The Open Sports Sciences Journal

Content list available at: https://opensportssciencesjournal.com

RESEARCH ARTICLE

Inflammatory Indices during and after a Randomized Controlled Trial on Exercise in Old Adults: Could Moderate-intensity Exercise be Safe Enough? (Active Elderly and Health – Clinicaltrials.Gov, NCT03858114)

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Abstract:

Background:

Aging is characterized by a progressive increase in chronic diseases. According to WHO's guidance, there is a need to develop strategies to monitor, maintain and rehabilitate the health of older people. The present research aims to elucidate whether or not a moderate physical activity intervention in older adults can cause an increase in inflammatory biomarker indices such as C-reactive Protein (CRP) and erythrocyte sedimentation rate (ESR). It is a valuable tool for promoting health that can be considered tolerable in the over-65 population.

Methods:

120 males and females over 65 years of age participated in a randomized controlled trial (RCT NCT03858114) in two groups of 60 individuals of similar size and underwent moderate physical activity or cultural and recreational activities. The exclusion criteria were being younger than 65 years old, being unable to participate in physical activity for medical reasons, and a Body Mass Index of greater than 35. Blood samples from participants were collected for the pre-treatment period (t0), at the end of the study of 12 weeks (t1), and 20 weeks after the end of the study (t2) for measurement of inflammatory indices CRP and ESR.

Results:

The commonly routine tests for inflammatory reactions (ERS and CPR) showed no change at the end of an RCT on mild-to-moderate exercise.

Conclusion:

The results on inflammatory indices confirm the safety of this type of intervention and encourage its long-term use and testing.

Keywords: Randomized controlled trial, C-reactive protein, Erythrocyte sedimentation rate, Old adults, Physical activity, Chronic diseases.

Article History	Received: April 22, 2022	Revised: November 2, 2022	Accepted: December 7, 2022

1. INTRODUCTION

Physical activity has a positive effect on the immune system, resulting in a reduced risk of cardiovascular disease, diabetes, chronic obstructive pulmonary disease, colon and breast cancer, dementia, and depression [1 - 4]. In this phenomenon, also stem cells present in different organs [5] seem to be linked to exercise and physical activity [6]. The underlying mechanism of this widespread benefit is a reduction in the body's state of inflammation. A chronic level of inflammation, in fact, is likely to underlie these pathological conditions: evidence is the presence of high levels of substances in the body, such as interleukin-6 and C-reactive protein, mediators of inflammation.

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In addition, it is found that most patients with microtrauma, a condition in which the patient typically presents with localized pain, improve with activity modification and rehabilitation. Microtrauma is followed by an inflammatory process and subsequent fluid and electrolyte shifts. During the progression of these events, muscle spasms may be present, aggravating the overall condition. Exercise has an anti-inflammatory action, and therefore, in the long term, regular physical activity can protect against the development of chronic diseases [7]. However, for this reason, in assessing the appropriateness of a physical activity intervention, one must consider how much intensity may interact with levels of inflammation. In fact, there is a limit to physical activity beyond which the body's immune defense functions tend to decrease rather than increase. In a sense, the immune system's response can be said to be biphasic: there is an improvement up to a certain level of physical activity, but if you go beyond that a worsening takes over. According to Guidelines Exercise in Old Adults is a Preventive Tool Contrasting Cognitive and Functional Decline Instead [8 - 12], Physical Inactivity is a Determinant of Dementia [11 - 18]. Physical Activity Limits Disability Related to Chronic Diseases and has Positive Effects on Quality of Life and Biological Rhythms [19]. Scientific reading shows that moderate activity, for example, can have an important effect on the inflammatory state. However, there are still controversies about the definition of standards to be used in clinical indications, *i.e*., duration and kind of exercises (aerobic and/or anaerobic) and level of intensity. Some studies have also evaluated the appropriateness of vigorous physical activity intervention in similar populations; however, more research is needed to strengthen the confidence with which a certain intensity of physical activity can be suggested or indicated in an older population (older adults). Randomized controlled trials in research studies adopted high-intensity exercises with up to five sessions per week [12]. In fact, this model is difficult to introduce as common practice in old people living in the community, in which mild/moderate chronic diseases (hypertension, diabetes and so on) are usual.

Evaluating the results of an RCT proposing a type of physical activity intervention, conducted three times a week, accessible to older adults with mild chronic cardiovascular or dysmetabolic disorders, improved cognitive performance in the older adults was found after three months [20, 21]. An exercise of this type could be continued in the long term if safety and the absence of secondary consequences were guaranteed. Vigorous physical exercise increases the flow of muscle oxygen and causes intracellular events that can lead to an increase in oxidative damage [22]. Exercise could thus paradoxically induce harm if carried out with excessive intensity. Senescent organisms are more sensitive to oxidative stress during exercise due to age-related ultrastructural and biochemical changes [23, 24].

The previous clinical trial mentioned above (NCT03858114) [20, 21], aims to measure, through a randomized controlled trial, whether an intervention based on moderate physical activity can improve the quality of life and motor skills of community-dwelling older adults (primary outcomes). The secondary objectives are to measure whether physical activity improves (1) cognitive performance, (2) pain perception, (3) biological rhythms and immune response related to metabolic control, and (4) community assets (environments, mobility, safety, social cohesion). In comparison to the previously described studies, the current study seeks to determine whether moderate physical activity in older adults can lead to a possible change in inflammation markers (VES and CRP), similar to the damage seen in vigorous physical activity [20, 21]. ESR is the rate at which red blood cells treated with anticoagulant descend in one hour in standardized conditions. It is a test used as a non-specific measure of inflammation. CRP is a blood plasma pentameric protein, whose circulating concentrations rise in response to inflammation. It is a ring-annular protein of hepatic origin that increases in relation to interleukin-6 macrophages and T-cell secretion. CRP activates the complement system *via* C1q of dead or dying cells, promoting phagocytosis by macrophages (Fig. **1**).

2. METHODS

2.1. Design

We included in a Randomized Controlled Trial 120 males and females over 65 years of age into two groups of similar size and gender. The experimental group (60) consisted of 44% males and 56% females. While the control group (60) was composed of 36% males and (64%) females. The samples were well balanced for the main known confounding factors (age, between 71 and 73 years old, gender, and educational level). The experimental group underwent moderate physical activity and the control group cultural and recreational activities focused on education on wellness, cooking, and the history of local culture.

2.2. Participants

Were recruited through public notices and referrals from primary health care services. The Italian Olympic Committee (Italian National Olympic Committee-CONI) was contributing to the study through support in recruiting older adults (through radio, TV and newspaper spots) and by selecting gyms and training staff for the intervention. Subjects (N = 120) were assigned by randomization to the active interventional protocol (physical activity) or the control intervention. All participants were assessed before the treatment (t0), at the end of the 12-week trial (t1), and 20 weeks after the end of the trial (t2). In the two weeks prior to treatment, participants received physical, medical, and psychological assessments, and were subjected to blood sampling to evaluate the indices of blood inflammation. The description of setting and the recruitment methods has been extensively described in the previous articles already published. All participants-were required to have a medical certificate for non-competitive physical activity. Exclusion criteria included: a Body Mass Index of greater than 35, the presence of diseases that preclude moderate physical activity (as determined by a medical examination), and participation in a physical activity program. Participants were enrolled at the Department of Medical Sciences and Public Health (coordination actions and data analysis), Movement Analysis Laboratory at the Citadel of Monserrato (biomechanical and neuropsychological medical assessments

and blood assays), Laboratory of Clinical Biochemistry and Molecular Biology at the University Hospital Company (AOU) of Cagliari (blood tests), at 4 gyms that participated in previous joint studies between the University of Cagliari and CONI (active intervention), and the Rehabilitation Center of the AOU Cagliari (control condition).

2.3. Study Tool

The hematic values of erythrocyte sedimentation rate (ESR), within the normal range is 0 to 22 mm/hr for men and 0 to 29 mm/hr for women [25] and C-reactive protein (CRP), within the normal range of 0,5 mg/l and 10 mg/l, with variability depending on the age and sex of the patient [26], were examined. A sedimentation with capillary photometry technology was adopted for measuring ESR by the TEST-1 device (Alifax, Padova, Italy). Serum CRP concentrations were measured using an immunoturbidimetric high-sensitive assay (Modular RR analyzer, Roche, Basel, Switzerland). Blood samples were collected at t0, t1 and t2.

2.4. Interventions

The exercise was conducted in 3 weekly sessions. The effort was not to exceed 60% of the heart rate reserve (HRR). The active phase included aerobic and anaerobic exercises. After signing informed consent, enrolled subjects were randomly assigned to the experimental treatment by blocks of randomized permutations at a 1:1 rate; codes have been masked. Medical and psychological examiners will not know whether participants were assigned to the active intervention or control condition. The project coordinator arranged meetings with participants before each appointment to instruct them not to disclose the treatment they had received. The control group condition consisted of cultural and recreational activities around the main sites of cultural interest of the city, supported by a health educator. Participants were divided into groups of the same size with the same active intervention times.

The control group condition involved participants for the same amount of time used as the intervention condition, but without the involvement of physical activity, in order to provide a comparator lacking the expected effective stimulus, while all other effects (*e.g.*, sociability, fun, bonding, time sharing, companionship) were taken into account.

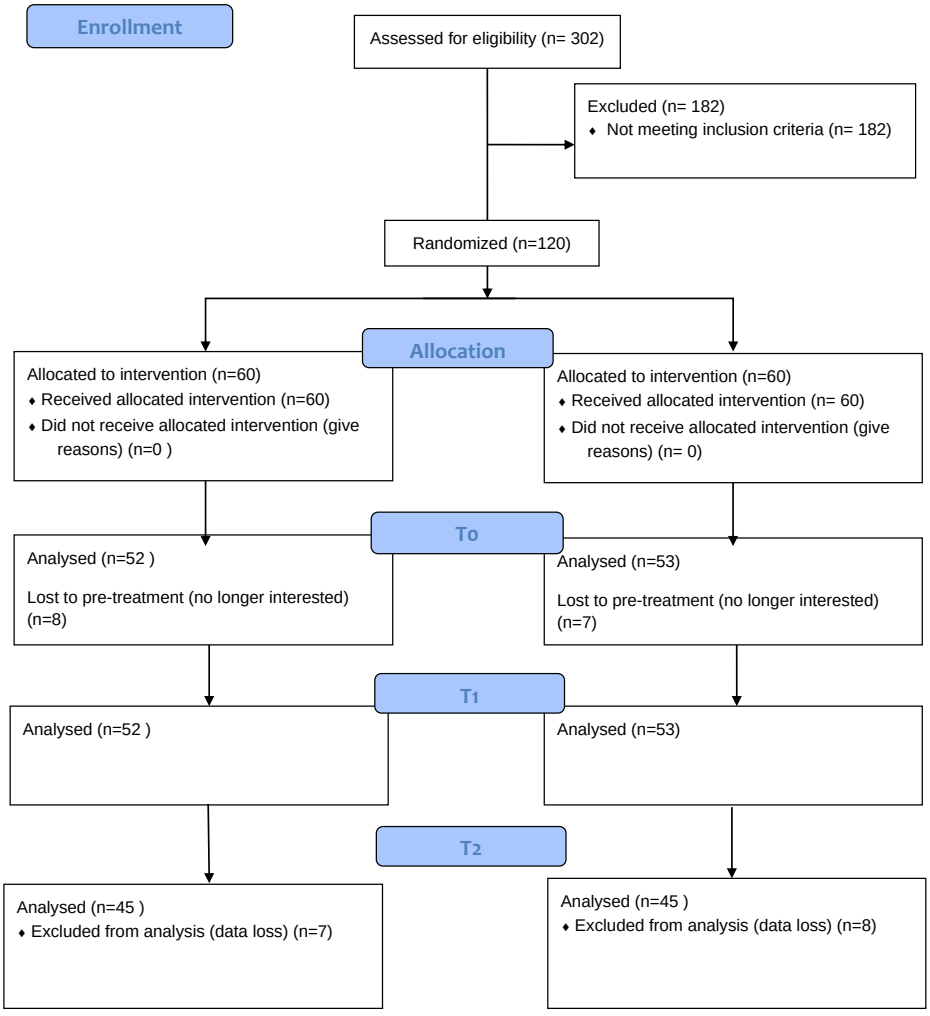

Fig. (1). CONSORT 2010 flow diagram.

Table 1. Mean ± standard deviation of blood rate of ESR and CRP in intervention and control group at t0, t1 and t2.

ESR/CRP	T0	T1	Anova Boferroni	P	T2	Anova Boferroni	P
Exercise ESR	15.95±8.28 (N=52)	15.56±11-70 (N=52)	df1,102,103 F=0.098	0.845	15.02±9.34 (N=45)	df 1,95,96 F=0.270	0.604
Control group ESR	15.26±8.66 (N=53)	12.95±8.87 (N=53)	df1,104,105 F=1.840	0.1789	14.45±9.66 (N=45)	df 1,96,97 F=0.641	0.425
Exercise CRP	2.49±4.56 (N=52)	2.15±3.15 (N=52)	df1,102,103 F=0.186	0.659	1.76±1.99 (N=45)	df 1,95,96 F=0.989	0.322
Control group CRP	1.79±2.62 (N=53)	3.26±8.28 (N=53)	df1,104,105 F=1.508	0. 22	1.71±2.57 (N=45)	df 1,96,97 F=0.022	0.822

Legend: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; dF, degrees of freedom for each origin of variance. Statistic F: the factor (batch) mean square divided by the error mean square. Prob > F: the p-value (P). T0, blood samples collected in the pre-treatment period for the measurement of inflammatory indices CRP and ESR; T1, blood samples collected at the end of the 12-week study for the measurement of inflammatory indices CRP and ESR; T2, blood samples collected 20 weeks after the end of the study for the measurement of inflammatory indices CRP and ESR.

Table 2. Individual with ESR rate ≥25 and CRP rate ≥8 in the intervention and control group at t0; t1 and t2.

ESR/CRP	T0	T1	Chi square With Yates correction	P	T2	Chi square With Yates Correction	P
Exercise ESR	(N=6/52)	(N=8/52)	0.385	0.535	(N=6/45)	0.001	0.999
Control group ESR	(N=8/53)	(N=5/53)	0.476	0.322	(N=6/45)	0.148	0.701
Exercise CRP	(N=3/52)	(N=3/52)	0.000	1.000	(N=1/45)	0.133	0.716
Control group CRP	(N=2/53)	(N=3/53)	0.001	0.999	(N=1/45)	0.0001	0.999

Legend: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Prob > F: the p-value (P); T0, blood samples collected in the pre-treatment period for the measurement of inflammatory indices CRP and ESR; T1, blood samples collected at the end of the 12-week study for the measurement of inflammatory indices CRP and ESR; T2, blood samples collected 20 weeks after the end of the study for the measurement of inflammatory indices CRP and ESR.

2.5. Statistical Analysis

The analysis of variance (ANOVA) test has been used to conduct studies on the experimental groups and the control group. To fully understand the differences between the groups in an ANOVA, a "multiple comparison analysis" was conducted using the Bonferroni test. The experimental and control groups were measured three times in parallel by comparing the total average levels (ESR and CRP), setting the score at T0 as a pivot, and comparing this average score with the scores. The comparison of the frequency of the number of people with an evaluated measure above the threshold within the same group (experimental or control) was then conducted between T0 *versus* T1 and T0 *versus* T2 by means of a chi-square test.

2.6. Ethical Issues

Each participant signed an informed consent to participate in the study. All participants received insurance for trial by a company. The study was carried out according to the Declaration of Helsinki and its revisions [27]. The Committee for Medical and Health Research Ethics of the "Azienda Ospedaliera Universitaria di Cagliari", has approved the study with reference number PG/2018/15546 (approved on October 25, 2018).

3. RESULTS

At the end of the trial, after 12 weeks, 105 people (87%) completed the Trial; 20 weeks after the end of the trial 90 people (75%) were evaluated as it is possible to see in the tables. Table **1** shows no differences in the Mean ± Standard Deviation of blood rate of an ESR and CRP of the participants. In Table **2**, the number of individuals with an ESR rate ≥25 and a CRP rate ≥8 equally did not show any difference.

4. DISCUSSION

The study found the blood levels of the two commonly routine tests for measuring inflammatory reactions (ESR and CPR) did not vary over time at the end of the trial and 20 weeks later of an RCT that compared moderate physical activity for 12 weeks against socializing cultural activity. The already published RCT has highlighted an improvement in cognitive performance in the group subjected to exercise [20, 21] but not in the control group. The exercise conducted during the trial improves pain perception and depressive symptoms, but these conditions worsen again a few months after the end of the exercise.

However, it may be possible to consider a longer period of moderate exercise administration if this proves to be safer than vigorous exercise. In fact, high-intensity exercise can induce micro-traumas. Hence, it may be associated, particularly over a long time, with an increase in routine inflammatory indices caused by micro-traumas [22]. On the other hand, it has been observed that in old adults, even a sedentary lifestyle is associated with an increase in inflammatory indices such as ESR. This is probably linked to a lower antioxidant response

and metabolic abnormalities (as obesity and related metabolic syndrome) [28].

Similarly, mild to moderate physical activity has been found to lower inflammatory response rates in autoimmune diseases [29, 30] or conditions with increased inflammatory response [31]. However, protocols with moderate intensity and mixed anaerobic and aerobic exercises have not been sufficiently tested in healthy adults. Given the lower expected differences between RCT groups in cognitive performance and other indicators, larger samples would have been required, than with vigorous exercise trials [21].

The large trial from which this work is derived is the first that has demonstrated in a large sample of healthy older adults, that mild-moderate activity can improve cognitive performance even in the short term [20, 21]. Previous physical activity protocols involving older adults were mainly aimed at verifying their impact on other outcomes such as quality of life, perception strongly associated with regularity of social rhythms and inclusion [32]. In addition, this type of intervention can have a very important significance in secondary prevention, such as the one indicated for older adults, aiming to intervene early at the first signs of aging. This study adds to the evidence that mild physical activity did not increase indices of routine inflammation as high-intensity exercise did, most likely because of microtrauma caused by physical activity. For these reasons, the practice of moderate-intensity physical exercise in older adults seems to be a fundamental tool of public health to counteract the loss of autonomy in an aging world population [8, 33] even in conditions of high stress, such as that of the recent pandemic, in which it seems to act as a protective factor [34]. Practically speaking, mild-moderate activity improves subjects' cognitive function and reduces depressive symptoms, at least temporarily. Inflammatory indices' effects support the safety of this kind of intervention, promoting its long-term use and verification.5.

5. LIMITATION OF THE STUDY

In the present study, there are some limitations. The sample size was established for the main outcomes of the RCT, however, a sample size check was not performed on secondary outcomes such as inflammatory indices or fidelity to the treatment. For this reason, more methodologically adequate studies would be highly recommended.

CONCLUSION

The commonly routine tests for inflammatory reactions (ERS and CPR) did not vary over time at the end of an RCT on mild-moderate exercise as well as 20 weeks later. The same trial has demonstrated that mild-moderate activity improves cognitive performance, pain perception, and symptoms of depression even in the short term in old adults, but many of these indicators regress when exercise is stopped. The results on inflammatory indices confirm the safety of this type of intervention and encourage its use and verification in the long term.

LIST OF ABBREVIATIONS

CRP	=	C-reactive Protein
ESR	=	Erythrocyte Sedimentation Rate
RCT	=	Randomized Controlled Trial
HRR	=	Heart Rate Reserve

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Committee for Medical and Health Research Ethics of the "Azienda Ospedaliera Universitaria di Cagliari", has approved the study with reference number PG/2018/15546 (approved on October 25, 2018).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Each participant signed an informed consent form to participate in the study.

STANDARDS OF REPORTING

CONSORT guidelines and methodology were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are made available by the corresponding author [A.S].

FUNDING

The study received funding or grants from the following sources: A grant of "Fondazione di Sardegna" 2018; P.O.R. Sardegna F.S.E. 2014-2020.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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