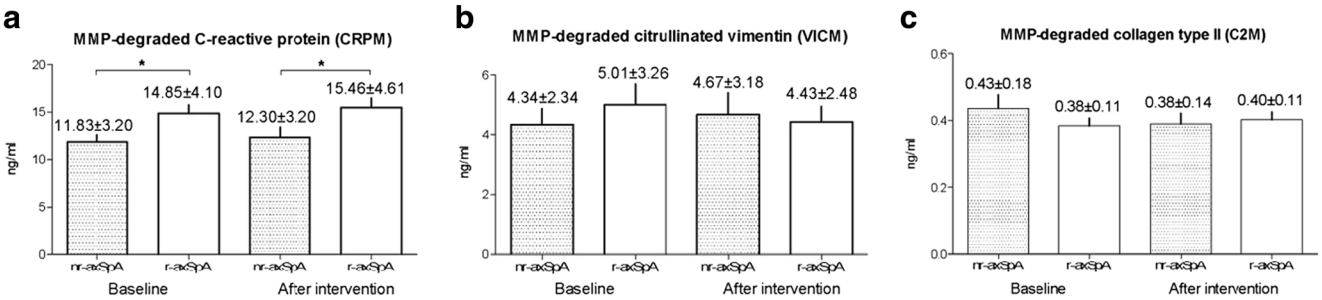

Fig. 2 The biomarkers of the extracellular matrix turnover at baseline and after the exercise intervention. Explanation—on the top of bars are data characterised as the mean ± standard deviation, only significant differences are marked, the * means $p < 0.05$. Statistical analysis—*p* value was calculated for r-axSpA and nr-axSpA groups between baseline and after intervention using the Wilcoxon matched pairs test. The Mann-Whitney unpaired test was used for calculating intergroup differences at baseline and after the intervention. r-axSpA radiographic axial spondyloarthritis, nr-axSpA non-radiographic axial spondyloarthritis

[10]. Cytokines IL-6 and TNF-α may induce protease secretion, and they are in the cascade that produces the serological biomarkers investigated in the current study. Thus, by not inhibiting these cytokines, inhibition of protease-derived ECM fragments is not present. Physical activity is a complex process with immune, metabolic and endocrine consequences [25], thus investigation into the exact relationships among exercise therapy, long-term axSpA outcomes and biomarkers associated with disease progression are needed.

In conclusion, we found that exercise therapy improved the subjective evaluation of disease activity and pain mainly in the nr-axSpA group and should be recommended as a therapeutic option. The ECM turnover biomarkers were not influenced by exercise intervention. This finding indicates that exercise therapy is important for patient health but does not affect ECM turnover.

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Compliance with ethical standards All patients signed informed consent (approved by the Ethics Committee of the Institute of Rheumatology) and have all data and biomarkers analysed after study conclusion. Principles of Good Clinical Practice and the Declaration of Helsinki were reflected in this study.

Disclosures None.

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