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REVIEW

Effects of physical exercise on oxidative stress biomarkers in hypertensive animals and non-diabetic subjects with prehypertension/hypertension: a review

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Abstract

Background Oxidative stress (OS) is a condition that alters different functions of the organism inducing high blood pressure (HBP). Although physical exercise is recommended for the treatment of HBP, it is not clear which exercise method is more efficient to reduce OS biomarkers in subjects with HBP and non-type 2 diabetes mellitus (T2DM). Therefore, this review aimed to determine the effect of physical exercise on the OS biomarkers of HBP animal models and non-T2DM prehypertensive/hypertensive human adults.

Methodology An online search was done in WoS, Scopus and PubMed (MeSH) databases with the following combination of keywords: "hypertension" AND "oxidative stress" AND "exercise".

Results A total of 1128 articles were identified, from which only six articles on animal research and six on human research fulfilled the inclusion and exclusion criteria. In animal models, exercise reduced OS biomarkers and decreased systolic blood pressure. In humans, five of these articles showed a significant decrease in OS biomarkers along with a decrease in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and a single study found an increase in OS biomarkers co-occurring with a decrease in SBP/DBP.

Conclusions Based on the analyzed articles, it is concluded that physical exercise, in its different modalities, allows the reduction of OS biomarkers, together with a significant decrease in SBP/DBP. Moderate intensity aerobic exercise presents a higher body of evidence compared to resistance training and flexibility training. For this reason, it is recommended to conduct more randomized clinical trials with these last two methods.

Keywords Hypertension · Endurance training · Resistance training · Reactive oxygen species · Antioxidant response elements

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Introduction

Hypertension or high blood pressure (HBP), is one of the chronic diseases with the highest prevalence in the world, affecting millions of people [1]. It is considered as a risk factor for the development of cardiovascular diseases such as stroke, heart failure and coronary artery disease, among others [1–4]. Additionally, HBP has been associated with alterations in the renin–angiotensin–aldosterone system, increased sympathetic tone, endothelial dysfunction and a state of oxidative stress (OS) [1, 5]. The last one refers to an imbalance between oxidant and antioxidant factors in favor of oxidants [6]. Oxidizing factors include reactive oxygen species (ROS) such as the free radicals (FR) superoxide anion ($O_2^{\cdot-}$), hydroxyl free radical ($OH^{\cdot}$), singlet oxygen and hydrogen peroxide (H_2O_2). In turn, reactive nitrogen species (RNS) include nitric oxide (NO) and peroxynitrite anion ($ONOO^-$). All these reactive species are short half-life, highly reactive elements, capable of interacting with different biomolecules such as lipids, proteins and nucleic acids, leading to damage in different cellular structures such as cell membrane, mitochondria, and cell nucleus [7, 8]. The damage can be observed through the evaluation of biomarkers of oxidative stress in the blood; malondialdehyde (MDA), which is produced by lipid peroxidation; protein carbonyls (PC) produced by damaged proteins that oxidize aldehyde groups and F8-isoprostanes derived from non-enzymatic oxidation of the arachidonic acid present in phospholipids. Additionally, it can be useful to evaluate the activity of antioxidant enzymes like superoxide dismutase (SOD) [8, 9], which is present in our organism in the inside and outside faces of the cell membrane, catalase (CAT) [8, 9] located in mitochondria and peroxisomes and glutathione peroxidase (GPX) [8, 9] found in the mitochondrion and hepatic cells cytosol's. Non-enzymatic antioxidants can also be evaluated, as is the case of reduced glutathione (GSH) [8, 9], which is a tripeptide constituted by the amino acids glutamic acid, cysteine y glycine [10, 11]. Moreover, non-enzymatic antioxidants act as a first line of defense against ROS, as they are prepared to act when a variety of stressful situations, an acute myocardial stroke among these, generate a sudden increase of ROS [8, 12].

HBP subjects show a chronic OS condition, exhibited by higher levels of MDA and F8-isoprostanes due to lower plasma antioxidant capacity and lower SOD, CAT and GPX enzyme activity in red blood cells [11], along with lower GSH reserves [11].

The origins of ROS in HBP are diverse, on a view that they can be associated to enzymatic processes of NADPH oxidase (NOX), xanthine oxidase (XO), endothelial nitric oxide synthase (eNOS), mitochondrial dysfunction, and obesity [1, 5, 13]. At the renal level, there is an increase in the production of angiotensin II in HBP subjects, which acts on AT1 receptors stimulating the transcription of different NADPH oxidase subunits [3, 5]. The production of ROS and the induction of second messengers by NADPH, leading to the overregulation of inflammatory mediators such as chemokines, adhesion molecules and cytokines, which furthermore leads to renal insufficiency and vascular damage [14].

At the vascular level, there is a deregulation of the enzymes xanthine oxidase (XO) and nitric oxide synthase (NOS) [5, 15]. XO is a source of FR generated through the reduction of oxygen to superoxide anion in the last two steps of hypoxanthine purine metabolism. In studies on humans and spontaneously hypertensive Wistar Kyoto rats, a relationship has been observed between the increases of endothelial XO, ROS production, and systemic blood pressure [16, 17]. Additionally, the NOS enzyme is present in various isoforms: as endothelial nitric oxide synthase (eNOS), neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS). All of them produce nitric oxide (NO), which is a paracrine regulator of vascular tone. NO prevents the formation of the atherosclerotic plaque [18, 19] and thrombus; it also prevents leukocyte-endothelial cell adhesion, proliferation and migration of vascular smooth muscle cells (VSMC) and platelet aggregation to maintain a healthy vascular endothelium. To keep an adequate endothelial function, eNOS uses L-arginine and tetrahydrobiopterin (BH4) to produce NO [14, 20]. Thus, deficiencies in the activity of eNOS or the amounts of L-arginine and BH4 can affect the synthesis of NO and therefore, the endothelial ability to induce vasodilation. One consequence of this is an increase in total peripheral resistance, which entails an increase in systemic blood pressure and endothelial dysfunction. Moreover, the presence of eNOS in a pro-oxidant environment can generate peroxynitrite ($ONOO^-$), a reactive nitrogen species capable of causing endothelial damage [20].

Furthermore, the mitochondrion has an essential function in cell death and metabolic homeostasis [13, 21]. Additionally, it generates cellular energy in the form of ATP utilizing the electron transport chain (ETC) and the tricarboxylic acid cycle (TCA). It is important to mention that this process is not perfect, as roughly 2% of the O_2 which is consumed by the mitochondrion is incompletely reduced, generating ROS such as $O_2^{\cdot-}$ (superoxide radical anion) [22] and $OH^{\cdot}$; and at the same time, vascular homeostasis is affected by the processes of mitochondrial fission and fusion [13]. These processes are associated with a deregulation of ROS production and can damage the mitochondrial membrane, enzyme activities, and DNA [23–25].

The high production of ROS in patients with HBP due to the reasons mentioned before, generates a depletion in the reserves of endogenous antioxidants, in addition to a

decrease in the activation of various antioxidant enzymes, so subjects with HBP are more susceptible to oxidative damage induced by other cardiovascular pathologies associated with HBP, such as acute myocardial stroke [1, 5, 26].

As a result, the supplementation of radical scavenging antioxidants such as vitamins C and E is a good strategy for co-treatment of this pathology [11]. Additionally, another co-treatment for HBP is physical exercise; however, it generates acute OS and increased production of FR, ROS, RNS [27, 28] and especially H_2O_2 [29]. This can enable the modulation of different cell functions through modifications of redox balance, activating different transcription factors associated to the mitochondrial biogenesis, the increase of endogenous antioxidant defense and inflammatory processes such as transcription factors peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [29], nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [30], nuclear Factor Kappa B (NF-κB) [31], and Heat Shock Proteins (HSP) [32].

Physical exercise has proved to be an effective way of reducing SBP and DBP [1]. Additionally, it increases the activity of antioxidant enzymes such as SOD, CAT and GPX in oxidative stress-associated pathologies like obesity and T2DM [10]. In this way, the total antioxidant capacity in the plasma is improved, together with an increase in the reserves of GSH in blood cells, and therefore, the concentration of oxidative stress biomarkers decreases [10]. Nevertheless, even though there are variety of exercise programs for the treatment of non-type 2 diabetes prehypertensive or hypertensive subjects, the role of physical exercise in the OS of this population still needs to be defined. For this reason, the aim of the present review is to describe the effects induced by physical activity and different physical exercise protocols on the OS biomarkers of HBP animal models and non T2DM prehypertensive/hypertensive human adult, in addition to summarizing the mechanisms of action of exercise based on studies of hypertensive animal models and their effect on the OS.

Methodology

Literature search

A search was carried out in PubMed, WoS and Scopus databases with the keywords “hypertension” AND “oxidative stress” AND “exercise” OR “resistance training” OR “circuit based training” OR “muscle stretching exercises” OR “high-intensity interval training”; only considering articles written in English. In the case of the PubMed database, the MeSH metasearch engine was used. Additionally, a manual search of the references lists of the articles found was made, besides a free literature review of specialized journals. Regarding publication dates, the inclusion criteria considered articles published from January 2008 to May 2018. The search was carried out on May 23–May 31, 2018. As a result, 1128 articles were identified as matching keywords and previously described criteria (Table 1).

Selection of publications

Analyzed studies were carried out from 2008 to 2018. Inclusion criteria of the investigations carried out in animal models were spontaneously HBP rats (SHR), Dahl salt-sensitive rats, with a training program of at least 2 weeks, and rats/mice/hamsters older than 3 months. On the other hand, the selection of articles on human subjects consisted of a study population of overweight and obese men and women who were 25 years of age or older. They had prehypertension or hypertension and participated in an exercise program for at least 2 weeks. Regarding the exclusion criteria, in the case of investigations in animal models, it was HBP induced by kidney damage (DOCA-Salt, subtotal nephrectomy, renovascular hypertension) and ovariectomized. The exclusion criteria in human subjects included smokers and subjects with cancer, type 2 diabetes mellitus, kidney failure, pulmonary hypertension and heart failure, together with subjects who received a nutritional co-intervention such as antioxidant supplementation or any diet modifications. Additionally, systematic reviews, meta-analysis, literature reviews, book chapters and case studies were excluded. The analysis of the articles was done individually with the PEDro [33] scale and blindly by VF, PJ, HF (Tables 2 and 3).

Key findings

From a total of 1128 articles found in the databases, 133 duplicates were removed with EndNote, leaving 995 articles left. The title and abstract of these 995 were screened, selecting 146 articles.

Table 1 Results of the search in PubMed, Scopus and WoS databases

	PubMed (MeSH)	Scopus	WoS
1. Hypertension	238,058	700,802	375,361
2. Oxidative stress	110,234	265,006	299,565
3. Exercise	162,936	545,331	359,098
4. Resistance training	6,411	15,547	21,409
5. Circuit-based training	31	3118	1439
6. Muscle stretching exercises	1380	4390	2609
7. High-intensity interval training	351	2206	2764
8. 3 OR 4 OR 5 OR 6 OR 7	165,199	704	369,932
1 AND 2 AND 8	50	691	439
1 + 2 + 3	50	689	439

Table 2 Summary of results of animal models of HBP

Author	Sample	Intervention	Effects on SBP, DBP or MBP	Effects on OE biomarkers	Another relevant outcomes
Bertagnoli [34].	SHR of 15 weeks of age. SHR SED SHR EX	An aerobic training was on a treadmill (5 days/week, 10 weeks, 1 h/day) at a speed of 20 m/min for 1 h.	SHR EX v/s SHR SED ↓MAP ↓SBP ↓DBP	SHR EX v/s SHR SED ↓ Lipid peroxidation in cardiac tissue. ↑ SOD (U/mg protein in cardiac tissue) ↔CAT (U/mg protein in cardiac tissue) ↔GPX (U/mg protein in cardiac tissue) ↑ Total nitrates/nitrites in cardiac tissue	SHR EX v/s SHR SED ↓Norepinephrine concentration in cardiac tissue. ↓Heart weight
Kimura [35]	SHR of 14 weeks. They SHR SED $n=10$ SHR EX $n=10$	Free aerobic workout on a treadmill for 10 weeks, recording the total distance traveled at the end of the training, which was 4615 ± 2165 m/day.	SHR EX vs SHR SED ↔PAS	SHR EX v/s SHR SED ↑Mn SOD in aorta ↔CuZn SOD in aorta	
Soares de Andrade [36].	SHR rats and WKY rats of 8–21 weeks old divided in four groups: WKY SED $n=14$ WKY EX $n=10$ SHR SED $n=15$ SHR EX $n=14$	An aerobic training in a treadmill was performed five times a week at 55% VO_{2max} for 60 min for 13 weeks.	WKY SED v/s WKY EX ↓PAS SHR SED v/s SHR EX ↓PAS	WKY SED v/s WKY EX ↔ Lipid hydroxyperoxidation in left ventricle ↔ Hydroxynonenal in left ventricle SHR SED v/s SHR EX Lipid ↓hydroxyperoxidation in left ventricle ↓Hydroxynonenal in left ventricle	WKY SED v/s WKY EX ↑ Cardiomyocyte diameter ↓ Heart rate SHR SED v/s SHR EX ↔ Cardiomyocyte diameter ↓ Heart rate

Table 2 (continued)

Author	Sample	Intervention	Effects on SBP, DBP or MBP	Effects on OE biomarkers	Another relevant outcomes
Campos [37].	SHR and WKY male rats aged 12–22 weeks divided in three groups: Groups: WKY SED SHR SED SHR EX	Swimming training for 5 days a week for 60 min for 10 weeks. At the end of each session, the rats ran on a treadmill for 10 min.	WKY SED v/s pre- intervention ↔SBP SHR SED v/s pre- intervention ↑SBP SHR EX v/s pre-intervention ↓SBP	SHR SED v/s WKY SED post- intervention ↑ Lipid peroxidation in heart extract ↑ Protein carbonyls peroxidation in heart extract SHR EX v/s WKY SED post-intervention ↔ Lipid peroxidation in heart extract ↔ Protein carbonyls peroxidation in heart extract	SHR SED v/s WKY SED post-intervention ↔Atrogin protein levels SHR EX v/s WKY SED post-intervention ↔Atrogin protein levels WKY SED v/s pre- intervention ↓VO_{2max} SHR SED v/s pre- intervention ↓ VO_{2max} SHR EX v/s pre- intervention ↑ VO_{2max} SHR EX v/s pre- intervention ↑ VO_{2max}
Jordao [38].	SHR and WKY rats. SHR SED $n=10$ WKY SED $n=10$ SHR EX $n=10$ WKY EX $n=10$.	Swimming training of 5 days a week for 1 h for 10 weeks, with an additional workload of 4% of the animal's body weight.	WKY SED v/s pre-intervention ↔MBP WKY EX v/s pre-intervention ↔MBP SHR SED v/s pre- intervention ↔MBP SHR EX v/s pre- intervention ↓MBP	WKY SED v/s WKY EX ↔ Nox1 Aorta expression ↔ Nox4 Aorta expression ↔eNOS Aorta expression ↔Vascular nitrite SHR EX v/s SHR SED ↔ Nox1 Aorta expression ↓ Nox4 Aorta expression ↔ eNOS Aorta expression ↑Vascular nitrite	WKY SED v/s WKY EX ↔ Relative maximal endothelium-dependent vasorelaxation induced by ACh SHR EX v/s SHR SED ↑ Relative maximal endothelium-dependent vasorelaxation induced by Ach WKY SED v/s pre -intervention ↔ VO_{2max}, ↔ HR WKY EX v/s pre- intervention ↑VO_{2max},↓HR SHR SED v/s pre- intervention ↔VO_{2max},↔ HR SHR EX v/s pre- intervention ↑ VO_{2max}, ↓HR

Table 2 (continued)

Author	Sample	Intervention	Effects on SBP, DBP or MBP	Effects on OE biomarkers	Another relevant outcomes
Silva [39].	SHR and WKY male rats from 11 to 12 weeks of age. WKY SED SHR SED WKY EX SHR EX.	An aerobic training on a treadmill at 0% incline for 8 weeks, with sessions of 1 h a day, 5 days a week.	WKY SED v/s pre- intervention ↔MBP WKY EX v/s pre- intervention ↔MBP SHR SED v/s pre- intervention ↑MBP SHR EX v/s pre- intervention ↔MBP	WKY SED v/s pre- intervention ↔CAT activity, ↔CAT expression ↔SOD expression, ↔GPX expression ↔Prdx expression, ↔Txn expression ↔Ho-1 expression WKY EX v/s pre- intervention ↔CAT activity, ↔CAT expression ↑SOD expression, ↑GPX expression ↑Prdx expression, ↑Txn expression ↔Ho-1 expression SHR SED v/s pre- intervention ↔CAT activity, ↔CAT expression ↔SOD expression, ↔GPX expression ↓Prdx expression, ↑Txn expression ↔Ho-1 expression SHR EX v/s pre- intervention ↔CAT activity, ↔CAT expression ↑SOD expression, ↑GPX expression ↑Prdx expression,↑Txn expression ↔Ho-1 expression	SHR SED v/s WKY SED ↑ Collagen content in LV SHR EX v/s WKY SED ↔ Collagen content in LV SHR EX v/s SHR SED ↓ TNFα expression in heart ↓NF-κβ translocation ↓IL-1β expression ↑ IL-10 expression

↑ significant increase, ↓significant decrease, ↔ no significant changes, *WKY* Wistar Kyoto Rats, *WKY SED* Wistar Kyoto rats sedentary, *WKY EX* Wistar Kyoto rats exercised, *SHR* spontaneously rat, *SHR SED* spontaneously rat sedentary, *SHR EX* spontaneously rat exercised, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* median blood pressure, *Ach* acetylcholine, *SOD* Superoxide dismutase, *Mn SOD* manganese superoxide dismutase, *CuZn SOD* copper zinc superoxide dismutase, *CAT* Catalase, *GPX* glutathione peroxidase, *Prdx* peroxiredoxin, *Txn* thioredoxin, *Ho-1* heme oxygenase 1, *BW* body weight, *LV* left ventricle

Table 3 Summary of results on non DMT2 prehypertensive/hypertensive subjects

Authors	Sample	Intervention	Blood pressure (BP)	Effect of OS biomarkers	Other clinical effects
Feairheller [40].	$n=94$ Subjects with HBP	Aerobic training group 6 months 3 sessions a week for 45–60 min at 50–70% VO_{2max}	SBP (initial) 133 DBP (initial) 87 SBP (final) 130 ↔ DBP (final) 86 ↔	Training group ↓ NOx ↓ NADPH	Training group ↑ VO_{2max}
Tsukiyama [41].	Female $n=64$ and Male $n=120$	Number of weeks: 4 5 days a week Static bicycle for 1 h Both trained at 60% HR_{max}	SBP (initial)130 DBP (initial) 79 SBP (final)128↔ DBP (final) 76↓	↔SOD ↑CAT ↑GPX1 ↑ NO_2^-	↔Arginase I ↓L-Arginine ↔L-Citrulline ↔L-Ornithine ↑Urea
Lamina [42].	$n=357$ Subjects between 50- and 70-years-old with mild to moderate stable HBP. Sedentary	Group 1 HIIT training Number of weeks: 8 3 sessions per week for 45–60 min Group 2 Continuous training Number of weeks: 8 Three sessions per week for 45–60 min Group 3 Control Only daily physical activity for 8 weeks.	Group 1 SBP (initial)130 DBP (initial) 80 SBP (final) 120 ↓ DBP (final) 72 ↓ Group 2 SBP (initial) 31 DBP (initial) 81 SBP (final) 119 ↓ DBP (final)74 ↓ Group 3 SBP (initial) 129 DBP (initial) 80 SBP (final)130↔ DBP (final) 80↔	Group 1 HIIT training ↓ SUA Group 2 continuous training ↓ SUA	Group 1 HIIT training ↑ VO_2 max Group 2 continuous training ↑ VO_2 max
Cook [43].	Group 1 African American $n=14$ Group 2 Caucasian American $n=18$	Resistance training Groups 1 and 2 1-RM bench press Number of weeks: 6 Three sessions per week for 60 min	Group 1 African American SBP (initial) 132 DBP (initial) 76 SBP (final) 133↔ DBP (final) 74 ↔ Group 2 Caucasian American SBP (initial) 131 DBP (initial) 76 SBP (final) 127↓ DBP (final) 73 ↔	Group 1 African American ↓8-IsoP Group 2 Caucasian American ↔8-IsoP	Group 1 African American ↔Size ↓Weight ↓IMC ↓ %Body Fat ↔sICAM ↔TNF-α Group 2 Caucasian American ↔Size ↑Weight ↑IMC ↔ %Body fat ↓sICAM ↔ TNF-α
Fernandes [44].	Resistance group $n=13$ Control group $n=12$	Number of weeks: 10 Resistance group Three series of ten repetitions of nine different exercises Control group No exercise	Resistance group SBP (initial) 142 DBP (initial) 68 SBP (final) 137 ↔ DBP (final) 64 ↓ Control group SBP (initial) 139 DBP (initial) 67 SBP (final) 144 ↔ DBP (final) 72↔	Resistance group ↓MDA ↓ NO_2^- Control group ↑MDA ↔ NO_2^-	Resistance group ↔Glucose ↔Total cholesterol ↔Triglycerides ↔ IMC Control group ↔Glucose ↔Total cholesterol ↔Triglycerides ↔ IMC
Patil [45].	$n=57$ men 60–80 years Control Group = 28 Yoga Group = 29	Yoga group 3 months 6 days a week for 1 h Yoga poses Control group Flexibility and stretching 15–20 min, hike 35–40 min, 5 min rest six times a week	Yoga group SBP (initial) 146 DBP (initial) 74 SBP (final) 133 ↓ DBP (final) 73 ↔ Control Group SBP (initial) 145 DBP (initial) 75 SBP (final) 146 ↔ DBP (final) 74↔	Yoga group ↓ MDA ↑ GSH ↑ Vit C ↑ SOD Control group ↑ MDA ↔ GSH ↓ Vit C ↔ SOD	Yoga group ↔Glucose ↔Serum triglyceride ↔ HDL cholesterol Control group ↔Glucose ↔Serum triglyceride ↔ HDL cholesterol

↓ significant decrease, ↑ significant increase, ↔ no significant changes, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, VO_{2max} maximum oxygen uptake, *ET-1* endothelin 1, *LOOH* lipid hydroperoxide, *RSNO S*-nitrosothiol, *MDA* malondialdehyde, *GSH* glutathione, *SOD* superoxide dismutase, *NOx* nitrites/nitrates in urine, *SUA* serum uric acid, *sICAM* soluble intercellular adhesion molecule-1, NO_2^- nitrogen dioxide

Then, the full text of the selected 146 articles was reviewed against the inclusion and exclusion criteria, resulting in the exclusion of 135 articles. From these, seven were excluded for dealing with cancer and diabetes, 13 for acute exercise, 5 for pulmonary hypertension or disease, four for heart failure, 19 involved no hypertensive animals/subjects, 13 for age range, 40 were literature reviews, two were in another language than English, three were in models with renal failure, nine considered another outcome not relevant for this review, 12 used supplementation, two were animal models ovariectomized, two considered pregnant subjects, two were pharmacological studies, one was in a cellular model, and one was a cross-sectional study. Additionally, one article in humans was manually added; therefore, six articles on animal models and six articles on human subjects were finally considered for this review (Fig. 1). For the methodological analysis of the human research, articles in non-diabetic subjects with pre-hypertension/hypertension were analyzed with the PEDro scale [33] (see Table 4 at the end of the results section).

Results

Effects of exercise on the OS biomarkers of animal models of hypertension

In the study of Bertagnoli et al. [34], they utilized a group of 14 SHR of 15 weeks of age. They were divided into two groups, sedentary SHR group (SHR SED) and exercised SHR group (SHR EX). The aerobic training was on a treadmill (5 days/week, 10 weeks, 1 h/day) at a speed of 20 m/min for 1 h. The SHR EX group significantly decreased MAP ($p < 0.05$), SBP ($p < 0.05$) and DBP ($p < 0.05$) compared with the SHR SED group. In addition, the SHR EX group showed a decrease in norepinephrine concentration in cardiac tissue ($p < 0.05$), lipid peroxidation in cardiac tissue ($p < 0.05$), an increase in total nitrates/nitrites ($p < 0.05$), an increases in SOD activity ($p < 0.05$) in cardiac tissue and an decreases in heart weight ($p < 0.05$), compared with SHR SED group. However, no significant changes were observed in the amount of CAT and GPX.

Kimura et al. [35] used 20 male SHR of 14 weeks. They were randomly divided into two groups, ten rats in

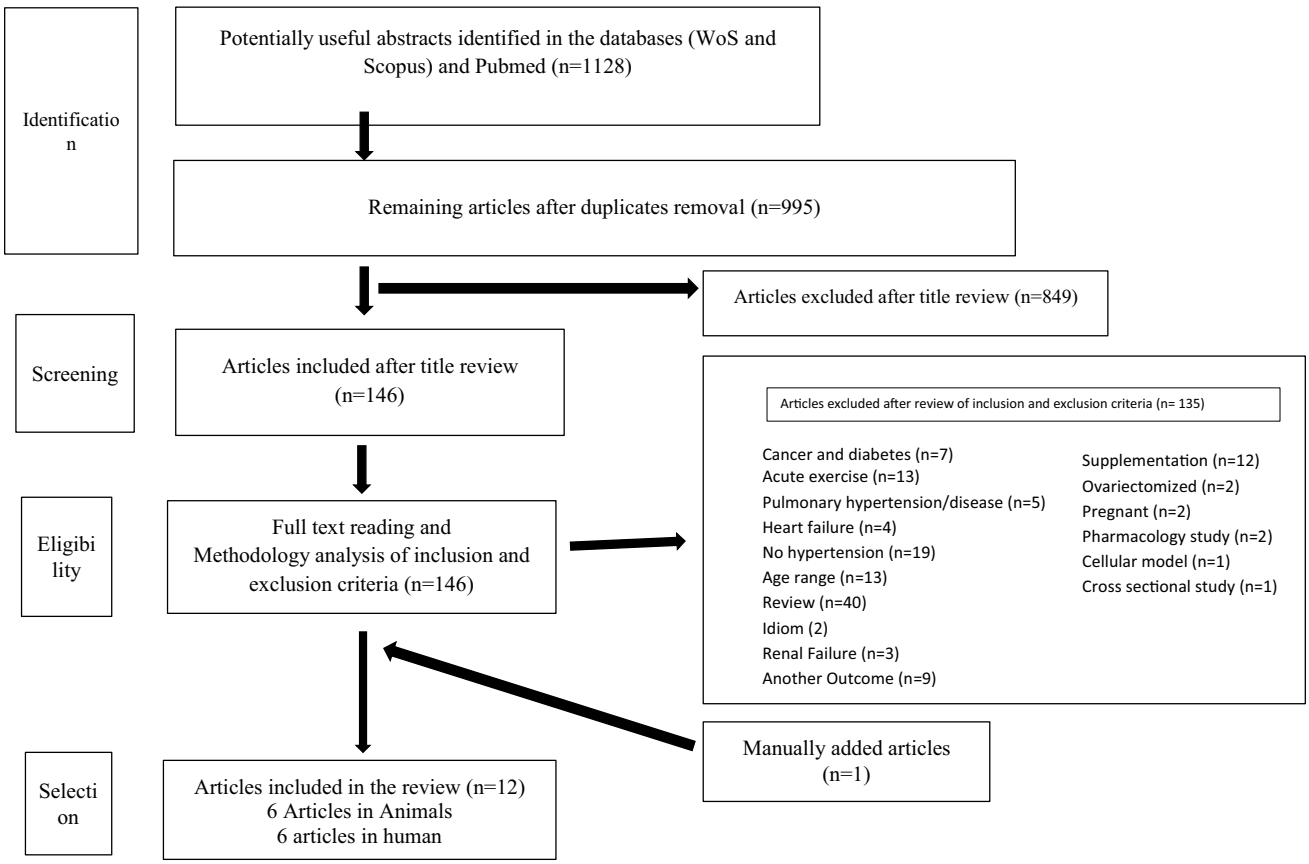

Fig. 1 Article selection process

Table 4 Articles on humans analyzed using PEDro scale

No of criterion	Criteria	Feairheller [40]	Tsukiyama [41]	Lamina [42]	Cook [43]	Fernandes [44]	Patil [45]
1	Eligibility	YES	YES	YES	YES	YES	YES
2	Random allocation	NO	NO	YES	NO	YES	YES
3	Concealed allocation	NO	NO	NO	NO	YES	NO
4	Baseline comparability	YES	YES	YES	YES	YES	YES
5	Blind subjects	NO	NO	NO	NO	YES	NO
6	Blind therapists	NO	NO	NO	NO	UNCLEAR	NO
7	Blind assessors	NO	NO	NO	NO	YES	NO
8	Adequate follow-up	YES	YES	NO	YES	YES	YES
9	Intention-to-treat analysis	NO	NO	NO	NO	NO	NO
10	Between-group comparisons	YES	YES	YES	YES	YES	YES
11	Point estimates and measures of variability	YES	YES	YES	YES	YES	YES
TOTAL		5/11	5/11	5/11	5/11	9/11	6/11

the control group SHR SED and ten rats for the exercised group SHR EX. They performed a free aerobic workout on a treadmill for 10 weeks, recording the total distance traveled at the end of the training, which was 4615 ± 2165 m/day. After the exercise program, MnSOD in aorta had a significant increase in the SHR EX compared with the SHR SED group, although there were no significant differences in either of the two SHR groups in Cu/Zn SOD. At the end of the training, a decrease in body weight was also detected, especially in the SHR EX group. Regarding the SBP, there were no significant decreases in either of the two groups.

In the investigation of Soares de Andrade [36], 53 rats were used; 14 sedentary Wistar rats (WKY SED), ten exercised Wistar rats (WKY EX), 15 SHR SED and 14 SHR EX. Aerobic training in a treadmill was performed for 13 weeks, five times a week at 55% VO_{2max} for 60 min. A decrease was observed in the SBP of the SHR EX group compared with the SHR SED group ($p < 0.05$), in addition to a significant decrease in 4-hydroxynonenal and lipid hydroxyl peroxidation in the left ventricle ($p < 0.05$), while in the WYK SED and EX groups there were no significant differences in SBP, 4-hydroxynonenal and lipid hydroxyl peroxidation in the left ventricle.

In another study, carried out by Campos et al. [37], a group of SHR male rats aged 12–22 weeks were intervened and used WKY rats for control. They performed 10 weeks of swimming training; 5 days a week for 60 min. At the end of each session, the rats ran on a treadmill for 10 min. The SHR EX shows a significant decrease in SBP compared with SHR SED ($p < 0.05$). Furthermore, SHR SED presented a higher lipid peroxidation compared with SHR EX ($p < 0.05$) and a higher concentration of protein carbonyl levels in heart lysate compared to the WKY SED group ($p < 0.05$). However, the SHR EX group did not show significant changes in lipid peroxidation and protein carbonyls in the heart compared with WKY SED.

Jordao et al. [38] used 40 rats (SHR SED $n = 10$, WKY SED $n = 10$, SHR EX $n = 10$, and WKY EX $n = 10$). They underwent a swimming training of 5 days a week for 1 h for 10 weeks, with an additional workload of 4% of the animal's body weight. After the training, the rats were euthanized to analyze their aortic tissue. A significant decrease in the systolic pressure of SHR EX was found ($p < 0.05$), alongside a decrease in the levels of Nox4 compared with SHR SED group ($p < 0.02$) and a significant increase of vascular nitrite compared with SHR SED group ($p < 0.02$). The eNOS levels were maintained in both groups (SHR SED and SHR EX). Additionally, the SHR EX group show a significant increase of VO_{2max} ($p < 0.05$) and a significant decrease in their heart rates (HR) ($p < 0.05$). At a higher dose of ACh (10–4 M), both the maximal endothelium-dependent vasorelaxation response and the vasodilator response in the SHR EX group were significantly improved compared with SHR SED group ($p < 0.01$).

Silva [39] used SHR and WKY male rats from 11 to 12 weeks of age. The rats were divided into four groups, WKY SED, SHR SED, WKY EX, and SHR EX. They performed aerobic training on a treadmill at 0% incline for 8 weeks, with sessions of 1 h a day, 5 days a week. After the 8 weeks of intervention, the study showed a significant increase in mean arterial pressure (MAP), in the SHR SED group. However, the SHR EX group did not present an increase in MAP, but it showed a higher expression of SOD, GPX, peroxiredoxin and thioredoxin after the exercise training program, without presenting changes in the activity and expression of CAT in the heart homogenate. Furthermore, SHR SED group increases the expression of inflammatory cytokines such TNF-α ($p < 0.05$) and IL-1β ($p < 0.05$) compared with WKY SED group, while SHR

EX group don t have differences in inflammatory cytokines expression compared with WKY SED group, but shows a significant increases in IL-10 expression ($p < 0.05$), an anti-inflammatory cytokine, compared with WKY SED group. At last, the SHR SED group shows at higher translocation of NF-κβ ($p < 0.05$) after the time of intervention, while the SHR EX group do not show differences.

Effects of aerobic exercise on the OS biomarkers of subjects with HBP

In Feairheller's study [40], 94 participants (44 men and 50 women) who had pre-HBP or stage 1 HBP and also C242T and A640G polymorphisms were recruited. They underwent aerobic training for 6 months, with three sessions of 45–60 min at 50–70% VO_2 max per week. At the end of the 6 months' term, there were significant reductions of NO*x* (nitrites and nitrates in urine) and NADPH; however, no considerable decrease in SBP and DBP were found.

Tsukiyama [41] studied a healthy group of 120 men and 64 women from 45- to 48-years-old. The group trained in stationary bicycles at 60% HR_{max}, with five sessions of 1 h for 4 weeks. As a result of this training, L-arginine was significantly reduced; DBP was reduced in all subjects, there was an increase in NO_2 levels as well as in the expression of CAT and GPX in monocytes, and no changes were found in SOD1 expression.

A third investigation, conducted by Sikiru Lamina [42], presented a double-blind, randomized study of 357 sedentary subjects aged between 50 and 70 years with mild to moderate stable hypertension. The intervention lasted 8 weeks, with three 45–60 min' sessions per week at 60–79% HR_{max}. Concluding that period, there was an important reduction in SBP, DBP and SUA (serum uric acid).

Effects of strength training on the OS biomarkers of subjects with HBP

In Cook's research [43], 32 pre-HBP sedentary participants from 18- to 35-years-old were recruited for 6-weeks resistance training. Participants were divided into two groups, the first one conformed by 18 African American subjects and the second one by 14 Caucasian American subjects. Both groups did a 1 Rep Max (1RM) bench press training and strength training for 6 weeks, consisting of three weekly sessions of 1 h each. Plasma and serum samples were taken, leading to the identification of a decrease in the SBP of Caucasian subjects, but not in African American subjects. Even though the groups did not present significant differences, there was a main effect of time (training) for DBP ($p = 0.033$). Additionally, circulating levels of MMP-2 and 8-IsoP did not differ, but baseline sICAM levels were higher in Caucasian subjects ($p < 0.010$).

Furthermore, a significant time x group interaction was found for MMP-9 ($p = 0.036$). In African American subjects, MM-9 was lower before the training ($p = 0.018$) and decreased considerably after the training ($p < 0.001$). Additionally, their 8-IsoP decreased after the resistance training, which did not happen in Caucasian subjects ($p = 0.039$).

Another study was carried out by Fernandes [44], who studied non-smoker hypertensive women from ages 60 to 75 who were not physically active for at least 6 months. First, they were divided into a control group and a training group. The training group underwent strength training for 10 weeks, which consisted of two weekly sessions during the first 5 weeks and three weekly sessions during the remaining weeks. In each training, they performed ten reps of each exercise with the lowest load. The results showed a significant reduction of SBP and DBP in the training group and a higher reduction of plasma MDA concentration in comparison with the control group.

Effects of flexibility training on the OS biomarkers of subjects with HBP

Patil's study [45] recruited 57 elderly male individuals from 60- to 80-years-old. They were divided into two groups, one control group and a study (yoga) group. The yoga group practiced yoga early in the mornings (06:00–07:00 am), 6 days a week for 3 months with the supervision of a yoga instructor. The control group did flexibility or stretching exercises for 15–20 min and 35–40 min walks followed by a 5 min rest in the same conditions as the yoga group (1 h in the mornings, 6 days a week for 3 months with the supervision of a qualified instructor). Blood samples were withdrawn through venipuncture, showing no significant differences between the two groups at the beginning of the intervention. Moreover, baseline levels of fasting blood glucose, serum triglyceride, total cholesterol and HDL cholesterol were within a normal range in all subjects. At the end of the intervention, while the yoga group presented a reduction of serum MDA ($p < 0.001$), the MDA of the control group was considerably higher ($p = 0.04$). Compared with the control group, the yoga group presented significant improvements in plasma antioxidant capacity, together with increased levels of both SOD ($p = 0.007$) and GSH ($p = 0.002$). Serum Vit C levels also increased ($p = 0.002$) in the yoga group, contrarily to the decreased levels of the control group ($p = 0.015$). Lastly, the yoga group presented reductions of SBP ($p < 0.001$), PP ($p < 0.001$) and MAP ($p < 0.001$) which were not found in the control group.

Discussion

The present review dealt with the effects of different exercise methods on the OS biomarkers of hypertensive animal models without kidney damage and non-diabetic pre-HBP and

HBP subjects. In animal models (SHR), an aerobic exercise protocol decreased SBP [34, 36, 37], DBP [34] and MAP [34], in addition to decreasing biomarkers of oxidative stress damage such as lipid peroxidation in cardiac tissue [34, 36] and preventing oxidative damage. Moreover, an exercise in SHR rats increases the expression, content and activity of SOD [34, 35, 39] and increases expression of GPX [39].

Jordao et al. [38] observed a lower expression of Nox4 in the aorta along with a higher bioavailability of nitrites after a program of exercises in SRH. Additionally, the levels of relaxation induced by ACh in SHR EX rats were similar to those of the WKY SED; however, the SHR SED presented a lower relaxation induced by ACh. Additionally, while Bertagnolli et al. [34] observed that exercise decreases norepinephrine levels and lipid peroxidation in cardiac tissue, Silva et al. [39] observed a decrease in ANG II in plasma and cardiac tissue after a program of aerobic exercise, together with a lower accumulation of collagen in cardiac tissue associated with less pathological cardiac remodeling. These results allow us to presume that exercise decreases the sympathetic modulation, allows a lower release of ANG II. ANG II stimulates the activity of Nox4 so when levels of ANG II decreases induce a lower activation of Nox4, and in this way, exercise reduced the activity of some of the most critical ROS sources, which in turn allows a greater bioavailability of nitrites and more efficient vasodilation [38].

In human studies, Feairheller [40], Tsukiyama [41] and Sikiru Lamina [42] research pointed out a decrease in the different sources of ROS, such as NOX and xanthine oxidase due to aerobic exercise. Furthermore, concentrations of SUA, which is an independent risk factor for HBP, also decreased. Studies on strength training [43, 44] indicate a reduction of sICAM and 8-IsoP damage mechanisms, which are related to inflammatory markers that contribute to HBP. Additionally, flexibility training also decreased OS biomarkers (MDA) and improved SOD, GSH and Vit C detoxification systems [45].

Interestingly, in Cook's study [43] on the effect of strength training in African American and Caucasian participants, only the BP of the latter decreased after the intervention, even though the FR levels in the former also decreased. Details of this situation were not given. Nevertheless, the reduction of BP should have entailed a reduction of FR due to the functions of NO. However, a possible explanation for this is the influence of genetic factors since subjects were non-respondent [43]. Additionally, it has to be borne in mind that BP is not only caused by OS, so other factors such as diet, sleep quality and occupation, among others, should be analyzed to explain the lack of BP reduction in the African American subjects. Moreover, the effect of other types of exercise, together with variations in the intensity and duration of the routines could be investigated to further account for changes in the BP of these subjects.

Flexibility, strength, and aerobic exercises are known to help in reducing ROS biomarkers, mainly because they produce an increase in endogenous antioxidant defenses. Additionally, a decrease in SBP and DBP is observed in the different types of exercise, which is related to hemodynamic, hormonal and neuronal factors, and an increase of NO; all of which contributes to improve the antioxidant system and diminish inflammation. Despite the few studies about flexibility training, it can be said that this type of exercise is especially helpful to decrease BP because poor flexibility is associated with arterial stiffening [46].

In addition to decreasing biomarkers of OS, physical exercise is recommended both for the prevention and treatment of metabolic pathologies since it improves the cardiorespiratory function [10], allows the increase of muscle strength [47], improves body composition [48], improves insulin sensitivity [10, 49], lowers cytokine levels and induces an augment in the expression and content of antioxidant enzymes through "hormesis" [27, 50, 51].

Paradoxically, exercise (resistance and endurance) is a stressful event, which induces the liberation of catecholamine and cytokines secreted in the skeletal muscle (like IL-6) and also generates a sharp increase of FR, associated to a rise in oxidative stress biomarkers [52, 53]. The explanation for this is that during physical activity there is a higher activity both of the mitochondrial respiration and eNOS, XO and NOX2 enzymes, thereby producing a transient redox imbalance. This phenomenon is known as "exercise-induced oxidative stress" [27, 54, 55].

NOX2 enzymatic complex is one of the main sources of ROS. Produced in muscles during exercise, NOX2 is present in the sarcolemmal membrane, transversal tubules and sarcoplasmic reticules of skeletal muscles. Pannexin channels release ATP in the depolarization phase of the muscle fibers, activating purinergic receptors associated with signaling pathways of IP_3. Additionally, the sarcoplasmic reticules (RS) release Ca^{2+}, activating calcium-dependent protein kinases (CDPKs). CDPKs phosphorylate cytoplasmic subunits of NOX2 (p47-phox), generating a union with the membrane subunits of NOX2 and the return to a NOX2 functional active complex [56, 57]. Other sources of ROS in the muscle is activation of different enzymes such as phospholipase A_2 (PLA_2), neuronal nitric oxide synthase (nNOS) and, to a lesser degree, the production of $O_2^{\cdot-}$ by the mitochondrial electron transport chain. Additionally, the endothelium of the blood vessels that irrigates muscle tissue is involved in the production of ROS. Among the most important ones are the enzymes xanthine oxidase (XO) and endothelial nitric oxide synthase (eNOS) [20].

High-intensity interval training in a short term basis can also have as a consequence acute production of ROS of short duration, increasing the levels of oxidative stress biomarkers like MDA and PC in the blood for 24–48 h [54]. These ROS

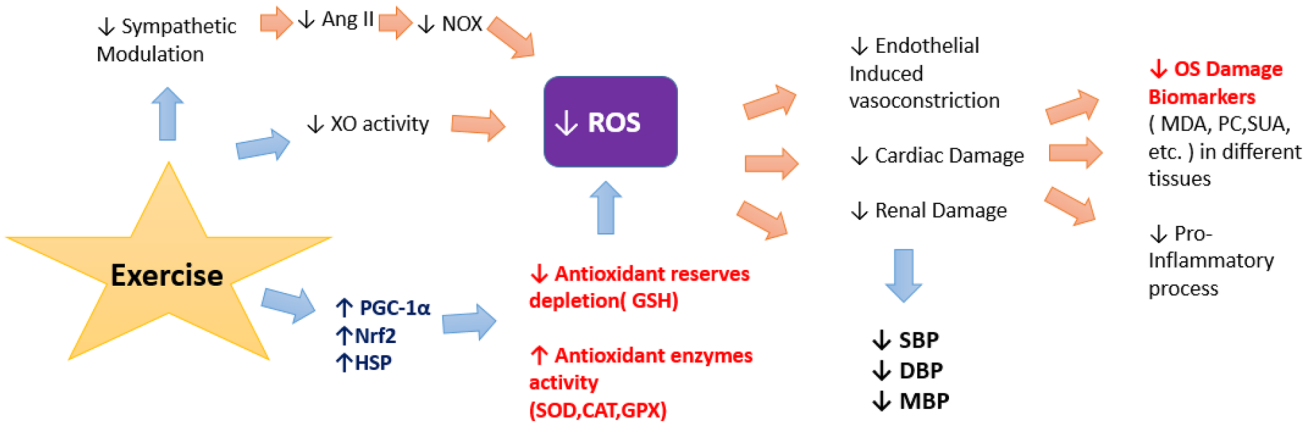

Fig. 2 Schematic effects of exercise in ROS and OS in HBP. In BPH, there is an increase in the sympathetic modulation that generates an increase in the secretion of ANG II, in turn, ANG II stimulates the activity of NOX, in addition to a higher activity of XO in the BPH. NOX and XO generate a chronic increase of ROS, which leads to a depletion of antioxidant reserves and a reduction in the expression, content and activity of SOD, CAT and GPX enzymes. The increase of ROS and the decrease of the antioxidant defense generates a state of chronic oxidative stress damaging different cellular structures of the endothelium, cardiac tissue and kidney, which allows the increase of SBP, DBP and MBP in the BPH. The damage of the various tissues by ROS generates an increase in the EO damage biomarkers such as MDA, PC, among others. Exercise induces a decrease in sympathetic modulation, decreasing ANG II levels, and this decreases NOX activity. Furthermore, exercise allows the activation of transcription factors such as PGC-1α, Nrf2, and HSP inducing an increase of antioxidant enzymes such as SOD, CAT and GPX in addition to the GSH content. The lower production of ROS and the increase in antioxidant defense allows to decrease the damage of endothelium, heart tissue and kidneys, which allows a decrease in SBP, DBP and MBP in addition to reducing the biomarkers of EO damage in different tissues and blood. It is for the above that physical exercise can be a useful tool for the treatment of BPH

generated during endurance and resistance training produce adaptations using the "hormesis" principle, allowing the activation of signaling pathways which in turn activate the PGC-1α [29], Nrf2 [30], NF-κB [31] and HSP [32].

PGC-1α works as a transcriptional coactivator through the recruitment and correlation of transcription factors that regulate muscle gene expression. It incorporates Nrf2, gives rise to mitochondrial biogenesis and increases the expression of antioxidant enzymes [58]. An increment can also activate PGC-1α in the production of H_2O_2 via AMPK. H_2O_2 is capable of decreasing the production of ATP from the mitochondrion, lowering the ATP/ATM ratio and allowing for the activation of AMPK, which directly phosphorylates PGC-1α [59]. While redox modifications produce the extraction of Nrf2 after physical exercise, Keap1 keeps Nrf2 inside the cytosol. Oxidative stimulation helps to covalently modify thiol groups of Keap1 to dissociate from the Nrf2, enabling the transfer to the nucleus by unions with ARE (antioxidant response elements) and increasing the manifestation of antioxidant enzymes [30].

In the NF-κB complex, ROS divided the trimeric complex preformed by the inhibitory protein IκB (inhibitor of NF-κB) and the p50/p65 protein dimers. The phosphorylation of IκB subunits is produced immediately as a consequence of redox changes. When this subunit is detached from the p60/p65 heterodimer, it can be translocated to the nucleus and subsequently bound to DNA to begin transcription associated with cytokines such as IL-6 [56].

HSP is a family of proteins that recognize misfolded proteins and allow the maintenance of the cell's structural integrity. The most characteristic HSPs are Hsp70 and Hsp60 [60]. After an exercise program, a transient increase in ROS activates the JAK/STAT pathway, which mediates H_2O_2-induced Hsp70 expression [61]. Furthermore, ROS can generate reversible oxidation of proteins that allow the activation of the stress response, in addition to damage at a muscular level, increasing the protein content of Hsp70.

Along with the above, ARE have been identified in the promoters of Hsp70, indicating a putative role for Nrf2 in the redox regulation of Hsp70 [60]. It has been observed that an increase in Hsp70 allows cardioprotection against ischemia/reperfusion processes. Additionally, detraining processes significantly decrease the content of Hsp70 in the myocardium [62].

Physical exercise enables the activation of Nrf2, NF-κB, PGC-1α and HSP, causing an increase in the activity and content of SOD, CAT and GPX enzymes in red blood cells [31, 32, 51, 63, 64] and cardiac tissue. These enzymes, in turn, enhance glutathione levels, mitochondrial biogenesis and antioxidant capacity of tissues, improving antioxidant defenses and thus decreasing the concentration of oxidative stress biomarkers [34, 36]. Besides, exercise can decrease plasma levels of norepinephrine and consequently, the levels of ANG II in plasma and cardiac tissue. Lower levels of ANG II generate lower Nox4 activity, higher nitrite bioavailability and a better eNOS function. All these factors together

allow a cardioprotective effect on the protein structure of the heart, which permits a lower remodeling and cardiac hypertrophy induced by HBP [39]. Additionally, exercise can induce lower lipid peroxidation and reduced expression of inflammatory cytokines in heart samples of SHR EX compared with SHR SED (Fig. 2) [34, 36–38].

Therefore, physical exercise generates a decrease in oxidative stress damage biomarkers in different tissues, since it can reduce the activity of the sources that generate ROS and the ones that can generate damage to cardiac tissue, aorta and endothelium. Additionally, it can increase the content and activity of antioxidant enzymes in heart and plasma, and improve the bioavailability of nitrites and the capacity of relaxation of the endothelium. Because of this, a reduction in blood pressure is achieved, besides protecting the heart from oxidative damage, which leads to less pathological remodeling [39].

Concerning the presence of HBP and T2DM in obese subjects, also called metabolic syndrome, it has been observed that the production of NO is 40–50% lower than the one of non-obese subjects [53], which generates a lower response to vasodilator stimuli. In subjects with diabetes, an increment in proinflammatory cytokines (TNF-α) is found, which further decreases the production of NO and increases the production of superoxide anion [65].

Notwithstanding the above, further studies on the effects of exercise on non-diabetic subjects with HBP are needed, as several reviewed articles considered indirect markers of oxidative stress, such as uric acid. Furthermore, to better assess the levels of biomarkers of oxidative stress in this subjects it is necessary to consider direct ROS damage biomarkers, like MDA, F2-isoprostanes and protein carbonyls, activity and content of antioxidant enzymes such as SOD and CAT and finally the intracellular redox balance assessed by the GSH/GSSG ratio [10].

Conclusion

Physical exercise is associated with a reduction of both blood pressure and oxidative stress biomarkers. Although animal models, and particularly SHR, have shown the beneficial effects of exercise on ROS biomarkers, clinical studies in humans have presented contradictory evidence. Nevertheless, the exclusion of systematic reviews and meta-analyses, together with the heterogeneity of the training and measurement methodologies in the selected human articles, constitute limitations for this review and create difficulties in making recommendations. Despite this, it can be concluded that to enhance the effects of exercise on the reduction of blood pressure and OS biomarkers it is necessary to consider aerobics, strength and flexibility exercises together, which can be combined into a concurrent training model.

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Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

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

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