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The Effect of Exercise Training on the Levels of Anti-Inflammatory Factors (IL-4 and IL-10): A Meta-Analysis Study

Mohammad Rahman Rahimi[1], Hassan Faraji[2*], Sasan Kamangar[1]

1. Department of Exercise Physiology, University of Kurdistan, Sanandaj, Iran.
2. Department of Physical Education and Sport Sciences, Islamic Azad University, Marivan Branch, Marivan, Iran.

Corresponding Author's Email: faraji.hassan@iau.ac.ir

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Abstract

Background: Anti-inflammatory markers play a crucial role in chronic diseases.. Regular training is a valuable method to control inflammation.

Aim: This meta-analysis aims to explore the impact of exercise training on anti-inflammatory indicators like IL-10 and IL-4.

Martials and methods: Various databases, including PubMed, Cochrane, Embase, Web of Science, EBSCO, and Google Scholar, were systematically searched for randomized controlled trials from 2007 to 2023. Studies focusing on IL-10 and IL-4 indicators in individuals undergoing exercise training were selected. According to the study inclusion criteria, ultimately, 40 articles were finally selected as study samples for the meta-analysis. The meta-analysis was conducted using fixed and random effects models to analyze the effect sizes, taking into account factors such as age, gender, health status, type and duration of exercise, and BM..

Results: Aerobic training significantly increased IL-10 levels (p=0.00, 95% CI=0.267:0.723, ES=0.495), while the increase after resistance training was not significant (ES=0.295, 95% CI-0.020:0.610, p=0.067). Both aerobic training (ES=-282, 95% CI=-0.795:0.185, p=0.237) and resistance training (ES=0.227, 95% CI=-0.389:0.843, p=0.471) had no significant effect onIL-4 levels. Subgroup analysis revealed a significant increase in IL-10 associated withBMI subgroups (p=0.019), with the highest increase in BMI group 18 to 25 (p=0.001). Subgroup meta-analysis for IL-4 showed no significant differences between subgroups (p>0.05).

Conclusion: Aerobic training was associated with a significant increase in IL-10 levels in healthy and unhealthy subjects, but aerobic and resistance training had no significant effect on IL-4 levels. Further randomized controlled studies are essential, especially focusing on resistance training and different training scenarios.

Keywords: Aerobic Training, Resistance Training, Interleukin-10, Interleukin-4, Systemic Inflammation

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1. Introduction

Chronic inflammation, marked by the extended activation of lymphocytes and macrophages, along with the proliferation of blood vessels and connective tissue, diverges from the protective role of acute inflammation essential for maintaining tissue homeostasis [1]. When inflammation persists over a long period, it is associated with an increase in lymphocytes and macrophages and the growth of blood vessels and connective tissue. Research suggests that ongoing inflammation is linked to tumor progression, influencing cell proliferation, metastasis, and resistance to treatment. [2] Biomarkers of chronic inflammation play a significant role in the development of various conditions, including cardiovascular diseases, type 2 diabetes, osteoporosis, cancer progression, blood clotting disorders, immune responses, and allergies [1, 3-5].

Cytokines, proteins or glycoproteins primarily produced by leukocytes and occasionally by other cell types, facilitate communication between immune and non-immune cells, regulating essential biological processes. While they act as signaling molecules, they do not function in isolation [6]. Cytokine production can swiftly adjust in response to inflammatory triggers, exhibiting either transient or sustained responses. [7] Categorized by their roles, cytokines are primarily divided into pro-inflammatory and anti-inflammatory types. Pro-inflammatory cytokines contribute to inflammation development and progression, whereas anti-inflammatory cytokines are released in response to inflammation, aiming to constrain and reverse the inflammatory process [5]. Besides impacting immune cells, cytokines can influence various other cell types through autocrine, paracrine, and endocrine signaling, influencing processes like proliferation, differentiation, and cell death. Moreover, cytokines play a pivotal role in immune system regulation. [8] Among cytokines, interleukins (ILs) represent a diverse group with over 40 identified types to date. In the context of cancer growth and development, the equilibrium of cytokines significantly influences the progression and metastasis of cancer. Alterations in inflammatory and anti-inflammatory factors can shape the course of cancer development. [2] Anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and potentially IL-6 help reduce inflammation by inhibiting the activity of the pro-inflammatory cytokine.. IL-10, a potent anti-inflammatory cytokine, plays a crucial role in preventing inflammatory and autoimmune pathologies. [9] IL- Produced by TH2 cells, IL-10 primarily targets T helper cells (Th1), inhibiting IL-2 and interferon gamma. It diminishes antigen presentation, MHC class II expression in dendritic cells, macrophage co-stimulatory molecules, th17 cell responses, and suppresses IL-12 production in macrophages. [10] IL-10's anti-tumor effect stems from enhancing NK cell activity, with some attributing this effect to CD8+ or CD4+ cells . [11] By counteracting TNF-α's inflammatory

impact on insulin signaling in adipocytes, IL-10 can potentially mitigate insulin resistance related to adipocytes, emphasizing its primary role in inflammation reduction [12].

IL-4, another interleukin potentially involved in the immune response during physical activity, is situated on chromosome q5 and is produced by CD4 and TH2 cells, impacting both B and T cells. [13] IL4-Known for its pleiotropic activity, it is commonly synthesized by helper T cells, exerting diverse effects on various cell types. Notably, it stimulates human B lymphocytes to generate immunoglobulin E and G, enhances the expression of cell surface molecules like MHC on B lymphocytes and macrophages, thereby boosting their antigen presentation capability. IL-4 promotes Th2 cell differentiation and proliferation, inhibits IFN-gamma activation in macrophages, and enhances mast cell proliferation within the body. [14] Additionally, in collaboration with IL-13, IL-4 contributes to biological effects linked to allergic inflammation and parasite defense. [15] Recent evidence suggests that IL-4 receptors are pivotal in cancer cell proliferation, migration, invasion, and are crucial for type 2 immune response induction and maintenance, correlating with atopic conditions like asthma and atopic dermatitis [16]. IL-4 triggers STAT6 activation, suppressing inflammation by inhibiting pro-inflammatory mediator production such as TNF-α and IL-1 from monocytes. [14, 17]

Regular physical activity is widely acknowledged as a key non-pharmacological approach to prevent and mitigate the risk of various diseases. Studies concentrating on inflammatory profiles suggest that consistent physical training may exhibit an inverse relationship with systemic inflammation markers [18-20]. However, interventional studies examining the definitive impact of chronic physical training on inflammation remain scarce, lacking conclusive and specific outcomes. While some experimental research indicates that regular exercise correlates with elevated levels of IL-4 and IL-10 [21-25], other studies do not consistently report the effects of exercise on these anti-inflammatory markers. [26, 27] Despite some meta-analyses and reviews underscoring the positive influence of exercise training on inflammatory markers [18, 28] contrasting studies exist that do not confirm these effects. [28, 29]

Variations in exercise type, age, gender, health condition, exercise duration, and publication bias could potentially explain these conflicting outcomes. Moreover, there appears to be a lack of research specifically examining the impact of different exercise modalities on IL-4 and IL-10 markers, highlighting insufficient data in this area. Consequently, this meta-analysis was undertaken to explore the influence of chronic exercise training on IL-4 and IL-10 levels, aiming to enhance understanding in this domain.

2. Materials and Methods

The systematic review and meta-analysis protocol was relied on aggregated data from

previously published RCT studies, it did not necessitate ethical approval.

2.1. Data Sources and Searches

Published studies from 2007 to 2023 exploring the impact of exercise on anti-inflammatory markers were retrieved without language limitations from Google Scholar, EBSCO, WOS, PubMed, Embase, and Cochrane databases. Search terms included keywords like "anti-inflammatory agents," "exercise training," "biological markers," "cytokines," "interleukin," "IL-10," "IL-4," "strength training," "aerobic training," and "chronic diseases." Systematic reviews, meta-analyses, and reference lists were also reviewed for additional studies.

2.2. Study Inclusion and Exclusion Criteria

Using the PICO framework, this article included healthy individuals, overweight or obese men and women, and patients above 18 years with any history of sports training. The intervention encompassed any form of chronic exercise, while the comparison involved studies with control groups not engaging in exercise. RCTs providing adequate data on circulating IL-4 and IL-10 levels in both intervention and control groups were considered. Exclusion criteria comprised non-RCT studies, those involving children or animals, duplicate publications, literature reviews, letters to the editor, conference abstracts, and studies evaluating acute exercise effects. Articles without full text or raw data were also excluded. Data analysis involved random and fixed effects models, with effect size reported in terms of mean standard deviation and 95% confidence interval (Appendix Table 1).

2.3. Initial Search Results

The initial search yielded 383 articles related to the topic. Following an initial review of titles and abstracts, 282 irrelevant or duplicate articles were eliminated. Of the remaining studies, 14 involved animal subjects and were excluded during a secondary review. Four articles lacked full text and focused on professional athletes, while one was excluded due to inadequate independent sports training. Ultimately, 40 articles were chosen as study samples for the meta-analysis, as illustrated in the article selection flowchart in Figure 1.

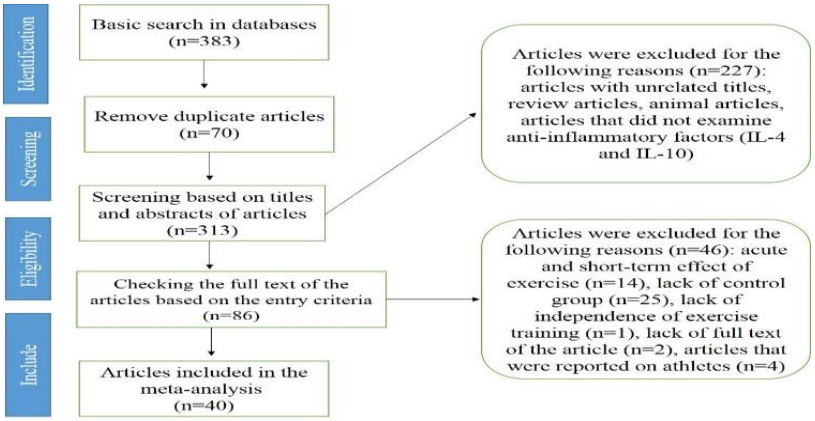

Figure 1. Flowchart of the selection process of the current research articles

2.4. Data Extraction and Quality Assessment

Two authors independently reviewed titles and abstracts of eligible studies, resolving discrepancies with a neutral researcher's assistance. Information was extracted including authors' names, publication year, participant details, exercise interventions, anti-inflammatory factors (IL-4 and IL-10), and their concentrations pre and post-intervention. The quality of studies was assessed using Pedro's 11-item scale, omitting blinding items due to the research nature. A scoring system from 0 to 9 was utilized, with higher scores indicating better quality (Appendix Table 2).

2.5. Statistics

Mean, standard deviation, and sample size were utilized for analysis. For studies reporting median and interquartile range, these were converted to mean and standard deviation. Study characteristics such as exercise type, intensity, duration, frequency, age, gender, disease type, BMI, and supplement intake were recorded. Data analysis was conducted using CMA software, assessing variables between exercise and control groups via effect size (ES) with a 95% confidence level. The random effects model handled heterogeneity, while the fixed effects model was used in its absence. Significance was set at $p<0.05$. Forest diagrams and funnel plots assessed publication bias, with subgroup analysis categorizing studies based on subgroups [30].

Initially, an accumulation graph of all articles was constructed using mean and standard deviation data from pre-test and post-test results of aerobic-control and resistance-control training groups to assess the average effect across studies. Publication bias was evaluated using a funnel plot (effect size versus standard error) and Egger, Begg, and Mazumdar tests to determine bias ($P\leq0.05$) or non-bias ($P\geq0.05$). To address publication bias impact, the Trim and Fill method was employed.

3. Results

3.1. The effect of exercise training on IL-10 levels

Among the 40 articles initially reviewed, 29 focused on aerobic exercises and 6 on resistance exercises. Due to high effect sizes causing heterogeneity, 5 articles were excluded. Ultimately, 35 articles were included in the meta-analysis (Figure 2). Given an I-squared value exceeding 50% (52.73), the random effects model was used to determine the overall effect size (p>0.00). Analysis revealed that exercise training significantly increased IL-10 levels, with an effect size of 0.495 pg/ml (p=0.00, 95% CI=0.267:0.723). Linear regression tests indicated no rejection of the null hypothesis regarding bias, with p values of 0.23 and 0.051, signifying non-bias (Figure 3). The funnel plot displayed symmetrical effect sizes, implying high research validity. Out of the included articles, 24 showed non-significant effect sizes, while 11 exhibited significant effects.

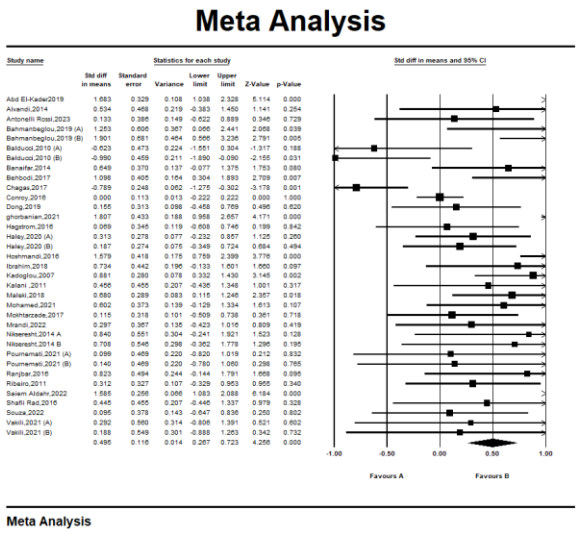

Figure 2. Forest diagram of standardized difference in means (SMD) related to the effect of exercise training on IL-10

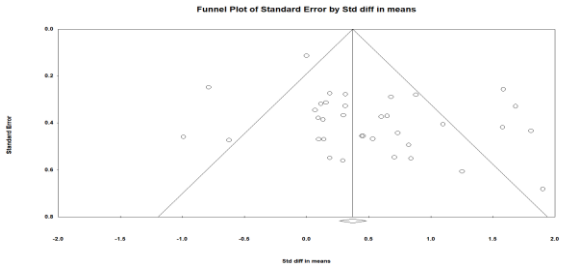

Figure 3. Funnel plot showing the influence of exercise training on IL-10 concentration

3.2. The effect of aerobic training on IL-10

In the meta-analysis examining the impact of aerobic exercise on interleukin-10 levels, data from 29 articles were analyzed. Due to the heterogeneity of the data, as indicated by an I-squared value exceeding 50% (77.25%), a random effects model was employed to assess the overall effect size of the studies (p > 0.0001, Figure 3). The forest plot analysis (figure 4) revealed that aerobic exercise significantly increased interleukin-10 concentrations, with an

effect size (ES) of 0.527 pg/mL (p = 0.0001, 95% CI = 0.260:0.794, ES = 0.527).

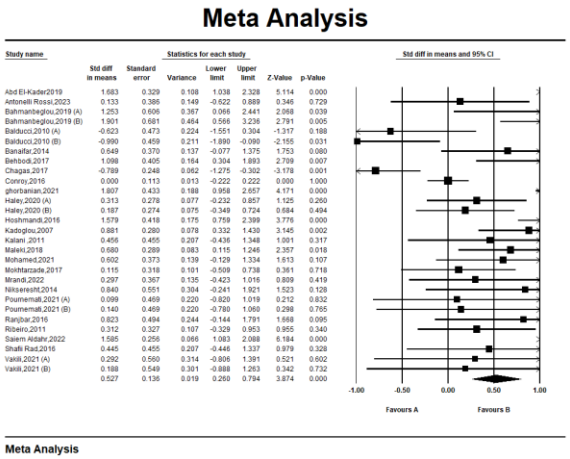

Figure 4. Forest plot of the effect of aerobic training on IL-10

Linear regression tests by Egger, Begg, and Mazumdar tests to assess potential bias yielded p-values of 0.38 and 0.07, respectively. These results indicate that the null hypothesis of these tests was not rejected, suggesting that the study is not biased. The effect sizes in the funnel plot are symmetrical, indicating high validity (Figure 5). Additionally, the analysis showed that 18 articles had insignificant effect sizes, while 11 articles had significant effect sizes.

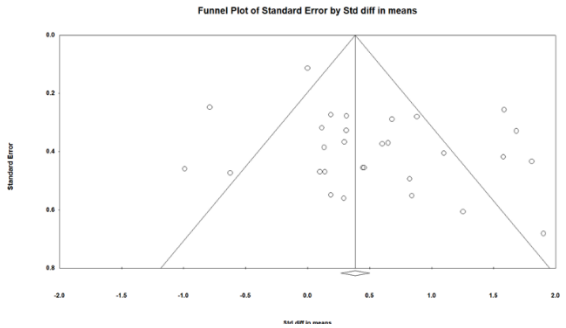

Figure 5. Funnel plot showing the influence of exercise training on IL-10 concentration

3.3. The effect of resistance training on IL-10

The meta-analysis included eight articles to analyze the effect of resistance training on IL-10 levels. Two articles were excluded due to a high effect size, leaving six articles for the main review. The I-squared value obtained due to the heterogeneity of the data was less than 50% (0.00), so the fixed effects model was used to check the amount of data (p<0.67) (Figure 6). The forest diagram related to the studies showed that the total effect size of resistance training studies on IL-10 with a confidence interval (-0.20, 0.610) tended to increase (0.067), but since it was in contact with the reference line, this increase was not significant (ES= 0.295, 95% CI-0.020: 0.610, p=0.067, Fig. 6).

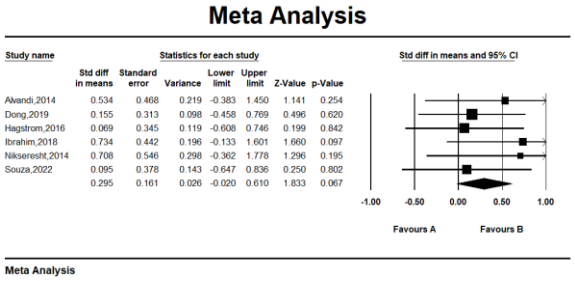

Figure 6. Forest plot illustrating the the effect of resistance training on IL-10

The results of the linear regression tests indicated that there was no bias (p=0.259) and a significant p value (p=0.03). When using the right-side completion method, the number of articles was adjusted to 2, resulting in a decrease in the effect size value from ES=0.295 to ES=0.174. Furthermore, the results revealed that 6 articles had non-significant effect sizes, as depicted in (Figure 7).

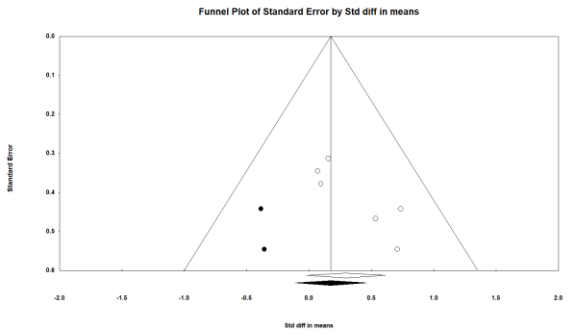

Figure 7. Funnel plot showing the influence of resistance training on IL-10 concentration

3.4. The effect of exercise training on IL-4

The meta-analysis included 13 articles analyzing the effect of exercise training on IL-4 levels, with 11 studies related to aerobic exercises and 2 studies on resistance exercises. The random effects model was used due to the heterogeneity of the data, with an I-squared value of 81.587%. The effect of exercise training on interleukin-4 level was not significant, with an effect size of ES=-0.212 pg/ml (ES=-0.212, 95% CI=-0.628:0.204, p=0.318, Figure 8).

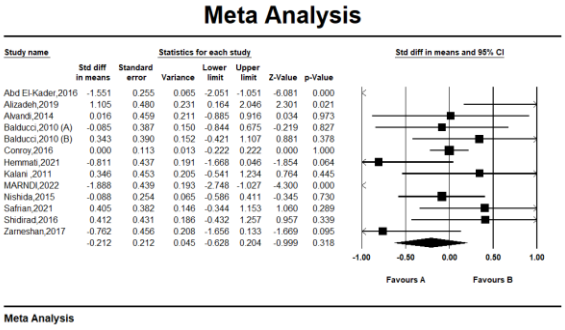

Figure 8. Funnel plot showing the influence of exercise training on IL-4 concentration

Based on the results of the regression tests, the p-values for bias and non-bias were found to be 0.95 and 0.78, respectively. These values indicate that the null hypothesis for these tests is not rejected, suggesting that our research has not suffered from distortion. Additionally, the size of the effects in the funnel diagram shows symmetry, indicating high validity of the research. The case study revealed that 10 studies had no significant effect, while 3 articles had a significant effect.

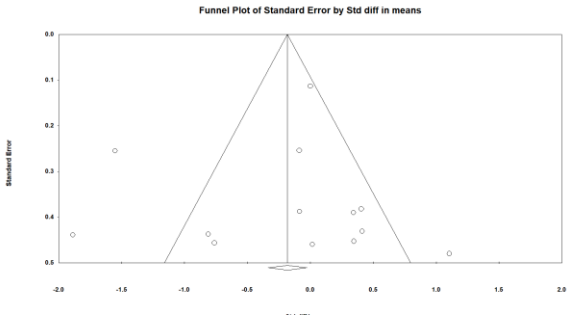

Figure 9. Funnel plot showing the influence of exercise training on IL-4 concentration

3.5. The effect of aerobic training on IL-4

The present meta-analysis included 11 articles that examined the effect of aerobic training on IL-4 levels. The analysis showed that the effect size of aerobic exercise studies on IL-4 level was not significant, with an effect size of ES=-0.282 pg/ml (ES=-0.282, 95%CI=-0.795:0.185, p =0.237). Additionally, 2 articles were included in the meta-analysis to analyze the effect of resistance training on IL-4 levels. The analysis revealed that the effect size of resistance training studies on IL-4 level was also not significant, with an effect size of ES=-0.227 pg/ml (ES=-0.227, 95% CI=-0.389:0.843, p= 0.471).

3.6. Subgroup analysis the effect of exercise training on IL-10 and IL-4

Furthermore, the meta-analysis conducted a stratified analysis of the effect of exercise training on IL-4 and IL-10 levels based on various factors such as age, gender, health status, BMI, duration, and type of training. The average effect size, 95% confidence interval, heterogeneity test results, and p-value of intra-subgroup and inter-subgroup comparisons were investigated. In the analysis of the results of the heterogeneity test, a value of $p>0.05$ indicates publication bias. The significance level of intra-subgroup and inter-subgroup comparisons is calculated as $p<0.05$, and values with this level are considered significant.

The results of the sub-class meta-analysis related to IL-10 indicate that the average effect size of the effect of exercise training on IL-10 level in all subgroups of the classes, except for the "both" subgroup related to gender and the "resistance exercises" subgroup, was significant. This was observed in subgroups related to the type of exercise and number of weeks more than 16 weeks, as well as BMI 25 to 30 and 30 to 35. However, in the comparison between the subgroups of classes, only the subgroup related to BMI had a significant difference in terms of the increase of IL-10 ($p=0.019$), with the highest increase observed in the 18 to 25 subgroup corresponding to the BMI group ($p=0.001$). On the other hand, the results of the sub-class meta-analysis related to IL-4 show that in none of the subgroups, except for exercises less than 8 weeks, the effect size does not have a significant difference between the pre- and post-test values ($p> 0.05$).

4. Discussion

The study aimed to investigate the impact of regular exercise training on IL-4 and IL-10 levels, as well as the potential effects of training variables and subjects' conditions on these anti-inflammatory markers. The overall results of the meta-analysis revealed that exercise training was linked to a significant increase in IL-10 levels ($p=0.00$, 95%CI=0.267:0.723, ES=0.495). Also, the meta-analysis showed that aerobic exercise significantly increased interleukin-10 concentrations, with an effect size (ES) of 0.527 pg/mL ($p = 0.0001$, 95% CI = 0.260:0.794, ES = 0.527), however, resistance training did not have a significant effect on IL-10 levels (ES=0.295, 95%CI-0.020:0.610, $p=0.067$).

IL-10, also known as human cytokine synthesis inhibitory factor (CSIF), is a cytokine that plays a crucial role in immune regulation and inflammation. It acts as an anti-inflammatory cytokine and is primarily produced by antigen-presenting cells, including activated T cells, monocytes, B cells, and macrophages. [31] One of its key functions is inhibiting the transcription of nuclear factor kappa B, thereby preventing pro-inflammatory responses. [32] This meta-analysis aimed to investigate the effects of various aerobic exercise programs, differing in intensity and duration, on the concentration of IL-10 in individuals. The overall findings of this

meta-analysis revealed a significant impact of exercise training on the concentration of IL-10, with an effect size (ES) of 0.495 and a 95% confidence interval ranging from 0.267 to 0.723. These results clearly demonstrate the influence of exercise training on the concentration of this inflammatory factor. Further analysis of individual studies indicated that only 11 articles exhibited a significant effect size. These findings align with previous research that has explored the impact of aerobic exercise on IL-10 levels in individuals. During exercise training, various molecular mechanisms are triggered, initiating intracellular signaling cascades that activate a network of molecular pathways responsible for the anti-inflammatory effects of exercise. Muscle contractions produce IL-6, which stimulates the production of anti-inflammatory cytokines such as IL-1 receptor antagonist and IL-10, while also inhibiting the release of the pro-inflammatory cytokine TNF-α [33, 34]. The anti-inflammatory effects of IL-10 can be mediated through the indirect actions of the signal transducer and activator of transcription 3 (STAT3) on target inflammatory genes such as TNF-α [35].

Also, The mechanisms by which exercise training increases IL-10 concentrations may be attributed to the enhancement of immune cell function, such as macrophages, which play a crucial role in the immune response. These cells produce IL-10, contributing to the anti-inflammatory effects of exercise [34].

According to the meta-analysis of Babaei et al. (2021), exercise training increases the amount of IL-10 in metabolic syndrome patients with a value of 0.480 pg/ml and a 95% confidence interval between 0.10 and 0.86 and a significant effect on the increase of IL-10 (p=0.02), but the effect of resistance training alone on IL-10 concentration was not significant (p=0.22) (p=0.22) [36]. In addition, Khalafi et al. (2023) in a meta-analytical study by examining 11 studies reported that the effect of exercise training in hypoxia in adults significantly increased the concentration of IL-10 (p=0.006) with an effect size of 0.606 with a 95% confidence interval between 0.176 up to 1.37 [37]. However, in a study of 720 people, the effect of 6 and 12 months of regular aerobic exercise on serum levels of IL-10 in postmenopausal women in the Alberta Physical Activity and Breast Cancer Prevention Trial Alpha Group (320 people, 225 min/week versus no activity in the controls) and the Alberta Breast Cancer and Exercise Trial The beta group (400 people, 300 (HIGH) versus 150 (MODERATE) min/week) was investigated, and the results showed that the concentration of IL-10 did not change in the alpha (p=0.84) and beta (p=0.64) groups. [26] Exercise training has the ability to modulate the immune system by downregulating genes that are involved in inflammatory responses. This shift towards an anti-inflammatory state leads to an increase in the levels of IL-10, which is well-known for its anti-inflammatory properties. Endurance

training, in particular, promotes the development of new mitochondria and enhances their density and function. This upregulation of mitochondrial oxidative phosphorylation (OXPHOS) is associated with improved energy efficiency and capacity, which may contribute to the elevated production of IL-10 [38]. Research has demonstrated that endurance trained athletes have a higher proportion of regulatory T cells (Tregs) in their bloodstream compared to individuals who lead a sedentary lifestyle. Tregs are known to produce IL-10, and their increased presence may play a role in the higher levels of IL-10 observed following chronic endurance exercise. [39] Additionally, intense endurance exercise can induce changes in the transcription of genes in peripheral blood leukocytes, particularly those involved in protein production, such as ribosomal proteins. This increase in protein synthesis may support the enhanced production of IL-10. [38] It is also possible that the secretion of IL-6, which is stimulated by regular endurance physical activity, may contribute to the secretion of anti-inflammatory cytokines like IL-10 . [40] Another potential mechanism for the increase in IL-10 levels after endurance exercise is the reduction of adipose tissue, including visceral fat, due to increased fat oxidation. Studies have shown that the decrease in fat mass, along with a reduction in the infiltration of macrophages into adipose tissue and a shift in macrophage phenotype from pro-inflammatory (M1) to anti-inflammatory (M2), leads to an increase in anti-inflammatory cytokines like IL-10 and a decrease in pro-inflammatory cytokines [41].

Regular aerobic endurance training has been found to have a positive impact on chronic inflammatory diseases by enhancing endogenous immune modulating pathways through the increase in IL-10 levels. This is exemplified by studies demonstrating that the administration of IL-10-inducing agents through subcutaneous delivery can effectively slow down the progression of atherosclerosis and exhibit protective effects in neuroinflammation models. [42] Moreover, IL-10 plays a crucial role in safeguarding the body against an uncontrolled immune response, primarily through the activation of the Jak1/Tyk2 and STAT3 signaling pathways. [43] Additionally, IL-10 targets various types of leukocytes, inhibiting their activation and function, thereby impeding the dissemination of inflammatory cytokines and preserving the integrity of host tissues. [44]

The sub-group related to BMI exhibited a significant difference in terms of the increase of IL-10 among the sub-groups within the classes, with the highest increase observed in the 18 to 25 subgroup of the BMI group. Regular aerobic exercise may lead to a smaller increase in IL-10 levels in overweight and obese individuals compared to those with normal weight. This difference could be attributed to the varying inflammatory states present in these groups. Overweight and obese individuals typically have elevated levels of inflammation and pro-

inflammatory cytokines, which could potentially counteract the rise in IL-10. [45]

The current study findings indicated that resistance exercises did not have a significant impact on IL-10 levels. Furthermore, no significant difference was noted between subgroups in terms of the effect of resistance exercises on IL-10 levels within the classes. It appears that regular resistance and strength training do not elicit the same response in IL-10 levels as aerobic training due to the distinct physiological reactions they trigger. Acute alterations in circulating cytokine levels, such as IL-10 induced by resistance exercise, have been reported differently. A recent systematic review and meta-analysis in 2023 demonstrated that resistance exercise had a small to moderate positive effect on IL-6 and a large positive effect on IL-1ra, but this effect was not observed for IL-10. [46] However, the lack of a significant increase in IL-10 levels could also be attributed to an acute inflammatory response resulting from resistance exercise-induced muscle damage, which might overshadow anti-inflammatory signals [47].

IL-4 is a crucial player in the regulation of immune responses, particularly known for its role in supporting the differentiation and function of Th2 cells, which are linked to anti-inflammatory responses. This cytokine can hinder cellular immunity while boosting humoral immunity. Research suggests that the rise and synthesis of glucocorticoids, notably cortisol during stress like physical activity, can lead to increased IL-4 production. [48] IL-4 has the ability to suppress the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 by macrophages and other cells. [49] IL- Furthermore, IL-4 triggers the alternative activation of macrophages (M2 macrophages) associated with tissue repair and anti-inflammatory functions, and influences B cells to enhance the production of IgE and IgG1, which play roles in allergic responses and inflammation reduction. [50] By activating STAT6, IL-4 can inhibit the production of pro-inflammatory cytokines. [51] Our study data revealed that neither aerobic nor resistance exercises had a significant impact on IL-4 levels. In fact, exercise was shown to decrease IL-4 by -0.212 pg/ml with a 95% confidence interval ranging from -0.628 to 0.204, although this effect was not statistically significant (p=0.318). Consistent with current research, both domestic and international studies have indicated that sports training does not significantly affect IL-4 levels. In a meta-analysis, Ting et al. (2018) discovered that the impact of aerobic exercise on IL-4 concentration in adults was not significant, with a 95% confidence interval between -0.02 and 0.03 (p=0.76). [18] A study involving 720 individuals, including the Alberta Physical Activity and Breast Cancer Prevention Alpha group (320 individuals) and the Alberta Breast Cancer and Exercise Trial Beta group (400 individuals), demonstrated that IL-4 concentrations in both the Alpha (p=0.54) and

Beta (p=0.32) groups did not change significantly [26].

The association between regular training and IL-4 levels remains somewhat ambiguous. While certain research indicates that exercise does not directly elevate circulating IL-4 levels, other studies propose that the rise in IL-6 due to exercise may enhance the gene expression of IL-4 receptors, potentially heightening sensitization and leukocyte response to IL-4 . [52] This suggests a potential indirect anti-inflammatory impact of exercise mediated by IL-6 rather than IL-4 itself. Moreover, consistent physical activity has been demonstrated to boost IL-4 expression in muscle tissue over time following repeated exercise sessions. [53] This implies that although circulating IL-4 levels may not undergo significant changes, there could be localized effects within muscle tissue contributing to the anti-inflammatory profile. Our data analysis reveals no notable disparity in the effect size of IL-4 between pre-test and post-test values across the subgroups (except for exercises lasting less than 8 weeks). Given the limited number of studies focusing on exercises lasting less than 8 weeks, further investigation is warranted to validate this observation.

This study is subject to limitations, notably the scarcity of literature pertaining to resistance training, particularly concerning IL-4, which impacts the outcomes of the subanalysis. Furthermore, a more comprehensive examination involving other markers such as IL-8, IL-6, TNF-a, and IL-2 could provide a clearer understanding of the relationship between these markers and regular physical activity, a consideration that should be addressed in future research endeavors.

5. Conclusion

This meta-analysis demonstrated that participating in aerobic exercises leads to a significant increase in IL-10 levels in both healthy individuals and those with illnesses. Individuals with a BMI between 18 and 25 experienced a more significant increase in IL-10 due to exercise. Additionally, the study found that exercise did not have a noticeable impact on the blood concentration levels of IL-4 in individuals with illnesses or in healthy individuals, suggesting that its effects may be localized to the muscles. These two anti-inflammatory interleukins are crucial in the development of chronic diseases such as cardiovascular diseases, diabetes, cancer, chronic lung diseases, multiple sclerosis, immune system disorders, and others.

Conflict of interest

The authors declared no conflicts of interest.

Authors' contributions

M.R.R; Conceptualization, Methodology, Software, Supervision and Writing. H.F.; Visualization, Investigation, Validation, Writing- Reviewing and Editing. S.K.; Data curation, Writing- Original draft preparation. All authors read and approved the final manuscript.

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Ethical considerations

The author has completely considered ethical issues, including informed consent, plagiarism, data fabrication, misconduct, and/or falsification, double publication and/or redundancy, submission, etc.

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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Appendix

Table 1. Characteristics of selected studies in the present study

Study	Sampling	Factors measured (Study Results)	Exercise Parameters	Type of disease	BMI	Supplement or drug use	Age range	sex	Number of subjects	Groups
Chagas et al. 2017 (۵۴)	random	IL-10 (↓)	20 weeks, 3 sessions per week, %50-60 Vo2max	Healthy	30.6	No	50-79	Female	35	Exercise
					32.8				35	Control
Dong et al. 2019 (۵۵)	random	IL-10 (↑)	12 weeks, 3 sessions per week, Progressive resistance	Sarcopenia	18.96±3.08	No	43-68	both	2	Exercise
					20.49±3.41				20	Control
Niksereshet et al. 2014 (۵۶)	random	IL-10 (↑)	12 Weeks, 3 sessions per week, %80-90 HR Max	Healthy	–	No	34-46	Man	12	Aerobic periodicity resistance
									12	
									10	Control
Alvandi et al. 2014 (۲۷)	random	IL-10 (↑) IL-4 (↑)	10 Weeks, 3 sessions per week, %70-80 1RM	Healthy	29±1.8	No	20-30	Man	10	Exercise
					27.3±1.6				9	Control

Hagstrom et al. 2016 (۵۷)	random	IL-10 (↑)	16 weeks, 4 sessions per week, %80 1RM	Cancer survivors	27.6 ± 4.2	No	18-70	Female	19	Exercise
					29.9 ± 6.46				15	Control
Hajizadeh Maleki et al. 2017 (58)	random	IL-10 (↑)	24 weeks, 4-6 seessions per week %56-69 Vo2max	IBS	25.1 ± 3.5	No	18-41	Female	24	Exercise
					25.3 ± 3.1				27	Control
Ibrahim et al. 2018 (۵۹)	random	IL=10 (↑)	12 weeks, 3 sessions per week, circuit exercise	Healthy	18.3±6.8	probiotics	19-26	Female	12	Exercise
					21.1±6.4				9	Exercise-probiotics
					20.5±6.4				10	probiotics
					18.6±7.3				10	Control
Shafieerad et al. 2018 (۱۲)	random	IL-10 (↑)	8 weeks, 3 sessions per week, 3 times %50-70 HR Max	Healthy	28.47±2.29	No	40-50	Female	11	Exercise
					29.51±1.75				9	Control
Mokhtarzade et al. 2017 (۶۰)	random	IL-10 (↑)	8 Weeks, 3 sessions per week, %60-65 Wmax	ms	27.08±2.49	No	20-40	Female	2	Exercise
									18	Control
					26.21±1.67					
Ribeiro et al. 2011 (۶۱)	random	IL-10 (↑)	8 Weeks, 3 sessions per week, %65-75 HR Max	Infarction	28.4 ± 4.0	No	44-64	both	20	Exercise
					26.6 ± 4.6				18	Control
Tadayon Zadeh et al. 2021 (۶۲)	random	IL -10 (↑)	8 Weeks, 3 sessions per week, %40-70 HR Max	ms	25.2±2.6	No	25-40	Female	15	Exercise
					24.3±2.7				15	Control
Mohamed et al. 2021 (۶۳)	random	IL-10 (↑)	2 Weeks, 3 sessions per week, %60-75 HR Max	Covid-19	24.65 ± 1.31	No	24-45	both	15	Exercise
					23.95 ± 1.21				15	Control
Behbodi et al. 2017 (۶۴)	random	IL-10 (↑)	6 Weeks, 3 sessions per week, %60-75 HR Max	Healthy	32.03±1.26	No	30-40	Female	15	Exercise
					32.07±1.33				15	Control
Souza et al. 2022 (۶۵)	random	IL-10 (↑)	12 Weeks, 3 sessions per week, %50-75 1RM	Sarcopenia	_	No	67-81	both	14	Exercise
									14	Control
Ranjbar et al. 2016 (66)	random	IL-10 (↑)	8 Weeks, 3 sessions per week, %65-80 Wmax	Type 2 diabetes	26.7±3.1	No	33-53	Female	10	Exercise
					28.8±1.7				8	Control
Balducci et al. 2010 (۶۷)	random	IL-10 (↓) IL-4 (↓)	52 weeks, 2 sessions per week, %70-80 Vo_2max and %80 1RM	Metabolic syndrome Type 2 diabetes	30.5±0.9	No	40-75	both	22	aerobic resistance
					29.4±1.1				20	aerobics Intense
					30.0±1.0				20	intensity low
					30.9±1.1				20	Control
Hoshmandi et al. 2017 (۶۸)	random	IL-10 (↑)	8 Weeks, 3 sessions per week, %40-70 VO_{2max}	MS	25.44±4.41	No	24-37	Female	15	Exercise
					24.15±3.78				15	
										Control
Vakili et al. 2021 (۶۹)	random	IL-10 (↑)	8 Weeks, 3 sessions per week, %60-65 HRR	Healthy	27.14±1.21	No	13-18	Man	9	short interval
					26.72±1.39				10	long interval
					27.30±2.18				10	Control

Emamdoost et al. 2020 (۷۰)	random	IL-10 (↑)	12 Weeks, 3 sessions per week, %40-60 1RM	Healthy	32.79±0.75	No	23-35	Man	11	strong resistance
					32.69±1.27				10	Low intensity resistance
					32.13±1.4				11	Medium resistance
					32.55±1.43				11	Control
Fatahpour Marandi et al. 2021 (71)	random	IL-4 (↑) IL-10 (↑)	12 Weeks, 3 sessions per week, %65-75 HR Max	Breast Cancer	_	No	35-45	Female	15	Exercise
									15	Control
Banai Far et al. 2013 (۷۲)	random	IL-10 (↑)	6 Weeks, 3 sessions per week, %55-70 HR Max	Healthy	31.88±2.8	No	36-48	Female	17	Exercise
					33.15±1.69				14	Control
Pournemati et al. 2021 (۷۳)	random	IL-10 (↑)	12 Weeks, 3 sessions per week, %50 Vo2max	menopausal women with breast cancer	28.27±1.80	No	53-61	Female	13	high intensity
					28.74±2.94				13	Low intensity
					27.60±1.88				14	Control
Khosravi et al. 2017 (۷۴)	random	IL-10 (↑)	10 Weeks, 3 sessions per week, %50-65 Vo2max and %60-70 1RM	Type 2 diabetes	27.99±4.11	No	44-58	Female	8	Aerobic
					28.11±3.33				8	Resistance
					26.82±4.85				8	Control
Zarneshan et al. 2017 (۷۵)	random	IL-4 (↑)	12 weeks, 3 sessions per week, %60-80 HR Max	Asthma	31.8±4.9	No	28-40	Female	12	Exercise
					30.9±4.9				9	Control
Safarian et al. 2021 (۷۶)	random	IL-4 (↑)	8 Weeks, 3 sessions per week, %70-85 HR Max	Schizophrenia	23.51±4.41	No	25-45	Man	14	Exercise
					22.25±4.98				14	Control
Shahidi Rad et al. 2020 (۷۷)	random	IL-4 (↑)	8 weeks, 3 sessions per week, %40-60 1RM	MS	_	No	25-40	Female	11	Exercise
									11	Control
Alizadeh et al. 2019 (۲۱)	random	IL-4 (↑)	6 Weeks, 3 sessions per week, %90 HR Max	Healthy	27.8±0.6	No	17-19	Man	10	Exercise
					28.5±0.6				10	Control
Ghorbanian et al. 2021 (۷۸)	random	IL-10 (↑)	12 weeks, 3 sessions per week, %45-70 HR Max	Breast Cancer	24.47±0.91	No	46-58	Female	15	Exercise
					25.12±1.01				15	Control
Kadoglou et al. 2007 (۲۲)	random	IL-10 (↑)	26 Weeks, 3 sessions per week, %50-75 Vo2max	Type 2 diabetes	32.1±3.19	No	56-66	both	29	Exercise
					31.99±3.41				27	Control
Taheri Kalani et al. 2010 (۷۹)	random	IL-10 (↑) IL-4 (↑)	10 Weeks, 3 sessions per week, %70-80 HR Max	Healthy	28.6±1.7	No	20-30	Man	11	Exercise
					27.3±1.6				9	Control
Vahdat et al. 2018 (۸۰)	random	IL-10 (↑)	6 weeks, 3 sessions per week, %85-90 HR Max	Healthy	26.73±1.50	No	35-45	Man	10	Exercise
					26.25±1.08				10	Control
Abd El-Kader et al. 2016 (۸۱)	random	Il-4 (↑)	12 weeks, 5 sessions per week, %60-80 HR Max	COPD	22.83±3.57	No	35-55	both	40	Exercise
					20.88±3.16				40	Control
Hemmati et al. 2022 (۸۲)	random	Il-4 (↑)	12 weeks, 3 sessions per week, %65-85 HR Max	Kidney transplant	23.75±4.03	No	18-45	both	13	Exercise
					24.41±3.93				10	Control

Conroy et al. 2016 (۲۶)	random	IL-10 (↔) IL-4 (↔)	12 weeks, 5 sessions per week, %70-80 HRR	Healthy	29.1 ± 4.5	No	50-74	Female	155	Exercise
					29.2 ± 4.3				156	Control
Antonelli Rossi et al. 2023 (۸۳)	Non-random	IL-10 (↑)	8 weeks, 3 sessions per week, %60-75 HR Max	Sickle cell anemia	–	No	25-28	both	14	Exercise
									13	Control
Nishida et al. 2015 (۸۴)	random	IL-4 (↑)	12 weeks, 3 sessions per week, OBLA	Healthy	24.2±3.7	No	65-85	Female	31	Exercise
					22.5±2.5				31	Control
Beglou et al. 2019 (۸۵)	random	IL-10 (↑)	8 weeks, 3 sessions per week, %80-100 and %75-95 Vo2peak	blood pressure	–	No	45-51	Man	8	short interval
									9	long interval
									10	Control
Aldahr et al. 2022 (۸۶)	random	IL-10 (↑)	24 weeks, 3 sessions per week, %70-80 HR Max	Type 2 diabetes	34.15±3.39	No	62-66	both	40	Exercise
					33.82±.47				40	Control
Abd El-Kader et al. 2019 (۸۷)	random	IL-10 (↑)	26 weeks, 3 sessions per week, %60-80 HR Max	Healthy	–	No	61-67	both	25	Exercise
									25	Control
Haley et al. 2020 (۸۸)	random	IL-10 (↑)	20 weeks, 75 minutes a week, 150minutes a week, 300minutes a week, %70-80 HR Max	Exposed to breast cancer	26.8 ± 6.3	No	27-41	Female	41	Control
									38	Low dose aerobics
									37	High dose aerobics

↑: increase, ↓:decrease, ↔: no change, HR Max: Hart rate max, HRR: Hart rate RESERVE,

Table 2. Scores related to the articles that can be reviewed in the meta-analysis based on the PEDro scale

Research index	Pedro's total score	Measurement in steps and intervals	Comparison of intergroup statistics	Analysis of willingness to treat	Collecting the initial factor from 85% of subjects	Blindness of researchers	Similarity of pre-test characteristics	Subject division by an unrelated person	Random division	Eligibility
Shafieerad et al. 2018	6	1	1	0	1	0	1	0	1	1
Hajizadeh Maleki et al. 2017	5	1	1	0	0	0	1	0	1	1
Marani et al. 2021	6	1	1	0	1	0	1	0	1	1
Nishida et al. 2015	6	1	1	0	1	0	1	0	1	1
Antonelli Rossi et al. 2023	7	1	1	1	1	0	1	1	0	1
Conroy et al. 2016	6	1	1	0	1	0	1	0	1	1
Abd El-Kader et al. 2019	6	1	1	0	1	0	1	0	1	1
Alvandi et al. (2014)	6	1	1	0	1	0	1	0	1	1
Abd El-Kader et al.	7	1	1	0	1	0	1	1	1	1

2016										
Kadoglou et al. 2007	6	1	1	0	1	0	1	0	1	1
Balducci et al. 2010	6	1	1	0	1	0	1	0	1	1
Souza et al. 2022	7	1	1	1	1	0	1	0	1	1
Aldahr et al. 2022	7	1	1	0	1	0	1	1	1	1
Ribeiro et al. 2011	6	1	1	0	1	0	1	0	1	1
Ibrahim et al. 2018	6	1	1	0	0	1	1	0	1	1
Hagstrom et al. 2016	6	1	1	0	1	0	1	0	1	1
Dong et al. 2019	7	1	1	1	1	0	1	0	1	1
Chagas et al. 2017	5	1	1	0	0	0	1	0	1	1
Haley et al. 2020	7	1	1	0	1	0	1	1	1	1
Beglou et al. 2019	5	1	1	0	0	0	1	0	1	1
Hemmati et al. 2022	6	1	1	1	1	0	1	0	1	1
Alizadeh et al. 2019	6	1	1	0	1	0	1	0	1	1
Tadayon Zadeh et al. 2021	6	1	1	0	1	0	1	0	1	1
Mokhtarzade et al. 2017	6	1	1	0	1	0	1	0	1	1
Nikseresht et al. 2014	6	1	1	0	1	0	1	0	1	1
Shahidi Rad et al. 2020	6	1	1	1	1	0	1	0	0	1
Safarian et al. 2021	6	1	1	0	1	0	1	0	1	1
Behbodi et al. 2017	6	1	1	0	1	0	1	0	1	1
Banai Far et al. 2013	6	1	1	0	1	0	1	0	1	1
Pournemati et al. 2021	6	1	1	1	0	0	1	0	1	1
Vakili et al. 2021	5	1	1	0	1	0	1	0	0	1
Khosravi et al. 2017	6	1	1	0	1	0	1	0	1	1
Emamdoost et al. 2020	6	1	1	0	1	0	1	0	1	1
Ranjbar et al. 2016	6	1	1	0	1	0	1	0	1	1
Hoshmandi et al. 2017	6	1	1	0	1	0	1	0	1	1
Ghorbanian et al. 2021	6	1	1	0	1	0	1	0	1	1
Vahdat et al. 2018	6	1	1	0	1	0	1	0	1	1
Zarneshan et al. 2017	5	1	1	0	1	0	1	0	0	1
Taheri Kalani et al. 2010	6	1	1	0	1	0	1	0	1	1