Curcumin as adjuvant therapy to Meloxicam in treatment of patients with knee Osteoarthritis; Evaluation of antioxidant activity

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Abstract:

Osteoarthritis (OA) is a chronic degenerative joint disease that doubled in prevalence since the mid of 20th century most commonly due to obesity and aging. Osteoarthritis can affect any joint in the body. The pathogenesis of OA is multifactorial influenced by range of biochemical and mechanical factors.

Oxidative stress is described to play an important role in many diseases including OA. Accumulating evidences suggested the beneficial effect of anti-oxidants for reducing OA severity. Curcumin is a well-known antioxidant agent that acts by different mechanisms in modulating oxidative stress status. This study was designed to evaluate the antioxidant effect of curcumin as adjuvent therapy to a non-steroidal anti-inflammatory drug, meloxicam, in the management of knee osteoarthritis. This prospective open-labelled randomized controlled study was carried out on forty-two eligible patients who were allocated in two groups, serum superoxide dismutase 3 (SOD3) and glutathione reductase (GR) were measured at baseline and after 3 months of the study. Pain and physical function assessment were evaluated by oxford knee score (OKS). Results illustrated highly significant improvement in pain and physical function scores when curcumin used as adjuvant to meloxicam, also curcumin supplementation resulted in significant increase in SOD3 serum level and only a modest decrease in GR serum level when compared to meloxicam alone. In conclusion, this study demonstrated benefit of curcumin when used in combination with meloxicam over using meloxicam alone in modulating antioxidant parameters in blood, in addition to significantly improving pain and physical function after 3 months of treatment.

Key words: osteoarthritis, curcumin, oxford knee score, antioxidants, superoxide dismutase 3, glutathione reductase.

الكركم كعلاج مساعد لمضادات الالتهاب غير الستيروئيدية لمعالجة مرضى التهاب المفاصل غير الرثوي في الركبة ; تقييم فعالية مضادات الأكسدة.

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الخلاصة:

التهاب المفاصل غير الرثوي هو مرض المفاصل التنكسية المزمن الذي تضاعف انتشاره منذ منتصف القرن العشرين غالبا بسبب السمنة والشيخوخة . من الممكن ان يصيب التهاب المفاصل غير الرثوي اي مفصل في الجسم. اسباب التهاب المفاصل غير الرثوي متعددة العوامل تتأثر بمجموعة من العوامل الكيميائية والميكانيكية. يقوم الإجهاد التأكسدي بدور مهم في العديد من الأمراض بما في ذلك التهاب المفاصل غير الرثوي. وقد اشارت الأدلة على التأثير المفيد لمضادات

الأكسدة للحد من شدة المرض. الكركم هو أحد مضادات الأكسدة المعروفة التي تعمل عن طريق آليات مختلفة في تعديل حالة الإجهاد التأكسدي. تم تصميم هذه الدراسة التجريبية لتقييم تأثير مضادات الأكسدة للكركم كعلاج مضاف لعقار مضاد للالتهابات غير الستيرويدية ، ميلوكسيكام ، في علاج التهاب المفاصل في الركبة. وقد أجريت هذه الدراسة المحتملة مفتوحة التسمية والمسيطر عليها على اثنين واربعين مريضا مؤهلا والذين تم تقسيمهم في مجموعتين. وقد تم قياس مستوى الاوكسيد الفائق3 والجلوتاثيون المختزل في مصل الدم في نقطة البدايه وبعد ثلاث اشهر من العلاج وتم تقييم التحسن في مستوى الالم والوظيفة البدنية عن طريق مجموع نقاط اوكسفورد للركبة. أوضحت النتائج تحسنًا كبيرًا في درجات الألم والوظائف الجسدية عندما استخدم الكركم كعلاج مساعد للميلوكسيكام لوحظ ايضا عند اضافة مكملات الكركم زيادة في مستوى الاوكسيد الفائق3 وايضا الى انخفاض متواضع للجلوتاثيون المختزل بالمقارنة مع استخدام الميلوكسيكام فقط. في الختام أظهرت هذه الدراسة تفوق الكركم عند استخدامه جنبا الى جنب مع ميلوكسيكام على الميلوكسيكام وحده في تعديل العوامل المضادة للأكسدة في الدم. أيضا في تحسين الألم والوظيفة الجسدية بشكل كبير بعد 3 أشهر من العلاج.

الكلمات المفتاحية: التهاب المفاصل غير الرثوي, الكركم, مجموع نقاط اوكسفورد للركبة, مضادات الاكسدة, الاوكسيد الفائق 3, الجلوتاثيون المختزل.

Introduction

Osteoarthritis is highly prevalent chronic degenerative disease [1] that doubled in prevalence since the mid of 20th century and affecting 4% of world population [2]. OA has a profound impact that exceeding individuals' quality of life to substantial burden on health care systems all over the world. Almost every synovial joint can be affected by osteoarthritis. However, it particularly targets the knees, hands, and hips [3]. Etiology of osteoarthritis is multifactorial. Several person-level risk factors are recognized, including socio-demographic factors, genetic factors, obesity, diet-related factors, and high bone density/mass [4], as well as joint-level risk factors, including specific bone/joint shapes and injury [5]. Osteoarthritis possesses notable differences of clinical presentation with some common features such as crepitus, bony swelling, joint line tenderness, pain and stiffness [6]. Therefore, osteoarthritis is typically diagnosed on the basis of medical history, physical exam, relevant signs and symptoms along with consistent radiographic features [7], in addition to various clinical assessment questionnaires developed to accurately measure symptoms and physical function limitation of OA patients, for instance; oxford knee score [8].

Osteoarthritis has long been perceived as a degenerative joint disease nevertheless accumulating evidence indicated that inflammation and oxidative stress plays substantial role in OA pathogenesis. Chondrocytes maintain a delicate balance between synthesis and breakdown of the extracellular matrix (ECM), free radicals can induce structural and functional alteration of the extracellular matrix because these toxins pack in bones and synovial joints, and together with inflammatory mediators they can result in extensive structural damage, inflammation and eventually cell death [9].

No drug has been found yet to retard or stop OA progression, therefore many researches have been devoted to find drug or adjuvant to meet these demands. Curcumin a natural polyphenolic compound known for centuries for its powerful anti-inflammatory and antioxidant properties which has implicated in management of many diseases including OA [10].

Aim of study: This study was designed to evaluate the potential therapeutic effect of curcumin supplement through antioxidant effects when combined with non-steroidal anti-inflammatory drug, meloxicam, in the management of knee osteoarthritis.

Patients and Methods

This interventional prospective randomized controlled study was designed to evaluate role of curcumin on antioxidant status of osteoarthritis patients and to assess pain and physical function improvement over the course of treatment. Fourty two patients with confirmed

radiological evidence of knee OA were selected from the outpatient clinic at Baghdad teaching hospital and enrolled in this study after obtaining written informed consent from each patient. Eligible patients were allocated into two groups as follow:
Group A: 21 patients treated with; meloxicam 15 mg once daily.
Group B: 21 patients treated with; meloxicam 15 mg once daily and curcumin 800 mg 2 caps once daily.
Patients were recommended to take meloxicam once daily after food while curcumin 2 caps once daily before breakfast according to label recommendations. Patients followed up for a total of 12 weeks and regular clinical evaluation of their knee symptoms were done at 0, 4, 8 and 12 weeks in accordance with oxford knee score (OKS) clinical assessment questionnaire, this has 12 items each item is followed by 5 responses. The scoring is from 0–4, where 0 = worst and 4 = best outcome. The total score is calculated as the sum of scores from responses to all 12 items as a total of 48. Patients were also objectively assessed for antioxidant parameters superoxide dismutase 3 (SOD3) and glutathione reductase (GR), thence ten milliliters of venous blood was withdrawn from each patient at baseline before starting treatment and after 12 weeks at end of treatment. Statistical analysis was carried out by SPSS where $P<0.05$ is considered to be significant and $p<0.01$ is highly significant.

Results

The mean of patient's age was as follow: in group A, it was 49.52± 8.07, whereas in group B, it was 50.52± 9.90, non-significant statistical differences observed between both groups ($P>0.05$). In regard to smoking, there was non-significant differences between group A and B, same thing was observed concerning duration of symptoms as presented in table (1).

Table (1): demographic data and disease characteristics.

Study groups			
Variable	**Group A**	**Group B**	**P-value**
Age (year)	49.52± 8.07	50.52± 9.90	0.722^{NS}
Gender	**n (%)**	**n (%)**	
Female **Male** **Total**	19 (90.5) 2 (9.5) 21 (100)	17 (81.0) 4(19.0) 21 (100)	0.378^{NS}
Smoking	**n (%)**	**n (%)**	
Yes	2 (9.5)	3 (14.3)	0.634^{NS}
No	19 (90.5)	18 (85.7)	
Total	21 (100)	21(100)	
Duration of symptoms (year)	**n (%)**	**n (%)**	
<1	9 (42.9)	9 (42.9)	1.0^{NS}
1 to 5 years	11 (52.4)	11 (52.4)	
>5	1 (4.8)	1 (4.8)	

*Data presented as mean ± SD
Number of patients (n), Percentage (%), NS: No significant differences ($P>0.05$).
Two-sample *t*-test is used for statistical analysis of (age)
Paired *t*-test is statistically used to compare between pre- and post-treatment results in same group
Chi-square test is used for statistical analysis of (Smoking, Gender, Duration of symptoms)

The outcome obtained from this study showed a highly significant improvement of pain and physical function score (oks) after 3 months of treatment between both groups with a higher percent of change within group B than with group A ($p<0.01$), as shown in table (2) and figure (1).

The changes in SOD3 serum level related data were presented in table (3) and figure (2) which showed that both groups A and B were comparable in mean values at baseline ($P>0.05$). However, significantly higher level of improvement in the outcomes of SOD3 serum level was seen in group B compared to that in group A after three months of treatment ($P<0.05$).

A non-significant decrease in SOD3 serum levels was demonstrated after three months of treatment with meloxicam alone compared to baseline levels ($P>0.05$), while addition of curcumin to meloxicam resulted with highly significant increase in SOD3 serum levels after three months of treatment in respect to baseline levels ($P<0.01$).

Table (2): Effect of treatment with Meloxicam alone and in combination with Curcumin on Oxford Knee Score (OKS) in patients with knee OA.

Variable	Study groups		
OKS	**A (Meloxicam)**	**B (Meloxicam + Curcumin)**	**P-value**
Baseline	26.52± 4.95	23.67± 6.27	0.109^{NS}
After 1 month	31.71± 3.94	35.33± 7.70	0.065^{NS}
After 2 months	35.62± 4.35	40.00± 6.40	0.013*
After 3 months	37.86± 5.01	43.00± 6.08	0.005**
P-value	<0.001**	<0.001**	

Data presented as mean ± SD.

NS: No significant differences ($P>0.05$), (*) Significant difference ($P<0.05$), (**) Highly Significant difference ($P<0.01$).

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

Two-sample *t*-test is used to compare pre or post treatment between group A and group B patients.

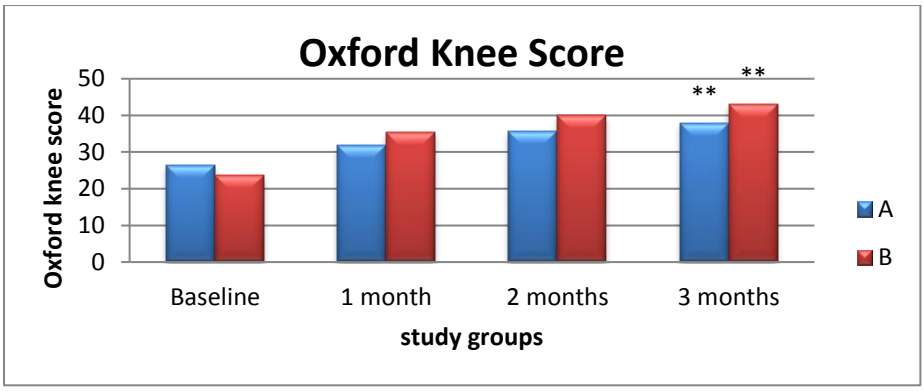

Figure (1): Effect of treatment with meloxicam alone or in combination with curcumin on Oxford knee Score (OKS) in patients with knee osteoarthritis.

Table (3): Effect of treatment with meloxicam alone and in combination with curcumin on SOD3 serum level in patients with knee osteoarthritis.

Variables	Study Groups		
SOD3 (pg/ml)	**Group (A)**	**Group (B)**	***P* – value**
Pre-treatment	13.03 ± 9.95	12.88 ± 8.94	0.958 ^{NS}
Post-treatment	12.06 ± 7.37	20.58 ± 12.64	0.011*
P – value	0.67 ^{NS}	0.009 **	

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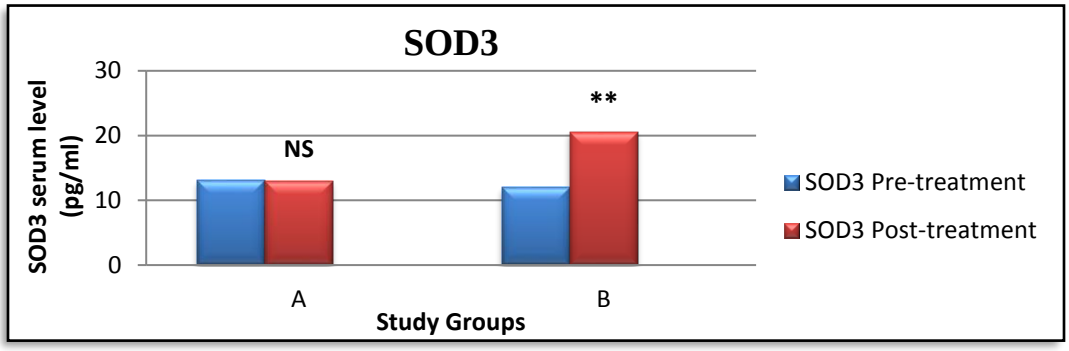

Figure (2): Effect of treatment with meloxicam alone and in combination with curcumin on SOD3 serum level in patients with knee osteoarthritis

There was a significant statistical difference in GR levels after three months of treatment between both groups (P<0.05). Also, the results showed a highly significant decrease in GR serum level after three months of treatment with meloxicam alone in respect to pretreatment level (P<0.01), while when meloxicam is combined with curcumin, there was no significant reduction in serum level of GR after three month of treatment compared to pretreatment level (P>0.05).

Table (4): Effect of treatment with meloxicam alone and in combination with curcumin on glutathione reductase (GR) serum level in patients with knee osteoarthritis.

Variables	Study Groups		
GR (pg/ml)	**Group (A)**	**Group (B)**	**P - value**
Pre-treatment	339.41 ± 70.59	297.74 ± 55.07	0.055 ^{NS}
Post-treatment	226.17 ± 52.44	270.30 ± 74.79	0.025 *
P – value	0.00 **	0.157 ^{NS}	

NS: Non-significant differences (P>0.05), (*) significant differences (P<0.05), (**) highly significant differences (P<0.01).

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

Two-sample *t*-test is used to compare pre or post treatment between group A and group B patients.

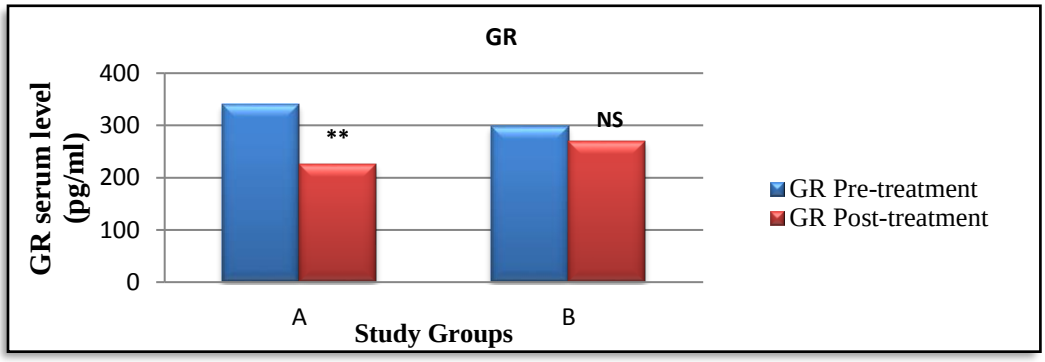

Figure (3): Effect of treatment with meloxicam alone and in combination with curcumin on glutathione reductase (GR) serum level in patients with knee osteoarthritis.

Discussion

Age of the 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 mean of age 55.3 years in Jordan [11] and 57.5 years in Iran [12], our findings come in accordance with another study carried out in Iraq [13]. Only 5 out of 42 patients participating in this study were smoking on daily basis. According to some studies there is a link between smoking and OA it was found that smoking increases the risk of cartilage loss due to increase toxins in blood and raise level of oxidative stress in body which is one of the important contributors to OA and cartilage loss. Meanwhile, other studies suggested protective effect of smoking on OA which account mostly for nicotine content of tobacco [14,15].

Pain and physical dysfunction are the two main symptoms of knee OA. In the current study, there was a highly significant improvement in pain and function scores in respect to oxford knee subscales for both groups comparing to pre-treatment scores. Even though, the overall patient's pain and functional assessments were better with the combination therapy which implies a further effect on pain reduction and in turn amelioration of physical function when curcumin used in combination with meloxicam. These results approved the analgesic effect of curcumin as many studies reported similar effect. There was a study from India showed beneficial effect of curcumin complex for reducing pain and other related symptoms of OA patients when used for 12 weeks [16]. Kuptniratsaikul *et al* (2014) demonstrated that curcuma domestica extract is as effective as ibuprofen in improving Western Ontario and McMaster universities WOMAC pain and function scores when used for patients with knee OA [17]. Analgesic and antinociceptive effect of curcumin was reported in several studies pre-clinical and clinical [18,19]. However, the exact molecular mechanism is still undefined but it's believed that this polyphenolic compound targets diverse pathways to reduce pain [20]. There is a study conducted in Brazil demonstrated the effect of curcumin on targeting different signaling pathways to reduce superoxide anion-induced hyperalgesia [21].

Moreover, curcumin has the ability to inhibit PGE2 production by inhibition of COX-2 gene expression. A random double-blind study on knee OA patients compared the ability of curcuminoids and the NSAID diclofenac to inhibit COX-2, both groups significantly (p <0.001) reduced COX-2 secretions by similar efficacies. Furthermore, curcumin can stimulate cortisol production by adrenal gland via inhibiting the bTREK-1potassium channels, and has the capacity to deplete nerve endings of the neurotransmitter substance P [22, 23].

Thus, in the present study, when curcumin concurrently administered with meloxicam, this combination adds synergestic effect by acting on different mechanisms of antinoceception with lower tendency to develop side effects.

Oxidative stress is an imbalance between free radicals and antioxidants ratio in the body [24]. Number of previous studies have reported elevated levels of pro-oxidant species and altered antioxidants levels in plasma and synovial fluid of patients suffering from OA [25- 27].

Results of the current study have revealed benefit of adding curcumin to meloxicam over meloxicam alone in amelioration of antioxidant status evinced by elevation of serum SOD3 level. Previous study by Panahi Y. *et al* (2016) reported elevated SOD serum level of osteoarthritis patients after six weeks supplementation with curcumin [28], another study curried out on rats suffering from hepatic damage and raised level of oxidative stress described an increase of SOD activity and the overall

hepatic antioxidant capacity after curcumin use [29].

Curcumin has been known to be a bifunctional antioxidant that exerts its effect by scavenging ROS and simultaneously inducing an antioxidant response [30]. It has been demonstrated that curcumin stimulates cytoprotective enzymes such as glutathione-S-transferase (GST), heme oxygenase-1 (HO-1), and c-glutamyl cysteine ligase (c-GCL). Furthermore, curcumin induces endogenous antioxidant and anti-inflammatory defense mechanisms through modulating transcription factors like nuclear factor erythroid-derived 2 (Nrf2), activator protein-1 (AP-1) and nuclear factor kappa B (NFkB) [31].

In general, the antioxidant activity of polyphenols is linked to the number of hydroxyl groups existing on the aromatic ring structures, in addition to the presence of a highly activated carbon atom that can serve as potent H-atom donors in scavenging free radicals [32].

The results also evidenced significant decrease of glutathione reductase serum level (which catalyses the reduction of glutathione disulphide (GSSG) to reduced glutathione (GSH) [33] when meloxicam administered alone. However, in patients of the other group who used curcumin in addition to meloxicam exhibited only a modest decrease in glutathione reductase, it falls slightly out of baseline level which means that curcumin alleviate meloxicam side effect on antioxidant enzymes and keep it marginally close to normal level. Earlier studies in rats reported that curcumin feeding to rats resulted in the induction of glutathione linked enzymes [34- 36]. Thus, curcumin may act by inducing the antioxidant enzymes and these enzymes may detoxify reactive oxygen species (ROS).

Conclusion:

from this study we concluded that the use of curcumin as adjuvent therapy to meloxicam yielded a better effect on pain and functional status of knee OA patients. Moreover, curcumin supplement plus meloxicam demonstrated a marked increase of SOD3 level and only a slight non-significant reduction of GR serum level, whereas meloxicam showed no significant effect on SOD3 and marked reduction of GR.

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