

Effectiveness of Yoga in reducing IL-6 serum level in elderly with knee osteoarthritis



Nila Wahyuni^{1*}, Nyoman Adiputra¹, I Putu Gede Adiatmika¹,
Luh Putu Ratna Sundari¹, Agung Wiwiek Indrayani²

ABSTRACT

Introduction: Osteoarthritis (OA) is a progressive degenerative disease. Yoga exercise is one of the non-pharmacological treatments for knee OA. It can improve joint function through a mind-body connection mechanism. It is also non-invasive and relatively safe to do at all ages, including the elderly. Interleukin-6 is one of the circulating inflammation biomarkers in knee OA. This study showed yoga's effectiveness objectively by measuring inflammatory biomarkers' changes, namely interleukin-6 (IL-6) in knee OA cases.

Methods: This research was a randomized control trial. The study was conducted in 8 weeks when the blood sampling and serum IL-6 level quantifications were taken.

Results: There was a significant difference ($p < 0.005$) and large Effect Size ($ES > 0,8$) in serum IL-6 levels before and after treatment between yoga and the control group.

Conclusion: Therefore, we conclude that yoga is a lifestyle modification intervention that improves the clinical condition of knee OA by altering the inflammatory control pathways activity. We highly recommend that future studies use a larger sample size and analyze more specific biomarkers describing joint degradation in knee OA cases.

Keywords: Elderly, knee osteoarthritis, interleukin-6, yoga, degenerative, inflammation.

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¹Department of Physiology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia, 80234;

²Department of Pharmacology and Therapy, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia, 80234.

*Corresponding author:

Nila Wahyuni;
Department of Physiology, Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia, 80234;
wahyuninila08@unud.ac.id

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INTRODUCTION

Osteoarthritis (OA) has been associated with functional limitations and disabilities. Populations with OA have risk factors for developing functional limitations and disabilities¹. OA is the fourth cause of disability in the world. Most cases of disability due to OA are caused by hip and knee OA².

Indonesia, as a Southeast Asian country, is experiencing population growth where the proportion of elderly continues to increase. The increasing number of elderly proportion causes high OA prevalence in Southeast Asia³. Apart from causing functional impairments and disabilities, knee OA also impacts the global economy. Average costs spent per patient with knee and hip OA are 11.1, 9.5 and 4.4 euros for total costs, direct and indirect costs, respectively⁴. Knee OA also has a negative impact on health-related quality of life (HRQoL). Knee OA

negatively impacts physical, psychological, social and economic aspects⁵.

OA management guidelines begin with the introduction of non-pharmacological treatment for knee OA. Yoga is a safe lifestyle modification intervention that has been shown to improve the clinical condition of patients with knee OA by attenuating pain and improving various functional parameters⁶. Yoga is also effective in improving the QoL in patients with knee OA⁷.

Circulating interleukin-6 (IL-6) is associated with radiographs and knee cartilage loss in the older population with knee OA⁸. This study aimed to investigate yoga's effectiveness in improving clinical knee OA by measuring IL-6 as a biomarker that plays a role in the pathophysiology of knee OA. To the best of our knowledge, no studies have examined the effectiveness of yoga in reducing levels of interleukin-6 as a biomarker of inflammation in knee OA. Our findings can be used as a reference

for considering yoga as one of the current safe and effective non-pharmacological treatments in patients with knee OA.

MATERIALS AND METHODS

Materials

The diagnosis of knee OA was established using the American College of Rheumatology (ACR classification) criteria. Using these criteria, the diagnosis of knee OA is based on the presence of clinical symptoms of knee pain accompanied by at least 3 of the following 6 criteria: age > 50 years old, morning stiffness < 30 minutes, crepitus on knee motion, bony tenderness, bony enlargement, and no palpable warmth⁹.

The guidelines used for body mass index (BMI) classification are the BMI criteria of WHO. Table 1 shows the classification of BMI based on WHO criteria¹⁰.

Participants' weight measurements were carried out using an anthropometer

made in Japan with a decimal number of one decimal point in kilograms. Height measurements were carried out using an anthropometer made in the USA, with a decimal number of one decimal point in centimeters. IL-6 examination was carried out before and after treatment. We used a human IL-6 ELISA kit * (Thermo, catalog no-LS-thermo-BMS213-2).

Methods

This research was a randomized control trial involving respondents that were elderly with knee OA and was conducted in Denpasar, Bali, Indonesia. The study design and respondents' recruitment strategy are summarized using the CONSORT statement flow diagram in Figure 1. The randomization method used was simple random sampling with a random number table. The sample size in this study was 33 respondents. Respondents were randomly allocated (using blocked randomization) into 2 groups: yoga and control. The protocol did not state the block size, so the investigators were blinded. Respondents were allocated to the yoga group (n=18) and the control group (n=15). Respondents' data analyzed in the control and yoga group were 15. Ethical clearance for this study had been issued by the Research Ethics Commission, Faculty of Medicine, Udayana University/ Sanglah Hospital, Denpasar (Ethical Clearance No. 2068/UN14.2.2.VII.14/LP/2018). An explanation of the procedures and benefits of the study was conducted on all respondents before the commencement of the study. The signing of informed consent showed the respondents' agreement. The yoga group was given yoga training for 8 weeks, 2 times a week, and the total duration of the exercise was 60 minutes per session. The control group was a negative control that was not given any intervention.

Participants in this study were elderly with knee OA in Denpasar City, Bali. The study respondents were established according to eligibility criteria, which age of more than 50 years, experiencing clinical symptoms of OA in the last 6 months, being willing to follow the study, and having a normal BMI (based on WHO criteria, using the formula: mass (kg)/height (m)²). Respondents were

Table 1. BMI criteria based on WHO classification¹⁰

Classification	BMI (kg/m ²)
Underweight	< 18.5
Normal range	18.5-24.9
Overweight (preobese)	25.0-29.9
Obese	≥ 30
Class I	30-34.9
Class II	35.0-39.9
Class III	≥ 40.0

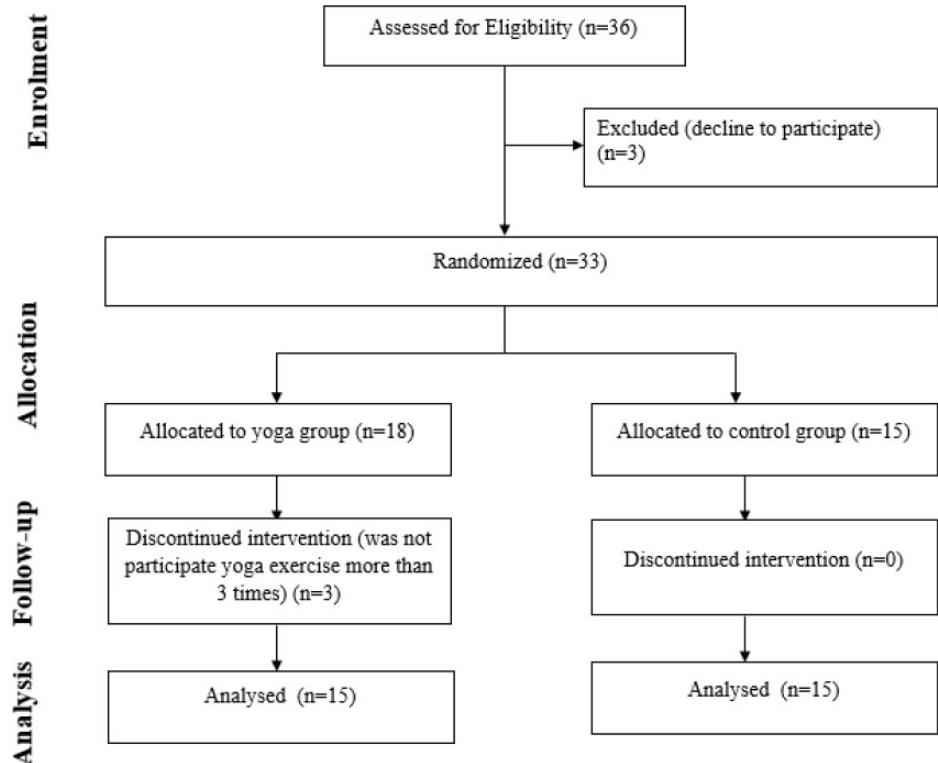


Figure 1. CONSORT statement of respondent recruitment.

excluded if they experienced balance disorders, had a history of corticosteroid injection therapy to treat knee OA in the last 3 months, had injection therapy for hyaluronic acid to treat knee OA in the last 6 months, had knee surgery in the last 2 years, using a knee brace, cane or walker for a long time, taking pain relievers and anti-inflammatory drugs. Respondents dropped out when they could not complete the treatment given, suffered injuries during the study, or resigned by themselves.

Yoga exercise was under the supervision of a yoga trainer and medical team. The yoga exercise began with active stretching as a warming-up for 5 minutes and consisted of 10 postures, and each posture was done for 1 minute with 5 repetitions. Yoga postures were accompanied by

breathing control (Table 2). At the end of the session, the subject relaxed, namely, Shavasana posture, for 5 minutes.

Blood sampling was taken at 08.00 AM and twice, 24 h before yoga training (pretest) began and 24 h after it (posttest). Venous blood taken using a syringe stood for 1-2 hours, so serum/plasma and other blood components were separated. After 1-2 hours, a new 300 rpm centrifuge was carried out for 10 minutes. Seen and observed formed supernatant (serum/plasma) were separated from other blood components. The supernatant was put in a 1.5 ml microcentrifuge tube and stored in the freezer at -20 / -80°C.

Interleukin-6 level was measured using the ELISA technique. We used a human IL-6 ELISA kit * (Thermo catalog no-LS-thermo-BMS213-2; sensitivity 1.03 ng/L).

Table 2. Details of Yoga Exercise Intervention

Practices	Duration	Repetition	Total duration
Warming up	5 minutes	1	5 minutes
Tadasana	1 minute	5	5 minutes
Virabhadrasana	1 minute	5	5 minutes
Dandasana	1 minute	5	5 minutes
Supta tadasana	1 minute	5	5 minutes
Supta padangustasana	1 minute	5	5 minutes
Urdva hastasana	1 minute	5	5 minutes
Ardha uttanasana	1 minute	5	5 minutes
Baddha konasana	1 minute	5	5 minutes
Virasana	1 minute	5	5 minutes
Swastikasana	1 minute	5	5 minutes
Cooling down (Shavasana)	5 minutes	1	5 minutes

Table 3. Characteristics of respondents based on age and sex

Variable	Frequency (f)	Percentage (%)
Age		
>60 years old	30	100
Sex		
Yoga group		
Male	6	40
Female	9	60
Control group		
Male	7	46.7
Female	8	53.3

Table 4. p values, CI and ES of serum IL-6 in the pre-test, post-test and decline after intervention in yoga and control group

Serum IL-6 levels	p value	Confidence Intervals	ES
Before intervention			
Yoga group	0,900	73.038-76.825	0.022
Control group		74.845-76.320	
After intervention			
Yoga group	0,000*	12.302-28.539	0.852**
Control group		72.921-73.598	
Decline before and after intervention	0,000*	1.497-3.146	0.852**

Notes:

CI: Confidence Interval

ES: Effect Size

*significant p-value

**Large Effect Size (ES)

The manufacturer had prepared reagents, samples, standard solutions and assay procedures according to protocol.

RESULTS

Characteristics of Participants

In our study, the respondents were elderly in Denpasar. The respondents were characterized by age and by sex. All respondents were more than 60 years old, and the numbers of females were more than male in both groups (Table 3).

The standard Deviation (SD) of IL-6 levels before and after intervention in the yoga group is 3,42 pg/mL and 14,66 pg/mL. The standard Deviation (SD) of IL-6 levels before and after intervention in the control group is 1,33 pg/mL and 0,61 pg/mL (figure 1).

The decline of IL-6 Level in the Yoga and Control Group

We found a significant difference in IL-6 level after intervention in the yoga group

compared to the control group [SE = 0.852 (large); p = 0.000]. A significant difference in IL-6 levels reduction was also established in the yoga group compared to the control group [SE = 0.852 (large); p = 0.000] (Table 4).

The mean IL-6 level after intervention and the decline of IL-6 level between yoga and control groups showed significant differences (Figure 2).

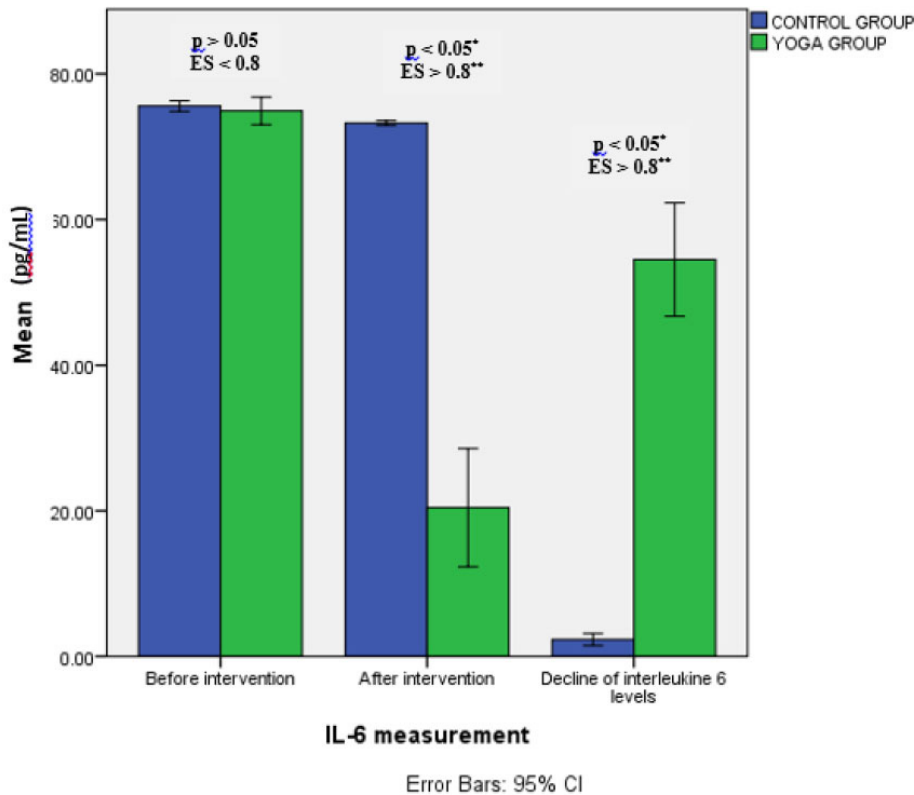
DISCUSSION

Characteristics of Respondents Based on Age

This study was carried out to evaluate the effect of yoga on the IL-6 serum of the elderly with knee OA in Bali. We found that all our respondents were more than 60 years old (Table 3). The incidence rate of knee OA tends to increase with age which is linear with a meta-analysis done by Blagojevic et al., in which knee OA is associated with an age of > 50 years¹¹. The aging process in the musculoskeletal system is the biggest risk factor compared to other factors. The underlying pathological processes in aging are extra and intra-articular tissue structural changes¹². Over 60 respondents have suffered aging-related degradation of the joint structure. Joint structural degradation is known to be associated with senescence-associated secretory phenotype (SASP). SASP is a pro-inflammatory cellular phenotype that can be induced by several stimuli, one of which is DNA damage, where DNA damage is related to the development of OA. In fibroblast, SASP is established by the biogenesis of several cytokines and matrix-metalloproteinases (MMPs) such as IL-1 β , IL-6, IL-8, MMP-3, and MMP-13. These cytokines and MMPs are also found in joint tissues with osteoarthritic changes¹³. Mitochondrial reactive oxygen species (ROS) also promote the expression of proinflammatory cytokines¹⁴.

Characteristics of Respondents Based on Sex

In our study, the characteristics of respondents by sex showed more female respondents than males. This finding is in line with a study sponsored by the Centers for Disease Control and Prevention and the National Institutes of Health. This study reveals differences in the incidence



Notes:
 *significant p-value
 **large Effect Size (ES)

Figure 2. The mean of IL-6 in the pre-test, post-test and decline after intervention between yoga and the control group.

and severity of OA between male and female populations and between racial and ethnic groups¹⁵. The difference in response to sex hormones between men and women also partially contributes to differences in the development of knee OA between men and women. Chondrocytes, a protective factor in knee OA, are target cells for estrogens because these cells express ER α and ER β receptors. A decline in estrogen levels in menopausal women is a risk factor for OA. Therefore, the prevalence of OA is higher in menopausal women¹⁶.

Effectiveness of Yoga in Decreasing Serum IL-6

Yoga is one of the mind-body therapeutic modalities available for various diseases and disorders. Mind-body interventions involving stress management with physical activity may exert their beneficial effects via multiple mechanisms and may be well suited for investigating OA and inflammatory immune-mediated diseases such as rheumatoid arthritis (RA)¹⁷. The effectiveness of yoga in

reducing serum IL-6 levels in our study can be attributed to various theories, one of which is mechanistic explanations for yoga's potential mental and physical health benefits via the attenuation of sympathetic autonomic nervous system (SANS) tone¹⁷.

Our findings are also supported by study conducted by Awasthi et al., where intensive yoga therapy in knee OA patients promotes the improvement of inflammatory biomarkers and physical functions¹⁸. Inflammation is related to depression and stress conditions. Stress conditions will increase the action of the inflammatory cytokines IL-6¹⁹. Yoga training is believed to reduce inflammatory cytokines biogenesis via its mitigative effect in decreasing stress conditions^{20,21}.

In our study, all yoga postures were done while doing breath control (pranayama). Pranayama trains concentration and provides a relaxing effect on research respondents. Combining yoga postures with concentration and relaxation are underlying factors for yoga to be categorized as a mindfulness-based

intervention. Meditation as a part of yoga may affect the regulation of histone deacetylases (HDACs) and inflammatory pathways, which account for the therapeutic potential of mindfulness-based interventions²².

Yoga postures in our research involve physical movements, concentration and relaxation of the mind, thus can be classified as mind-body therapy. Mind-body therapy studies, including yoga studies, had been conducted to elucidate the mechanisms underlying the effectiveness of these therapies²³. However, the study was focused on gene expression alterations²⁴. In the past two decades, mind-body interventions (MBIs) have been gaining empirical support and recognition by mental health professionals. Yoga is a type of MBI that has a strong physical component. MBIs are known to affect physical health by altering gene expression²⁵.

Our study's decrease in serum IL-6 levels may be attributed to downregulated expression of pro-inflammatory genes. Creswell et al. found that the 8-week Mindfulness-Based Stress Reduction (MBSR) program downregulated NF- κ B-associated gene expression profile. Downregulated NF κ B activity is associated with various stress management interventions to reduce the risk of inflammation. The underlying mechanism is that MBSR reduces stress and inflammation through modulation of the HPA axis and sympathetic nerves²⁶, both known to produce stress mediators (e.g., cortisol, norepinephrine, epinephrine) that can modulate NF κ B activity and pro-inflammatory gene expression²⁷. Yogic meditation also might alter the activity of inflammatory control pathways that shape immune cell gene expression. It is in line with the research carried out by Black, D.S et al., which led to the conclusion that Kirtan Kriya Meditation (KKM) for 12 minutes daily for 8 weeks can reduce the activity of NF κ B transcription factors and increase the activity of Interferon Response Factors (IRF) which is a key factor in Integrated Stress Response (ISR)²⁸.

Our findings also align with the study by Vijayaraghava, which concludes that yoga effectively reduces and suppresses increased levels of interleukin-6. The

underlying reason is that yoga gives physical stress to the body so that it causes adaptation, which ultimately has a protective effect on the immune system²⁹. Meditation is an important part of yoga. Kaliman et al. investigated the effects of intensive 8-h mindfulness meditation on several circadian, modulatory chromatin and inflammatory genes. Mindfulness meditation can alter the biochemical, neural and behavioral processes that will affect the regulation of HDACs and inflammatory pathways. In a recent interesting review by McDougall, OA is hypothesized as a neuropathological entity in which a possible brain-joint axis may have important roles in OA pathobiology³⁰. In the near future, it is intriguing to test the effect of our yogic intervention on this hypothesized brain-joint connection based on the findings that yoga beneficially modulates mental and physical health.

This body of evidence leads us to a notion that yoga can be an effective strategy in managing pathological entities underlined by chronic inflammation²², such as knee OA. Based on the studies we cited in this paper and our findings, we assume that our next biggest homework is to reveal the exact molecular mechanisms of yoga on knee OA from epigenetic and other plausible perspectives.

CONCLUSION

We conclude that yoga effectively attenuates serum IL-6 levels among elderly individuals with knee OA. Yoga is a lifestyle modification-based intervention that improves the clinical condition of knee OA by altering the inflammatory control pathways activity. We recommend yoga as an adjunct therapy in managing knee OA. The limitations of our study were the involvement of a relatively small sample size and quantification of serum IL-6 level only. Therefore in future studies, a larger sample size is needed to determine whether study results can be generalized to the broader populations. We also recommend studies using more comprehensive arrays of biomarkers that will give a good molecular picture of knee OA's degradation process.

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AUTHOR CONTRIBUTION

All authors contributed equally in the writing of this article

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

This study had been ethically approved with ethical clearance no. 2068/UN14.2.2.VII.14/LP/2018

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STATEMENT OF INFORMED CONSENT

All research respondents were willing to participate in the study by signing an informed consent.

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