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SYSTEMATIC REVIEW

The impact of physical activity on serum levels of inflammatory markers in rheumatoid arthritis: a systematic literature review

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Abstract

This review aims to determine the specific effects of PA on systemic levels of interleukins and inflammatory markers. A systematic literature search was conducted in three computerized bibliographic databases (Medline, Embase, CENTRAL) to identify randomized controlled trials and matched case studies. Applied key words were: RA and PA including the terms exercise, exercise therapy, gymnastics and exercise movement techniques. Inclusion criteria were data on all types of pro-inflammatory interleukins (IL), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). For data synthesis, the populations, interventions and outcomes were described according to the PRISMA statement. A total of 1289 publications were found. Fifteen papers, related to 14 different study populations, met the inclusion criteria. No study revealed a significant change regarding IL or CRP levels in response to the intervention (PA). In three study populations, a significant reduction of the ESR was identified, but the effect from PA was not discernible from effects of changes of the anti-rheumatic medication in these studies. The strong variability in study designs, cohort size and types of physical training programs remains an obstacle in the assessment of the measurable effects of PA on inflammatory markers in patients with RA. At present, there is no sufficient evidence to conclude that PA has a significant impact on systemic levels of inflammatory markers in RA.

Keywords Physical activity · Rheumatoid arthritis · Disease activity · Aerobic · Strength · Immunological parameters · Inflammation

All authors certify they not have signed any agreement with a commercial interest related to this study which would in any way limit publication of any and all data generated for the study or to delay publication for any reason.

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Introduction

Physical activity (PA) has been established as an essential part of a multimodal therapeutic approach in the treatment of patients with rheumatoid arthritis (RA) [1–3]. Preserving joint function and maintaining muscle strength are principal goals of PA. Concerns about potentially increasing pain and exacerbated disease activity (DA), traditionally have been reasons to avoid high levels of PA in RA [4]. Specifically, dynamic exercises with high intensity to induce muscle growth and to increase physical fitness were suspected to cause joint damage. Exercises that set comparatively little stress on the joint, like range of motion and non-weight-bearing exercises were preferred. However, clinical studies have proven that more intense dynamic exercise is actually safe for patients with RA [3]. Today, the EULAR recommends PA as part of a general concept to optimize health-related quality of life. It fosters cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance [5, 6]. According to a systematic literature review, PA leads to pain relief, distraction from pain [7], improvement in joint

function and increased energy, and has not only physiological benefits but also positive effects on the mental state [8]. Despite the vast literature about the effects of PA on RA, there is no systematic review about the effects of PA on serum levels of inflammatory parameters in RA. Only few studies have addressed inflammatory markers as primary or secondary endpoints. These study results appear to be very heterogeneous and sample sizes within each study were generally small. Therefore, the aim of this review was to answer the question if PA has a lowering effect on the serum levels of inflammatory markers in patients with RA, which would further corroborate the concept that PA has potent anti-inflammatory effects, hence a reduction of rheumatic medication could be indicated as a result of PA. Furthermore, a proven positive effect of PA on immunological parameters would also suggest that patients with RA should undergo regular blood analyses for inflammatory markers to control the actual load of the body.

Materials and methods

Three computerized bibliographical databases were screened: Medline (National Library of Medicine), Embase (Elsevier Science Publishers) and CENTRAL (Cochrane Collaboration). In the EMBASE search, all Medline journals were excluded in advance. The keywords "rheumatoid arthritis", "physical activity", "exercise", "exercise therapy", "gymnastic" and "exercise movement techniques" were each searched as medical subject heading and in all fields combined with Boole's logical operators ("AND" or "OR"). The search was restricted to primary studies in English and German published until November 2016.

Eligibility criteria

Randomized controlled trials (RCT) and matched case studies reporting data on the immunological effects of physical activity in patients with RA over 18 years of age were included. To assess the quality of the included studies, only published articles were included in this review, while abstracts and conference proceedings were not taken into account. No limitations on type or timespan of activity intervention were applied. Pre-defined inclusion criteria were data on systemic levels of interleukins (IL), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). As part of a sensitive search strategy, no restriction was initially made to certain proinflammatory cytokines. Studies that did not provide any information about these common clinical rheumatoid immunological parameters, generated by taking blood samples, were excluded.

Study selection and data collection process

Two reviewers (RDB, AS) independently assessed each title and abstract to tag potentially relevant articles that met the inclusion criteria. If the title and abstract did not include adequate information to decide on the relevance to the systematic review, the full articles were read. Potentially relevant articles were scrutinized based on their full texts regarding inclusion and exclusion criteria. In case of disagreement between the reviewers, arguments were discussed, until agreement was reached. To ensure complete capture of all relevant studies, all articles from the bibliography of the selected studies were cross-referenced. All studies were graded by two reviewers according to the Cochrane Collaboration's tool for assessing risk of bias assessing the quality of RCTs [9] and the Newcastle–Ottawa Scale, assessing the quality of observational studies [10] Papers meeting the pre-defined inclusion criteria were coded using a data extraction sheet. Data extraction included study design, sample characteristics, sample size, type and characteristics of physical activity intervention, time of intervention, primary outcomes and immunological outcome parameter. This review is reported within the PRISMA guidelines (supplementary Table 1).

Results

A total of 901 studies were found in Medline, 235 in the CENTRAL and further 153 in EMBASE. The search strategy resulted in a list of 1289 paper titles. Removal of all duplicates lead to 1150 paper titles. Processing this list of titles and abstracts according to the inclusion and exclusion procedure yielded 62 potentially relevant papers, which resulted in 15 articles, related to 14 different study populations that met the inclusion criteria (Fig. 1). Two studies [11, 12] worked with the same study population. These two studies used a matched case design, whereas the remaining thirteen were prospective randomized controlled trials (RCT). The specific characteristics of the included trials are described in Table 1. In total, 766 patients with RA (range 8–220 per study) were included in this systematic review. Descriptive characteristics of the patients as well as details regarding the underlying methodology, type of PA and the relevant results are shown in Table 1.

In accordance with the study design of most publications, blinding the participants was not possible in any of the included studies. In seven study populations [11–17], the measurements were accomplished by blinded assessors. All papers included at least one control group (CG)

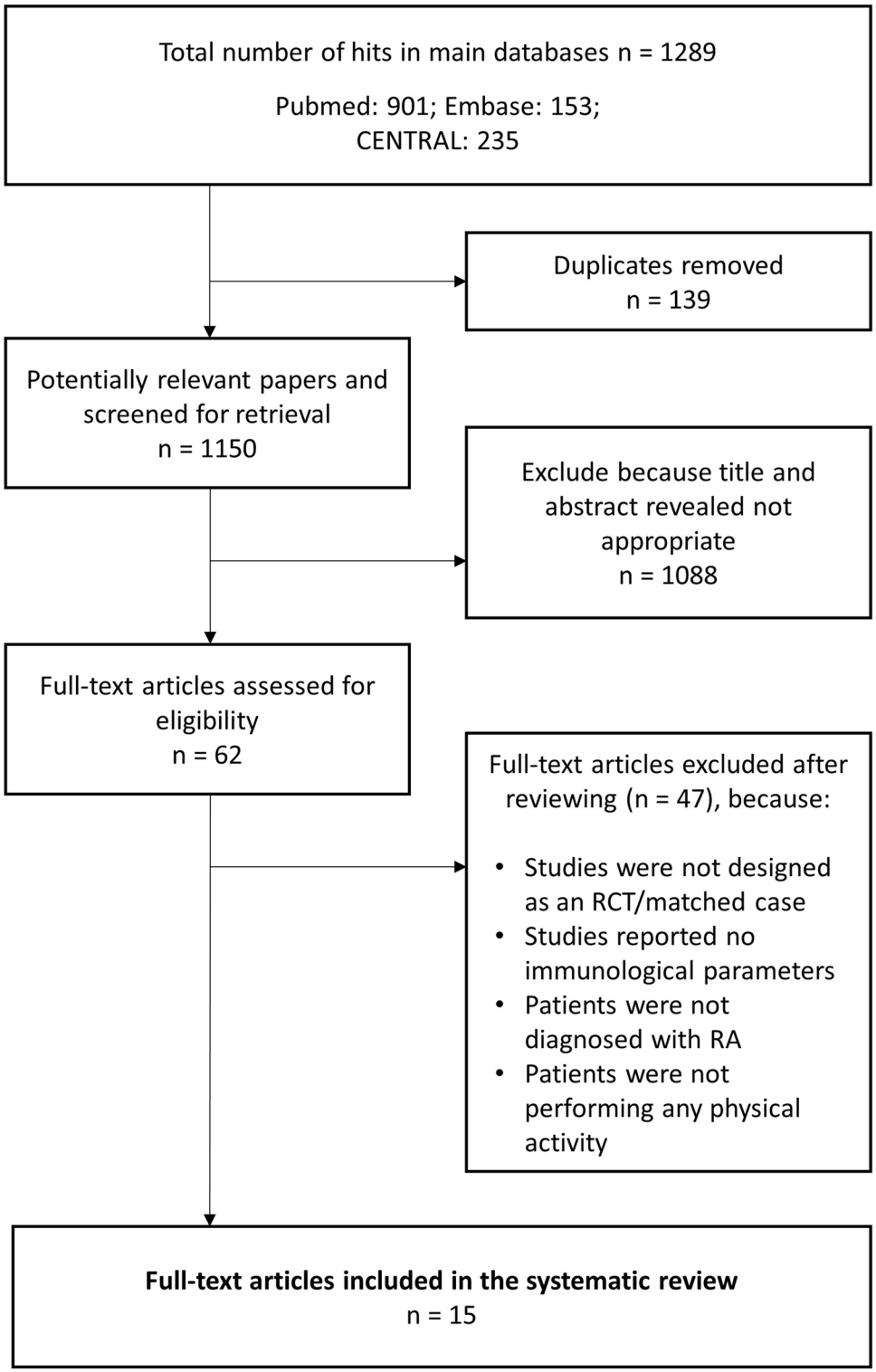

Fig. 1 PRISMA flow diagram of study selection

with varying characteristics. In most of the studies, the CG consisted of a randomized subgroup of RA patients participating not in any kind of intensive exercise program but rather in a PA program with minor intensity. Two studies included CG with healthy subjects performing the same exercise program [14, 18] (Table 1). Sandstad et al. designed their study in a cross-over design, in which participants function as their own CG [19]. For randomization, five RCTs used stratification systems as the modified method of minimization [4, 15, 16, 20, 21]. The other eight

Table 1 Data extraction including study design and characteristics, aim and reported outcomes

Author/year/location	RCT/group nr.	No. of patients/controls	RA participants age (Ø)	PA intervention type	Intervention description	Time of intervention	Primary outcomes	Immunological outcomes	Significance in primary outcomes	Significance in immunological outcomes
Aerobic exercises										
Baslund et al. 1993 Denmark	RCT	9:9	48	Aerobic	Progressive bicycle training under supervision vs. control	8 weeks 4–5 ×/week	Immune parameters (blood mononuclear cells, natural killer cells, cytokines, clinical chemistry)	Immune parameters (CRP, ESR, IL)	No	No
Melikoglu et al. 2006 Turkey	RCT (2 groups and healthy control)	19:17:14	48.4	Aerobic	Dynamic exercise (treadmill) vs. ROM exercise. vs. healthy control with dynamic exercise	2 weeks 5 ×/week for 20 min (individually supervised)	IGF-1, IGFBP-3	Disease activity (CRP, ESR)	Partially	No
Metsios et al. 2014 UK	Matched case design	18:18	53.9	Aerobic	Individualized resistance and aerobic exercise training intervention vs. advices about benefits of PA	6 months 3 ×/week for 60 min	Endothelial function, HAQ	Disease activity (CRP, ESR)	Yes	Yes: disease activity (DAS28) reduced significantly, but CRP did not significantly reduce. ESR-specific data not available
Stavropoulos-Kalinoglou et al. 2013 UK	Matched case design	18:18	53,9	Aerobic	Individualized resistance and aerobic exercise training intervention vs. advice about benefits of PA	6 months 3 ×/week for 60 min	Aerobic capacity (VO_2 max) cardiovascular risk factors, HAQ	Disease activity (CRP, ESR)	Yes	Yes: disease activity (DAS28) reduced significantly, but CRP did not significantly reduce ESR-specific data not available
Sandstad et al. 2015 Norway	Cross-over	12	33 (approx)	Aerobic	Spinning bicycle	35 min 2 ×/week	CVD risk factors	Disease activity (DAS28, CRP)	Yes	Trend towards lower CRP

Table 1 (continued)

Author/year/location	RCT/group nr.	No. of patients/controls	RA participants age (Ø)	PA intervention type	Intervention description	Time of intervention	Primary outcomes	Immunological outcomes	Significance in primary outcomes	Significance in immunological outcomes
Wadley et al. 2014 UK	Partial - "RCT"[a] (3 groups)	12:7	56	Aerobic	Moderate-intensity aerobic exercise	3 months 3×/week for 30–40 min	Markers of oxidative stress	Disease activity (DAS28), CRP, IL-8	Partially	Yes:disease activity (DAS28) reduced significantly, but ESR-specific data not available No change in CRP and IL-8
Strength exercises										
Lemmey et al. 2009 UK	RCT (2 groups)	13:15	58.1	Strength	High-intensity progressive resistance training supervised in a gym vs. ROM exercises at home	24 weeks 2×/week	Body composition, physical function	Disease activity (ESR)	Yes	No
Rall et al. 1996 USA	Partial - "RCT"[a] (4 groups)	8:8:8:6	41.8	Strength	RA strength training vs. healthy young strength training vs. elderly strength training vs. elderly control	12 weeks 2×/week	Immune response parameter	Immune response parameter	No	No
Combination of aerobic and strength exercises										
Ekdahl et al. 1990 Sweden	RCT	56 (in four groups)	NA	Combined	Dynamic exercise vs. static and stretching exercise	6 weeks	Muscle strength, function and endurance, aerobic capacity	Disease activity (CRP, ESR)	Yes	No

Table 1 (continued)

Author/year/location	RCT/group nr.	No. of patients/controls	RA participants age (Ø)	PA intervention type	Intervention description	Time of intervention	Primary outcomes	Immunological outcomes	Significance in primary outcomes	Significance in immunological outcomes
Häkkinen et al. 1994 Finland	RCT (2 groups)	21:18	43.2	Combined	Progressive dynamic strength training vs. maintain habitual physical activity	6 months 2-3 ×/week and 2 ×/week walking/swimming	Muscle strength (RI, HAQ)	Disease activity (ESR)	Yes	Yes: disease activity improved significantly (ESR reduced), but no information given about stable medication
Häkkinen et al. 2001 Finland	RCT (2 groups)	31:31	49	Combined	Dynamic strength exercise vs. ROM and stretching exercise	24 months 2 ×/week 45 min and 2 ×/week 45 min walking/swimming	Muscle strength, bone mineral density, physical function, joint damage, HAQ	Disease activity (ESR)	Yes	Yes: disease activity improved significantly (ESR reduced), but anti-rheumatic medication was being initiated
Neuberger et al. 2007 USA	RCT (3 groups)	68:79:73	55.5 (8.0 years with RA)	Combined	Low-impact aerobic exercise program at a gym vs. at home with videotape vs. control	12 weeks 3 ×/week for 60 min	Fatigue, pain, depression functional and diseases activity, aerobic fitness (grip strength and walking time)	Disease activity (CRP, ESR)	Yes	No
Seneca et al. 2015 Denmark	RCT (2 groups)	36	NA	Combined	Progressive high-intensity exercise program	30 min bicycle, 30 min strengthening 2 ×/week	Muscle strength physical fitness, pain, functional ability	Disease activity (DAS28-CRP)	Partially	Yes: disease activity (DAS28-CRP) reduced significantly CRP-specific data not available
van den Ende et al. 2000 Netherland	RCT (2 groups)	20:28	60 (8 years with RA)	Combined	Intensive strength vs. conservative exercise program and exercise on their own	24 weeks 5 ×/week and 3 ×/week bicycling	Pain, physical function	Disease activity (ESR)	Yes	Yes: disease activity improved significantly (ESR reduced)

Table 1 (continued)

Author/year/location	RCT/group nr.	No. of patients/controls	RA participants age (Ø)	PA intervention type	Intervention description	Time of intervention	Primary outcomes	Immunological outcomes	Significance in primary outcomes	Significance in immunological outcomes
van den Ende et al. 1996 Netherland	RCT (4 groups)	25:25:25:25	52 (10 years with RA)	Combined	High-intensity strength vs. low-intensity group vs. low-intensity individual vs. home exercise	12 weeks 3×/week 60 min	Physical condition, muscle strength, joint mobility daily function (HAQ)	Disease activity (CRP, ESR)	Yes	No

NA not available, *CRP* C-reactive protein, *CVD* cardiovascular disease, *DAS28* Disease Activity Score, *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *IGF 1* insulin-like growth factor 1, *IGFBP-3* insulin-like-growth factor-binding protein-3, *IL* interleukin, *PA* physical activity, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *RI* Richie's articular index, *ROM* range of motion, VO_2 *max* maximal oxygen capacity

[a]Partial "RCT": RCT with multiple groups of which only some have been randomized

papers did not address if a modified method of minimization was applied [3, 13, 14, 17–19, 22, 23]. Four of them negate significant differences between the groups at baseline [3, 13, 14, 18].

Study quality assessment

Supplementary Table 2 describes the Cochrane risk of bias assessment. All RCT articles were coded for risk of bias. Randomization was performed according to Cochrane criteria in all 13 (100%) RCTs. The description of allocation concealment was ensured in none of the cases. No risk assessment could be carried out. The blinding of participants was assured in two RCTs (15.4%). These two cases use only a single-blinding strategy for blinding the physical activity trainers carrying out the exercises. Also, the blinding of the outcomes assessment was only assured in two (15.4%) RCTs. The risk of incomplete data was low in ten (77%) RCTs. For all publications, the reporting bias cannot be conclusively assessed. The three coded other high-risk biases are based on the administration of anti-inflammatory drugs during the RCT, as a result of which valid statements about the effect of PA cannot be made precisely. Supplementary Table 3 describes the outcome of the Newcastle–Ottawa Scale for two included case–control studies. Both studies reach 7 out of 9 possible quality points to be achieved.

Aerobic exercises

Baslund et al. [4] studied 18 patients with RA and stable medication for at least 6 months. The intervention group (IG) performed aerobic exercises under supervision on a bicycle ergometer four to five times a week for 8 weeks. The CG did not train but continued with their routine daily activities. According to the authors, no significant differences were recorded in response to the aerobic exercise program between groups regarding CRP (mean change: IG + 27 vs. CG − 67 nmol/l) and ESR (mean change: IG + 1 vs. CG − 3 lU/min). Furthermore, in the IG, the plasma concentration of IL-1α (+ 84 pg/ml), IL-1β (− 7 pg/ml) and IL-6 (+ 366 pg/ml) presented no statistical significant changes.

Melikoglu et al. [14] included 36 patients with RA and 14 healthy controls. Patients displayed ACR criteria functional status class I or II with clinically inactive disease and stable medication for 3 months. The patients were randomly assigned to either a 2-week dynamic exercise training group (treadmill) ($n = 19$) or to a ROM training group ($n = 17$). The healthy CG performed dynamic exercise training on a treadmill for 2 weeks as well. Regarding their results, IGF-1 increased in the dynamic exercise group (+ 99.3 ng/ml; $p < 0.001$), while it decreased significantly in the ROM group (− 89.1 ng/ml; $p < 0.05$). They did not find

significant changes for IGFBP-3 (+264.5 ng/ml; n.s.), ESR (+1.1 mm/h; n.s.) or CRP (±0.0; n.s.).

The papers from Metsios et al. [11] and Stavropoulos-Kalinoglou et al. [12] analyzed the same study population. They included 36 patients with RA, no joint surgery in the preceding 6 months, stable DA and stable medication. The patients were matched either to an exercise program (IG) or just received a leaflet about benefits of exercise (CG). The exercise group trained 6 months three times a week for 60 min in a semi-supervised fashion individualized resistance and aerobic exercise training intervention (treadmill, bicycle, rowing, or arm ergometer). They found significant improvements in the IG for VO_2 max, blood pressure, triglycerides, HDL ratio, BMI, body fat, 10-year cardiovascular disease event probability, DAS28 (mean change: −0.8; $p<0.05$) and HAQ (mean change: −0.5; $p<0.001$) after 6 months. CRP did not reduce significantly in the exercise group after 6 months. However, the authors report a significant difference between the IG and the CG regarding CRP (mean change: IG+1.0 vs. CG+4.0; $p=0.042$) 6 months from baseline [12]. Metsios et al. [11] repeated these calculations with log-transformed nonparametric variables and replicate the significant group differences for log CRP ($p=0.047$). The authors state a significant improvement in DA and disease severity without providing specific data of ESR.

Sandstad et al. [19] performed a cross-over study in which both study groups switched after a 2 months washing-out period. They included patients with RA and juvenile idiopathic arthritis (JIA) with stable medication. The IG received a supervised 35 min exercise on a spinning bicycle twice a week. The CG received no intervention over the same period of time. Authors report no change in DA and pain. Nevertheless, they state a non-significant trend towards a decreased CRP in the IG (median change: −0.75 mg/l; $p=0.08$). No changes for other biomarkers were found. Regarding their results, high-intensity interval training has no negative effect on pain or DA but a positive effect on several CVD risk factors.

Wadley et al. [23] investigated the effect of a 3 month moderate-intensity aerobic exercise three times a week for about 30–40 min to reduce markers of oxidative stress and inflammation. Their investigation included an acute bout of exercise in an untrained group of 12 patients with RA on stable medication (IG). Seven patients, who received advice about potential benefits of PA served as CG. Training was performed either using a treadmill, bicycle, hand or rowing ergometer. The aerobic exercises did not increase markers of oxidative stress in RA patients. 3-Nitrotyrosine and DA (DAS28: −0.6; $p<0.05$) were decreased following exercise training. No alteration was found for IL-8 (mean change: IG −0.4 vs. CG+0.5 pg/ml; n.s.) or CRP (mean change: IG −4.3 vs. CG+2 mg/l; n.s.) in either the IG or the CG, also no significant difference between the two groups was detected.

Strength exercises

Lemmey et al. [21] performed a RCT with 28 patients with RA and stable medication for at least 3 months. Included patients were randomized either to a 24-week supervised high-intensity progressive resistance group training twice a week (PRT) ($n=13$) or a low-intensity ROM exercise group ($n=15$) at home. Optimized for the induction of muscle hypertrophy, three sets of eight repetitions with a load corresponding to 80% of the first cycle maximum load with less than 2 min rest between sets were performed with multistack machine exercises. No significant changes were found in DA (mean change DAS28: −0.2; n.s.) or ESR (mean change: −0.5 mm/h; n.s.) within the IG group or between the IG and CG (mean change DAS28: IG −0.2 vs. CG+0.3; $p=0.471$/ESR: IG −0.5 vs. CG+5.9 mm/h; $p=0.285$).

Rall et al. [18] studied eight patients with RA, good disease control and stable medication for 3 months, who performed a 12-week progressive resistance strength training. As CG, they used 8 healthy young (22–30 years), and 14 healthy elderly (65–80 years) individuals (8 with a training program and 6 non-training controls; randomly assigned). The training program comprised progressive resistance strength training of all major muscle groups, twice a week. Patients trained at 80% of their one-repetition maximum, on five different machines for the trunk (abdominal and back extension), upper body (chest press), and lower body (leg press and leg extension) strength. There were no significant differences in unstimulated IL-6 (mean change: ±0.0 ng/ml; n.s.), concanavalin A-stimulated IL-6 (mean change: ±0.0 ng/ml; n.s.), phytohemagglutinin-stimulated IL-2 (mean change: +7.4 kU/l; n.s.) and concanavalin A-stimulated IL-2 (mean change: +0.4 kU/l; n.s.) within the RA exercise group [18].

Combination of aerobic and strength exercises

Ekdahl et al. [13] studied 67 patients with RA in a RCT. Patients were randomly assigned into four groups; two dynamic and two static exercise 6-week training groups. In the dynamic group, different exercises were applied, e.g., jumping on a mat, ergometer cycling, dynamic exercises against body weight and home exercises such as walking or rubber band training. The static exercise consisted mainly of ROM training exercises. Twenty-one patients received steroid injections or changes in their anti-rheumatic medication during the study period. These patients were partially excluded from the statistic calculations. A significant improvement of muscle strength, function, endurance and aerobic capacity was found for the dynamic groups in

comparison to the static groups. No significant alterations in DA represented by ESR and CRP were detectable between these two groups.

Neuberger et al. [15] performed a RCT with three different training groups comprising a total of 220 patients with RA. The study was divided into an exercise group in a gym (GTG) or at home (HTG) and a no-exercise CG. The three times a week 60 min 12-week exercise program consisted of four parts: warm up, low impact (one foot always on the ground), aerobic exercise (no running or jumping exercises), strengthening and cool down. The GTG and HTG showed positive effects regarding walk time and grip strength. Overall symptoms for fatigue, pain, and depression were positively influenced. The aerobic fitness levels were enhanced in all three groups (GTG + 12%/HTG + 10%/CG + 7%). In contrast, neither ESR (mean change GTG: − 0.5 mm/h; n.s. vs. HTG: − 1.8 mm/h; n.s.) nor CRP (mean change GTG: − 0.2 mg/dl; n.s. vs. HTG: − 0.4 mg/dl; n.s.) changed significantly.

Häkkinen et al. [22] published an RCT including two groups of patients: recent onset RA and psoriatic arthritis. Thirty-nine patients with recent onset RA were included. A 6-month strengthening exercise program (two or three times a week) was combined with additional aerobic exercises (swimming, walking) twice a week. The training was individually tailored to fit each patient's physical capacity. The CG maintained their habitual activities. Significant improvements in muscle strength and a significant reduction of the ESR (mean change − 11.6 mm/h; $p < 0.05$) were found in the IG.

A further study by Häkkinen et al. [20] included only patients with recent onset RA who have not had any antirheumatic medication. Medication was initiated only with the beginning of the investigation. They included 62 patients who were divided into an IG and a CG. The IG received an individually adapted strengthening exercises (two or three times per week) combined with additional aerobic exercises twice a week. The study period was 24 months. In contrast, the CG performed range of motion and stretching exercises twice a week. Significant improvements in muscle strength and a significant reduction of the ESR were reported. They found significant differences between the IG and the CG for ESR (mean change IG − 16 vs. CG − 9.3; $p < 0.001$ at 18 month) and DAS28 (mean change IG − 2.4 vs. CG − 1.9; $p < 0.05$) until the third follow-up 18 months after baseline. At the time of measurement 24 months after launching the exercise intervention, no significant differences for DAS28 and ESR were calculable.

Seneca et al. [17] evaluated 36 patients with early RA less than 5 years from diagnosis aiming to analyze the differential effects of a partly supervised vs. a self-administered exercise program. Patients were randomly assigned into either a 6-week supervised, progressive, high-intensity exercise program followed by a further 6-week self-administrated exercise program (IG) or a 12-week just self-administrated exercise program (CG). Randomization was stratified according to age and gender. Treating physiotherapists were blinded to group allocation. The exercise program consisted of 30 min on an exercise bike and 30 min strength circle training. The exercises were the same for both groups (partly supervised vs. self-administrated). As expected, both groups showed increase in muscle strength and physical fitness, without difference between the two groups. DAS-CRP, however, showed a significant difference between the groups. The partly supervised group showed a significantly higher reduction in DAS-CRP than the self-administrated group (mean change IG − 0.58 vs. CG + 0.06; $p = 0.006$).

Van den Ende et al. [3] examined 100 patients with RA, stable medication and a low to moderate disease activity, which were randomly assigned to four different study groups. The four exercise groups were defined as a high-intensity exercise group program, a low-intensity exercise group program, an individually supervised low-intensity exercise program and a group who receive written instructions for home exercises only. The high-intensity exercise group trained 12 weeks, three times a week for 60 min. After a warm up, an interval program of 12 exercises in standard fashion was performed, followed by a 20 min bicycling program and closing with cooling down exercises. The interval training consisted of dynamic weight-bearing exercises for different muscle groups. Exercises were performed at a high pace. The program was adjusted every 4 weeks with higher exercise load. Cycling was performed with 70–85% of age-predicted maximum heart rate. The authors found a significant increase in aerobic capacity and joint mobility in the high-intensive exercise group compared to the remaining three groups. The DA represented by ESR remained nearly unchanged. No significant differences between and within the four groups (high-intensity exercise program: + 2 mm/h; n.s./low-intensity group exercise program: − 5 mm/h; n.s./low-intensity exercise program: + 7 mm/h; n.s./home exercise program: − 6 mm/h; n.s.) were reported.

In a further study, van den Ende et al. [16] studied 48 patients with RA, divided into an intensive exercise group (IG) or a conservative exercise program (CG), each for 24 weeks. All patients receive a usual conservative exercise program of ROM exercises and isometric exercises. In the IG, the program was supplemented with an individual intensive exercise program. This program consisted of knee and shoulder dynamic and isometric muscle strengthening exercises against resistance five times a week and conditioning bicycle training three times a week. Both groups were supervised by physical therapists. Muscle strength and functional ability improved significantly in the IG compared to the CG. DAS28 (mean change − 1.4) and ESR (mean change − 22 mm/h) improved, but differences between the groups

did not reach statistical significance. However, the number of swollen joints and ESR (mean change − 22 mm/h, $p < 0.05$) significantly decreased in the dynamic group after 24 weeks.

Discussion

The aim of this investigation was to provide a systematic review about the impact of physical activity on serum levels of inflammatory markers in rheumatoid arthritis. PA has distinct positive effects on metabolism and health and fosters the cardiorespiratory fitness, muscle strength, flexibility and neuromotor performance. Regarding the impact of physical activity on serum levels of inflammatory markers in RA, three studies report a significant reduction of the ESR in conjunction with the investigation of disease activity [16, 20, 22]. Two studies implied a significant improvement in disease activity without providing specific data on ESR [11, 12]. Seneca et al. [17] state a significant reduction in DAS-CRP but did not address the values of CRP itself, making their results for this review of limited value. None of the other studies could show a reliable change of the CRP within the IG in course of PA. Two of the included studies [4, 18] directly use an immunological parameter as the primary outcome, but do not report any significant results either. Accordingly, Baslund et al. [4] conclude that conditioning exercise training had no effect on immunocompetent cells in the blood of patients with RA. Some studies, reporting positive trends for changing immunological parameters with PA, do not achieve any significance. Van den Ende [16] speculates that a reduction of joint inflammation in course of PA might be explained by increased joint stabilization through improved muscle function.

In consideration of all included studies, it is suggested that on average PA has no effect on CRP, ESR and IL, and does neither increase nor decrease systematic inflammation in patients with RA. To ensure high study quality, only matched case studies and RCTs were utilized in this review. Nevertheless, the analysis showed a high heterogeneity for CRP between the included studies. Large differences in effect sizes or confidence intervals indicate systematic differences between studies. This restricts the reliability of the pooled overall result [24]. Therefore, the significance of the pooled studies concerning the change of CRP cannot be reliably interpreted.

The vast literature on effects of PA in RA reveals a distinct heterogeneity in the details of the employed exercises. Caspersen published a paper defining PA, exercise and physical fitness. He states that PA is "any bodily movement produced by skeletal muscles that results in energy expenditure" occurring while sleeping at work or at leisure. In this regard, exercise is a subset from PA, however, containing a planned, structured and repetitive character with the objective to improve or maintain physical fitness. Physical fitness is defined as "a set of attributes that are either health or skill related" [25]. In response to this, Tierney et al. [26] emphasizes the importance to research PA in its entirety and not exercise as single component. Therefore, the mix of different type of sports (aerobic/strength) in our analysis has been conceptually accomplished. The aim was not to evaluate the effect of individual types of exercise, but rather the global effect of physical activity on proinflammatory parameters.

Furthermore, it cannot be ruled out that some positive changes in immunological parameters were not caused by PA but by change in medication. One study [20] investigating disease activity included patients who did not take any anti-rheumatic drugs. The anti-rheumatic medication was initiated at the beginning of the study, making it impossible to discuss the impact of PA on immunological parameters. Even van den Ende et al. [3] produces this kind of bias by allowing 5 out of 100 patients to change their anti-rheumatic medication during the study. In their further study [16], all patients received a modulation of their anti-rheumatic medication. At least they conclude that the decline in disease activity is most likely related to the intensification of the medical treatment. Ekdahl states that 21 of his patients received either steroid injections or a modulation of their anti-rheumatic medication [13]. Later, he excluded these patients from statistical calculations. However, his depictions are not clearly documented. Sandstad et al. [19] included only patients with stable medication, however, changes in cortisone up to 5 mg were allowed, which would be enough to create a significant change of CRP values. The paper by Rall et al. [18] proposed an interesting study design by trying to elucidate the effects of PA on in vivo and in vitro immune parameters. However, the number of eight included subjects seems in regard of the expected measurable parameters, too small to achieve results with a level of significance. In addition, two of their patients (25%) changed their anti-rheumatic medication during the study period creating a substantial bias in their results. When changes were made, this was mainly to ensure painless physical activity for the patients. The American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis from 2015 recommends medication therapy for all patients with rheumatoid arthritis [27]. In context of meaningful clinical research, it is therefore necessary to work with this patient population. Medication and medication changes are common in the everyday life of patients. Overall, in all studies that initiated a change in medication, a relevant bias regarding the examined parameters cannot be rejected.

Further, no conclusions can be made about the effect of PA in elderly patients. The average age of the RA participants was between 33 and 60 years. Based on this systematic review and the current study situation, no statements can be

made about the suitability of PA in old age or the effects of PA for the elderly. At least, Häkkinen et al. [22] emphasize that individually tailored dynamic muscle strength training had no negative effects on disease activity or structural joint damage. In the majority of the included studies, the disease activity (DAS28), pain and swollen joints are reduced and muscle strength, physical fitness, and functional ability increased (see Table 1). In contrast, serum markers cannot be used to measure the benefits of PA on RA. Although it is likely that there is a positive measurable effect, and accordingly trends can be observed, currently available evidence is insufficient to support that conclusion.

Strength and limitations

Several limitations of this review should not be left unrecognized. First, the search was limited to studies published in German or English. Second, most studies did not include immunological parameters of inflammation as primary endpoints in the study design. Third, the differences in type of exercise, intensity of training, time frame of the intervention (8 weeks up to 2 years), patient demographics, number of cases ($N = 18$ to $N = 220$), and inclusion–exclusion criteria varied considerably between studies, creating limited comparability. In addition to type and intensity of physical activity performed, the disease duration itself can also influence the review results. It can be assumed that diseases that have existed for years are more difficult to influence. Unfortunately, only 2 of the 15 studies included provide information about the duration of the disease. Moreover, there may still be unpublished research results, which could not be covered by the literature research, as only the published articles were included in this systematic review. A further limitation can be seen in the incomplete documentation of medication during the study periods. Anti-rheumatic medical therapy was initiated at the beginning of the study [20] in some, but medication was changed during the intervention period in others [3, 13, 19]. The strengths of this review is its systematic and comprehensive literature search of a clinically relevant topic that has not been addressed this way before. The number of scientific papers found shows that so far there have been only a few sufficient studies on this topic.

Conclusion

Current studies show that PA has a major influence on physical and mental functioning. PA is recommended by the EULAR as an important element in the treatment of rheumatic diseases. This supplementary review reveals that up to date there is no clear evidence to support a measurable independent effect of PA on the systemic concentration of inflammatory markers in patients with RA. Prospective randomized trials with serum inflammatory markers as primary endpoints will have to be performed to find out whether the trends observed in available studies actually reflect a clinically meaningful beneficial effect of physical activity on inflammatory markers in the serum of patients with RA.

Author contributions RDB and AS conceived and designed the systematic review. RDB, AS and MAK performed the review. RDB and AS selected and analyzed the included studies. RDB, AS, MAK, WR and AN wrote, critically reviewed and revised the manuscript.

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Compliance with ethical standards

Conflict of interest Rolf-Dieter Burghardt, Murteza Ali Kazim, Wolfgang Rüther, Andreas Niemeier and André Strahl declares that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants and/or animals performed by any of the authors.

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