CLINICAL TRIAL

Evaluation of the Anti-inflammatory Effect of Curcumin as an Additive Therapy to Meloxicam in Management of Knee Osteoarthritis

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ABSTRACT

Background: Osteoarthritis (OA) is one of the most prevalent chronic degenerative arthritis diseases and a major cause of pain and physical disability among elderly patients. It can affect any joint in the body but most commonly, hip and knee joints. The etiology of the disease is multifactorial, OA affected by a range of mechanical and biochemical factors. Various studies provided compelling evidence that low-grade inflammation and synovitis are playing a pivotal role in its pathogenesis along with oxidative stress. Unfortunately, there is no cure for the disease; thus, most current treatments are prescribed for alleviating symptoms only. Curcumin, a natural polyphenolic compound, has been used for centuries in ayurvedic medicine that gained an increasing surge of interest to explore its potential properties. Many *in vitro* and *in vivo* studies reported powerful anti-inflammatory and antioxidant capacity for treating various pathological conditions, including OA, curcumin has shown chondroprotective potential on osteoarthritis disease.

Aim of the Study: This study was designed to evaluate the anti-inflammatory effect of curcumin as an additive therapy to a non-steroidal anti-inflammatory drug, meloxicam, in the management of knee osteoarthritis.

Patients and Method: This prospective open-labeled randomized controlled trial was conducted among patients with mild to moderate knee OA. Sixty-two patients were enrolled in this study; only 42 patients completed the study. Patients were assigned randomly into two groups; group (A) 21 patients treated with meloxicam alone (15 mg/day), group (B) 21 patients treated with a combination of meloxicam (15 mg/day), and curcumin (1600 mg/day) for 12 weeks. Inflammatory biomarkers (IL-1β, IL-6, and TNF-α) serum levels were evaluated at the time of enrolment and after 12 weeks of treatment.

Results: Results gained from this study showed that treatment of knee OA patients with a combination of meloxicam and curcumin has a better effect on overall pain and physical function in addition to a remarkable decrease in serum pro-inflammatory biomarkers (IL-1β, IL-6, TNF-α) level (-39%, -24%, -30%) respectively after 12 weeks of treatment in respect to baseline levels. However, this reduction was significant only for IL-6. While those patients treated with meloxicam alone demonstrated no significant reduction.

Conclusion: Curcumin represents a safe and effective anti-inflammatory product that exhibits a synergistic effect when used in combination with meloxicam, resulting in pain and physical activity improvement, which its anti-inflammatory effect may reflect.

Keywords: Curcumin, Inflammation, Knee osteoarthritis, Meloxicam.

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INTRODUCTION

Osteoarthritis (OA) is the most prevalent form of chronic arthritis and the major cause of pain and disability among the adult population.[1] OA affected more than 4% of the world's population.[2] OA has a profound impact that exceeds an individual's quality of life to a substantial burden on health care systems all over the world.[3]

The disease is also known as a degenerative joint disease that involves the whole joint organ, which is characterized pathologically by inflammation of the synovium and localized loss of cartilage. As OA worsens over time, more pathological changes can be seen, including remodeling of subchondral bone, formation of bone spurs at the joint edges, degeneration of ligaments and menisci, and thickening of the joint capsule.[4]

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The etiology of OA is multifactorial, and it is usually associated with certain risk factors, including age, obesity, inflammation, and joint injuries.[5,6] Inflammation is now well known to play a substantial role in OA pathogenesis; it occurs early in the course of OA due to interactions between the immune system and factors, including metabolic dysfunction and local tissue damage.[7] Excreted inflammatory molecules, such as pro-inflammatory cytokines, seem to be driving the production of the proteolytic enzymes that degrade the ECM. Matrix Metalloproteinases (MMPs) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) are examples of these enzymes.[8,9] It is widely recognized that IL-1β is the key cytokine at all stages of OA.[10] Furthermore, IL-1β activity along with the activity of TNF-α derives the activity of prostaglandin E2 (PGE2) that subsequently exacerbates joint inflammation and pain.[11]

Unfortunately, no drug can stop or retard disease progression, y*et al*l medications currently used, such as NSAIDs, are for managing symptoms only. However, they are known for multiple serious adverse effects, particularly on long-term use.[12] Therefore, extensive research focuses on finding new effective drugs or adjuvants with the lowest possible side effects.

Curcumin is a polyphenolic compound widely used for its anti-inflammatory and powerful antioxidant activity and good analgesic effect.[13] Curcumin has demonstrated important chondroprotective effects and anti-catabolic activities in OA. Studies have shown that oral administration of curcumin has been significantly found to slow down disease progression, through the reduction of synovitis, proteoglycan loss, cartilage erosion through down-regulation of cyclooxygenase enzymes, PGE-2, pro-inflammatory mediators such as IL-1β, IL-6, IL-8, TNF-α and adipokines in chondrocytes, in addition, to reduce the synthesis of reactive oxygen species.[14,15] Accordingly, curcumin appears to be a promising agent for treating OA, especially it has a high safety profile.

This study is designed to evaluate the effect of adding curcumin to one of the semi-selective COX-2 inhibitors of NSAIDs group: meloxicam for treating knee OA patients.

PATIENTS AND METHODS

A randomized open-labeled controlled trial was conducted to evaluate the effect of adding curcumin to meloxicam in patients with knee OA. A total of 62 patients were selected from the outpatient clinic at Baghdad teaching hospital and enrolled in the study. Written informed consent was obtained from all subjects before participation. Patients were eligible to study if they were fulfilling the criteria of diagnosing knee OA and had a confirmed diagnosis of mild to moderate painful knee osteoarthritis according to physical examination and radiological features based on Kellgren-Lawrence (KL) classification system, also if they were aged 18-70 regardless the gender. The exclusion criteria were severe cases of OA, patients with DM and cardiovascular diseases, patients with renal and hepatic dysfunction, patients with diagnosed ulcer diseases, also pregnant and breastfeeding women, and patients receiving steroid injections within 2 months before the study, or other steroid administration within 4 weeks before the study as well as patients who are allergic to any of the known tested drugs.

Eligible patients were randomly allocated in two groups as follow:

Group A: 21 patients treated with NSAIDs; meloxicam 15 mg once daily.

Group B: 21patients treated with NSAIDs; meloxicam 15 mg once daily and Curcumin 800 mg 2 caps once daily

Meloxicam was administered orally with a dose of 15mg once daily after food, while curcumin two caps (800 mg) were administered orally once daily before breakfast for a period of 3 months.

Clinical outcomes were evaluated by measuring serum levels of the pro-inflammatory parameters (IL-1β, IL-6, and TNF-α) at baseline and after 3 months of treatment.

RESULTS

Sixty-two patients have initially entered this trial, but only 42 patients completed the 3 months of study and were included in the final analysis. The baseline demographic data have shown that both study groups were comparable regarding gender, age, and BMI, were no statistical differences in the baseline characteristics were noticed Table 1.

Study results showed that the change in serum IL-1β level was statistically non-significant between groups at baseline or after 3 months of treatment. However, there was a higher decrease in serum IL-1β level in group B patients after 3 months of treatment than with group A compared to baseline, but there was a non-significant statistical difference in serum level of IL-1β pre and post treatment for both groups, ($p > 0.05$). Table 2, Figure 1.

Treatment with a combination of meloxicam and curcumin resulted in a significant reduction in IL-6 serum level after three months of treatment in respect to the baseline level ($p < 0.05$). At the same time, no significant statistical changes in IL-6 serum level were noticed after treatment with meloxicam alone in respect to the baseline level. Nevertheless, a non-significant change was observed in IL-6 serum levels after

Table 1: Patient's demographic data and disease characteristics

Variable	*Group A*	*Group B*	*P-value*
Gender	n (%)	n (%)	-
Female	19 (90.5)	17 (81.0)	0.378^{NS}
Male	2 (9.5)	4(19.0)	
Total	21 (100)	21(100)	
Age (year)	49.52 ± 8.07	50.52 ± 9.90	0.722^{NS}
BMI (kg/m^2)	30.25 ± 3.75	30.71 ± 4.90	0.735^{NS}

Data presented as mean ± SD

Number of patients (n), Percentage (%), NS: No significant differences ($p > 0.05$).

The two-sample *t*-test is used for statistical analysis of (age, BMI)

Paired *t*-test is statistically used to compare pre-and post-treatment results in the same group

Chi-square test is used for statistical analysis of (gender)

Table 2: Effect of treatment with meloxicam alone or in combination with curcumin on serum IL-1β level in patients with knee osteoarthritis.

Variable	*Study groups*		
IL-1β (pg/mL)	*Group A*	*Group B*	*P-value*
Pre-treatment	8.072 ± 7.32	8.45 ± 10.82	0.895 ^{NS}
Post-treatment	7.356 ± 8.24	5.152 ± 2.346	0.247 ^{NS}
P-value	0.313 ^{NS}	0.144^{NS}	

Data presented as mean ± SD.
NS: Non-significant differences (p > 0.05).
Paired *t*-test is statistically used to compare pre-and post-treatment results in the same group.
A two-sample *t*-test is used to compare pre or post-treatment between group 1 and group 2 patients.

Table 3: Effect of treatment with meloxicam alone or in combination with curcumin on serum IL-6 level in patients with knee osteoarthritis.

Variables	*Study groups*		
IL-6 (pg/mL)	*Group A*	*Group B*	*p-value*
Pre-treatment	253.69 ± 212.7	381.65 ± 206.3	0.055 ^{NS}
Post-treatment	296.33 ± 302.6	286.4 ± 194.88	0.900 ^{NS}
p-value	0.568 ^{NS}	0.044*	

NS: Non-significant differences (*P* > 0.05), (**) highly significant differences (*P* < 0.01).
Paired *t*-test is statistically used to compare pre-and post-treatment results in the same group.
The two-sample *t*-test is used to compare pre or post-treatment between group A and group B patients.

Table 4: Effect of treatment with meloxicam alone or in combination with curcumin on serum TNF-α level in patients with knee osteoarthritis.

Variables	*Study groups*		
TNF-α (pg/ml)	*Group (A)*	*Group (B)*	*P-value*
Pre-treatment	3504 ± 923.11	3874.6 ± 3083.4	0.6 ^{NS}
Post-treatment	3830.7 ± 1177.8	2675.1 ± 1036.1	0.002 **
P - value	0.147 ^{NS}	0.075 ^{NS}	

NS: Non-significant differences (p > 0.05), (**) highly significant differences (p < 0.01).
Paired *t*-test is statistically used to compare pre-and post-treatment results in the same group.
A two-sample *t*-test is used to compare pre or post-treatment between group A and group B patients.

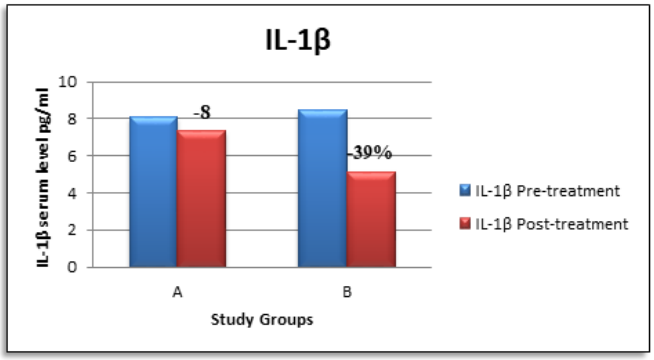

Figure 1: Effect of treatment with meloxicam alone, and in combination with curcumin, on serum level of IL-1β in patients with knee osteoarthritis.

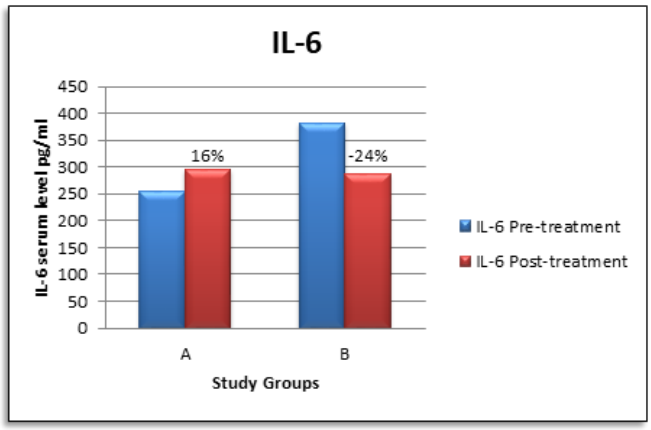

Figure 2: Effect of treatment with meloxicam alone and in combination with curcumin on IL-6 serum level in patients with knee osteoarthritis.

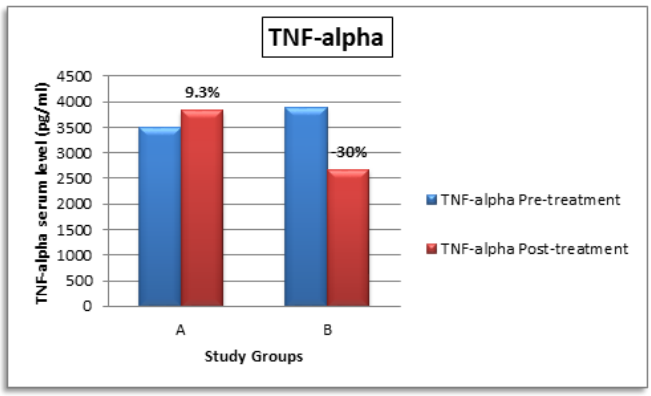

Figure 3: Effect of treatment with meloxicam alone and in combination with curcumin on TNF-α serum level in patients with knee osteoarthritis.

three months of treatment between both groups A and B. Table 3 and Figure 2.

In regard to TNF-α; within each group, the results of this study showed a non-significant difference in the serum levels of TNF-α after three months of treatment in respect to the baseline levels. However, 30% reduction and 9.3 % elevation of TNF-α levels were noticed in group B and group A patients, respectively, after completing the study.

In comparison between the two groups, there were no significant differences in TNF-α serum levels before treatment and highly significant differences after three months of treatment (p < 0.01). All these data are displayed in Table 4 and Figure 3.

DISCUSSION

In the current study, both genders were assigned, but women are highly predominant to men in both group's ratios. This finding comes in accordance with earlier studies.[16,17] Worldwide estimates are around 18% of women and 10% of men aged over 60 years.[18] The tendency of women to develop KOA more than men may be due to multiple factors like anatomical structure differences and hormonal and genetic factors.[19] In regard to age, both groups were matched, all patients in the present study

aged between 30 to 70 years with a mean age 49.52 in group (A) and 50.52 in group (B), which may point toward a lower age onset of KOA in Iraqi population comparing to other studies in middle east patients with a mean of age 55.3 years in Jordan[20] and 57.57 years in Iran,[21] our findings come in accordance with another study carried out in Iraq.[17]

In the current study, there was found a strong association between increased BMI and knee OA prevalence; patients in both groups (A) and (B) had BMI > 30. Being overweight is an important risk factor for developing OA.[22] The findings are almost similar when compared to other studies conducted in Iraq and nearby regions.[23,24] These findings suggested the common shared pathogenic role for metabolic factors with knee OA. The possible mechanism might involve adipokines such as leptin which is attributed to approximately half of the total effect of obesity on knee OA.[25,26] On the other hand, the mechanical effect that puts extra stress on weight-bearing joints plays a comparable role in knee OA development.

Osteoarthritis is now well recognized to have an inflammatory component as a critical contributor to its pathogenesis. Inflammatory cytokines produced by the synovium and chondrocytes, including interleukin 1ß (IL-1ß), tumor necrosis factor-α (TNF-α), IL-6, and others, seem to play vital roles in cartilage destruction. These cytokines are produced by the synovium and chondrocytes and are expressed there and in the synovial fluid. Some studies indicate that this local inflammation may be reflected systemically.[27]

In the present study, orally administered curcumin as an adjuvant to meloxicam remarkably decreased inflammatory biomarkers such as IL-1β, IL-6, and TNF-α (-39, -24, and -30% respectively), although some of them were not statistically significant) but the reduction was enough to affect treated knee OA patients positively. These results are supported by the work of Belgaro *et al*. (2010), who reported a significant reduction in all markers of inflammation after 8 months of use of meriva[a] (a Curcumin-phosphatidylcholine Complex) in knee OA patients.[28] The observed downregulation of those circulated inflammatory biomarkers is mostly attributed to the inhibitory effect of curcumin on NF-κB activation and MAPK signal pathway. Hence, the remarkable clinical improvements noticed seem to have an apparent mechanistic basis that supported previously *in vitro* observation on OA joint tissues.[29]

In vitro and *in vivo* studies have demonstrated that curcumin can suppress the production of pro-inflammatory cytokines such as IL-1ß and TNF-α by macrophages. It is suggested that curcumin attenuates inflammation by interrupting the nuclear factor-kB (NF-kB) signaling transcription factors.[30] Thus, it has the potential to protect chondrocytes from the negative downstream outcomes of IL-1β such as inhibition of collagen type II and β1-integrin expression and up-regulation of COX-2, MMP-9, and MMP-3.[31]

Curcumin has been shown to have a chondroprotective effect *in vitro* and significantly slows down disease progression in an osteoarthritis mouse model. Curcumin also exerts potent anti-apoptotic and anti-catabolic effects on IL-1β-stimulated cultures of articular chondrocyte.[32] Further study by Huang and his colleagues (2013) showed that curcumin dramatically mitigate the progression and severity of collagen-induced arthritis in mice and inhibits the production of the B-cell-activating factor that belongs to the TNF family.[33] Curcumin also inhibits COX-2, LOX, and inducible NOS enzymes, which are important in the inflammatory process, thereby acting as an anti-inflammatory agent.[34]

In respect to this study, meloxicam treated group revealed a non-significant increase in IL-6 and TNF-α; this finding is consistent with other studies that used meloxicam for osteoarthritis treatment that reported similar results.[35,36] IL-6 is thought to have partial anti-inflammatory activity because of the induction of acute-phase proteins. Nevertheless, the production of some of these proteins is a sensitive indicator of inflammation and of the production of pro-inflammatory cytokines, IL-1 and TNF-α.[37]

The overall results of this clinical trial showed a significant inflammatory biomarkers reduction by curcumin supplementation. This finding and the improvement of OA-associated pain symptoms uphold the idea that this polyphenol can suppress pro-inflammatory pathways linked with different low-grade inflammatory diseases, including osteoarthritis, and obviously can mitigate disease progression. Moreover, clinical trials with curcumin demonstrated safety, high tolerability, and nontoxicity.[38,39] Thus, it sounds rational to consider the treatment of OA with highly effective nutraceuticals such as curcumin even alone or as an adjunct to other best-known treatments for OA like NSAIDs.

CONCLUSION

A combination of meloxicam and curcumin demonstrated a remarkable decrease in serum levels of pro-inflammatory biomarkers, contrary to treatment with meloxicam alone.

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