Evaluation of the Clinical use of Metformin or Pioglitazone in Combination with Meloxicam in Patients with Knee Osteoarthritis; using Knee Injury and Osteoarthritis outcome Score

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Abstract

Osteoarthritis is the most prevalent arthritic disease and a leading cause of disability. The pathogenesis of osteoarthritis involves multiple etiologies, including variable degree of synovial inflammation. Metformin and pioglitazone could potentially reduce the levels and activity of inflammatory mediators. This may consider as a new therapeutic approach added to the current used drugs in an attempt to decrease the pain, inflammation, and improve daily activity and quality of life in patients with knee osteoarthritis.

This study designed to evaluate the clinical utility of using metformin or pioglitazone as anti-inflammatory agents in combination with non-steroidal anti-inflammatory drugs (NSAID) of selective type of cyclooxygenase-2 (COX-2) inhibitor, meloxicam, in the treatment of knee osteoarthritis (OA).

Randomized, double blinded clinical study was performed on 98 patients who have symptomatic and radiologic evidence of painful OA of the knee (57 patients only completed the study). Patients were allocated into three groups, group (A); 20 patients treated with meloxicam (15mg/day) alone, group (B); 20 patients treated with metformin (1000mg/day) + meloxicam (15mg/day) and group (C); 17 patients treated with pioglitazone (15mg/day) + meloxicam (15mg/day). The treatment was followed for 12 weeks through measurement of the clinical effects of drugs each 7 days, using the Knee Injury and Osteoarthritis Outcome Score (KOOS) system.

The results showed that metformin or pioglitazone, when used in combination with NSAID resulted in significant improvement in the components of KOOS, higher than that produced by meloxicam when used alone. In conclusion, administration of metformin or pioglitazone as adjuvant therapy to NSAID, meloxicam, in OA patients produced very well characterized analgesic and anti-inflammatory activities, and improves the therapeutic profile of meloxicam.

Keywords: Metformin, Pioglitazone, Osteoarthritis, Knee injury, KOOS.

تقييم الفعالية السريرية للمتفورمين او البايوكليتازون كعلاج مساند للميلوكسيكام في المرضى المصابين بالتهاب الركبة غير الرثوي، باستخدام نظام كوز لتقييم حالة المريض

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الخلاصة

مرض التهاب المفاصل غير الرثوي هو المرض الاكثر انتشارا بين امراض المفاصل والسبب الرئيسي في جعل المريض غير قادر على الحركة بصورة طبيعية , أسباب المرض متعددة من ضمنها الالتهاب الزليلي في المفاصل بدرجاته المتفاوتة, حيث لايوجد علاج شافي لمرضى التهاب المفاصل غير الرثوي , لذلك نجد ان الاستراتيجيات العلاجية الحالية تهدف في المقام الاول الى الحد من الألم وتحسين وظيفة المفصل . أشارت العديد من الدراسات المصممة على النماذج الحيوانية او على الانسان الى فاعلية كلا من عقار المتفورمين وعقار البايوكليتازون في الحد من مستويات ونشاط وسطاء الالتهاب, مما يجعلهما نهجا علاجيا جديدا يضاف الى مضادات الالتهاب غير الستيرويدية المستخدمة حاليا في محاولة للتقليل من الالم والالتهاب وتحسين الفعالية اليومية ونوعية حياة المرضى المصابين بالتهاب مفصل الركبة غير الرثوي . وبناء على ذلك صممت هذه الدراسة لتقييم الفائدة السريرية الناجمة عن استخدام عقار المتفورمين او البايوكليتازون مع احد مضادات الالتهاب غير الستيرويدية المثبطة لانزيم الاكسدة الحلقي - 2- لثالميلوكسيكام, في علاج التهاب مفصل الركبة غير الرثوي.

أجريت هذه الدراسة على 98 مريضاً ممن لديهم أعراض وأدلة سريرية على الأصابة بالتهاب مفصل الركبة المسبب للألم (أكمل الدراسة 57 مريضاً فقط). وتم تقسيم هؤلاء المرضى الى ثلاث مجاميع : المجموعة -أ- (20 مريض) تم علاجهم بعقار الميلوكسيكام (15 ملغم يوميا), المجموعة –ب- (20 مريض) تم علاجهم بعقار الميلوكسيكام (15 ملغم يوميا) إضافة الى عقار المتفورمين (500 ملغم كل 12 ساعة), المجموعة –ج- (17 مريض) تم علاجهم بعقار الميلوكسيكام (15 ملغم يوميا) إضافة الى عقار البايوكليتازون (15 ملغم يوميا).

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وتم مراقبة المرضى وتقييم فعالية الادوية المستخدمة من خلال فحص الاستجابة السريرية للعلاج اسبوعياً باستخدام نظام KOOS.
أظهرت نتائج الدراسة بأن استخدام عقار المتفورمين او البايوكليتازون مع عقار الميلوكسيكام يؤدي الى تحسن معنوي في مستوى المعايير الخاصة بنظام KOOS مقارنة بتلك التي يسببها عقار الميلوكسيكام لوحده.
يمكن الاستنتاج بأن ا ضافه عقار المتفورمين أو البايوكليتازون لعقار الميلوكسيكام يحدث تأثيراً واضحاً في التقليل من مستوى الالم والاعراض المصاحبة له كما يحسن الفعالية اليومية ونوعية حياة المريض من خلال التأثير المضاد للالتهاب والمسكن للألم . كما ان استخدامه مع مضادات الالتهابات غير الستيرويدية يسهم في تحسين فعاليتها العلاجية.
الكلمات المفتاحية : متفورمين، بايوكليتازون، التهاب الركبة غير الرثوي، اصابة الركبة، نظام كوز لتقييم حالة المريض اسبوعيا.

Introduction

Osteoarthritis (OA) is a progressive musculoskeletal condition that involves the deterioration of articular cartilage and subsequent subchondral bone erosion [(1)]. Although the exact pathophysiology of the condition has not been uncovered yet, it is generally considered to be caused by a combination of cumulative mechanical stresses from aging, destructive biochemical changes taking place in the synovial membrane, and apoptosis of chondrocytes [(2)]. Clinically, there are several classes of treatments for OA, including non- pharmacological , pharmacological , and surgical treatment modalities. However, these treatments provide largely symptom relief, and do not halt the progression of the disease [(3)].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used medications to treat OA. However, these drugs may elicit adverse effects particularly gastrointestinal ulcerations [(4)]. Moreover, some of these agents have been reported to disrupt extracellular matrix metabolism, particularly proteoglycans synthesis [(5)]. Prolonged consumption of these drugs can result in severe adverse effects. Consequently, there is an urgent need for new strategies in OA therapy which can improve symptoms and are safe for clinical use over long periods of time [(6)]. The ability of metformin and pioglitazone to reduce the intensity of pain and inflammation that contributed to the pathophysiology of OA, with no serious adverse effects, has been reported in many animal model studies [(7,8)]. This may considered a new therapeutic approach added to the currently used NSAIDs to improve pain, inflammation, and quality of life in patients with knee OA. It has been shown that metformin can serve as potential drug to treat inflammation-related disorders [(8)]. The specific anti-inflammatory mechanism of metformin is not clearly understood. However , several studies demonstrated that the pharmacological action of metformin goes beyond mere glycemic control , decreasing markers of inflammation and contributing to the reduction of oxidative stress [(9,10)]. Metformin dose-dependently reduced the production of nitric oxide (NO) and prostaglandin E2 (PGE2) and suppressed the mRNA and protein levels of inducible nitric oxide synthase (iNOS) and COX-2 in lipopolysaccharides-activated macrophages [(11)]. Pioglitazone is potent and highly selective agonist for the nuclear receptor peroxisome proliferator-activated receptors gamma (PPAR-γ) and to a lesser extent PPAR-α [(12)]. Through PPAR-γ-mediated effects, pioglitazone improve insulin sensitivity and also have pleiotropic effects on insulin secretion, lipid and adipose tissue metabolism, body fat distribution, and vascular endothelial function [(13)].The anti-inflammatory effects of PPARs are mainly mediated by either inhibiting the induction of pro-inflammatory cytokines or stimulating the production of anti-inflammatory molecules [(14)]. Many *in vitro* studies have been shown that PPAR-γ is expressed and functionally active in chondrocytes, and those PPAR-γ activators modulate the expression of several genes considered essential in the pathogenesis of OA. PPAR-γ activation inhibits the IL-1-induced expression of iNOS, metalloproteinase-13 (MMP-13), COX-2, and PGE2 in chondrocytes [(15- 17)].

This study designed to evaluate the clinical utility of using metformin or pioglitazone as anti-inflammatory agents in combination with NSAID of selective type of COX-2 inhibitor, meloxicam, in the treatment of knee osteoarthritis (OA).

Patients and Methods

A double blind clinical study was carried out on (98) randomly selected patients (29 males and 69 females) with painful osteoarthritis (OA) of the knee, at the outpatients clinic in Baghdad Teaching Hospital with age range 36-71 years (59.2 ± 7.3). All selected patients have symptomatic and radiological evidence of OA in one or both knee joints. They were informed about the nature and the aim of the study. During selection of patients, certain exclusion criteria

were followed to exclude unsuitable patients including; 1. Patient with hypertension, ischemic heart diseases or diabetes mellitus. 2. Patient with hepatic or renal impairment and those who are on treatment with drugs, which interfere with the tested drugs. 3. Patients who have active peptic ulcer or damage. 4. Patients with end-stage radiological events of joint destruction. 5. Patients with positive history of bladder cancer. 6. Patients with positive history of allergic reactions to any one of the known tested drugs. 7. Patient who misses one time of blood sampling or treatment assessment indicated in this study and/or his medication for any reason. 8. Pregnant or lactating female patients.

The selected patients were randomly allocated into three groups as follow: Group A, includes 32 (11 males and 21 females) patients with negative GIT risk factors, treated with meloxicam tablets (15mg/day) taken at night for 12 weeks (20 patients only completed the study). Group B, includes 36 (9 males and 27 females) patients with negative GIT risk factors, treated with meloxicam tablets (15mg/day) taken at night and metformin (500mg/12 hours) for 12 weeks (20 patients only completed the study). Group C, includes 30 (9 males and 21 females) patients with negative GIT risk factors, treated with meloxicam tablets (15mg/day) taken at night and pioglitazone (15mg/day) for 12 weeks (17 patients only completed the study). Effects of drug treatment were assessed each seven days by clinical evaluation and direct interview with patients through a questionnaire method known as Knee Injury and Osteoarthritis Outcome Score (KOOS) [(18)]. The results were expressed as mean ± SEM; paired t-test and ANOVA were used to examine the degree of significance; P values less than 0.05 were considered significantly different.

Results

Effect on pain score

Before enrolment in the study (zero time), OA patients demonstrated poor pain control with their previous therapy, manifested by low pain score which indicate severe or extreme symptoms of pain in most of patients (table 1). Treatment with meloxicam alone resulted in significant increase in pain score from the first week (22.11%) compared to pre-treatment value, reaching maximum level at week twelve (88.81%) at the end of the study. However, combination of meloxicam with metformin resulted in significantly higher levels of improvement in the pain score started from the first week of treatment (51%) and remain elevated to the end of the study (170.95%). While addition of pioglitazone to meloxicam resulted in significant increase in pain score started from the first week (30.07%) reaching maximum level at week nine (146.62%), and remain around this level until the last week of the study (twelve weeks) (table 1).

The obtained data showed that maximum level of improvement in pain score was gained in patients treated with combination of meloxicam and metformin which was significantly higher than that observed in patients treated with combination of meloxicam and pioglitazone at corresponding durations. However; these two groups demonstrated significant improvement in pain score compared to patients treated with meloxicam alone at corresponding duration.

Effects on symptom score

At zero time (before starting treatment), all selected OA patients showed poor management of OA symptoms, manifested by low score of symptoms according to the outcome of KOOS (table 2). Treatment with meloxicam alone resulted in significant elevation in symptom score compared to pre-treatment value from the first week (15.57%) with maximum elevation at the last three weeks of the study (54.52%, 56.01%, and 55.03%). Treatment with combination of meloxicam and metformin resulted in significantly higher levels of improvement in the symptom score started from the first week of treatment (21.99%) and maximum score achieved at week eight (113.64%) and remain elevated to the end of the study. However, the combination of pioglitazone and meloxicam resulted in time dependent significant increase in symptom score, reaching maximum level at the last two weeks of the study (87.08%, and 86.52%) relative to pre-treatment value, respectively. Parallel improvement in symptoms score were obtained by using combinations of meloxicam with either metformin or pioglitazone through first seven weeks of treatment. From week eight to the end of study; combination of meloxicam with metformin showed significant improvement compared to that of meloxicam and pioglitazone combination at corresponding duration. Both of these combination groups showed significantly different improvement in symptom score along the study period compared to patients group of meloxicam alone-treatment (table 2).

Table(1): Effects of treatment with meloxicam alone, combination of meloxicam + metformin, and meloxicam + pioglitazone on pain score in osteoarthritic patients.

Duration (Weeks)	Pain Score of KOOS		
	Meloxicam (15 mg/day) No. of Patient=20	**Meloxicam(15mg/day)+ Metformin(1000mg/day) No. of Patient=20**	**Meloxicam (15mg/day)+ Pioglitazone(15mg/day) No. of Patient=17**
0	32.07 ± 1.08	29.98 ± 1.08	31.53 ± 1.45
1	39.16 ± 1.14 * **a**	45.27 ± 1.16 * **b**	41.01 ± 1.13 * **a**
2	44.16 ± 1.05 * **a**	52.08 ± 0.94 * **b**	49.67 ± 0.89 * **c**
3	47.24 ± 0.92 * **a**	56.66 ± 1.02 * **b**	54.08 ± 1.04 * **c**
4	49.3 ± 0.85 * **a**	61.38 ± 1.01 * **b**	58.17 ± 1.27 * **c**
5	52.08 ± 0.85 * **a**	66.11 ± 0.87 * **b**	61.92 ± 0.91 * **c**
6	52.91 ± 0.84 * **a**	71.58 ± 0.83 * **b**	66.99 ± 0.95 * **c**
7	55.41 ± 0.79 * **a**	76.65± 0.89 * **b**	74.01 ± 1.04 * **c**
8	55.83 ± 0.8 * **a**	79.42 ± 0.76 * **b**	75.8 ± 0.85 * **c**
9	57.49 ± 0.83 * **a**	80.98 ± 0.72 * **b**	77.76 ± 1.09 * **c**
10	59.16 ± 0.73 * **a**	80.81 ± 0.64 * **b**	77.76 ± 1.01 * **c**
11	60.41 ± 0.78 * **a**	81.09 ± 0.77 * **b**	77.76 ± 0.82 * **c**
12	60.55 ± 0.85 * **a**	81.23 ± 0.8 * **b**	76.78 ± 0.75 * **c**

- Data are expressed as mean ± SEM.
- * $P<0.05$ significant difference compared to pre-treatment value within the same group.
- Values with non-identical superscripts (a, b & c) among different groups are significantly different ($P<0.05$) at corresponding duration.

Table (2): Effects of treatment with meloxicam alone, combination of meloxicam + metformin, and meloxicam + pioglitazone on symptoms score in osteoarthritic patients.

Duration (Weeks)	Symptoms Score of KOOS		
	Meloxicam (15 mg/day) No. of Patient=20	Meloxicam(15mg/day)+ Metformin(1000mg/day) No. of Patient=20	Meloxicam (15mg/day)+ Pioglitazone(15mg/day) No. of Patient=17
0	35.71 ± 1.37	34.1 ± 1.69	37.39 ± 1.37
1	41.27 ± 1.02 * **a**	41.6 ± 1.01 * **a**	43.48 ± 0.76 * **b**
2	44.28 ± 0.91 * **a**	48.22 ± 0.92 * **b**	48.1 ± 1.07 * **b**
3	48.03 ± 0.99 * **a**	52.32 ± 1.08 * **b**	52.73 ± 1.13 * **b**
4	51.07 ± 0.86 * **a**	56.07 ± 0.74 * **b**	55.04 ± 0.87 * **b**
5	51.97 ± 0.71 * **a**	62.85 ± 0.79 * **b**	62.6 ± 1.06 * **b**
6	53.22 ± 0.93 * **a**	66.23 ± 0.65 * **b**	66.8 ± 0.96 * **b**
7	52.5 ± 0.69 * **a**	69.28 ± 0.75 * **b**	69.32 ± 0.69 * **b**
8	52.85 ± 0.88 * **a**	72.85 ± 0.95 * **b**	68.69 ± 0.78 * **c**
9	54.1 ± 0.94 * **a**	72.14 ± 0.85 * **b**	68.2 ± 0.92 * **c**
10	55.18 ± 0.75 * **a**	70.89 ± 0.83 * **b**	69.3 ± 0.76 * **c**
11	55.71 ± 0.79 * **a**	72.67 ± 0.87 * **b**	69.95 ± 0.75 * **c**
12	55.36 ± 0.84 * **a**	72.49 ± 0.78 * **b**	69.74 ± 0.54 * **c**

- Data are expressed as mean ± SEM.
- * $P<0.05$ significant difference compared to pre-treatment value within the same group.
- Values with non-identical superscripts (a, b & c) among different groups are significantly different ($P<0.05$) at corresponding duration.

Effects on Daily Living Activity (ADL) score

In table 3, ADL score was found relatively low before starting treatment in all patients (zero time) enrolled in study. In patients group treated with meloxicam, ADL score showed significant increase, started after one week of treatment and reaching maximum score at the end of the study (13.98% and 80.82%) compared to pre-treatment value, respectively, with no significant differences among the mean values of last three weeks of the study. These values are significantly lower than those produced by combination treatment of meloxicam with metformin and meloxicam with pioglitazone at the same period of time.

Addition of metformin to meloxicam resulted in significant improvement of ADL score after one week treatment (32.73%) compared to pre-treatment value and reach maximum improvement at the last four weeks of the study. The levels of improvement in ADL score produced by treatment with meloxicam and pioglitazonee combination remained significantly higher than baseline from week one (33.78%) to the end of study (106.53%), with maximum level of improvement recorded at week eight (118.58%) as shown in (table 3). Treatment with combination of meloxicam and metformin showed higher improvement of ADL scores which are significantly different compared to that resulted by treatment with meloxicam alone, and with combination of meloxicam and pioglitazone, particularly at the last five weeks of study.

Table (3): Effects of treatment with meloxicam alone, combination of meloxicam + metformin, and meloxicam + pioglitazone on Daily Living Activity (ADL) score in osteoarthritic patients.

Duration (Weeks)	ADL Score of KOOS		
	Meloxicam (15 mg/day) No. of Patient=20	**Meloxicam(15mg/day)+ Metformin(1000mg/day) No. of Patient=20**	**Meloxicam (15mg/day)+ Pioglitazone(15mg/day) No. of Patient=17**
0	34.77 ± 1.72	38.38 ± 1.37	37.36 ± 1.06
1	39.63 ± 0.99 * **a**	50.94 ± 0.89 * **b**	49.98 ± 1.04 * **b**
2	42.35 ± 1.1 * **a**	57.35 ± 0.93 * **b**	56.13 ± 1.33 * **b**
3	45.44 ± 1.12 * **a**	62.94 ± 0.88 * **b**	66.17 ± 0.91 * **c**
4	51.46 ± 0.87 * **a**	65.88 ± 0.8 * **b**	70.67 ± 0.86 * **c**
5	53.22 ± 0.87 * **a**	75.36 ± 0.99 * **b**	77.85 ± 0.64 * **c**
6	54.4 ± 0.93 * **a**	79.88 ± 0.83 * **b**	80.45 ± 0.64 * **b**
7	56.83 ± 0.84 * **a**	82.19 ± 0.78 * **b**	81.66 ± 0.78 * **b**
8	51.82 ± 0.98 * **a**	84.38 ± 0.73 * **b**	81.66 ± 0.96 * **c**
9	60.95 ± 0.66 * **a**	85.99 ± 0.8 * **b**	81.35 ± 0.8 * **c**
10	62.65 ± 0.81 * **a**	87.46 ± 0.79 * **b**	78.98 ± 0.84 * **c**
11	62.57 ± 0.7 * **a**	86.94 ± 0.72 * **b**	77.68 ± 0.79 * **c**
12	62.87 ± 0.8 * **a**	86.87 ± 0.84 * **b**	77.16 ± 0.99 * **c**

- Data are expressed as mean ± SEM.
- * P<0.05 significant difference compared to pre-treatment value within the same group.
- Values with non-identical superscripts (a, b and c) among different groups are significantly different (P<0.05) at corresponding duration.

Effects on sport/recreation score:

Table 4; revealed low sport/recreation score at zero time levels before starting drug treatment with treated drugs. Treatment with meloxicam alone resulted in significant increase in sport/recreation score started after first week (16.19%) compared to pre-treatment value, reaching maximum level (59.05%) at the end of the study (12 weeks).

Combination of meloxicam with metformin resulted in significantly higher level of improvement in sport/recreation score after the first week of treatment, which found to be comparable to those produced by combination of meloxicam with pioglitazone (28.7%, 17.04%) compared to pre-treatment values, respectively. At the end of the study; significant difference was achieved between the two combination groups, with preference to meloxicam and metformin group over meloxicam and pioglitazone group in improving sport/recreation score (117.39%, 75% compared to pre-treatment value, respectively) (table 3). Both of combination groups revealed a significant elevation in sport/recreation score compared to patients group treated with meloxicam alone at the same period of study.

Table (4): Effects of treatment with meloxicam alone, combination of meloxicam + metformin and, meloxicam + pioglitazone on Sport/Recreation score in osteoarthritic patients.

Duration (Weeks)	Sport / Recreation Score of KOOS		
	Meloxicam (15 mg/day) No. of Patient=20	Meloxicam(15mg/day)+ Metformin(1000mg/day) No. of Patient=20	Meloxicam (15mg/day)+ Pioglitazone(15mg/day) No. of Patient=17
0	26.25 ± 0.8	28.75 ± 1.35	25.88 ± 1.23
1	30.5 ± 0.8 * **a**	37 ± 1.11 * **b**	30.29 ± 1.17 * **a**
2	32 ± 0.76 * **a**	44 ± 1.12 * **b**	35.59 ± 1.04 * **c**
3	33.75 ± 0.8 * **a**	46.75 ± 0.98 * **b**	38.24 ± 1.05 * **c**
4	34.75 ± 0.68 * **a**	48.5 ± 0.73 * **b**	38.82 ± 1.01 * **c**
5	36.75 ± 0.98 * **a**	49.75 ± 0.92 * **b**	40 ± 0.96 * **c**
6	37 ± 1.05 * **a**	54.5 ± 1.02 * **b**	40.88 ± 1.15 * **c**
7	37.5 ± 0.85 * **a**	59 ± 0.93 * **b**	41.76 ± 1.05 * **c**
8	39.25 ± 0.75 * **a**	59.75 ± 0.85 * **b**	43.24 ± 0.73 * **c**
9	39.5 ± 0.88 * **a**	62.25 ± 0.68 * **b**	44.12 ± 0.77 * **c**
10	39.25 ± 0.83 * **a**	62.75 ± 0.77 * **b**	45.59 ± 0.84 * **c**
11	41.25 ± 0.95 * **a**	62.5 ± 0.85 * **b**	45.59 ± 0.95 * **c**
12	41.75 ± 0.91 * **a**	62.5 ± 0.93 * **b**	45.29 ± 0.8 * **c**

- Data are expressed as mean ± SEM.
- * $P<0.05$ significant difference compared to pre-treatment value within the same group.
  Values with non-identical superscripts (a, b & c) among different groups are significantly different ($P<0.05$) at corresponding duration .

Effects on Quality of Life score (QOL)

At zero time (before treatment), all patients showed relatively low QOL score. There is a clear evidence for good response to treatment with all used medications concerning QOL score, indicating that drug therapy improves not only the disease state and clinical features, but also the patient's mood. During the first week of treatment , all groups demonstrated time-dependent improvement in QOL score compared to baseline value of each group, with the priority to patients group treated with combination of meloxicam and metformin (28.87%). The presented data also showed that treatment with meloxicam alone resulted in a slower improvement pattern of QOL score compared to that produced by treatment of meloxicam and metformin combination at the end of the study (50%, 89.98%) compared to pre-treatment values, respectively. Addition of pioglitazone to meloxicam resulted in significant improvement in QOL score compared to that of meloxicam alone at corresponding duration, particularly within the last few weeks of study. The presented data, clearly demonstrated the advantage of adding metformin to meloxicam concerning improvement of QOL score in comparison to that produced by meloxicam alone and combination of meloxicam with pioglitazone (table 5).

Table (5): Effects of treatment with meloxicam alone, combination of meloxicam + metformin, and meloxicam + pioglitazone on Quality of Life (QOL) score in osteoarthritic patients.

Duration (Weeks)	QOL Score of KOOS		
	Meloxicam (15 mg/day) No. of Patient=20	**Meloxicam(15mg/day)+ Metformin(1000mg/day) No. of Patient=20**	**Meloxicam (15mg/day)+ Pioglitazone(15mg/day) No. of Patient=17**
0	25 ± 1.36	28.13 ± 1.4	25.37 ± 1.56
1	27.81 ± 1.24 * **a**	36.25 ± 0.86 * **b**	27.57 ± 1.52 * **a**
2	32.19 ± 0.94 * **a**	40.63 ± 0.96 * **b**	28.31 ± 1.21 * **c**
3	33.13 ± 0.92 * **a**	42.78 ± 1.04 * **b**	30.15 ± 1.23 * **c**
4	33.75 ± 0.84 * **a**	44.69 ± 0.82 * **b**	33.09 ± 0.71 * **a**
5	34.69 ± 0.85 * **a**	45.63 ± 0.8 * **b**	35.29 ± 0.92 * **a**
6	35.31 ± 0.94 * **a**	46.88 ± 0.85 * **b**	35.66 ± 0.89 * **a**
7	35.94 ± 0.89 * **a**	47.5 ± 0.95 * **b**	36.38 ± 0.96 * **a**
8	35. 63 ± 0.92* **a**	50.63 ± 1.01 * **b**	38.97 ± 1.01 * **c**
9	36.25 ± 0.86 * **a**	51.88 ± 1.02 * **b**	39.34 ± 1.04 * **c**
10	37.49 ± 0.9 * **a**	53.13 ± 0.85 * **b**	39.71 ± 0.92 * **c**
11	37.5± 0.78 * **a**	53.76 ± 0.84 * **b**	40.44 ± 0.95 * **c**
12	37.5± 0.78 * **a**	53.44 ± 0.96 * **b**	41.18 ± 0.94 * **c**

- Data are expressed as mean ± SEM.
- * P<0.05 significant difference compared to pre-treatment value within the same group.
- Values with non-identical superscripts (a, b & c) among different groups are significantly different (P<0.05) at corresponding duration.

Discussion

Osteoarthritic pain is generally described as a sharp ache or a burning sensation in the associated muscles and tendons. OA can cause a crackling noise (called "crepitus") when the affected joint is moved or touched and patients may experience muscle spasms and contractions in the tendons. Occasionally, some patients reported increased pain with movement, cold weather, high humidity, and/or a drop in barometric pressure [19]. The pain of OA includes both nociceptive and non-nociceptive components and is associated with abnormally excitable pain pathways in the peripheral and central nervous systems [20, 21]. Furthermore; unrelieved pain leads to serious negative consequences, like those observed with poor pain score belong to OA patients before treatment (table 1), with many other physiological effects associated with increased catabolic demands [22].

There is evidence that NSAIDs are superior to paracetamol for pain relief in patients with osteoarthritis [23], but they are also associated with more adverse effects. The major concern is serious gastrointestinal, renal and cardiovascular complications, with risk increasing with age, concurrent use of other medications and duration of therapy. NSAIDs help relieve pain, swelling and stiffness but they do not alter the progression of osteoarthritis [24].

Since cartilage tissues of osteoarthritic patients contain no pain receptors. So, sensation of pain likely results from inflammatory mediators. Pro-inflammatory agents interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), as well as the growth

factors have all been shown to induce COX-2 expression which produces measurable quantities of prostaglandins. On the other hand, the anti-inflammatory cytokines IL-4 and IL-13, as well as the immunosuppressive glucocorticoids, were shown to decrease COX-2 levels [(25)].

In this respect, the beneficial effects of metformin and pioglitazone in reducing pain and symptoms in patients with OA can be explained according to the nature of the biological activity which can be attributed to many factors including the anti-inflammatory and antioxidant effects. The mechanism by which metformin or pioglitazone regulate the inflammatory response is poorly understood, but many studies on animal models demonstrated their inhibitory effect on the expression of the pro-inflammatory mediators and oxidative stress markers. Metformin, the well-known adenosine monophosphate-activated kinase (AMPK) activator, can suppress COX-2 and iNOS mRNA and protein expression dose dependently [(26)]. Metformin ability to reduce the intensity of pain, mainly associated with its effects on the profile of inflammatory cytokines (i.e., TNF a, IL-1β, IL-6, and IL-10) and adipokines [(27)], it significantly prevented the increased levels of pro-inflammatory mediators like TNF-α, IL-1β, IL-6, and IL-18 in many inflammatory disorders, Moreover; metformin prevented the expression of COX-2, iNOS, and decreased the levels of NO and PGE2 in cell culture media [(28)], an evidence which support the observed effect of reducing the consequence of pain in OA patients.

Pioglitazone is potent and highly selective agonist for the nuclear receptor, PPAR-γ. Activation of PPAR-γ has been shown to exhibit anti-inflammatory and anti-catabolic properties and to be protective in animal models of OA [(29)]. Study by (Mrgenweck, 2013) reported that PPAR-γ could be emerged as a new pharmacotherapeutic target for chronic pain; PPAR-γ activation blocks the development of, and reduces established neuropathic pain [(30)], the possible mechanism of neuroprotection by PPAR-γ agonist, pioglitazone, may involve modulation of inflammatory reaction and oxidative stress [(31)]. Pioglitazone, via PPAR-γ activation, reduce the effects of IL-1β-induced COX-2 expression by interfering with oxidative stress and role of ROS [(32)]. PPAR-γ agonist, pioglitazone, has been reported to reduce the severity of experimental OA. This effect was associated with a reduction in the levels of MMP-13 and IL-1β, which are known to play an important role in the pathophysiology of OA lesions [(33)]. The lack of satisfaction of patients and doctors with NSAIDs treatment reflected by that fewer than 20% of patients with hip or knee OA, in whom NSAIDs treatment initiated, are still taking the same drug 12 months later [(18)].

The typical patient with OA is middle aged or elderly, and complains of knee, hip, hand, or spine pain. In most cases, the patient experience pain and stiffness in and around the affected joint, causing a decrease in function and activity. The onset of these symptoms is mostly insidious, and pain typically worsens with the use of the affected joint, but usually is alleviated with rest, while morning stiffness is lasting less than 30 minutes in common [(34)].

Osteoarthritis is a common debilitating joint disorder, affecting large sections of the population, which results in high morbidity; significant disability and impaired quality of life [(35)]. Accordingly, the primary goals of OA treatment are to relief pain, minimizing disability and limit the progression of the disease. Because most patients with OA are elderly people who have co-morbidities and are more susceptible to side effects of chronically used medications, care must be taken to individualize therapy on the bases of a patient's need and to minimize potential drug toxicity [(36)].

In this study, the high level of improvement in pain score observed with the use of metformin compared to meloxicam alone or in combination with pioglitazone (table 3 and 5) may correspond to the reported improvement in the daily activities and quality of life score, where metformin, and to less extent pioglitazone, improve all parameters in KOOS system when added to meloxicam, compared to using meloxicam alone. According to the results of this study, the addition of either metformin or pioglitazone to NSAIDs could constitute a new promising way to reversing or retarding the progression of degenerative processes that predispose to pain and other consequent symptoms in OA.

Conclusion

Co-administration of metformin or pioglitazone with meloxicam, in OA patients produced very well characterized analgesic and anti-inflammatory activities, and improves the therapeutic profile of meloxicam.

References

1. Goldring SR, Goldring MB. Clinical aspects, pathology and pathophysiology of osteoarthritis. J Musculoskelet Neuronal Interact. 2006; 6(4): 376–378.

2. Hugle T, Geurts J, Nüesch C, Müller-Gerbl M, Valderrabano V. Aging and

osteoarthritis: an inevitable encounter J Aging Res. 2012; 2012: 950192.

3. Kim, J.E.; et al: Effect of self-assembled peptide–mesenchymal stem cell complex on the progression of osteoarthritis in a rat model. International Journal of Nanomedicine 2014; 9 (1): 141-152.

4. Wolfe MM, Lichtenstein DR, Singh C. Gastrointestinal toxicity of NSAIDs. New Engl J Med 1999; 340 : 1888-1899.

5. DeVeries BJ, Van deBerg WB, Van depute EB. The influence of anti-rheumatic drugs on basal and accelerated breakdown of articular proteoglycans. Agents Actions 1988; 23: 52.

6. Leong, D.J.; Choudhury, M.; Hirsh, D.M.; Hardin, J.A.; Cobelli, N.J. and Sun, H.B.: Nutraceuticals: potential for chondroprotection and molecular targeting of osteoarthritis. Int J Mol Sci. 2013 Nov 21; 14(11): 23063-85.

7. Kalariya, N.M.; Shoeb, M.; Ansari, N.H.; Srivastava, S.K. and Ramana, K.V.: Antidiabetic drug metformin suppresses endotoxin-induced uveitis in rats. Invest Ophthalmol Vis Sci. 2012; 53: 3431–3440.

8. Yuan, H.; Li. L.; Zheng, W.; Wan, J.; Ge, P.; Li, H. and Zhang, L.: Antidiabetic drug metformin alleviates endotoxin-induced fulminant liver injury in mice. Int Immunopharmacol. 2012; 12:682–688.

9. Andrews, M,; Soto, N. and Arredondo, M.: [Effect of metformin on the expression of tumor necrosis factor-α, Toll like receptors 2/4 and C reactive protein in obese type-2 diabetic patients]. Rev Med Chil. 2012 Nov; 140(11):1377-82.

10. Esteghamati, A.; Eskandari, D.; Mirmiranpour, H.; Noshad, S.; Mousavizadeh, M.; Hedayati , M . and Nakhjavani, M.: Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: a randomized clinical trial. Clin Nutr. 2013 Apr; 32(2):179-85.

11. Hyun, B.; Shin, S.; Lee, A.; Lee, S.; Song, Y.; Ha, N.J.; Cho, K.H. and Kim, K.: Metformin Down-regulates TNF-α Secretion via Suppression of Scavenger Receptors in Macrophages. Immune Netw. 2013 Aug; 13(4):123-32.

12. Waugh, J.; Keating, G.M.; Plosker, G.L.; Easthope, S. and Robinson, D.M.: Pioglitazone: a review of its use in type 2 diabetes mellitus. Drugs, 2006; 66(1): 85-109.

13. Shah, P. and Mudaliar, S.: Pioglitazone: side effect and safety profile. Exp. Opin. Drug Saf. 2010; 9(2): 347-54.

14. Kostadinova, R.; Wahli, W. and Michalik, L.: PPARs in diseases: control mechanisms of inflammation. Curr Med Chem. 2005; 12(25):2995-3009.

15. Li, X.; Afif, H.; Cheng, S.; Martel-Pelletier, J.; Pelletier, J.P.; Ranger, P. and Fahmi, H.: Expression and regulation of microsomal prostaglandin E synthase-1 in human osteoarthritic cartilage and chondrocytes. J Rheumatol 2005; 32:887-895.

16. Fahmi, H.; Di Battista, J.A.; Pelletier, J.P.; Mineau, F.; Ranger, P. and Martel-Pelletier, J.: Peroxisome proliferator-activated receptor γ activators inhibit interleukin-1β-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes. Arthritis Rheum 2001; 44:595-607.

17. Fahmi, H.; Pelletier, J.P.; Mineau, F. and Martel-Pelletier, J.: 15d-PGJ2 is acting as a 'dual agent' on the regulation of COX-2 expression in human osteoarthritic chondrocytes. Osteoarthritis Cartilage 2002; 10:845-848.

18. Hussain, S.A.; Jassim, N.A.; Numan, I.T.; Al-Khalifa, I.I. and Abdullah, T.A.: Anti-inflammatory activity of silymarin in patients with knee osteoarthritis. A comparative study with piroxicam and meloxicam. Saudi Med J. 2009 Jan; 30(1):98-103.

19. de Figueiredo, E.C.; Figueiredo, G.C. and Dantas, R.T.: "Influence of meteorological elements on osteoarthritis pain: a review of the literature". Rev Bras Reumatol. 2011 Dec : 51(6): 622–8.

20. Mease, P.; Hanna, S.; Frakes, E. and Altman, R.: Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. J Rheumatol 2011; 38: 1546-51.

21. Mandl, L.: Treating the pain of osteoarthritis-where do we go from here? J Rheumatol 2011; 38(8): 1535-7.

22. Carr DB, Jacox A. Acute pain management: Operative or medical procedures and trauma. Rockville, MD, Agency for Health Care Policy and Research, U.S. Department of Health and Human Services, 1992, AHCPR Publication, pp. 92-132.

23. Towheed, T.; Maxwell, L.; Judd, M. et al: Acetaminophen for osteoarthritis. Cochrance Database Syst Rev 2006 (1): CD004257.

24. Zhang, W.; Moskowitz, R.; Nuki, N. et al: OSARI recommendations for the management of hip and knee osteoarthritis, Part II: OSARI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008; 16 (2): 137-62.

25. Crofford, L.J.: COX-1 and COX-2 tissue expression: implications and predictions. J. Rheumatol. 1997; 24:15–19.

26. Kim, S.A.; Choi, H.C.: Metformin inhibits inflammatory response via AMPK-PTEN pathway in vascular smooth muscle cells. Biochem Biophys Res Commun. Sep 7, 2012; 425(4):866-72.

27. Labuzek, K.; Liber, S.; Suchy, D. and Okopieå, B.A.: A successful case of pain management using metformin in a patient with adiposis dolorosa. Int J Clin Pharmacol Ther. 2013 Jun; 51(6): 517-24.

28. Nilesh, M. K.; Mohammad, S.; Naseem, H. A.; Satish, K. S. and Kota, V. R.: Antidiabetic Drug Metformin Suppresses Endotoxin-Induced Uveitis in Rats. Ophthalmol. Vis. Sci. June 8, 2012; 53 (7): 3431-3440.

29. Nebbaki, S.S.; El Mansouri, F.E.; Afif, H.; Kapoor, M.; Benderdour, M.; Duval, N.; Pelletier, J.P.; Martel-Pelletier, J. and Fahmi. H.: Egr-1 contributes to IL-1-mediated down-regulation of peroxisome proliferator-activated receptor γ expression in human osteoarthritic chondrocytes. Arthritis Res Ther. 2012 Mar 28; 14(2): R69.

30. Morgenweck, J.; Griggs, R.B.; Donahue, R.R.; Zadina, J.E. and Taylor, B.K.: PPARγ activation blocks development and reduces established neuropathic pain in rats. Neuropharmacology. 2013 Jul; 70: 236-46.

31. Kim, H.; Hwang, J.; Park, S.; Nahm, S.F.; Min, S.; Lim, C.; Park, K. and Han, S.: A peroxisome proliferator-activated receptor gamma agonist attenuates neurological deficits following spinal cord ischemia in rats. J Vasc Surg. 2014 Apr; 59(4): 1084-9.

32. Martín, A.; Pérez-Girón, J.V.; Hernanz, R.; Palacios, R.; Briones, A.M.; Fortuño, A.; Zalba, G.; Salaices, M. and Alonso, M.J.: Peroxisome proliferator-activated receptor-γ activation reduces cyclooxygenase-2 expression in vascular smooth muscle cells from hypertensive rats by interfering with oxidative stress. J Hypertens. 2012 Feb; 30(2): 315-26.

33. Kobayashi, T.; Notoya, K.; Naito, T.; Unno, S.; Nakamura, A.; Martel-Pelletier, J. and Pelletier, J.P.: Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, reduces the progression of experimental osteoarthritis in guinea pigs. Arthritis Rheum. 2005 Feb; 52(2):479-87.

34. Hinton, R.; Moody, R.L.; Davis, A.W. and Thomas, S.F.: Osteoarthritis: Diagnosis and therapeutic considerations. Am. Fam. Phys. 2002; 65(5): 841-848.

35. Sharma, A.R.; Jagga, S.; Lee, S.S. and Nam, J.S.: Interplay between Cartilage and Subchondral Bone Contributing to Pathogenesis of Osteoarthritis. Int J Mol Sci. 2013 Sep 30; 14(10): 19805-30.

36. Morehead, K. and Sack, K.E.: Osteoarthritis. What therapies for this disease of many causes? Postgrad Med. 2003; 114 (5): 11-7.