Sports Med (2015) 45:269–278
DOI 10.1007/s40279-014-0265-8

SYSTEMATIC REVIEW

The Response of Matrix Metalloproteinase-9 and -2 to Exercise

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Published online: 25 September 2014

Abstract

Background Matrix metalloproteinases (MMPs) are a major group of enzymes that play essential roles in normal functioning of diverse tissues during growth, development, and aging. However, among the MMPs little is known regarding the role of exercise in MMP-9 and MMP-2 function in humans.

Objective The aim of this study was to provide a systematic comprehensive review of the literature examining the effect of different exercise interventions on MMP-9 and MMP-2 in human investigations.

Data Sources A comprehensive systematic database search was performed, including PubMed/MEDLINE, Scopus, ScienceDirect, and Web of Science.

Study Selection Both the acute and chronic effects of exercise were included for evaluation in this systematic review. Inclusion criteria included the use of any type of planned, structured, and repetitive movement and its effects on the MMP-2 and MMP-9 response (obtained from plasma samples), participants (humans only) of any age with or without diseases, sedentary participants and those involved in light, moderate, and vigorous activity, randomized controlled trials (RCTs) and clinical trials (CTs), full text article citations with no restrictions in terms of language, and scored at least 5/11 on the Physiotherapy Evidence Database (PEDro) quality scale.

Study Appraisal and Synthesis Methods The PEDro scale was used to appraise study quality of RCTs and CTs. Two reviewers independently reviewed the full texts of all potentially relevant articles for eligibility and disagreements were discussed and resolved.

Results Seven studies met the previously determined quality indicators and were reviewed; three were RCTs and four were CTs. In general, the quality of the studies ranged from 5 to 9 out of a maximum of 11 on the PEDro quality criteria scale. Results revealed that chronic aerobic training induces a decrease in MMP-9 and MMP-2 levels, possibly indicating a cardioprotective effect, while resistance exercise training displayed conflicting results.

Conclusion Alterations in MMP-9 and MMP-2 plasma concentrations may be valuable biomarkers to reflect the influence of exercise on the inflammatory state. Nevertheless, the limited evidence available regarding the effects of exercise on the MMP-9 and MMP-2 response in human participants suggests that further studies are needed to fully define the connection between the role of exercise on the MMP-9 and MMP-2 response.

Electronic supplementary material The online version of this article (doi:10.1007/s40279-014-0265-8) contains supplementary material, which is available to authorized users.

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Key Points

Matrix metalloproteinase-9 (MMP-9) and MMP-2 have emerged as important effectors in a variety of homeostatic functions, such as bone remodeling, tumor progression, cell death, immunity, and inflammation.

Although clear scientific evidence of the benefits of exercise exists, there are several challenges to a comprehensive understanding of the modulatory effects of exercise on MMPs and their significance as a muscle adaptation and inflammatory state.

The role of exercise on MMP-9 and MMP-2 in humans remains to be determined.

1 Introduction

Matrix metalloproteinases (MMPs) play essential roles in normal functioning of diverse tissues during growth, development, and aging [1]. Moreover, MMPs belong to a major group of enzymes that regulate cell–matrix composition and are zinc-dependent endopeptidases known for the ability to cleave one or several extracellular matrix constituents.

MMPs have emerged as important effectors in a variety of homeostatic functions, such as bone remodeling, tumor progression, cell death, immunity, and inflammation [2]. Among the known MMPs, MMP-2 and MMP-9 are recognized to play an important homeostatic role in extracellular matrix during muscle growth, development, and repair processes [1, 3]. Both MMP-2 and MMP-9 degrade type IV collagen, a major component in the basement membrane, and an essential constituent in the cellular arrangement of skeletal muscle fibers [4]. A previous study demonstrated that MMP-9 increases in the myocardium during the first hours of ischemic/reperfusion and the neutrophils are the predominant source of MMP-9 production [5]. In addition, altered expression of MMP-9 and MMP-2 promotes erosion and thrombosis in subjects with metabolic syndrome [4]. In humans, the high expression of plasma MMP-9 is recognized as a valuable tool to predict increased risk of intra-hospital cardiac events in patients with type 2 diabetes mellitus versus non-diabetic patients [6]. Moreover, MMP-2 and MMP-9 are independent predictors for kidney disease progression and are independently associated with increased risk of mortality [7].

Additionally, previous studies with humans and exercise have demonstrated that exercise can affect the levels of MMPs following acute and chronic interventions [8, 9]. To date, among the MMPs analyzed, MMP-9 and MMP-2 are the main markers included in human studies with exercise [3, 8–13].

Interestingly, MMP-9 and MMP-2 levels have been found to reach peak values within a relatively short time following a single bout of exercise, indicating their participation in the early adaptive response to exercise [8, 14]. However, studies have used different methods for determining MMP-9 and MMP-2 measures, such as muscle biopsies and plasma concentrations. Consequently, the reported results from plasma MMP-9 and MMP-2 may not be an accurate reflection of local skeletal muscle adaptation in response to exercise. Moreover, acute exercise may induce acute inflammation with long-term compensatory suppression of inflammation, accompanied by chronic anti-inflammatory effects.

Considering that limited information exists regarding the effect of exercise training on MMP-9 and MMP-2 levels in humans [15], this information might aid in the understanding of which type of exercise and intensity can specifically modulate the MMP-9 and MMP-2 response.

Thus, the aim of this systematic review was to examine the effects of different exercise interventions on MMP-9 and MMP-2 levels in humans. We also aimed to verify possible relationships between training adaptations with MMP-9 and MMP-2, and to suggest areas for further research.

2 Methods

2.1 Search Strategy

For this systematic review we considered the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. We considered the study of Sampson et al. [17] for determining the search strategies. Studies were identified by searching the following electronic databases: PubMed/MEDLINE (via National Library of Medicine) (1990–present), Scopus (1990–2013), ScienceDirect (1990–present) and Web of Science (1990–present). The last search was conducted in April 2013.

In order to broaden or narrow retrieval, we used the Boolean Operators (AND, OR) and the proximity operator (W/n) considering the tutorial of each electronic database. Of note, we made minor adjustments to adapt the strategy to the other search electronic databases (Electronic Supplementary Material [ESM], Table S1). To facilitate the replication of the results and any future update of this

review, we reported the search strategy with enough detail and we used the same developing search proposed by Major et al. [18]. Once the abstracts were reviewed, the complete versions of the articles that met the criteria described in Sect. 2.3 were obtained. The reference lists of the articles that fulfilled the inclusion criteria were analyzed for the identification of additional studies. The study design, methodology, and clinical relevance were assessed.

2.2 Definition of Terms

For the search of potentially relevant references related to exercise and MMPs, we used the following thesaurus terms registered in the database from Medical Subject Headings (MeSH): 'resistance training', 'strength training', 'resistance exercise', 'exercise', 'physical exercise' and 'aerobic exercise' associated with the search terms 'matrix metalloproteinases', 'matrix metalloproteinases 2', '72-kDa Type IV Collagenase', 'gelatinase A', 'matrix metalloproteinases 9', '92-kDa Type IV Collagenase', 'gelatinase B', 'metallopeptidases', and 'skeletal muscle'.

2.3 Inclusion and Exclusion Criteria

Studies included in this systematic review met the following inclusion criteria: present the acute and chronic effects of exercise—that is, the use of any type of planned, structured, and repetitive movement and its effects on MMP-2 and MMP-9 response; participants (only humans) of any age, with or without diseases; sedentary participants and those involved in light, moderate, and vigorous activity; randomized controlled trials (RCTs) and clinical trials (CTs); only plasma MMP-2 and MMP-9 measures; only full-text article citations with no restrictions to language; and trials that scored at least 5 on the Physiotherapy Evidence Database (PEDro) quality scale. We included this cut-off point because scores rating 5 or more are considered moderate- to high-quality studies [19, 21]. Meeting abstracts, unpublished data, observational, correlation studies, and review articles were excluded.

2.4 Data Selection and Analysis

One author conducted the search and after removing the duplicates, the papers were screened using the eligibility criteria. The search strategy is presented in the ESM, Table S1. The quality assessment of all eligible papers was evaluated independently by two authors using a modified version of the PEDro scale [20] (ESM, Table S2). Disagreements were discussed and solved in case of occurrence. This scale was used to rate the quality of RCTs and CTs. The World Health Organization (WHO) defines CTs as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes [22]. The PEDro scale is an 11-item scale. Each satisfied item (except for item 1, which, unlike other scale items, pertains to external validity) contributes one point to the total PEDro score (score = 0–10 points). The items of the scale are: (1) eligibility criteria were specified; (2) subjects were randomly allocated to groups; (3) allocation was concealed; (4) groups were similar at baseline; (5) subjects were blinded; (6) therapists who administered the treatment were blinded; (7) assessors were blinded; (8) measures of key outcomes were obtained from more than 85 % of subjects; (9) data were analyzed by intention to treat; (10) statistical comparisons between groups were conducted; and (11) point measures and measures of variability were provided. The PEDro scale was chosen due to its sufficient reliability for use in systematic reviews.

3 Results

Results of the research strategy are shown in ESM, Table S1. Among 297 papers fully assessed in this review, a total of seven studies were included in the present systematic review, which consisted of three RCTs [8, 9, 12] and four CTs [3, 10, 11, 13] (ESM, Table S2).

Twenty-seven of the 34 articles retrieved for eligibility were excluded due to the following reasons: 20 studies presented a quality score of <5, two did not evaluate or assess MMP, two did not use an exercise intervention, two used mice and one used muscle biopsy analysis (Fig. 1).

3.1 Quality Assessment

Quality assessment of the studies according to the modified PEDro scale is summarized in the supplemental material (ESM, Table S2). The quality of scores ranged from 5 to 9. The highest quality studies were the RCTs. The most common methodological deficiencies that were not scored positively in the majority of the seven studies were the intention to treat analyses [3, 8–12], blinded outcome assessors [3, 8–13] and adverse events reported [8–10, 13]. Measures of variability and statistics between groups were not well reported in three studies [3, 9, 12]. Considering this, the calculation of the effect size and clinical significance of the results were compromised. Subjects were randomly selected in only three [8, 9, 12] of the seven studies. Five studies specified eligibility criteria [3, 10–13], three compared groups at baseline [9, 10, 12], one did not state if training supervision was used [8], four did not state compliance [3, 8, 9, 13], and one did not report whether participant dropouts occurred [13].

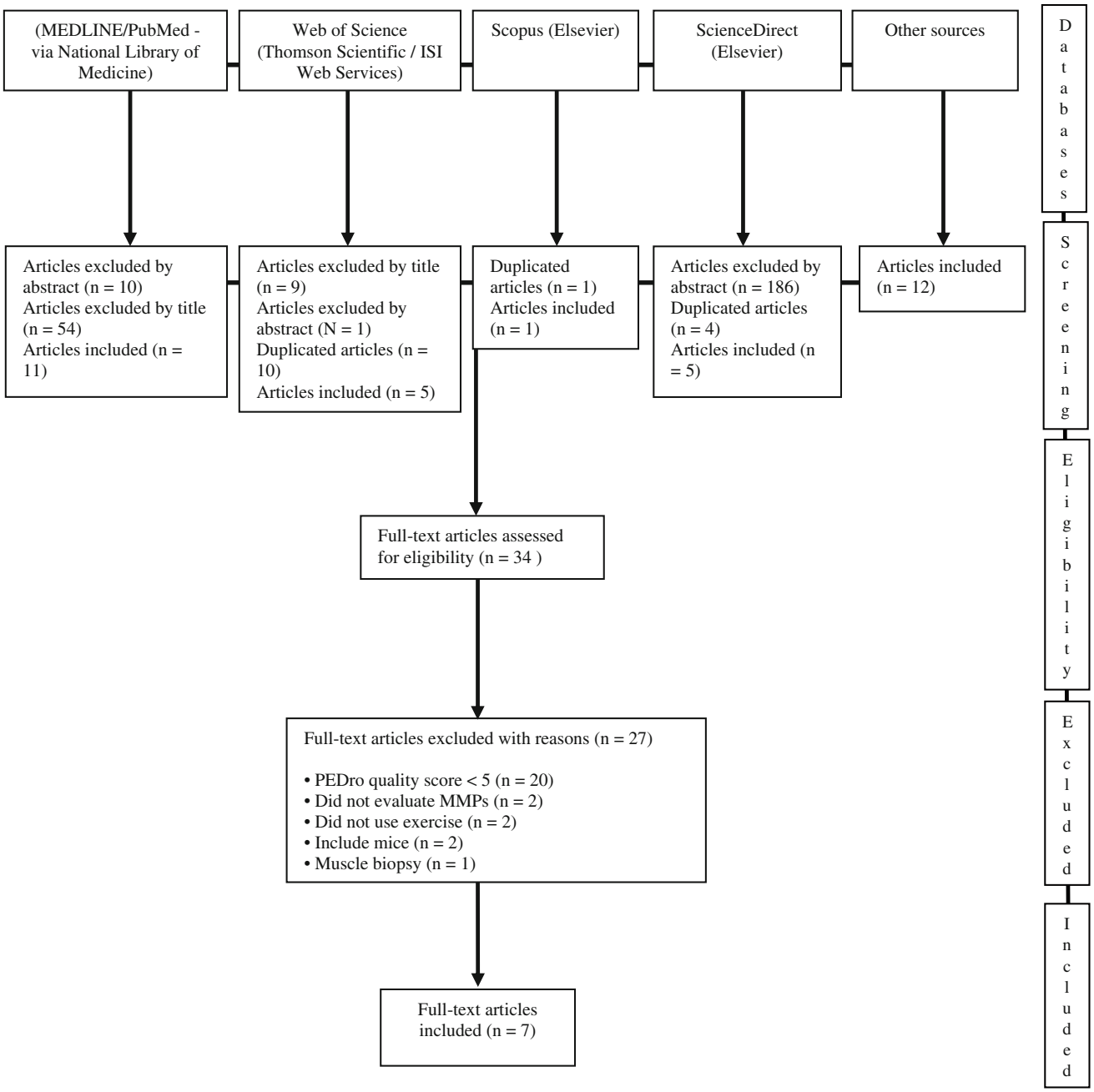

Fig. 1 Summary of search results. *PEDro* Physiotherapy Evidence Database quality score, *MMPs* matrix metalloproteinases

Overall, the quality of the included trials was only moderate (mean 6.42 ± 1.39, range 5–9/11).

3.2 Intervention Characteristics

The seven trials included a total of 203 participants. Only one study had a sample of <20 participants [3], and the study with the largest number of participants had 50 [12]. Only two studies had control groups [10, 12] (Table 1).

Two studies did not report the training status of the subjects [9, 12]. Three trials included subjects with asymptomatic cardiovascular disease [11], type 2 diabetes (T2DM) [12] and T2DM and metabolic syndrome [9]. In addition, some studies were composed of sedentary individuals [3, 10, 13] and active individuals [8].

Sex was reported in all studies. All studies provided age ranges for the participants. The youngest participants were 21 years of age [3] and the oldest 73 years [13].

The intensity of the exercise programs was clearly described in six [3, 8–10, 12] of the seven articles. For the resistance training (RT) protocols, the intensity ranged between 40 to 120 % of 1RM and for aerobic training

Table 1 Exercise intervention characteristics of the studies included in the systematic review

Study	Participants (*n*)	Study groups	Training status	Sex (M:F)	Age [mean (SD)]	Exercise modality	Exercise frequency (day/week)	Exercise intensity	Exercise duration (min)	Program length (week)	MMP-2	MMP-9	TIMP-1
Büyükyazı et al. [10]	24	EG (12) CG (12)	Sedentary	EG (0:12) CG (0:12)	45–62	Walking program exercises	5	60–65 % HRR	30–60	8	NE	↔ EG ↔ CG	↔ EG ↔ CG
Niessner et al. [11]	32	EG (32)	Patients[a]	EG (18:14)	49 (1.8)	Endurance training	3	NR	30	12	NE	↓ EG	NE
Kadoglou et al. [12]	50	EG[b] (25) CG[b] (25)	NR	EG + CG (17:33)	55–65	Brisk walking	4	50–70 % VO_{2peak}	30–60	16	↔ EG ↔ CG	↓ EG ↔ CG	↔ EG ↔ CG
Lucotti et al. [9]	47	EG1[c] (30) EG2[c] (20)	NR	EG1 (17:13) EG2 (13:7)	58.1 (9.9) 61.5 (11.5)	EG1 = aerobic exercise divided between row ergometer and cycle ergometer EG2 = aerobic plus resistance exercise (5 exercises for the upper and 4 exercises for the lower body)	5	EG1 70 % of HR_{max} EG2 1 set, 10 rep, 1-min RI between exercises (40–60 % 1-RM)	EG1 = 30 EG2 = 30 plus 15	3	↓ EG1 ↔ EG2	NE	NE
Fiotti et al. [13]	17	EG (17)	Had not participated in regular physical activity in the previous 6 months	(0:17)	67 (62–73)	Exercises that involved synchronization, dexterity, flexibility, strength, and steadiness	2	NR	NR	24	NE	↓ EG	NE
Urso et al. [8]	42	CT1 (?) RT2 (?)	Recreationally active	(16:0)	29.6 (0.7) 26.6 (0.7)	CT = conditioning drills, distance running stressed RT = agility drills, load carriage road marching and weight training stressed	5	CT = NR RT = 3 sets, 10 rep, 30 sec RI between each exercise, 2–3 min between each group of exercises	CT = NR RT = 60	8	↓ CT after 4 weeks of training ↔ RT	↑ CT from week 4 of training to 8 weeks ↑ After 8 weeks	NE
Madden et al. [3]	14	EG (14)	Physically inactive	(14:0)	21.4 (3.2)	Eccentric task arm curl exercise	–	6 sets, 10 rep, 2 min RI (120 % 1RM)	–	Acute exercise intervention	NE	↔ EG	↔ EG

↓ Significant decrease in the mean value; ↔ no significant change in the mean value; ↑ significant increase in the mean value; – do not use exercise frequency or exercise duration

CG control group, *CT* callisthenic-specific training program, *EG* experimental group, *F* female, HR_{max} maximum heart rate, *HRR* heart rate reserve, *M* male, *MMP* matrix metalloproteinase, *NE* not evaluated, *NR* no reported, *reps* repetitions, *RI* rest interval, *RM* repetitions maximum, *RT* resistance training, *TIMP* MMP tissue inhibitors, VO_{2peak} peak oxygen consumption, *?* number of participants not clearly stated

[a] Asymptomatic coronary artery disease individuals

[b] Individuals with type 2 diabetes

[c] Individuals with type 2 diabetes and metabolic syndrome

Table 2 Summary of outcome measures in the studies included in the systematic review

Study	Outcome	EG1/EG [mean (95 % CI or SD)]				EG2/CG [mean (95 % CI or SD)]				
		Pre-exercise	Mid-exercise	Post-exercise	*p* value[a]	Pre-exercise	Mid-exercise	Post-exercise	*p* value[a]	*p* value[b]
Büyükyazı et al. [10]	MMP-9 (ng/dL)	374.9 (196.3–469.1)		373.5 (282.0–547.0)	NS	315.8 (198.3–440.9)		329.4 (168.5–485.0)	NS	
	TIMP-1 (ng/dL)	261.3 (236.5–271.1)		243.7 (216.4–267.9)	NS	258.9 (246.3–271.1)		245.2 (231.3–271.1)	NS	
	MMP-9/TIMP-1 ratio	0.42 (0.2–0.6)		0.48 (0.3–0.6)	NS	0.36 (0.2–0.5)		0.40 (0.1–0.6)	NS	
Niessner et al. [11]	MMP-9 (ng/dL)	750 (98)		490 (50)	0.005[c]					
Kadoglou et al. [12][d]	MMP-9 (ng/mL)	NR		NR↓	0.039[c]	NR		NR	0.492	0.028[e]
	MMP-9/TIMP-1 ratio	NR		NR↓	0.057[c]	NR		NR	0.631	0.038[e]
	TIMP-2 (ng/mL)	NR		NR↑	0.042[c]	NR		NR	0.807	0.022[e]
	MMP-2 (ng/mL)	NR		NR	NS	NR		NR	0.788	0.597
	TIMP-1 (ng/mL)	NR		NR	NS	NR		NR	0.906	0.229
Lucotti et al. [9][d]	MMP-2 (ng/mL)	NR		NR↓	0.01[c]	NR		NR	>0.05	0.0001[e]
Fiotti et al. [13]	MMP-1 (ng/mL)	4 (3.8–4.1)		4 (3.95–4.2)	NS					
	MMP-9 (ng/mL)	368 (208–508)		191 (65–303)	0.003[c]					
Urso et al. [8]	MMP-1 (ng/mL)[g,h]	2.9 (0.6)	2.3 (0.8)	2.5 (0.6)	NS	4.5 (0.6)	5.6 (0.7)[i]	5.2 (0.6)	0.05	
	MMP-2 (ng/mL)[g,h]	296.1 (37.4)	192.5 (12.4)[i]	195.6(14.6)[i]	0.05	195 (34.6)	201.9 (11.5)	217.1 (13.5)	NS	
	MMP-3 (ng/mL)[g,h]	25.2 (3.1)	15.3 (2.0)[i]	15.5 (2.2)[i]	0.05	15.6 (2.9)	14.7 (1.9)	16.8 (2.1)	NS	
	MMP-9 (ng/mL)[g,h]	213.8 (41.2)	110.2 (18.4)	254.2(41.7)[j]	0.05	128.0 (38.2)	230.3 (17.0)	256 (38.6)[i]	0.05	
Madden et al. [3][d]	MMP-9 activity	NR	NR	NR	NR	NR	NR	NR	NR	NR
	MMP-9 (ng/mL)									
	TIMP-1 (ng/mL)									

CG control group, *EG* exercise group, *NR* not reported, *NS* not significant, *MMP* matrix metalloproteinase, *TIMP* tissue inhibitor metalloproteinase, ↑ = increase; ↓ = decrease

[a] Difference within group

[b] Difference between groups

[c] Significant difference ($p < 0.05$) within group for pre- vs post-exercise

[d] Pre- and post-exercise scores not reported in tables or text (only graphically, if at all)

[e] Significant difference ($p < 0.05$) between groups for post-exercise EG1/EG vs post-exercise EG2/CG

[f] Significant difference ($p < 0.05$) between groups for pre-exercise EG1/EG vs pre-exercise EG2/CG

[g] Basal MMP throughout the 8-week exercise program

[h] Significant ($p < 0.05$) exercise group by time interaction

[i] Significant difference ($p < 0.05$) vs baseline

[j] Significant difference ($p < 0.05$) vs mid-exercise

protocols the exercise was prescribed based on percent of heart rate reserve (HRR; 60–65 %) [10], percentage of maximum heart rate (HR_{max}; 70 %) [9], and peak oxygen consumption (VO_{2peak}; 50–70 %) [12]. Two studies did not report the exercise program adequately [13, 14]. The duration of the exercise sessions ranged from 30 to 60 minutes. Only two studies did not report the exercise duration [3, 13]. The training programs ranged in length from 3 to 24 weeks.

Whether and how an exercise dose-response (intensity, volume, frequency and length) modulates the MMP-2 and MMP-9 plasma levels is a main topic to be considered for further randomized trials. A summary of the outcome measures is presented in Tables 1 and 2.

Considering the variability of the individuals' health status and age, and the lack of information presented in some of the studies, one should consider that the expression of MMP-9 and MMP-2 is affected by pathological conditions such as inflammation, disease, and age [1, 23]. The inclusion of individuals with T2DM, metabolic syndrome, coronary risk factors, or the elderly affect the response of the main analyzed variable. Moreover, the use of a practical tool to classify the trainability of the individuals must be included in futures studies to favor comparability and standardization. The existence of a high level of bias undoubtedly affected the quality of the analyzed trials.

3.3 Effects of Exercise on MMP-9 and MMP-2 in Sedentary Individuals

Physically inactive and individuals that had not participated in regular physical activity in the previous 6 months were qualified as sedentary individuals.

Büyükyazı et al. [10] aimed to investigate the effects of 8 weeks of walking exercise on MMP-9 levels, tissue inhibitor of metalloproteinase-1 (TIMP-1) levels and MMP-9/TIMP-1 in post-menopausal women. There was no exercise training effects on MMP-9 levels, TIMP-1 levels or MMP-9/TIMP-1 in sedentary post-menopausal women. We speculate that the training program length was too short (8 weeks) when compared with studies [11, 12], which used 12 and 16 weeks, respectively. Moreover, the intensity used during walking may be too low to modify MMP-9 plasma levels.

Fiotti et al. [13] evaluated functional exercises that involved synchronization, dexterity, flexibility, strength, and steadiness. They demonstrated that after 24 weeks of training in elderly individuals, there was a decrease in MMP-9, while MMP-1 plasma levels remained unchanged throughout the study. Unfortunately, the effects of intensity could not be determined since the parameters were not reported in this study.

One study used eccentric resistance exercise for the upper body [3]. Considering that acute eccentric exercise can exacerbate muscle damage and inflammation, MMP-9 plasma levels and TIMP-1 plasma levels might not be a reliable marker of eccentric exercise-induced muscle damage, because the protocol failed to increase systemic MMP-9 and TIMP-1 levels [3]. However, a possible explanation provided by the authors was that a single-arm eccentric exercise with 6 sets of 10 repetitions at 120 % of 1RM may not involve sufficient tissue volume to elicit a systemic increase in MMP-9 levels and TIMP-1 levels.

3.4 Effects of Exercise on MMP-9 and MMP-2 in Individuals with Pathological Conditions

The study of Niessner et al. [11] included individuals with risk of coronary events. They demonstrated that endurance training decreased circulating MMP-9 levels, indicating beneficial effects of exercise on inflammation in these patients. Again, exercise intensity was not reported. The study of Kadoglou et al. [12] demonstrated that brisk walking (50–70 % of VO_{2peak}) in patients with T2DM reduced plasma levels of MMP-9, offering further insight into the cardioprotective mechanisms of exercise in patients with T2DM. In addition, exercised individuals decreased MMP-9/TIMP-1 and increased TIMP-2 when compared with the control group. There were no changes in MMP-2 and TIMP-1. Moreover, Lucotti et al. [9] demonstrated that in individuals with T2DM and metabolic syndrome who completed row ergometer, aerobic training cycle ergometer MMP-2 plasma levels displayed a decrease, which was not observed with concurrent training (resistance plus aerobic training).

3.5 Effects of Exercise on MMP-9 and MMP-2 in Recreationally Active Individuals

Urso et al. [8] investigated the response of MMP levels to an acute resistance exercise test (ARET) consisting of 6 sets of 10-RM barbell squats prior to 8 weeks of RT or callisthenic-type (CT) exercise training and then a repeat of the ARET. In the CT group, basal MMP-2 decreased by 35 % after 4 weeks of training. In the RT group, there was no effect of training on basal MMP-2 levels. The responses of MMP-9 to RT and CT were different. In the CT group, there was a 130 % increase from week 4 of training to 8 weeks post-training, with no differences between pre- and post-training. In the RT group, basal MMP-9 levels increased throughout the 8 weeks of training. Thus, the circulating MMPs' response to a single bout of high-intensity exercise appears to be dependent on the mode of exercise training and may facilitate training-specific adaptations.

After reviewing the response of plasma MMP-9 and MMP-2 to exercise, we suggest that the alterations in

plasma MMPs may reflect the impact of exercise on inflammatory markers, as verified by studies [9, 11–13] in metabolic syndrome, T2DM, coronary risk factors or elderly individuals, with lower effects in non-pathological individuals. However, these results require further investigation, due to the methodological limitations found in the exercise protocols.

4 Discussion

The purpose of this systematic review was to examine the effects of exercise interventions on MMP-9 and MMP-2 response in humans. Another objective was to assess the relationship between training adaptations, MMP-9 and MMP-2, suggesting areas for further research.

To the best of our knowledge this is the first systematic review to examine the effects of exercise on MMP-9 and MMP-2 response in humans. Overall, the findings of this review suggest that aerobic exercise [9, 11, 12] has a cardioprotective effect by decreasing pro-inflammatory markers (MMP-9 and MMP-2) in T2DM, metabolic syndrome, coronary risk factors, or elderly individuals. Similar results were demonstrated by Fiotti et al. [13] in elderly females submitted to functional exercises including synchronization, dexterity, flexibility, strength, and steadiness exercises. Regarding RT, conflicting results were found for MMP response [3, 8]. The study by Madden et al. [3] considered that eccentric exercise could exacerbate muscle damage and inflammation but their protocol failed to increase systemic MMP-9 levels, while Urso et al. [8] indicated by their results that the MMP system is influenced by an acute exercise session and that training does not attenuate this response.

Some mechanisms are proposed to better understand the regulatory mechanisms of the exercise-related changes in MMP-9 and MMP-2 and the differences in the outcomes between different populations. Koskinen et al. [24] evaluated the effects of downhill running on the plasma levels of creatine kinase (CK), MMP-2, MMP-9, and TIMP-1 and TIMP-2. There was no correlation between increased serum CK, MMPs, and TIMPs. This might indicate that the plasma changes of MMPs and TIMPs are not useful measures of exercise-induced muscle damage and remodeling of extracellular matrix, as verified by Madden et al. [3].

Under pathological conditions such as metabolic syndrome and coronary risk events, the elevation of MMP-2 and MMP-9 are correlated with increased inflammation [25]. Thus, lowering levels of inflammatory markers might mediate the inhibitory effect of exercise on MMP-9 and MMP-2 levels [26]. The decrease in MMP-9 and MMP-2 as a consequence of chronic exercise training could be related to expression of their endogenous protein inhibitors, such as TIMPs, α2-macroglobulin, and protease degradation. Also, substrate availability and accessibility determine the degree to which MMP activity is used. Another possible mechanism is the reduction of tumor necrosis factor-alpha (TNFα) induced by exercise training, a known stimulator of MMP-9 production [25, 27].

This systematic review raised interesting hypotheses. Considering the association between elevated plasma MMP-9 levels and intra-hospital cardiac events [6], the decrease in MMP-9 levels could be associated with favorable long-term cardiovascular outcomes [26]. Furthermore, MMP-9 and MMP-2 accelerate atherosclerotic progression and destabilize vulnerable plaques [4]. In addition, we raised the hypothesis that alterations on MMPs' plasma concentrations might be a good reflection of the exercise effect on inflammatory markers verified by the cited studies [9, 11–13] in T2DM, metabolic syndrome, coronary risk, and elderly individuals. Thus, the reduction of MMP-9 and MMP-2 levels promoted by exercise in individuals with pathological conditions might indicate a cardioprotective effect of exercise.

5 Conclusion

There is clear scientific evidence of the benefits of exercise for the prevention of diabetes, hypertension, cancer, osteoporosis and dementia [28]. Although the reduction of MMP-9 and MMP-2 levels promoted by exercise in individuals with pathological conditions might indicate a cardioprotective effect of exercise, there are several challenges to a comprehensive understanding of the modulatory effects of exercise on MMPs and their significance as a muscle adaptation or indicative of an inflammatory state. Furthermore, studies must explore the exercise dose-response, and more RCTs involving exercise should be conducted. Considering the limited available literature and differential methodological trials, this review suggests that the role of exercise on the MMP response in humans remains to be determined.

Acknowledgments No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review. The first author would like to thank his family, and in particular his mother Rita Cunha and his son Nicolas Cunha.

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