

# Effect of Yogic Interventions on Serum Levels of Interleukin-6 & Interleukin- 10 in Patients with Osteoarthritis Knee

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## ABSTRACT

The present study was conducted to determine the role of Yoga on inflammatory markers Interleukin 6 (IL-6) and Interleukin 10 (IL-10) in subjects of KOA. One hundred and twenty patients of OA knee were randomized into two groups based on computer generated random table - Group A and Group B. Group A subjects were kept on conventional treatment along with an add-on integrated supervised yoga of 45 min duration in five days in a week of five set of Asanas. Group B subjects were kept on conventional treatment alone. Conventional treatment was in the form of Quadriceps drill exercises, hot saline fomentation, paraffin wax bath and analgesic drug on SOS basis. Patients were assessed at baseline and at 6-month interval by measurement of inflammatory biomarkers Interleukin 6 (IL-6) and Interleukin 10 (IL-10) of OA knee in both Group A & B. The Statistically significant fall in both biomarkers IL-6 and IL-10 level were found in the intervention Group A. Further there was a significant reduction in doses of analgesic drugs being given to the patients of Group A. Inflammation level rose significantly in those patients who left practicing yoga. In Group B there was also a decrease in IL-6 and increase IL-10, levels. However this difference was statistically significant. Therefore it can be concluded that yoga therapy resulted in significant decrease in the requirement of analgesic drugs and has also shown to have even complete withdrawal of the drugs in some KOA patients.

**Keywords:** Yogic asana, Interleukins, Osteoarthritis knee, Cartilage, Inflammation, ELISA

## INTRODUCTION

Osteoarthritis (OA) is the most common disease of joints in adults around the world. [1] Worldwide, it is estimated to be the fourth leading cause of disability. [2] Its prevalence increases gradually in individuals older than 40 years. Community survey data in rural and urban areas of India shows the prevalence of osteoarthritis to be in the range of 17 to 60.6%. [3-5]

It is non-inflammatory disorder of movable joint characterized by an

imbalance between the synthesis and degradation of articular cartilage leading to classic pathological change of wearing and destruction of cartilage. [6] In the current studies available, no specific cure for OA appears to exist and the severity of condition varies from individual to individual. Most of the patients have no option but to undergo joint replacement surgery which again is an option not without risk and limitations. Therefore, there is need for a treatment option which could avoid or

delay a joint replacement and make patient comfortable till surgery becomes an absolute indication. A more generic approach to current treatment methods revolves around some combination of non-pharmacological and pharmacological treatment modalities. [7]

The zest to provide patients with viable options to accomplish their exercise goals as part of the management protocol is unending and newer treatment modalities as well as old existing modalities with a new perspective are being evaluated. Exploration of alternative therapies for the management of chronic pain is one of these attempts. [8] Although significant attention has focused on stretching and strengthening the quadriceps muscles for reducing symptoms of knee OA. [9,10] Yoga is one of several practices that have the potential to be effective in OA as well. [11,12] Yoga is a mind-body practice in complementary medicine with origins in ancient Indian philosophy. The theory behind yoga practice is that the union of mind and spirit in exercise brings balance to the body and promotes healing. [13]

Although yogic philosophy addresses numerous aspects of well-being that might have an effect on health and disease, the use of the physical postures, or asanas, can be used as a form of exercise. Yoga improves both flexibility and strength and could theoretically be beneficial to some musculoskeletal problems. Hatha yoga emphasizes strength, flexibility, and relaxation, with particular attention to alignment of body structures (e.g., the relationship of the distal to the proximal extremities and the extremities to the spine and torso). [13,14] The Yogic asanas incorporate poses, breathing techniques, and meditation, can theoretically reduce pain and stiffness associated with OA by realigning the skeletal structure, strengthening muscles around the joints, and stretching tight joint structures. [15]

It is believed that while practicing the Yoga, joint are frequently moved which are believed to cause physiologic effects at

the cellular level. Because in vitro production of pro-inflammatory interleukin-1 and tumor necrosis factor decreases under low-level intermittent fluid pressure, yoga exercise may reduce fluid pressure, which, in turn, preserves cartilage that would allegedly be lost by immobilization. [16]

There are sporadic reports and case series that have shown the usefulness of Yoga for management of osteoarthritis knee patients. [17-19] Some researchers have also evaluated the efficacy of Yoga as part of a combination therapy comprising Yoga, Naturopathy and Physiotherapy. [20]

Despite availability of such sporadic literature, there is almost no systematic study available to evaluate the efficacy of Yoga in management of Osteoarthritis knee and to compare it with other conservative management techniques. Even if any study is available, it is basically done at pilot level and do not have strong evidence. More so, none of the studies has attempted to understand the physiological route of benefit derived by Yogic asanas. Radiological evaluations often do not provide adequate information about the change in patient status following treatment. However, biochemical markers have been reported to have a better sensitivity in order to assess the severity of disease in addition to monitoring of the efficacy and safety of disease-modifying OA drugs, with the potential to act as diagnostic tools. [21] The diagnostic power of cytokines in the interleukin family apart from other biochemical markers such as tumor necrosis factor- $\alpha$ , and vascular endothelial growth factor make these the best candidates for assessment. Evaluation of these pro-inflammatory and inflammatory markers helps to understand the mechanism and physiology through which a treatment response is obtained.

In osteoarthritis, inflammation occurs locally, within the synovium, and systemically, with inflammatory agents circulating in the blood. In the pathophysiology of OA, proinflammatory cytokines, such as IL-1 and IL-6 have been

shown to play important roles in the destruction of cartilage, synovitis, and pain. [22-25] On the other hand anti-inflammatory markers Countering the proinflammatory cytokines, antiinflammatory cytokines also play a role in the pathophysiology of OA. In particular, IL-10 and IL-4 contribute to the suppression of inflammation of the synovial membrane. [26,27] By reducing inflammation; these mediators can support cartilage production, acting as anabolic effectors which can slow the progression of OA.

Osteoarthritis is considered a non-inflammatory arthritis, but there is evidence that as the cartilage destruction proceeds, change in the joint occurs that are associated with inflammation. [28] Once the synovium is inflamed, the synoviocytes produce cartilage degradation enzymes, such as cytokines (IL-1, IL-6 and IL-10), which contribute to further decreased cartilage volume. [29] Inflammation is a robust and reliable predictor of all-cause mortality in older adults. [30] Pro inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-  $\alpha$ ), and C-reactive protein (CRP) play a role in cardiovascular disease, type II diabetes, arthritis, osteoporosis, Alzheimer's disease, periodontal disease, and frailty and functional decline. [31,32] Inflammation of the synovial joint is an inseparable part of knee OA and leads to pain and disability. [33] In addition to exercise and obesity, behaviour affects inflammation through other pathways; even relatively modest levels of anxiety and depressive symptoms can raise pro-inflammatory cytokine production. [33] In addition to pro-inflammatory cytokines, cytokines with predominantly counter-inflammatory actions have been identified. IL- 10 was first described as a product of TH2 lymphocytes that inhibits cytokine production by activated macrophages. IL-10 is an anti-inflammatory cytokine. In humans IL-10 is encoded by the IL10 gene. [34] In experimental settings, joint motion preserves cartilage that can be lost by immobilization. Correctly supervised yoga may be one way to provide the motion and

forces on joints needed to preserve integrity. [34] With this background, the current study is designed to analyze the serum cytokine (IL-1, IL-6 & IL-10) to evaluate the effect of "add on yoga asana with conservative management of OA knee. Pro inflammatory cytokine mediators have been reported to contribute to OA pathogenesis by increasing cartilage degradation and inducing hyperalgesia via a number of direct and indirect actions TNF $\alpha$  activates sensory neurons directly via its receptors and initiates a cascade of inflammatory reactions via the production of ILs 40. IL-6 is an interleukin that acts as both a pro-inflammatory and anti-inflammatory cytokine. It is secreted by T cells and macrophages to stimulate immune response IL-6 is also a "myokine," a cytokine produced from muscle, and is elevated in response to muscle contraction. [36] It is significantly elevated with exercise, and precedes the appearance of other cytokines in the circulation. During exercise, it is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery. [37]

With this background, the present study was planned with an aim to analyze the selected cytokine ( IL-6 & IL-10) levels in serum of the symptomatic OA knee and change in symptom patients managed by "add on" yogic asana and to compare it with those being managed conservatively in a systematic planned study with adequate number of patients.

## **MATERIALS AND METHODS**

### **Study Subjects**

One hundred and twenty Patients with osteoarthritis knee were randomized in the two groups i.e. Group A with conventional treatment with add-on yoga and Group B with conventional treatment of Knee Osteoarthritis without involving yoga therapy. They were assessed by measurement of inflammatory biomarkers (IL-6 and IL-10) by ELISA-kit method. Clinical parameters of severity of Osteoarthritis knee before and after giving

the add-on intervention of Yoga (follow up at the interval of 6 months). This Randomized control trial consisted of men and women above 40 years that fulfilled American College of Rheumatology (ACR) clinical and radiographic criteria for KOA. Sixty subjects in each Group A and B were recruited from the outpatient clinic of the Department of Orthopedics Surgery of King Georg's Medical University, Lucknow. The patients in both the groups were matched for age and sex. They were also profiled for demographic, clinical and radiological features. Age and sex were self reported. Patients were weighed with a calibrated balance beam scale to the nearest 0.1 kg in minimum possible clothing and standing height was measured (without shoes and shocks) with a Stadiometer in centimeters (cm). Body Mass Index (BMI) was recorded by Quetelet index. Among the 20 male and 40 female (including both groups) ages range from 40-60, mean age  $48.80 \pm 6.48$  and  $50.12 \pm 5.74$  years respectively. The protocol for research work was approved by the human ethics committee of King George's Medical University, Lucknow. Informed consent was obtained from the study subjects for inclusion in the study before intervention. The both group patients were asked to fill up the detailed questionnaire regarding their occupation, socioeconomic status, medical history, life style habits.

In our study the data of the patients was recorded immediately after which they were randomly allocated into two groups based on computer generated random table. After their first visit at OPD, a follow up was performed at 6 months interval for the biochemical testing of inflammatory cytokines.

The selected biomarkers, Interleukin-6 and Interleukin-10 levels were analyzed in the enrolled patients at following intervals i.e. at 1st visit and at 6th month interval. The peripheral venous blood (2 ml) was collected into EDTA coated vials between 9.00 AM to 11.00 AM by using a

sterile needle following which the biochemical examination was done by ELISA technique. The samples were stored in the vials at -20 degree Celsius.

### **Intervention for Yoga Group**

The study design was a randomized controlled trial, total no of 120 patients who met our inclusion criteria were randomized into two groups A & B. The patients under Group A were given 45 min of integrated yoga therapy practice for five days in a week for 6 months Five day in week (120 days) along with conventional clinical treatment including physiotherapy. Group B patients were given only conventional treatment including physiotherapy.

The integrated yoga therapy practice included Virbhadrasana, SuptaTadasana, Uttanpadasana, Dandasana, Paschimotasana, Traditional treatment in form of strengthening exercise Quadriceps drill, hot fomentation and paraffin wax bath to knee were given to both groups. Tab-Paracetamol, orally in divided doses were given in both groups for initial ten days of treatment to relieve the initial pain before and after giving the treatment at interval of 6th months.

### **Statistical Tools Employed**

All data were collected and analyzed using SPSS (Statistical Package for Social Sciences) Version 16.0 statistical Analysis Software. The values were represented in Number (%) and Mean $\pm$ SD. Wilcoxon signed rank test was used to evaluate the within group change.

## **RESULTS**

The mean age of subjects in both study group A and B was  $48.80 \pm 6.48$  and  $50.12 \pm 5.74$  respectively. When we compare the data after 6 months from baseline data in Group-A, statistically significant reduction in serum levels of IL-6 and IL-10 were found. In group B there was also a decrease in IL6 and IL-10 levels but value was not statistically significant.

**Table 1: Group wise distribution of patients**

SN	Group	Description	No. of cases	Percentage
1.	I	Group-A in whom management of knee osteoarthritis was done using add-on Yogic asana	60	50.0
2.	II	Patients in whom management of knee osteoarthritis was done without add-on Yogic asanas Group-B	60	50.0

**Table 2: Age wise comparison of patients in two groups**

SN	Age Group (Years)	Group A (n=60)		Group B (n=60)	
		No.	%	No.	%
1.	40-50 Years	38	63.3	33	55.0
2.	51-60 Years	22	36.7	27	45.0
Mean Age±SD (Range) in years		48.80±6.48 (40-60)		50.12±5.74 (40-60)	

t=1.388; p=0.241 (NS)

**Table 3: Gender wise comparison of patients in two groups**

SN	Gender	Group A (n=60)		Group B (n=60)	
		No.	%	No.	%
1.	Male	20	33.3	22	36.7
2.	Female	40	66.7	38	63.3

$\chi^2=0.147$ ; p=0.702 (NS)

**Table 4: Comparison of patients in two groups according to BMI**

SN	BMI Category	BMI Range (kg/m <sup>2</sup> )	Group A (n=60)		Group B (n=60)	
			No.	%	No.	%
1.	Normal	18.5-24.9	14	23.3	10	16.7
2.	Overweight	25.0-29.9	34	56.7	40	66.7
3.	Obese	>30	12	20.0	10	16.7

$\chi^2=1.335$  (df=2); p=0.513

**Table 5: Comparison of patients in two groups according to Educational Status (Ref. lawmin.nic.in/ncrcw/final report)**

SN	Educational Status	Definition	Group A (n=60)		Group B (n=60)	
			No.	%	No.	%
1.	Illiterate	Those who are unable to read and write or can read but not write	12	20.0	5	8.3
2.	Literate	Those who has the ability to read and write with understanding in any language	48	80.0	55	91.7

$\chi^2=3.358$  (df=1); p=0.067

**Table 6: Comparison of patients in two groups according to Lifestyle (Activity Profile) (Ref. Jill A.Benneet;journal of aging and physical activity:2006, 14,456-77)**

SN	Activity Profile	Group A (n=60)		Group B (n=60)	
		No.	%	No.	%
1.	Sedentary Less than 20 to 150 minutes / week of physical activity	16	26.7	26	43.3
2.	Moderate More than 150 to 300 mins/week	44	73.3	34	56.7
3.	Heavy More than 300mins/ week	0	0	0	0

$\chi^2=3.663$  (df=1); p=0.056

**Table 7: Comparison of patients in two groups according to analgesic (paracetamol 650 mg) intake at baseline and different follow up intervals**

SN	No. of daily analgesic dosages	Group A (n=60)		Group B (n=60)	
		No.	%	No.	%
Baseline					
1.	0	0	0	0	0
2.	1	0	0	0	0
3.	2	60	100	60	100
$\chi^2=0$ ; p=1					
6 months					
1.	0	52	86.7	0	0.0
2.	1	8	13.3	43	71.7
3.	2	0	0.0	17	28.3
$\chi^2=93.02$ (df=2); p<0.001					

**Table 8: Comparison of two groups for different inflammatory markers at different study intervals**

SN	Component	Group A (n=60)		Group-B (n=60)		Statistical significance	
		Mean	SD	Mean	SD	't'	'p'
IL-6							
	Baseline	4.28 ± 3.52	4.44 ± 3.84	-0.247	0.806	4.28 ± 3.52	4.44 ± 3.84
	6 months	1.25 ± 1.03	2.37 ± 2.33	3.396	0.001	1.25 ± 1.03	2.37 ± 2.33
IL-10							
	Baseline	0.80 ± 0.48	1.43 ± 0.93	0.060	0.952	0.80 ± 0.48	1.43 ± 0.93
	6 months	2.75 ± 2.25	2.73 ± 2.15	-4.688	<0.001		

## DISCUSSION

In present study, in both the groups females predominated over males. The male to female ratio was 1:2. These findings are in the concurrence with the findings of reported gender-associated higher risk of osteoporosis in women as compared to men. Knee osteoarthritis is more common in women, with female-to-male ratios varying between 1.5:1 and 4:1 and a dramatic rise in its prevalence has been reported around the time of menopause. [38-42] There could be several reasons to explain this gender related association. One of them could be the posture of the house hold women in our environment where they usually works with knee bent position in their house. In a study at Bangladesh, most of the house wives used to do their household works in the bent knee position. There is a significantly increased prevalence of osteoarthritis knee in road laborers and others engaged in knee-bending occupations.

In present study, majority of patients in both the groups were aged 40-50 years. Mean age of patients in two groups was  $48.80 \pm 6.48$  and  $50.12 \pm 5.74$  years respectively. The age profile of patients in present study was slightly lower as compared to that reported in previous studies which have reported majority of patients to be older than 70 years. [43,44] One of the reasons for relatively younger age profile of patients in present study was a strict inclusion and exclusion criteria. In present study, individuals above 60 years of age were not included mainly because they tend to fall in exclusion criteria like history of prolonged analgesic and anti-inflammatory medication.

In present study, majority of patients in both the groups were overweight and obese. In fact, only 20% of patients were in normal weight category. Obesity is one of the strongest and best-established risk factors of OA. [45-47] and the findings of present study tended to endorse this relationship.

In present study, among demographic and lifestyle factors, literacy, household work and sedentary to moderate activity were quite commonly observed among patients with knee osteoarthritis. As far as literacy is concerned, it primarily shows a shift from a more active to a sedentary lifestyle and as such could be strongly correlated with the sedentary to moderate activity profile of the patients. With respect to dominance of household work as the occupation, it could be mainly attributed to the relatively higher proportion of females among study subjects.

In our study the doses of Analgesics were reduced significantly in both the groups, more so in the group practicing yoga which is in accordance with the study done by the name J Women's Health 2009 and also supported by Tai Chi study. The results of our study has shown the beneficial effects of yoga and similar studies done by Chenchen Wang, Christopher H. Schmid, Patricia L. Hibberd Tai Chi has shown that Yoga is effective in treating knee osteoarthritis. [48] Use of Yoga to reduce pain has been reported among different patient groups. The efficacy of Yoga to reduce labour pain, [49,50] chronic low back pain, [51] osteoarthritis [52] and musculoskeletal pain [53] in general. Yoga exercises consist of physical postures, breathing techniques and meditation [51] and as such affect the individual not only physically but psychologically and physiologically too.

The present study showed that there is statically significant difference in the levels of Interleukins at third and six months. In relation to this a number of studies have done by van Valburg et al., have reported the positive association between the cellular effects of mechanical and fluid pressure on structures such as cartilage which suggest that yoga postures might alter joint function. Low levels of intermittent fluid pressure, as occurring during joint distraction, have been shown in vitro to decrease production of catabolic

cytokines, such as interleukin-1 and tumor necrosis factor- $\alpha$ .

The present study demonstrates that after an interval of 3 and 6 months from the baseline, Group A showed a considerable decrease in the levels of the inflammatory markers as compared to the patients of Group B. This might be due to decrease in inflammation in response to yoga practices.

In present study, a significant decrease in pro-inflammatory markers IL-1 and IL-6 levels and a significant increase in anti-inflammatory marker IL-10 levels as compared to baseline was observed in both the groups, however, mean values for pro-inflammatory markers were significantly lower in Group A as compared to Group B at both the follow up intervals (3 and 6 months) whereas mean values of anti-inflammatory marker IL-6 were significantly higher in Group A as compared to Group B at both the follow up intervals.

We observed that serum levels of IL-6 had a twofold increase in patients when compared to controls, comparable to a study that showed increased IL-6 in patients with more severe disease. [54] Similar observations have also been made for IL-10 too. [55]

All these observations indicated that Yoga had a physiologic effect too that helped in providing an improvement in functional quality of life of patients. Effect of Yoga module on pro-inflammatory and anti-inflammatory cytokines has also been enumerated by several other workers in different studies. [56, 54, 57]

The present study demonstrates that after an interval of 6 months from the baseline, Group A showed a considerable decrease in the levels of the inflammatory markers as compared to the patients of Group B. This might be due to decrease in inflammation in response to yoga practices.

## CONCLUSION

On the basis of result of our study we can conclude that Yoga can serve as an adjuvant with existing conventional treatment of osteoarthritis and prolong add-

on of yoga can even augment certain pathophysiological processes involved in progression of Osteoarthritis.

**Competing Interests:** Authors have declared that no competing interests exist.

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