Effect of Methotrexate in Treatment of Knee Osteoarthritis

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Abstract: Osteoarthritis (OA) is one of the most prevalent condition resulting to disability particularly in elderly population. Lacking of effective therapies available to relieve the symptoms of OA or to slow the disease associated structural progression is a major barrier for the reduction of the impact of OA. Emerging evidence is increasingly indicating a high prevalence of synovitis in OA that is found to be associated with severity of pain. The aim of this study is to determine the effect of Methotrexate (MTX) in treatment of knee osteoarthritis (KOA). This was a single blinded randomized controlled trial of parallel design, A total of 200 consecutive eligible patients with symptomatic radiographic primary KOA participated in the study that fulfilled ACR Criteria for radiologic and clinical KOA. Patients were recruited from the Rheumatology and Rehabilitation Outpatient Clinic of Al-Azhar University Hospital in Damietta, Egypt. The patients were randomized into two groups; (a) MTX-treated KOA group: included 100 patients that received oral MTX and (b) non steroidal anti inflammatory drugs (NSAIDs)-treated KOA group: included 100 patients were received NSAIDs. The study was done at the period between April to November 2016. Clinical parameters including pain, tenderness and Ontario and McMaster Universities arthritis index(WOMAC) score were significantly lower in the MTX-treated group than in the NSAIDs-treated group at 3 months and at 6 months from treatment. On US examination, at 3 months of treatment the OA severity was significantly lower in the MTX-treated KOA group as compared to the NSAIDs-treated KOA group and the difference of osteoarthritis (OA) severity between the two groups was more prominent at 6 months of treatment. From this study we found that MTX significantly reduced pain and tenderness and improved joint mobility. MTX had significantly improved synovitis and effusion and decreased cartilage damage. There was a significant improvement in physical function of MTX therapy. MTX may be a therapeutic option on the treatment of pain and inflammation related to KOA.
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1. Introduction

Osteoarthritis (OA) is one of the most prevalent condition resulting to disability particularly in elderly population and increasing to frequency; the number of patients with OA has increased by nearly 30% over the past 10 years **(2).**

OA is characterized by an imbalance between the synthesis and degradation of the articular cartilage, leading to the classic pathologic changes leading to destruction of cartilage **(3).** The breakdown and deterioration of cartilage leads to the formation of new bone at the joint surfaces (sclerosis) and margins (osteophytes) **(4)**. This process often results in joint pain and loss of mobility, which may lead to long-term disability. Although OA is considered a non-inflammatory form of arthritis, there can be a small inflammatory component. KOA is an important cause of pain and disability in old population, and it is becoming increasingly prevalent worldwide due to its association with an aging population and due to a growing prevalence of obesity **(5).** Current management guidelines for OA include pharmacological and non-pharmacological therapies including weight loss and exercise **(6).** Routine treatments for pain and disability in these patients have low efficacy, and some treatments, including hyaluronic acid injection therapy, have high costs. Lacking of effective therapies available to relieve the symptoms of OA or to slow the disease associated structural progression is a major barrier for the reduction of the impact of OA **(7).** Emerging evidence is increasingly indicating a high prevalence of synovitis in OA that is found to be associated with severity of pain**.** Synovial changes in OA are often identical to those observed in rheumatoid arthritis (RA), although they are confined only in a discrete region adjacent to sites of chondropathy in the affected joint. Increased levels of pro-inflammatory cytokines (such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6), reduced levels of anti-inflammatory cytokines (such as IL-10 and IL-1 receptor antagonist (IL-1Ra)) have all been demonstrated within OA fluid and tissue **(8)**. Methotrexate (MTX) is an effective and now commonly used anti-synovial treatment for inflammatory arthritis with good long-term safety data **(7)**. Given the high levels of pro-inflammatory

cytokines and the evidence of immune cell infiltration into OA joints, coupled with the strong correlations observed between synovitis and pain, there is rationale for the use of MTX for reducing symptoms in OA. Most patients tolerate MTX for long-term use **(9),** and the use of folic acid concomitantly with MTX reduces the incidence of side-effects **(10)**. The aim of our study is to determine the effect of Methotrexate (MTX) in treatment of knee osteoarthritis (KOA).

2. Patients and Methods

This is a single blinded randomized controlled trial of parallel design. A total of 200 consecutive eligible patients (males and females) with symptomatic radiographic primary KOA participated in the study that fulfilled ACR Criteria for radiologic and clinical KOA **(1).** Patients were recruited from the Rheumatology and Rehabilitation Outpatient Clinic of Al-Azhar University Hospital in Damietta, Egypt. The patients were randomized into two groups; (a) MTX-treated KOA group: included 100 patients that received oral MTX and (b) NSAIDs-treated KOA group: included 100 patients were received NSAIDs. The two groups were matched as regards age, sex, BMI, and duration of KOA. The study was done at the period between April to November 2016.

Exclusion Criteria:

Patients with any of the following were excluded from the study:

1. Inflammatory arthritis like RA and lupus arthritis.
2. Had intra articular hyaluronic acid in the knee within the four months prior to enrolment.
3. Had intra articular or systematic corticosteroids in the three months prior to enrolment.
4. Had previous significant knee injury or any knee surgery.
5. Have current signs or symptoms of severe, progressive or uncontrolled hepatic (Alanine transaminase >2 times upper normal limit), renal (serum creatinine >1.5 times upper normal limit), haematological (haemoglobin ≤8.5 g/dL, white blood cells count ≤3.5 × 109/L, neutrophils count ≤1.5 × 109/L or platelets ≤100 × 109/L), cardiac, pulmonary, gastrointestinal, endocrine, neurologic or cerebral disease were excluded from the study.
6. Patients with bleeding disorders.
7. Women who are pregnant, breast-feeding.
8. Female or male patients planning for pregnancy during the course of the study.
9. Patients who were taking medications other than NSAIDs.
10. Patients were on physical therapy or any other form of treatments specific to OA during the course of the study.

Baseline Evaluation:

All patients with primary KOA had been assessed as follows:

1-Detailed History Taking

2-Physical Examination: including

a. General Examination

b. Locomotor Examination:

To assess the musculoskeletal system and all body joints to exclude any other Rheumatological conditions.

c. Knee Joint Examination:

Inspection:

Swelling(diffuse or localized), redness, scar of operation or previous trauma.

Palpation:

Hotness, crepitus. swelling, synovial thickening or bony prominence.

Range of motion: of the affected knee joint for any limitation in the range of motion.

Special tests: to assess ligaments and menisci.

3. Laboratory Investigations:

Laboratory investigations were done for all participants to exclude patients with other diseases conditions. The following parameters were assessed: complete blood picture, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). In addition rheumatoid factor (RF), serum uric acid, serum creatinine, Alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine, blood glucose, and prothrombin time were also assessed.

4-Radiographic Examination

All participants were examined by plain x-ray antero-posterior standing position and lateral views for both knees.

5-Knee Joint Ultrasound Assessment: for

a-**Assessment of synovial effusion and synovial membrane thickening**

All ultrasound assessments were performed using the same machine (Toshiba Xario 200 machine) with a 10-18 MHz linear transducer. The scans were based on a protocol derived from EULAR guidelines **(12)**while the OMERACT guidelines for synovial effusion**(11)** were also met. Synovial effusion was defined as an abnormal anechoic or hypoechoic area in the joint that is displaceable and compressible and lacks Doppler signal; as per the OMERACT guidelines **(11).**

b-Grading of OA Severity According to Osteophytes

Osteophytes were assessed at the tibial and femoral sites in both knees, with 30^{o} of knee flexion. Osteophytes were defined as cortical protrusions at the joint margin seen in two planes **(13).** Grading of KOA was done according to a scale proposed by ***Mortada et al.*** **(14),** which depended on the shape of distal femoral osteophytes (Table 4). The scale consisted of 6 grades (0 – 5), where grade 0 denoted no OA and grade 5 denoted the most advanced grade of KOA.

c-Assessment of Thickness of Femoral Condylar Cartilage

The thickness of the femoral condylar cartilage was measured in the medial and lateral condyles and in the notch, with the knee in maximum flexion. Cartilage thickness was measured from the thin hyper-echoic line at the soft tissue-cartilage interface to the hyper-echoic line at the cartilage-bone interface. The probe was placed transversely to the leg and perpendicular to the bone surface, just above the superior margin of the patella **(15)**.

Randomization and Intervention:

After the baseline evaluation, participants were randomly allocated into two groups:

MTX-treated KOA Group:

This group contained 100 patients with primary KOA. Participants in this group were instructed to take oral MTX 7.5 mg weekly for two weeks, followed by 10 mg weekly for two weeks, 12.5 mg weekly for two weeks and 15 mg weekly for the remainder of the study if there is no toxicity. If participants developed toxicity to MTX upon dose escalation the dose is reduced to the maximum tolerated dose (with a minimum dose of 7.5 mg/week) and this was be maintained for the duration of the study **(16).** All participants were instructed to take oral folic acid 5 mg tablets to be taken on the six consecutive days after taking the weekly MTX dose.

NSAIDs-treated KOA Group:

This group contained 100 patients with primary KOA. Participants in this group were instructed to use the NSIDs only.

Outcome Measures:

All outcome measures were assessed at baseline (prior to randomization), at 3 months post-intervention and at 6 months post-intervention:

Pain

Pain was measured using a 10 cm VAS. Pain intensity is classified using a range from 0 to 10, in which 0 = no pain at all and 10 = the worst possible pain. Patients were asked to sign the place on the VAS scale that corresponded to their pain level **(17).**

Tenderness

Assessment of tenderness – Elicited by firm digital pressure over the joint margin, tenderness was assessed on a 0 to 3 scale **(18).**

Range of motion:

Knee ROM in flexion was determined in prone position using an international standard 360º goniometer. The validity and reliability of this measuring device has been demonstrated by other researchers **(19).**

3. Results

The average age of the patients in MTX-treated KOA group were 58 ±7.9 years (ranged from 43 to 71 years) and the average age of the KOA patients in NSAIDs-treated group were 57.4 ±7.9 years (ranged from 44 to 71 years). The MTX-treated KOA group included 72 females and 28 males while the NSAIDs-treated KOA group included 74 females and 26 males. The average BMI of the MTX-treated KOA group and the NSAIDs-treated KOA group were 28.3 ±3.7 kg/m^2 and 28.1 ±3.5 kg/m^2 respectively. From the patients in the MTX-treated KOA group 14% were smokers compared to 12% in the NSAIDs-treated KOA group. The average duration of KOA-treated KOA in the patients in the MTX-treated KOA group were 12.4 ±4.4 years while the duration of KOA-treated KOA in the NSAIDs-treated KOA group were 12.1 ±4.5 years (ranged from 5 to 20 years in the both groups).

At baseline evaluation the VAS-pain did not differ significantly between the MTX-treated KOA group and the NSAIDs-treated KOA group (5.2 ±1.9 and 5.1 ±2.0 respectively, p=0.690). However, after 3 months the VAS- pain was significantly lower in the MTX- treated KOA group as compared to the NSAIDs-treated KOA group (4.4 ±1.6 versus 4.9 ±1.9 respectively, p=0.042) while after 6 months of intervention, the difference of VAS-pain between the two groups was more prominent (1.4 ±0.6 in the MTX-treated KOA group versus 4.2 ±1.9 in the NSAIDs-treated KOA group). This difference was significant (95% CI, 0.4; 1.42, p<0.001) (Table 1).

At baseline, the average tenderness did not differ significantly between the two groups (2.0 ±0.8 and 1.9 ±0.8 respectively, p=0.606). After 3 months of intervention, the average tenderness was 1.6 ±0.7 in the MTX-treated KOA group compared to 1.8 ±0.8 in the NSAIDs-treated KOA group. This difference was significant (p=0.048). After 6 months of intervention, the difference of average tenderness score was more prominent (3.4 ±1.6 in the MTX-treated KOA group versus 1.7 ±0.8 in the NSAIDs-treated KOA group). This difference was significant (95% CI, 0.06; 0.46, p=0.011) (Table 1).

The average WOMAC total score at baseline in the MTX-treated group and in the NSAIDs-treated group was 46.9 ±14.4 and 45.9 ±15.9 respectively. This difference was insignificant (p=0.615). After 3 months of intervention, the WOMAC total score in the MTX-treated group and in the NSAIDs-treated group was 38.6 ±15 and 43.4 ±17.1 respectively. This difference was significant (p=0.036). After 6 months of intervention, the WOMAC total score in the MTX-treated group and in the NSAIDs-treated group was 34.5 ±15.6 and 39.9 ±17.9 respectively. This difference was also significant (95% CI, 0.25; 10.23, p=0.028) (Table 1).

At baseline, limited knee joint ROM was reported in 42% and 46% of the patients with KOA in the MTX-treated group and NSAIDs-treated respectively. After 3 months of intervention the

frequency of the reported limited ROM was significantly lower in the patients in the MTX-treated group than in the NSAIDs-treated group (26% versus 43% respectively, p=0.011). After 6 months of intervention, the frequency of the limited ROM was in the MTX-treated KOA group was 19% compared to 37% in the NSAIDs-treated group. This difference was significant (p=0.005) (Table 2).

At baseline, the average KL-grade did not differ significantly between the two groups (2.09 ±0.9 and 2.06 ±0.9 respectively, p=0.819). After 3 months of intervention, the average KL-grade was 2.15 ±0.96 in the MTX-treated KOA group compared to 2.41 ±0.87 in the NSAIDs-treated KOA group. This difference was significant (p=0.045). After 6 months of intervention, the difference of average KL-grade was 2.22 ±0.99 in the MTX-treated KOA group versus 2.49 ±0.89 in the NSAIDs-treated KOA group. This difference was significant (95% CI, 0.01; 0.53, p=0.044) (Table 3).

At baseline evaluation the average OA severity on US examination did not differ significantly between the MTX-treated KOA group and the NSAIDs-treated KOA group (2.93 ±1.37 and 3.12 ±1.29 respectively, p=0.314). However, after 3 months the OA severity was significantly lower in the MTX-treated KOA group as compared to the NSAIDs-treated KOA group (3.08 ±1.51 versus 3.51 ±1.41 respectively, p=0.039) while after 6 months of intervention, the difference of OA severity between the two groups was more prominent (3.16 ±1.44 in the MTX-treated KOA group versus 3.60 ±1.43 in the NSAIDs-treated KOA group). This difference was significant (95% CI, 0.04; 0.84, p=0.032) (Table 4).

At baseline, 21% and 19% of the patients with KOA in the MTX-treated group and NSAIDs-treated respectively had knee effusion. After 3 months of intervention the frequency of the reported effusion was significantly lower in the patients in the MTX-treated group than in the NSAIDs-treated group (7% versus 16% respectively, p=0.046). After 6 months of intervention, the frequency of the effusion was in the MTX-treated KOA group was 5% compared to 14% in the NSAIDs-treated group. This difference was significant (p=0.030) (Table 5).

At baseline, the average femoral medial condyle cartilage thickness did not differ significantly between the two groups (1.72 ±0.68 and 1.73 ±0.66 respectively, p=0.950). After 3 months of intervention, the average femoral medial condyle cartilage thickness was 1.85 ±0.65 in the MTX-treated KOA group compared to 2.23 ±0.75 in the NSAIDs-treated KOA group. This difference was significant (p<0.001). After 6 months of intervention, the difference of average tenderness score was more noticeable (1.89 ±0.66 in the MTX-treated KOA group versus 2.34 ±0.79 in the NSAIDs-treated KOA group). This difference was significant (95% CI, 0.25; 0.65, p<0.001) (Table 6).

Table 1. Comparison of the clinical outcomes between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group		**Student's t test**	
	MTX-treated	**NSAIDs-treated**	**t**	***p***
VAS-pain				
At baseline	5.2 ±1.9	5.1 ±2.0	0.400	0.690
After 3 months	4.4 ±1.6	4.9 ±1.9	2.045	0.042
After 6 months	3.4 ±1.6	4.2 ±1.9	3.553	<0.001
Tenderness				
At baseline	2.0 ±0.8	1.9 ±0.8	0.516	0.606
After 3 months	1.6 ±0.7	1.8 ±0.8	1.990	0.048
After 6 months	1.4 ±0.6	1.7 ±0.8	2.574	0.011
Womac total score				
At baseline	46.9 ±14.4	45.9 ±15.9	0.504	0.615
After 3 months	38.6 ±15.0	43.4 ±17.1	2.110	0.036
After 6 months	34.5 ±15.6	39.9 ±17.9	2.212	0.028

Table 2. Comparison of the frequency of limited ROM between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group				Chi square test	
	MTX-treated		NSAIDs-treated			
	n	%	n	%	X^2	*p*
At baseline	42	43	46	46	0.325	0.569
After 3 months	26	26	43	43	6.395	0.011
After 6 months	19	19	37	37	8.036	0.005

Table 3. Comparison of the KL-grade between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group				Student's t test	
	MTX-treated		NSAIDs-treated		t	*p*
At baseline	2.09	±0.9	2.06	±0.9	0.229	0.819
After 3 months	2.15	±0.96	2.41	±0.87	2.014	0.045
After 6 months	2.22	±0.99	2.49	±0.89	2.024	0.044

Table 4. Comparison of the OA severity according to osteophytes severity on US examination between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group		Student's t test	
	MTX-treated	NSAIDs-treated	t	*p*
At baseline	2.93 ±1.37	3.12 ±1.29	1.009	0.314
After 3 months	3.08 ±1.51	3.51 ±1.41	2.082	0.039
After 6 months	3.16 ±1.44	3.60 ±1.43	2.164	0.032

Table 5. Comparison of the frequency of knee effusion by US examination between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group				Chi square test	
	MTX-treated		NSAIDs-treated			
	n	%	n	%	X^2	*p*
At baseline	21	21	19	19	0.125	0.724
After 3 months	7	7	16	16	3.979	0.046
After 6 months	5	5	14	14	4.711	0.030

Table6. Comparison of the femoral cartilage thickness between the MTX-treated group and NSAIDs-treated group at baseline and after 3 and 6 months from intervention:

	KOA Group		Student's t test	
	MTX-treated	NSAIDs-treated	t	*p*
Medial condyle				
At baseline	1.72 ±0.68	1.73 ±0.66	0.063	0.950
After 3 months	1.85 ±0.65	2.23 ±0.75	3.788	<0.001
After 6 months	1.89 ±0.66	2.34 ±0.79	4.375	<0.001
Notch				
At baseline	2.22 ±0.80	2.27 ±0.79	0.488	0.626
After 3 months	2.41 ±0.85	2.99 ±0.97	4.563	<0.001
After 6 months	2.46 ±0.86	3.14 ±1.02	5.122	<0.001
Lateral condyle				
At baseline	1.86 ±0.62	1.89 ±0.60	0.429	0.668
After 3 months	2.06 ±0.73	2.56 ±0.86	4.375	<0.001
After 6 months	2.08 ±0.73	2.75 ±0.86	5.976	<0.001

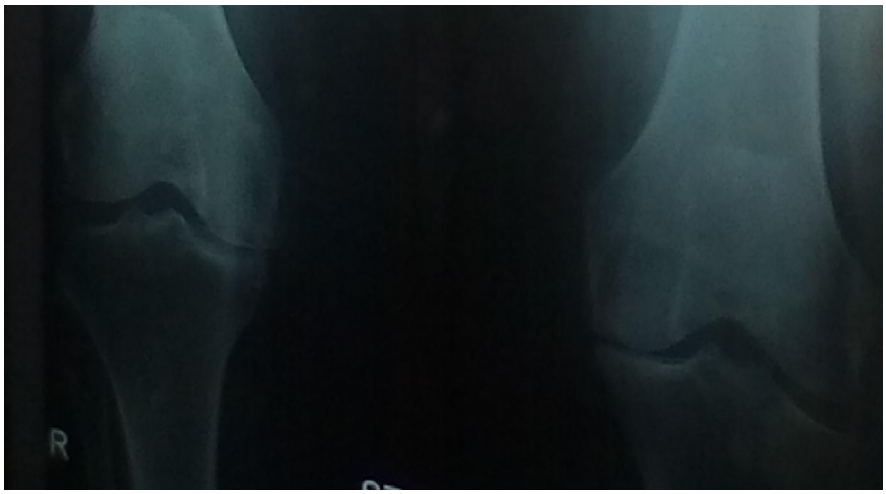

Figure 1. Plain X ray both knee A/P standing view for 53 years female patients before MTX therapy showing narrowing of medial compartment.

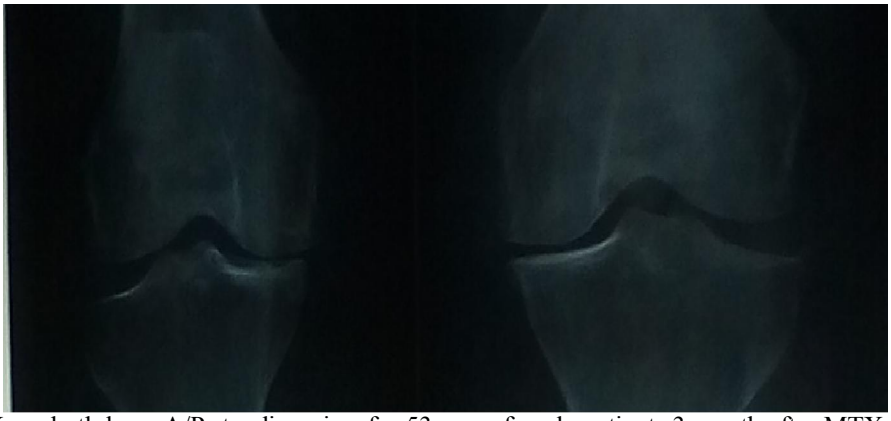

Figure 2. Plain X ray both knee A/P standing view for 53 years female patients 3 month after MTX therapy showing widening of medial compartment.

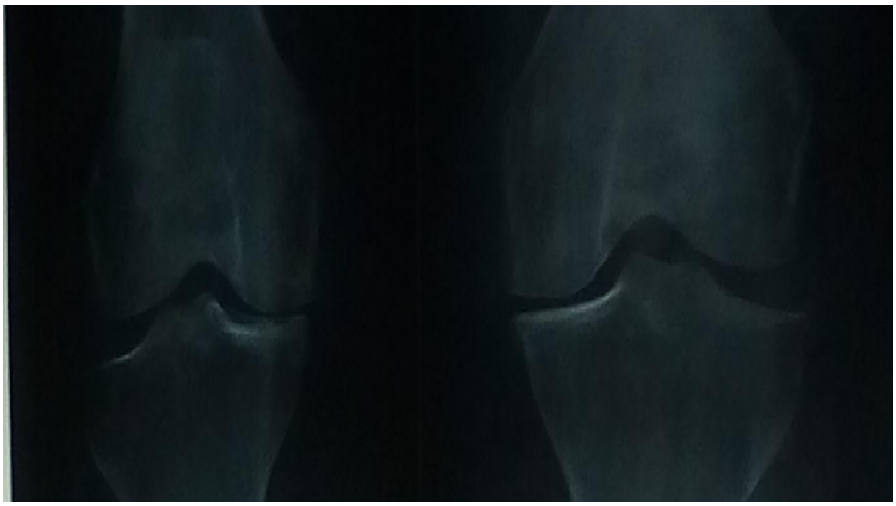

Figure 3. Plain X ray both knee A/P standing view for 53 years female patients 6 month after MTX therapy showing more widening of medial compartment.

4. Discussion

With a rapidly aging population, OA has become the fastest growing cause of disability worldwide **(20);(21).** Current estimates suggest that over 250 million people across the globe are affected by OA **(21).** OA is characterized by chronic joint pain and functional impairment, resulting inmarkedly reduced quality of life for individuals. OA also places an enormous burden on health services and health economies, and is the second leading cause of absence from work **(22)**.

One of the major barriers to reducing the impact of OA, both on individuals and society, is the lack of efficacious therapies available to treat the symptoms of OA or to slow the disease process and associated structural progression. Although current treatments are aimed at providing symptomatic relief, recent studies suggest that the large majority of people with OA live in constant pain despite use of available therapies **(23)**.

There is increasing evidence, particularly from imaging studies, of a high prevalence of synovitis in OA present from the earliest stages of the OA and associated with the presence and severity of pain **(24),(25)**. Another evidence for the inflammatory nature of the OA comes from the reported increased levels of pro-inflammatory cytokines, reduced levels of anti-inflammatory cytokines, infiltration of inflammatory cells within OA fluid and tissue **(26).** These observations suggest that modulating the inflammatory process may be an effective treatment target for OA.

MTX has an anti-inflammatory effect by inducing an increase in adenosine release from cells and was commonly used in inflammatory arthritis. Extracellular adenosine is a potent inhibitor of inflammation, suppressing the activity of inflammatory cells, thereby reducing secretion of inflammatory cytokines which drive synovitis **(27).**

Given the high levels of pro-inflammatory cytokines and the evidence of immune cell infiltration into OA joints, coupled with the strong correlations observed between synovitis and pain, there is rationale for the use of MTX for reducing symptoms in OA. However, to date only few trials of MTX for treating OA were performed and produced conflicting results. Therefore, we performed this study to determine the effectiveness of the MTX use in treatment of KOA.

A total of 200 consecutive eligible patients with symptomatic radiographic primary KOA participated in the study. All patients fulfilled ACR criteria for radiologic and clinical KOA. The patients were randomized into two groups; (a) MTX-treated KOA group: included 100 patients who received oral MTX and (b) NSAIDs-treated KOA group: included 100 patients were received NSAIDs.

The results of the current study had shown that pain, tenderness and Womac score were significantly lower in the MTX-treated group than in the NSAIDs-treated group at 3 months and at 6 months from treatment. After 3 months of intervention the VAS-pain was significantly lower in the MTX-treated KOA group as compared to the NSAIDs-treated KOA group (4.4 ±1.6 versus 4.9 ±1.9 respectively, p=0.042) while after 6 months of intervention, the difference of VAS-pain between the two groups was more prominent(1.4 ±0.6 in the MTX-treated KOA group versus 4.2 ±1.9 in the NSAIDs-treated KOA group, p<0.001).

In agreement with our findings**, *Wenham et al.*** (28), reported that after 24 weeks of treatment, MTX had significantly reduced pain in the patients with KOA. They reported that 50% of patients had achieved >20% reduction in pain, whilst 43% of patients had achieved >30% reduction in VAS pain of whom 23% had achieved >50% reduction in VAS pain. They also reported that MTX had resulted in improvement in patient-reported functional ability VAS of 20% at 12 weeks from MTX treatment and improvement in patient-reported functional ability VAS of 40% at 24 weeks from MTX treatment. Also in agreement with our findings, ***Hart (29),*** found that MTX had reduced pain and improved function in symptomatic KOA.

Abou-Raya et al. (2014)(9) performed a study to assess the efficacy of MTX in decreasing pain and inflammation in symptomatic KOA. They enrolled 144 patients with symptomatic KOA and were randomized into two equal groups to receive MTX up to 25 mg/week and placebo respectively. Pain and Womac score were evaluated at baseline and at the end of the study. In agreement with our results, they found a clinically relevant reduction in the MTX group compared with the placebo group for knee VAS-pain, physical function (Womac score) and ADL scores at 28 weeks of treatment. They also noted that 53% of the patients in the MTX group versus 24% in the placebo group had a reduction in VAS pain of >20%.

In a more recent study, ***Kingsbury et al.*** **(16),** demonstrated a clinically relevant reduction in knee pain and improvement in knee mobility and improvement in overall QOL in the group treated with MTX at 28 weeks. In the study of ***Kingsbury et al. (16)),*** a significantly higher proportion of patients in the MTX group (53%) showed a reduction in VAS measurement of pain of >20 mm compared to the placebo group (24%). These findings were consistent with our results.

On the other hand, ***deHolanda et al. (30),*** enrolled 58 patients in a double blinded controlled trial. The patients were randomized into two groups, and MTX group and placebo group. In that study no

statistically significant difference between both groups regarding WOMAC, Lequèsne Index and VAS pain was reported. The discrepancy between the results of the present study and the study of ***de Holanda et al. (30),*** can be attributed to the different methodology between the two studies. The study of ***de Holanda et al. (30),*** included much lower sample of patients than ours (29 patients in each groupin that study versus 100 patients in our study). Also, ***de Holanda et al. (30),*** provided MTX at a fixed dose of 7.5 mg/week for 4 months compared to our escalating dose from7.5 mg weekly for two weeks to 10 mg weekly for two weeks to 12.5 mg weekly for two weeks and then 15 mg weekly for the remainder of the study. Moreover we provided MTX in the current study for 6 months. In addition, the entry criteria in the previous study included a pain VAS of >50/100 mm (40% of patients in this study had VAS pain <5 mm) and participants had more structural damage, with over 90% having a KL score of 3, with 64.5% of the patients in our study had KL (**Kellgren and Lawrence system)** score 1 or 2. Our results had also shown that, plain radiography KL grade was significantly lower in the in the MTX-treated group than in the NSAIDs-treated group at 3 months and at 6 months from treatment. US was used in this study to explore possible synovial membrane changes that may occur with MTX treatment. Our results had shown that at 3 months of treatment the OA severity was significantly lower in the MTX-treated KOA group as compared to the NSAIDs-treated KOA group and the difference of OA severity between the two groups was more prominent at 6 months of treatment. Moreover, significantly less frequent patients in the MTX-treated group had effusion than the patients in the NSAIDs-treated group at 3 months and at 6 months from treatment. The US examination of the articular cartilage thickness of the current study had also revealed that the knee articular cartilage at the femoral condyles and notch was significantly more thick in the patients allocated in MTX-treated group than the patients allocated in the NSAIDs-treated group at 3 months and at 6 months from treatment.

Conclusion

MTX significantly reduced pain and tenderness and improved joint mobility. MTX had significantly improved synovitis and effusion and decreased cartilage damage. There was a significant improvement in physical function with MTX therapy. MTX may be a therapeutic option in the treatment of pain and inflammation related to KOA.

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