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Experimental Research

Effects of Otago Exercise Program on serum Interleukin-6 level in older women

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ABSTRACT

Background: Otago Exercise Program (OEP) has been demonstrated to minimize the risk of falling in older adults by improving muscular strength and balance. Meanwhile, reduced IL-6 level serves as a biomarker of regular physical activity.
Objective: Analyzing OEP effect on decreased IL-6 level in elderly women.
Methods: This study used a randomized control trial design from October 2020 to May 2021. 26 participants were divided into a treatment group (13 participants) and a control group (13 participants). The treatment group received OEP for 8 weeks, in which the OEP was carried out 3 times during the first week. On the other hand, the control group did not get intervention. The IL-6 level was measured 2 times, before and after OEP. The measurement results were analyzed using paired *t*-test and independent *t*-test, which were declared significant if $p < 0.05$.
Results: The participants' average IL-6 level at pretest and posttest was 4.77 ± 1.71 pg/mL and 4.57 ± 1.74 pg/mL, respectively. The IL-16 level of the treatment group at pretest and posttest was 4.22 ± 1.72 pg/mL and 3.97 ± 1.67 pg/mL, respectively ($t = 1.058$; 95% CI = −0.770 – 0.267; $p = 0.311$). Meanwhile, the IL-6 level of the control group at pretest and posttest was 5.30 ± 1.59 pg/mL and 5.16 ± 1.65 pg/mL, respectively ($t = 0.382$; 95% CI = −0.969 – 0.680; $p = 0.709$). The ΔIL-6 level in the treatment and control group was −0.25 ± 0.85 pg/mL and −0.14 ± 1.36 pg/mL, respectively ($t = 0.240$; 95% CI = −1.030 – 0.815; $p = 0.813$).
Conclusion: The OEP didn't lower serum IL-6 levels after eight weeks.

1. Introduction

The present public health system is concerned with the incidence of falls and their consequences among older adults. The number of older adults who died from falling incidents in the United States climbed from 8,613 (2000) to 25,189 (2016) [1]. As shown in a study conducted by Pengpid & Peltzer on 6,698 older adults in Indonesia, the incidence of falls that resulted in injuries was 12.8% in two years. According to the findings, older women had a 14% chance of having fall incidence. In comparison, men had an 11.5% chance of having fall incidence. About 7.6% had a single incidence, while 5.2% had a repeated history of falling [2].

There was an association between falling incidence in the elderly and decreased lower-extremity muscle mass and strength [3]. An increase in circulating cytokines, particularly interleukin-6 (IL-6), leads to a prolonged increase in muscle tissue catabolism, resulting in a loss of muscle mass and strength [4]. Even in older adults with previously excellent functional status, increased IL-6 level is associated with a loss of muscle mass and strength [5,6]. Serum IL-6 level increases with age. There is a significant increase in IL-6 found in older adults over 70 years [7].

A variety of methods have been developed to reduce inflammation associated with aging. Medical therapy may be an option. Fibrates, statins, ACE inhibitors, ACE receptor blockers, and nonsteroidal anti-inflammatory (NSAIDs) medications play a role in decreasing inflammation [8]. Anti-inflammatory usage has been limited due to common side effects such as indigestion, cardiovascular problems, and the financial burden of administering these drugs [9]. Physical exercise combined with a healthy lifestyle can help older adults overcome

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inflammation and physical deterioration. Regular moderate-intensity physical activity boosts skeletal muscle's anti-inflammatory action, which can be implemented as a therapeutic and preventive approach to minimize age-related degenerative processes and systemic inflammatory markers [10].

Physical exercise is an essential strategy for lowering the risk of age-related disease, and the current study has focused on its impact on the inflammatory profile [11]. Inflammatory markers are consistently lower in patients who engage in more regular and intensive physical activity, based on population-based cross-sectional and cohort studies [12,13]. Long-term physical exercise therapy can help reduce serum IL-6 levels. Regular physical activity has been shown to reduce fat mass and adipose tissue, contributing to systemic inflammation [14]. Compared to other sedentary adults, older adults who engage in regular physical activity have lower basal IL-6 levels [15].

Aerobic activity, muscle strengthening, flexibility, and balance are recommended exercises for the elderly, per the American College of Sports Medicine (ACSM). Exercise is divided into several phases, according to the elderly's abilities [16]. The Otago Exercise Program (OEP) is a multi-component moderate-intensity exercise program that includes flexibility, strengthening, balance, and walking. It has been demonstrated to minimize falling incidence in the elderly by boosting muscle strength and balance. The OEP is a low-cost, safe, and practical training program [17].

The effect of Otago exercise on serum IL-6 levels is still unknown, given the role of IL-6 as an inflammatory factor in the elderly and the relevance of physical exercise as a non-pharmacological approach to reduce it. The purpose of the study was to evaluate the OEP implementation in older women for eight weeks on the decrease in basal serum IL-6 levels.

2. Methods

2.1. Participants

The participant in the study was an Indonesian elderly woman who lived in a nursing home. The inclusion criteria were elderly, female, aged ≥60 years, a score on the Montreal Cognitive Assessment Indonesian Version (MoCA-Ina) of ≥26 [18,19], capable of understanding and following instructions, independent ambulation without the use of a walker, stable hemodynamics, and had sufficient visual and hearing capacity to follow the exercise. Exclusion criteria were those participating in other regular physical activity programs, having severe cardiorespiratory disorders, having a chronic disease that caused long-term disability, and having muscle pain and lower extremity joint pain with a Wong-Baker Face Scale of >4 and/or clinical signs of swelling, redness, and feeling warm. Participants who meet the participant criteria consciously fill out an informed consent form.

2.2. Study design

This study used a randomized control trial design that was carried out for the period October 2020 to May 2021. The number of participants in this study was twenty-six participants that were divided into treatment groups (13 participants) who received intervention and control group (13 participants) who did not get intervention. The intervention in this study was OEP conducted for 8 weeks, in which every participant was checked for vital signs before and after each exercise. The OEP was carried out 3 times a week, and the evaluation of OEP was assessed from the IL-6 level. The IL-6 level examination was carried out 2 times, before starting OEP (first week) and at the end of OEP (8th week).

2.3. Otago Exercise Program

The OEP is a physical exercise program specifically designed to reduce falls in the elderly, by increasing lower extremity muscle strength and improving balance [20]. Five types of strengthening exercises, 12 types of balance exercises, and a walking program are included in the OEP. Exercise types are based on the OEP protocol [21]. Based on the subject's capabilities during the exercise, the number of repetitions, the weight of the load on the ankles, and the level of balance training are gradually increased. This study used ankle cuff weights with 0.5 kg, 1 kg, and 2 kg loads. The subject received a 0.5 kg load at the beginning of the strengthening session. The load was gradually increased. The participants' maximum tolerance of ankle cuff weight was 2 kgs. The walking program was offered twice a week for 30 min each and could be divided into many sessions a day and performed on separate days with strengthening and balancing exercises. Two instructors supervised the exercises. The OEP's movements were demonstrated by one instructor, while the other was in charge of ensuring the exercise's safety and correcting improper subject movements. The control group received no treatment but was still allowed to go on with their daily routine at the nursing home.

2.4. Interleukin-6 level

This study measured the level of IL-6 in the basal serum. Data were measured twice, before and after the 8-week administration of OEP. The initial examination was conducted 48 h before the first OEP session began, and the final examination 48 h after the last OEP session. Before taking blood samples, the caretakers of the nursing home should ensure that all participants had not engaged in any strenuous physical activity in the previous 48 h using cross-check interviews. This step was required to exclude the IL-6 factor (myokine) released by muscle, yielding a pure basal IL-6 sample [22]. Blood was obtained from the peripheral veins, 5 cc for each participant in each collection. The pre-exercise blood sample was kept at −70 °C storage (sample stability up to 12 months). All samples were processed for serum separation after 8-week treatment. Serum IL-6 levels were then measured using human ELISA kits (R&D System, Inc., Minneapolis, USA). The level of serum IL-6 was measured in pg/mL units. Minimal IL-6 concentrations detection was 0.031 pg/mL.

2.5. Statistical analysis

Data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Data normality assumptions were verified by the Shapiro Wilk test. As assumptions were met, parametric tests were applied. The baseline characteristics of intervention and control groups were compared using an independent sample *t*-test. The comparison between IL-6 serum before and after the training session of intervention and control group using paired *t*-test. Between-group differences (delta) of IL-6 were compared using independent t-tests. The comparisons were considered statistically significant at $p < 0.05$.

3. Result

3.1. Characteristics of participant

The average age of the participants was 74.81 ± 7.6 years with a median value of 74 (71.3–81) years. The average age of the participants in control and treatment group was 74.31 ± 6.21 years and 75.31 ± 9.01 years, respectively ($t = 0.229$; CI 95% = −6.994 – 5.559; $p = 0.745$). The average weight of participants was 47.53 ± 9.93 kg, with a median value of 44.4 (39.7–55.72) kg. There was no significant comparison in participant weight between treatment (45.72 ± 9.04 kg) and control group (49.33 ± 10.79 kg; $t = 1.223$; 95% CI = −12.094 – 3.094; $p = 0.365$). The average participants' height was 147.88 ± 6.84 cm, with a median value of 147 (142.25–153) cm. The participants' average height in the treatment and control group was 148.85 ± 5.91 cm and 146.94 ± 7.78 cm, respectively ($t = 0.709$; 95% CI = −3.672 – 7.519; p

= 0.485). The participant's body mass index (BMI) value was 21.59 ± 3.44 kg/m^2 (treatment group = 20.55 ± 3.33 kg/m^2 vs control group = 22.61 ± 3.35 kg/m^2; t = 1.572; 95% CI = −4.767 – 0.645; p = 0.129; Table 1). Meanwhile, the median BMI of participants was 21.22 (19.8–23.75) kg/m^2.

3.2. Comparison of Interleukin-6 level in elderly woman with Otago Exercise Program

The participants' average IL-6 level at the pretest was 4.77 ± 1.71 pg/mL, with a median value of 4.78 (3.34–5.98) pg/mL. Meanwhile, the IL-6 level at the posttest was 4.57 ± 1.74 pg/mL, with a median value of 4.77 (3.27–5.51) pg/mL. In the treatment group, there was no significant comparison of IL-6 level between pretest and posttest (4.22 ± 1.72 pg/mL vs 3.97 ± 1.67 pg/mL; t = 1.058; 95% CI = −0.770 – 0.267; p = 0.311). In the control group, there was also no significant comparison in IL-6 level between pretest and posttest (5.30 ± 1.59 pg/mL vs. 5.16 ± 1.65 pg/mL; t = 0.382; 95% CI = −0.969 – 0.680; p = 0.709). The value of ΔIL-6 in the treatment and control group was −0.25 ± 0.85 pg/mL and −0.14 ± 1.36 pg/mL, respectively. The result was declared to have no significant comparison with t = 0.240, 95% CI = −1.030 – 0.815, and p = 0.813 (Table 2). Meanwhile, the participants' ΔIL-6 level was −0.46 ± 1.6 pg/mL, with a median of −1.20 (−1.48 – 0.08) pg/mL.

4. Discussion

Physical exercise is an essential strategy for lowering the risk of age-related diseases, particularly those with an inflammatory profile [11]. Inflammatory biomarker concentrations are consistently lower in older adults who engage in more intense and regular physical exercise, according to population-based cross-sectional and cohort studies [12,13]. Regular exercise can reduce fat mass and adipose tissue, further decreasing the risk of developing age-related diseases by contributing to systemic inflammation [10,14,23]. Contracting skeletal muscle during exercise releases IL-6, an anti-inflammatory cytokine that inhibits the production of pro-inflammatory cytokines such as IL-1 and TNF-α and promotes the release of anti-inflammatory and inhibitory cytokines, including IL-1ra and IL-10 [24].

The findings of this study contradicted the previous study from Nicklas et al., which found that prescribing multi-component exercise therapy consisting of strengthening, balance, aerobic, and flexibility exercises to 424 older male and female participants aged 70–89 for 12 months resulted in decreased IL-6 and CRP levels significantly [25]. Sadjapong et al. found that offering multi-component exercise therapy consisting of strengthening, balancing, and aerobic exercise for 12 weeks in 32 older adults in Phayao Province, Thailand, also resulted in a substantial decrease in serum IL-6 and CRP levels [26]. The disparities might be caused by the fact that the exercise in the two previous studies was moderate to high intensity, resulting in maximal muscle contraction capable of producing anti-inflammatory cytokines (myokine) while suppressing the production of pro-inflammatory cytokines from peripheral mononuclear cells. Meanwhile, the exercise delivered in this study was moderate-intensity exercise. The exercise intensity in this study was based on ACSM recommendations that suggested moderate-intensity exercise for elderly persons with sedentary lifestyles.

Table 1
Characteristic of participant.

Characteristic	Otago exercise program		95% CI	p
	Treatment	Control		
Age	74.31 ± 6.21	75.31 ± 9.01	−6.994 – 5.559	0.745
Weight	45.72 ± 9.04	49.33 ± 10.79	−12.094 – 3.094	0.365
Height	148.85 ± 5.91	146.92 ± 7.78	−3.672 – 7.519	0.485
BMI	20.55 ± 3.33	22.61 ± 3.35	−4.767 – 0.645	0.129

Note: BMI = body mass index; *significant <0.05.

Table 2
The effect of Otago exercise program on IL-6 levels.

Group	Otago exercise program		95% CI	p
	Pretest	Posttest		
Treatment group	4.22 ± 1.72	3.97 ± 1.67	−0.770 – 0.267	0.311
Control group	5.30 ± 1.59	5.16 ± 1.65	−0.969 – 0.680	0.709

Note: Comparation of ΔIL-6 level in treatment group and control group was p-value of 0.813.

High-intensity exercise should only be offered to older adults who are in good physical condition, have previous exercise experience and expertise, and are under expert supervision [27]. The exercise length is also a determining factor; in the previous study, the exercise was performed for 12 weeks to 12 months. However, in this study, the exercise was only given for eight weeks. Previous studies have found that the decrease in IL-6 level was directly proportional to the intensity and duration of the exercise, a phenomenon known as the dose-response relationship [28,29].

Phillips et al. found that after ten weeks of moderate to high-intensity strengthening exercises in large muscle groups in the upper and lower extremities, serum IL-6 levels in older women decreased significantly [30]. As the exercise duration was longer in previous studies, the strengthening exercise type given was more varied. The total number of active muscle groups/contractions throughout the study was higher, hence it had a significant result. This study only targeted lower extremity muscle groups and had limited types of strengthening exercises compared to previous studies.

Middlebeek et al. found that healthy male participants aged 40–55 years in a sedentary condition who had a moderate-intensity cycle ergometer exercise for two weeks had a significant drop in IL-6 levels [31]. The different result in the current study results was due to the lack of supporting examinations on a specific disease. In addition, there was no comprehensive and detailed recording of the physical activity scale on the subject throughout the study, resulting in a high basal serum IL-6 value at the beginning of the study. In contrast to Middlebeek et al. and Puzianowska-Kuznica et al., participants were selected through interviews, physical examinations, and additional assessment of the history of chronic diseases like cardiovascular disease, diabetes mellitus, stroke, and cancer. In-depth interviews about the physical activity before and during the exercise were also conducted [31,32]. In this study, the treatment group had a mean basal IL-6 level of 4.22 pg/ml, while the control group had a mean basal IL-6 level of 5.30 pg/mL. The participants in this study had higher basal serum IL-6 values than Puzianowska-Kuznica et al., who found 1.9 pg/ml in older women aged 70–74 years with a normal aging status [32]. Another study by Jankord & Jemiolo stated that subjects participating in the study should be carefully screened for disease to rule out an infectious condition and/or acute or chronic disease that might affect the basal serum IL-6 level to obtain good study results regarding the effect of exercise on basal serum IL-6 levels [28].

Another study by Lima et al. found that when 15 older adults, two men, and 13 women, with a mean age of 67 years, were given a combination of aerobic and strengthening exercises three times per week for ten weeks at a moderate intensity, their basal serum IL-6 levels did not improve [33]. According to Lustosa et al., applying moderate-intensity strengthening exercises to older women aged >65 years, three times per week for ten weeks, did not change the basal serum IL-6 levels [22]. The duration and intensity of exercise are linked to cytokine levels in the blood. In the acute phase of the exercise, anti-inflammatory cytokines such as IL-6 increase in the blood, while pro-inflammatory cytokines like CRP and TNF-α are inhibited. This condition helps improve chronic inflammatory conditions in older adults. This, in turn, also increases energy demands and adaptation to active body cells with regular exercise. There is an increase in IL-6 production in contracting muscles in acute post-exercise conditions (myokine). There was evidence stating that

skeletal muscle produced more IL-6 in low intramuscular glycogen reserves conditions. Muscle adaptation occurred after frequent physical exercise of the appropriate intensity and stimulus, resulting in increased intramuscular glycogen reserves and decreased IL-6 production by the muscles. It was hypothesized that as muscle produces less IL-6, the basal IL-6 level in serum would also decrease [29].

There are several limitations to this study. This study did not conduct additional examinations to identify a specific condition, instead only performed a physical examination and interviews with the participant. This study could not accurately control each patient's level of physical activity before and during the study. Recommendations for further study need to be specific for disease screening, using an activity scale for controlling the daily activities of participants and increasing the intensity and duration of Otago exercise.

5. Conclusion

The OEP includes strengthening, balance, flexibility, and walking carried out by elderly women to increase physical activity. An elderly woman has a high risk of fracture and OEP can be used to increase the muscle strength in elderly women. In this study, OEP cannot reduce IL-6 significantly but if carried out >8 weeks with a duration of 3 x/weeks it can reduce IL-6.

Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in Universitas Airlangga School Medicine, Surabaya, Indonesia (247/KEPK/FKUA/2020).

Sources of funding

None.

Author contribution

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Consent

All participants are required to fill out an informed consent.

Registration of research studies

Name of the registry: Health Research Ethics Committee in Universitas Airlangga School Medicine, Surabaya, Indonesia.

Unique Identifying number or registration ID: 247/KEPK/FKUA/2020.

Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

Imam Subadi is the person in charge of the publication of our manuscript.

Declaration of competing interest

I Dewa Gde Agung Mahendra, Imam Subadi, Indrayuni Lukitra Wardhani, Rwahita Satyawati, I Putu Alit Pawana, and Soenarnatalina Melaniani declare that they have no conflict of interest.

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