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EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION IN AUTOIMMUNE RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

EFFECTS OF PHYSICAL ACTIVITY ON VASCULAR FUNCTION IN AUTOIMMUNE RHEUMATIC DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT:

Objectives: To summarise existing evidence and quantify the effects of physical activity on vascular function and structure in autoimmune rheumatic diseases (ARDs). **Methods:** Databases were searched (up to March 2020) for clinical trials evaluating the effects of physical activity interventions on markers of micro- and macrovascular function and macrovascular structure in ARDs. Studies were combined using random-effects meta-analysis, which was conducted using the Hedge's g. Meta-analyses were performed on each of the following outcomes: (1) microvascular function (i.e., skin blood flow or responses to acetylcholine [ACh] or sodium nitropusside [SNP] administration); (2) macrovascular function (i.e., brachial flow-mediated dilation [FMD%] or brachial responses to glyceryl trinitrate [GTN%]; and (3) macrovascular structure (i.e., aortic pulse wave velocity [PWV]). **Results:** Ten studies (11 trials), with a total of 355 participants, were included in this review. Physical activity promoted significant improvements in micro- (skin blood flow responses to ACh [g = 0.92; 0.42 to 1.42]) and macrovascular function (FMD% [g = 0.94; 0.56 to 1.02]; GTN% [g = 0.53; 0.09 to 0.98]). Conversely, there was no evidence for beneficial effects of physical activity on macrovascular structure (PWV [g = -0.41; -1.13 to 0.32]). **Conclusions:** Overall, the available clinical trials demonstrated a beneficial effect of physical activity on markers of micro- and macrovascular function, but not on macrovascular structure, in patients with ARDs. The broad beneficial impact of physical activity across the vasculature identified in this review support its role as an effective non-pharmacological management strategy for patients with ARD.

Keywords: flow-mediated dilation, skin blood flow, rheumatoid arthritis, inflammatory diseases

Key messages:

- Changes in vascular homeostasis are integral to the cardiovascular pathophysiology in autoimmune rheumatic diseases (ARDs);
- This review demonstrates the benefits of physical activity on micro- and macrovascular function in ARDs;
- The available evidence supports the role of physical activity as vascular medicine for ARDs.

INTRODUCTION

Autoimmune rheumatic diseases (ARDs) are a group of diseases caused by immune dysregulation and characterised by local and chronic inflammation, deterioration of joint tissues, systemic manifestations and increased multimorbidity leading to reduced life expectancy (1). ARDs include conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SJ), systemic sclerosis (SSc), spondyloarthritis (SpA; which includes psoriatic arthritis [PsA], ankylosing spondylitis [AS]), systemic autoimmune myopathies (SAM) and systemic vasculitis (SV). Collectively, these diseases affect over 7% of the World's population (2), and usually appear in mid-life, mostly in women (~ 78 vs. 22%) (3).

Cardiovascular disease (CVD) represents the leading cause of mortality in many ARDs (4, 5). For instance, patients with RA present a 2-fold increased risk of myocardial infarction (6) when compared with healthy individuals (7). Similar estimates have been reported in patients with SLE (5), PsA (8) and SSc (9). The increased cardiovascular burden in ARDs is partly attributed to the presence of traditional cardiovascular risk factors (e.g., hypertension, insulin resistance) (10) but, importantly, also by the direct effects of inflammation upon the vasculature (11-13), leading to changes in vascular properties that precede the development of atherosclerosis (11).

ARD patients present with accelerated atherosclerosis and have a more unstable plaque profile, with increased prevalence of rupture-prone plaques (14, 15). The endothelium plays a major role in the regulation of vascular wall homeostasis (16) and endothelial dysfunction in micro- and macrocirculation is regarded as an early marker for atherosclerosis in many disease states, including ARDs (11, 12, 17). This process is aggravated by systemic and vascular inflammation, hallmarks of many ARDs, which interacts with intracellular regulatory processes promoting smooth muscle cell proliferation and arterial wall thickening (11). These maladaptive vascular processes are paralleled by impairment in the elastic properties of large arteries, with increase in stiffness in the central arteries (18). Consequently, measures of micro- and macrovascular endothelial function and macrovascular structure have been used as surrogate markers of cardiovascular risk in individuals with ARDs (19).

Changes in vascular function and structure play a central role in the pathophysiology of CVDs in ARDs and underscore the importance of therapeutics that can beneficially affect vascular health in ARDs. Physical activity (PA) has been recognised for some time as an important non-pharmacological therapeutic with beneficial effects on vascular function and structure (20). In

ARDs, PA has been linked with reduced disease activity (21), inflammation (22) and pain (23), and with improved cardiovascular risk profile (21, 24). Specific to the vasculature, cross-sectional studies have demonstrated improved vascular function in physically active compared with physically inactive ARD patients (25, 26). However, available clinical trials examining the effects of PA on vascular health in ARDs have elicited equivocal findings (27-29), which may be partially explained by small sample sizes and thus reduced statistical power. Additionally, the effects of PA on the vasculature may vary according to the vascular bed, with previous evidence demonstrating that physical activity may differentially impact the micro- and macrovasculature (30, 31), as well as vascular function and structure (32, 33). Finally, the magnitude of the improvement on vascular parameters promoted by PA in ARDs remains unclear. As even slight improvements in markers of endothelial function are associated with substantial reduction in the risk of cardiovascular events (34, 35), a better understanding of the effects of PA on vascular function and structure in ARDs may yield important clinical information to be used in the management of CVD in ARDs.

Resultantly, we conducted this systematic review and meta-analysis to summarise the existing evidence and to quantify the effects of PA on micro- and macrovascular function and macrovascular structure in ARDs. As a secondary outcome, we have also described the characteristics of existing PA programmes for this population and reviewed data on adherence to PA, and potential side effects.

METHODS

Registration

This systematic review with meta-analysis was reported according to the PRISMA statement and is registered in the PROSPERO database (CRD42020196023).

Search strategy and study selection

Searches were performed on 5 databases (PubMed, Web of Science, EMBASE, Cochrane Library and Scopus) by entering key words related to population, intervention and outcome (Supplementary Table S1). Searches were limited to peer-reviewed articles in English, published from the inception of each database up until March 2020.

For inclusion, studies were required to fulfill the following criteria: (1) randomised controlled trials (RCTs), non-RCTs or uncontrolled trials (UCT; pre vs. post only) with an

experimental condition that included a PA intervention; (2) interventions should have lasted ≥2 weeks, and should have been performed ≥1x week; (3) conducted on adults (≥18 years) with a diagnosis of SLE, RA, SpA, SJ, SSc, AS, SAM or SV; (4) included assessments of at least 1 of the following; brachial or lower-limb flow-mediated dilation (FMD%), or brachial responses to glyceryl trinitrate (GTN%), pulse wave velocity (PWV), cutaneous blood flow reactivity to pharmacologic, mechanical or local heat stimuli. Studies were excluded if they were protocol studies, observational studies, acute exercise studies, studies with physiotherapy interventions (e.g., joint manipulation, kinesio taping) or studies involving pediatric rheumatic diseases.

On completion of the searches, 2 members of the study team (TP and DL) independently selected the studies to be included based on the title, abstract and full text of each potential manuscript. Discrepancies were identified and solved through discussion with a third author (TS).

Data extraction

Two members of the study team (TP and SMS) independently extracted study data using a purpose developed data extraction sheet, after which a mutual consensus was reached. Discrepancies were identified and solved through discussion. Missing data were requested by contacting the corresponding authors of specific studies. The following characteristics were extracted from each selected study: (1) author (data); (2) study design; (3) participant information; (4) characteristics of the intervention; (5) outcome data.

Assessment of the risk of bias

Quality was appraised using the Cochrane risk-of-bias tool (RoB-2) (36), by two members of the study team (DB and TP). This tool considers bias arising from 5 domain (randomization process, deviations from the intended interventions, missing outcomes, measurement of the outcome and selection of reported results) and an overall bias analysis. The risk of bias of each domain and the overall risk were judged as “high”, “low” or “some concerns”. All studies were analysed with this tool, even non-RCTs and UCTs, assuming that they would already be at high risk due to their design.

Data analysis: Systematic Review

A narrative synthesis was performed to describe the data from the studies. Studies were described in the text and tables and were organized by key details, such as study design, summary of the population, intervention, comparison, and outcomes (divided by micro- and macrovascular function, and macrovascular structure). In addition, we reported data on participants' adherence to the interventions (i.e., the degree of compliance to the exercise sessions), and on the safety of the interventions (i.e., the occurrence of any health-related complications as a result of the intervention, such as disease relapses, acute flare-ups, cardiovascular complications, *etc*).

Data analysis: Meta-Analysis

Following data extraction, weighting, and missing data imputation, a meta-analysis was performed on each of the following outcomes: (1) microvascular function (i.e., skin blood flow or vascular conductance responses to acetylcholine [ACh] or sodium nitropusside [SNP] administration); (2) macrovascular function (i.e., FMD% or GTN%); (3) macrovascular structure (i.e., PWV). The UCTs were not included in the meta-analyses, but were qualitatively described along with the manuscript.

The effects of PA interventions on each vascular outcome were calculated as the standardized mean differences (SMD). The SMDs were estimated as the difference between the intervention and control group pre-post changes, divided by the pooled standard deviation for the changes. For microvascular function, we only used the post values due to the lack of available data to calculate pre-to-post changes. Studies were combined using random-effects meta-analysis, which was conducted using the Hedge's g (37). Cohens standard threshold values of 0.2, 0.5, 0.8 were used to describe effect sizes (based on the SMDs) as small, moderate and large, with values between 0 and 0.2 described as trivial (38). In addition, in order to infer the clinical relevance of PA on FMD%, we also calculated the absolute changes in FMD% as the mean difference (MD) between the intervention and control groups pre-post changes. To estimate the between-study variance we used restricted maximum-likelihood estimator (39). Meta-analyses were performed in RStudio version 4.02, with the 'metacont' function of the meta package.

RESULTS

Literature search

A total of 577 published articles were identified through independent searches in all the five databases. Following removal of duplicates (*n*=237), 340 publications were screened for inclusion. Of these, 322 records were excluded after reviewing the title and/or abstract. The remaining 18 papers were selected for full text reading and 8 were excluded for either not presenting any vascular outcome (*n*=7) or by not including PA as a major component of the intervention (*n*=1). Ultimately, 10 studies (11 trials) were included in the review and are listed in the qualitative analysis. Among these, 8 studies (9 trials) were suitable for inclusion in the meta-analysis, however we were unable to obtain relevant data from 2 studies (40, 41) (i.e., data were presented as median ± interquartile interval, and authors did not respond to emails soliciting original data or did not provide the required data). Therefore, 6 studies (7 trials) were included in the meta-analysis (Figure 1).

A general description of each study is detailed in Table 1. Among the 10 included studies, 3 were RCTs, 5 were non-RCTs and 2 were UCTs. These studies enrolled 355 middle-aged to older participants, with a large majority of women (88% *vs*. 12%). The included studies were conducted in participants with limited cutaneous SSc (lcSSC), axial SpA, SLE, RA and SAM.

Risk of bias

Nine studies presented a ‘high risk’ of bias and one study presented ‘some concerns’ considering the overall judgement (Figure 2A). Most of the methodological issues arose from the ‘randomisation process’ (7 out of 10 were not RCTs) or from ‘bias due to deviation from intended interventions’ (with most of the studies using ‘per-protocol’ analyses and/or presenting >5% drop out rates). The remaining domains were judged with ‘some concerns’ or ‘low risk of bias’ (Figure 2B).

Characteristics of the physical activity/exercise interventions

Most PA interventions lasted between 12-16 weeks and sessions were performed 2-3 days/week for 30-80 min/session (Table 1). All studies included a structured exercise programme and one study also employed a web- and pedometer-based PA programme (42). Exercise workouts comprised a mix of exercise types including high-intensity interval training (HIIT), moderate-intensity interval training (MIIT), moderate-intensity continuous training (MICT), resistance training (RT) and Tai-Chi. Aerobic exercise modalities included arm cranking, cycling, rowing,

swimming, and walking/running on a treadmill or in a public park. Aerobic exercise intensities ranged from low- (e.g., 35-60% of heart rate reserve) to high-intensity (e.g., 100% of maximal power output). RT sessions were composed of 4-10 whole-body exercises at 50-80% of 1 repetition maximum (Table 1). Interventions were either fully (6 out of 10) or partially (4 out of 10) supervised, and were conducted in different settings such as a hospital gyms (27, 40, 43-45), fitness/exercise centres (28, 29, 41), at home (40, 45), or in public gyms (42) or parks (46).

Effects of physical activity on vascular function

Microvascular function

Microvascular function was assessed in 4 studies (5 trials) via the evaluation of the responses of forearm skin blood flow or vascular conductance to ACh (endothelium-dependent) or SNP (endothelium-independent) iontophoresis (Table 1). Metsios *et al.* (40) reported increases in the skin blood flow response to ACh and SNP after 24 weeks of combined MIIT and RT in RA patients. In this same population, 12 weeks of MIIT promoted an increase in skin blood flow responses to SNP, but not to ACh (45). In patients with lcSSc, Mitropoulos et al (29) reported increased maximal forearm cutaneous vascular conductance in response to ACh after 12 weeks of upper-limb HIIT, however no benefits were observed after lower limb HIIT. Neither upper- or lower-limb training were able to improve microvascular responses to SNP. A latter study from the same group (28) observed that 12 weeks of combined HIIT and RT increased maximal forearm cutaneous vascular conductance in response to SNP, but not to ACh (Supplementary Table S2).

Overall, the meta-analysis revealed a large significant improvement in microvascular function responses to ACh in the PA group compared with the control group (Figure 3; [g=0.92; IC95%, 0.42 to 1.42]). On the other hand, no significant differences were found between PA and control groups in the microvascular responses to SNP (Figure 3; [g=1.62; IC95%, -0.27 to 3.51]).

Macrovascular function

Macrovascular function was assessed in 5 studies (5 trials) through the evaluation of FMD% (endothelium-dependent) and in 3 studies (3 trials) using the GTN% (endothelium independent) (Table 1). Van Zanten *et al*. (45) and Metsios *et al.* (40) reported increases in both FMD% and GTN% after 12 weeks of MIIT and 24 weeks of combined MIIT and RT, respectively, in RA patients. A study employing 1 day/week of Tai-Chi for 12 weeks also verified an increase

in FMD% in RA patients (44). Reis-Neto (46) observed increase in FMD% and no changes in GTN% after 16 weeks of moderate-intensity walking in a public park in patients with SLE. On the other hand, Misse *et al*. (43) did not observe increase in FMD% after 12 weeks of combined aerobic and RT in patients with SAM (Supplementary Table S2).

Overall, the meta-analysis revealed a large significant increase in FMD% (Figure 4 [g = 0.94; IC95%, 0.56 to 1.32]) and a moderate increase in GTN% (Figure 4 [g = 0.53; IC95%, 0.09 to 0.98]) favoring the intervention group. On average, FMD% increased 5.07% after the PA interventions (1.26 to 8.88) (Supplementary Figure S1).

Macrovascular structure

Macrovascular structure was assessed in 5 studies (5 trials) via the quantification of arterial stiffness by carotid-femoral PWV (cfPWV), aortic PWV, and augmentation index (AIx). Additionally, one study also included the assessment of carotid intima-media thickness (cIMT) as a measure of macrovascular structure (Table 1). The majority of studies (3 out of 5) did not observe changes in any marker of macrovascular structure following completion of a PA intervention in ARDs (27, 42, 43). On the other hand, Sveaas *et al*. (41) reported a decrease in arterial stiffness (AIx and cfPWV) after 12 weeks of combined HIIT or MICT and RT in patients with axial SpA, and Shin *et al*. (44) reported a reduction in cfPWV after 12 weeks of Tai-Chi in RA patients (Supplementary Table S2).

Overall, the meta-analysis revealed no significant effects of PA on PWV (Figure 5 [g = -0.41; IC95%, -1.13 to 0.32]).

Adherence and safety

Adherence to the PA sessions was >85% in 4 studies (27, 29, 40, 43). Sveeas *et al.* (41) reported that all participants in the intervention group attended the minimum requirement of ≥80% of the sessions, and Reis-Neto (46) did not report exclusion of any participants based on the minimum allowed attendance which was set at 75% of the PA sessions. Four studies did not report data on adherence to the PA interventions (28, 42, 44, 45).

Five studies reported no adverse effects related to the PA interventions (27-29, 41, 43). In one study (40), one participant was discontinued from the intervention due to arrhythmia, but it is

not clear if this was related to the intervention. Four studies did not report data on the safety of the PA interventions (42, 44-46).

Group mean disease activity measured using disease-specific tools was reported to be unchanged by the PA intervention in 4 studies (42, 44-46) and to be reduced in 2 (40, 41). Individual data on disease activity was reported by two studies only (41, 43). In one of them (41), 2 participants (out of 10) had a slight increase in their disease activity, while the others either decreased or did not change their disease activity. Four studies did not report data on the effects of the interventions on disease activity (27-29).

DISCUSSION

Our systematic review and meta-analysis summarised the evidence on the effectiveness of PA on vascular function and structure in ARDs. Although limited by the reduced number and low quality of the studies, data reviewed herein demonstrated a beneficial effect of PA on micro- and macrovascular function in ARDs. However, results from available studies observed no effect of PA on macrovascular structure. Furthermore, where this is reported, evidence suggests that PA is safe and well adhered by individuals with ARDs.

The results of the present review support the notion that PA may counter vascular impairment observed in ARDs (17, 47). More specifically, PA interventions were effective in improving micro- and macrovascular function, with clearer and larger effects observed on endothelium-dependent (FMD% and skin blood flow responses to Ach) as opposed to endothelium-independent (GTN% and skin blood flow responses to SNP) function. This information corroborates previous studies demonstrating that vascular adaptations promoted by PA are largely mediated by its direct effects on the endothelium rather than on smooth muscle vasodilator function (48, 49). Beneficial effects of PA on the endothelium are a consequence of repeated hemodynamic stimulation (e.g., shear stress and transmural pressure), which favors the production of nitric oxide and vascular relaxation (20). As for the clinical impact of these findings, PA yielded a ~5% increase in FMD% (Figure S1), which may be seen as clinically relevant, as there is an associated reduction in 12-13% in the risk of cardiovascular events for every 1% increase in FMD% (34, 35). Additionally, previous reviews indicated that patients with ARDs present 1-3% reduced FMD% compared to controls (17, 47); therefore, the present review indicates that PA may reverse the endothelial dysfunction observed in these patients. The effects

of PA on endothelial function are comparable with the effects of biologic modifying anti-rheumatic drugs (50) and statins (51), and superior to the use of non-steroidal anti-inflammatory drugs (52) and glucocorticoids (53), in ARDs.

The improvements in both macro- and microvascular endothelial function highlight the broad effects of PA across the vasculature in this population. These data prove relevant, as a recent study identified that changes in macrovascular and microvascular function may occur at different stages in the progression of CVD in ARDs, and reflect different and complementary aspects of vascular pathology (12). For instance, in an experimental model of adjuvant-induced arthritis, endothelial dysfunction in mesenteric arteries (i.e., microvasculature) occurred earlier than dysfunction in the aorta (i.e., macrovasculature) along the course of the disease. Moreover, microvascular dysfunction persisted even in the late stage of the disease, while macrovascular dysfunction returned to pre-disease values when inflammation was resolved (54). Data from cohort studies further support the different prognostic information provided by markers of micro- and macrovascular function, as the former seems to be a more powerful predictor of cardiovascular events in subjects without pre-existing cardiovascular conditions (55, 56), while the latter seems to be more important in subjects with existing CVD (35). Therefore, PA may beneficially affect ARD patients with different vascular phenotypes, in different stages of the cardiovascular continuum and along the course of the diseases.

The results of this review do not support the hypothesis that PA promotes positive changes in vascular structure in ARDs. Notwithstanding the reduced number of studies, the absence of any clear effects of PA on vascular structure may be explained by the small duration of most of the studies' interventions (~12 weeks). Changes in vascular function and structure in response to PA often follow a distinct time-course, with improvements in function preceding structural remodeling (20, 32). Therefore, it is likely that longer interventions (>16 weeks) might have elicited more consistent effects on vascular structure, as reviewed elsewhere (57). It is also possible that persistent inflammation may cause profound changes in vascular structure (*e.g.,* collagen and cholesterol deposition, fibrosis, plaque formation) that may be less prone to be reversed by PA (58). Finally, PA alone may also be a 'weak' intervention to produce consistent changes in vascular structure. In this respect, previous evidence suggests that multicomponent interventions (e.g., PA, low-fat diet, smoking cessation and lipid-lowering drugs) with intensive control of cardiovascular

risk factors may be the most effective strategy to produce consistent vascular remodeling in clinical populations (59, 60), which may also hold true for ARDs.

Studies included in the present review employed different protocols of PA. Five studies (28, 40-43) used a combination of aerobic training with RT, which is in compliance with public health recommendations for PA in ARDs (61). Exercise intensity ranged from moderate to very intense, which reveals the feasibility of more intense exercise interventions for this population, diverging from the previous notion that intense PA could be detrimental to ARDs (62). In fact, 3 studies (28, 29, 41) employed HIIT, which has only in the last two decades been recognised as a form of therapeutic exercise for clinical populations (63). Two studies (28, 41) also employed high-intensity dynamic RT, which has been recently advocated as a means to counteract functional decline in elderly and in population with chronic diseases, including ARDs (64). More importantly, the studies included in the review reported no serious adverse effects related to all these interventions, suggesting that PA is safe across a broad range of exercise types, modalities and intensities in ARDs. This information supports previous findings from studies addressing the safety of PA to ARDs (65, 66).

Data on adherence is also encouraging as it was reported to be above 75% across all studies that reported this variable, which is in agreement with previous studies specifically designed to assess adherence to PA interventions in ARDs (67, 68). However, it must be highlighted that most interventions included in this review were fully supervised and conducted in specialised exercise facilities (e.g., hospital gym and fitness centres). While intense monitoring by health professionals may be the most effective way to encourage adherence, it does not represent the real-world exercise setting for most of these patients. Interestingly, 2 studies (40, 45) employed a mixed monitoring approach with two supervised centre-based PA sessions and one unsupervised home-based session, also reporting good adherence (88% (24)) and benefits on vascular function. Future studies should examine the feasibility and effectiveness of even less controlled interventions (e.g., full time home-based PA, web-based or mHealth PA programmes), with the intent to subside public health initiatives that may be directly applied to this population.

Risk of bias

The generalisability of the present review findings are limited by the quality of the studies composing the review. In this regard, it should be noted that only 3 studies were RCTs, and one of

363 them (29) did not provide specific information about the randomisation process. Another aspect
364 that affected the overall risk of bias is the inherent difficulty to blind the participants and those
365 delivering the intervention to group allocation, which may have caused results to be impacted by
366 the expectations about the intervention, both by the participant and the intervention team. In this
367 scenario, additional effort must be given to blind the remaining personnel involved in the conduct
368 of the study, such as testing staff and outcome assessors. In fact, some of the vascular outcomes in
369 the present review present a degree of operator dependence for data analysis (69). Therefore,
370 absence of blinding of testing staff and, especially, data analysts may be considered an important
371 limitation of these studies. In the present review, only 4 studies reported that data assessors were
372 blinded for group assignment (27, 40, 41, 44). Overall, the high-risk of bias presented in all, but
373 one, of the studies included in this review highlight the incipience of this study area and points to
374 the urgent need of well-designed RCTs.
375
376 *Limitations*
377 This review is not without limitations. Firstly, due to the limited number of studies, the
378 results reported herein should not be generalized to all ARDs, therefore they should be interpreted
379 with caution. For the same reason, it was not possible to perform sensitivity and meta-regression
380 analyses to test the robustness of the observed outcomes and the potential effects of moderators on
381 the study results. For instance, the vascular responses to PA may vary across different ARDs and
382 protocols of PA, however the reduced number of studies precludes subgroup analyses. Secondly,
383 the included studies presented relatively small sample sizes and follow-up periods. As the ultimate
384 goal of PA is to reduce the number of clinically overt cardiovascular events in ARDs, future studies
385 should investigate the effects of long-term interventions on the occurrence of cardiovascular events
386 using adequately powered sample sizes. Thirdly, we included SpA (including PsA and AS) as
387 ARDs. In fact, these diseases are better classified as autoinflammatory rather than autoimmune
388 diseases, as they are not associated with the production of autoantibodies (70). However, these are
389 chronic inflammatory musculoskeletal conditions and previous studies have included them among
390 the ARDs (2, 71). Therefore, in order to preserve the original search strategy, we decided to
391 maintain SpA in the study review. Fourth, as considered in this review, arterial stiffness is largely
392 determined by aspects of the vascular structure, such as collagen/elastin ratio and smooth muscle
393 cell hypertrophy (72); however, factors related to vascular function (e.g., smooth muscle tone,

sympathetic activity) may also effect arterial stiffness (73), therefore arterial stiffness is sometimes seen as a marker of both vascular function and structure. Finally, we only searched and selected papers written in English, which may have caused some selection bias.

CONCLUSION

The present review provides evidence supporting the role of PA as vascular medicine for patients with ARDs. Overall, the available clinical trials with PA in ARDs demonstrated broad effects of PA across the vasculature, with larger and clearer effects on micro- and macrovascular endothelial function, and less consistent effects on endothelium-independent function and macrovascular structure. Furthermore, this review revealed that PA interventions including a broad range of types, intensities and volumes achieved a high rate of adherence and resulted in no adverse events. This augments the argument that PA is a feasible and effective non-pharmacological strategy in this population. This is the first review to address the effects of PA on vascular function in ARDs, a population characterised by a high cardiovascular morbidity and mortality. Data presented herein provides relevant information to health professionals working with ARDs, supporting evidence-based approaches regarding the management of cardiovascular risk in this population. Information provided by this review may also inform future study designs in this field.

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Conflict of interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLES

Table **1.** Methodological characteristics of studies.

Author (data)	Study design	Population			Intervention					Comparison	Outcomes
		Disease	*n* (Gender)	Age (mean ± SD)	Duration (weeks)	Frequency (days/week)	Type	Workout	Time (min)		
Mitropoulos et al. (2018)	Three-arm RCT	lcSSc	34 (31F, 3M)	65 ± 11*	12	2	I1: HIIT arm crank I2: HIIT cycling	Arm crank or cycling 30s 100% PO + 30s rest	40	Non-exercise control	Microvascular function: ACh CVC_{max}, SNP CVC_{max}
Mitropoulos et al. (2019)	RCT	lcSSc	32 (29F, 3M)	67 ± 12*	12	2	HIIT + RT	HIIT: arm crank/cycling 30s 100% PO + 30s rest RT: 5 upper-body exercises, 3 sets, 10RM	~70	Non-exercise control	Microvascular function: ACh CVC_{max}, SNP CVC_{max}
Sveaas et al. (2014)	RCT	axial SpA	24 (12F, 12M)	49 ± 12	12	3	HIIT + MICT + RT	HIIT: walking/running 4x4min 90-95%HR_{max} + 3min rest RT: 6 whole-body exercises, 2-3 sets, 8-10RM MICT: walking/running 40min 70%HR_{max}	40-60	Non-exercise control	Macrovascular structure: AIx, cfPWV
Soriano-Maldonado (2018)	Non-RCT	SLE	58 (58F)	44 ± 14	12	2	MICT + MIIT	Walking/running on a treadmill MICT: ~40-75 min 35-62.5% HRR MIIT: 2-8 x 5-20 min 50-75% HRR	~75	Usual care	Macrovascular structure: aPWV
Reis-Neto et al. (2013)	Non-RCT	SLE	38 (38F)	33 ± 8	16	3	MICT	Continuous walking at a public park HR(VT_1)	60	Non-exercise control	Macrovascular function: FMD, GTN%
Metsios et al. (2014)	Non-RCT	RA	36 (28F, 12M)	54 ± 10	24	3	MIIT + RT	MIIT: 3 circuit laps (walking, running, cycling, rowing) 3 x 3-4 min 70%VO_{2max} + 1 min rest RT: 4 whole-body exercises,	60-70	Lifestyle change advices	Microvascular function: ACh%, SNP% Macrovascular function: FMD%, GTN%

								3 sets, 12-15 rep, 70%1RM			
Sarajlic et al. (2018)	UCT	RA	29 (NR)	64 ± 11‡	52	5-7	MVPA + Circuit training (RT + MIIT)	MVPA (30 min): Web page- and pedometer to increase MVPA Circuit training: 3 circuit laps (45 min) RT: 10 whole-body exercises 10 rep, 50-80% 1RM MIIT: aerobic exercises 10 x 30 s, 60-85% HR_{max}	30-45	None	Macrovascular structure: AIx, cfPWV
van Zanten et al. (2019)	Non-RCT	RA	43 (29F, 14M)	52 ± 13*	12	3	MIIT	3 circuit laps (walking, running, cycling, rowing) 3 x 3-4 min 70%VO_{2max} + 1 min rest	60	Anti-TNFa treatment	Microvascular function: ACh%, SNP% Macrovascular function: FMD%, GTN%
Shin et al. (2015)	Non-RCT	RA	56 (56F)	64 ± 6	12	1	Tai-Chi	Twelve Movement tai Chi for arthritis (small and large degree of motion whole body movements)	60	Lifestyle change advices	Macrovascular structure: aPWV, cIMT Macrovascular function: FMD%
Misse et al. (2019)	UCT	SAM (DM and PM)	5 (5F)	44 ± 6	12	2	MICT + RT	MICT: walking/running between HR(VT_1-VT_2) RT: 6 whole-body exercises, 1 set, 8-12 RM	~60-80	None	Macrovascular structure: cfPWV Macrovascular function: FMD%

* weighted mean and standard deviation; † standard deviation was estimated from standard error; ‡ standard deviation was estimated from confidence intervals; ACh% = percentage increases in skin blood flow in response to acetylcholine administration; ACh CVC_{max} = maximal cutaneous vascular conductance in response to acetylcholine administration; AIx = augmentation index; aPWV = aortic pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; cIMT = carotid intima-media thickness; DM = dermatomyositis; F = female; FMD% = brachial artery flow-mediated dilation; GTN%= brachial artery responses to glyceryl trinitrate; HIIT = high-intensity interval training; HR = heart rate; HRR = heart rate reserve; I1 – intervention 1; I2 – intervention 2; lcSSc – limited cutaneous systemic sclerosis; M = male; MICT = moderate intensity continuous training; MIIT = moderate intensity interval training; MVPA = moderate-to-vigorous physical activity; Non-RCT = non-randomized controlled trial; NR = non reported; PA = physical activity; PO = maximal power output; PM = polymyositis; RA = rheumatoid arthritis; RCT = randomized controlled trial; RT = resistance training; SAM = systemic autoimmune myopathies; SLE = systemic lupus erythematosus; SNP% = percentage increases in skin blood flow in response to sodium nitropusside administration; SNP CVC_{max} = maximal cutaneous vascular conductance in response to sodium nitropusside administration; SpA – spondyloarthritis; UCT = uncontrolled clinical trial; VO_{2max} = maximal oxygen consumption; VT1 = first ventilatory threshold; VT2 = second ventilatory threshold.

FIGURE LEGENDS

Figure 1. Flow-chart of the systematic review. ARD, autoimmune rheumatic diseases; PA, physical activity.

Figure 2. Risk of bias of the included studies. Panel A depicts the risk-of-bias judgement for each study and bias domain. Panel B depicts the overall percentage of 'low risk', 'some concerns' and 'high risk' of bias in each of the bias domain.

Figure 3. Effects of physical activity on microvascular function. The upper panel presents the responses to Ach (i.e. endothelium-dependent function) and the bottom panel presents the responses to SNP (endothelium-independent function). SMD, standardised mean difference; CI, confidence interval; SD, standard deviation.

Figure 4. Effects of physical activity on macrovascular function. The upper panel presents the brachial flow-mediated dilation (FMD%; endothelium-dependent function) and the bottom panel presents the brachial artery responses to glyceryl trinitrate (GTN%; endothelium-independent function). SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.

Figure 5. Effects of physical activity on macrovascular structure as assessed by pulse wave velocity analysis. SMD, standardized mean difference; CI, confidence interval; SD, standard deviation.