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Original Article

Effect of Metformin as Add-on Therapy to Ibuprofen on the Disease Activity in Knee Osteoarthritis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract:

Background: *Osteoarthritis (OA) is the most common type of arthritis. This condition is highly debilitating, encompassing various physical symptoms like pain, stiffness, loss of function, and disability that negatively impacts patient's quality of life. Currently, there is no safe and effective therapy for OA. Metformin, a well-known drug used for type-II Diabetes Mellitus with excellent safety, shows anti-inflammatory properties. This study aimed to evaluate the effect of metformin as add-on therapy to ibuprofen in mild to moderate knee OA patients.*

Materials and Methods: *Adults with knee pain, radiologically diagnosed with mild to moderate (grade II-III) knee OA, participated in this double-blind, randomized, placebo-controlled trial. Patients were assigned randomly to two groups. Both groups received Ibuprofen tablet 400 mg twice daily for two weeks as standard of care. As add-on therapy, one group (n = 35) received metformin extended release (ER) tablets 500 mg orally once daily, and the other group (n = 35) received an identical inert placebo tablets for 8 weeks. The outcome of treatment regimen was evaluated using the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (normalized to scores of 0–100) at baseline, and at the end of 8th week.*

Results: *Following a 8-weeks treatment, there was a significant improvement in scores of knee pain (P=0.01), activity of daily living (ADL) (P =0.028), and knee-related quality of life (QOL) (P=0.013) and total scores (P=0.02) of the KOOS questionnaire in the metformin group compared to the placebo group.*

Conclusion: *Metformin as add-on therapy may have beneficial effects on improving knee pain, ADL, and QOL in mild to moderate knee OA patients.*

Keywords: Metformin, Osteoarthritis, KOOS.

Introduction:

Osteoarthritis (OA) is the most common type of arthritis and is more prevalent in older people.[1] OA is a serious, disabling, and highly prevalent condition, and it affected 7.6% (595 million) of the global population in 2020.[1,2] Individuals with OA experience increased pain, stiffness, swelling, disability, exhaustion, depression, insomnia, limited activities, and loss of involvement in regular social, communal, and professional activities.[3] The economic cost connected with OA is enormous,

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spanning from direct treatment costs ($65.5 billion) to lost work productivity ($71.3 billion).[4]

The pathological changes observed in OA joints include degeneration of the articular cartilage and ligaments, thickening of the subchondral bone, formation of osteophyte, variable degrees of synovial inflammation, and hypertrophy of the joint capsule.[5] Normally, AMPK enzyme is essential to maintain the metabolic homeostasis of bone. It has been found that abnormal AMPK activity was associated with synovial pathological changes in OA. Aging, low-grade inflammation, mechanical injury, and metabolic syndromes result in decreased AMPK activity. Impaired AMPK activity reduces the level and activity of SIRT1, FoXO3a, and ULK-1, resulting in mitochondrial dysfunction, increased oxidative stress, reduced autophagy, and increased inflammation-mediated cartilage breakdown. Conversely, increased production of p-P65, p-mTOR1, and c-Fos leads to NF-κB, ER stress, and osteoclastogenesis, which in turn causes chondrocyte apoptosis, inflammation of the synovium, and aberrant subchondral bone remodeling.[6,7]

Currently, there is no safe and effective treatment that can prevent, stop, or even delay the progression of OA.[8] Acetaminophen and Nonsteroidal Anti-inflammatory drugs (NSAIDs) are the primary treatments for OA pain, but NSAIDs produce significant gastrointestinal, renal, hepatic and cardiovascular side effects which restricted their usage to the lowest dose and shortest possible duration and have negative effect on articular cartilage.[9,10] Opioid therapy has the potential for tolerance, dependence, respiratory depression, and constipation.[11] Intra-articular corticosteroid therapy (ICS) only provides short-term relief for acute knee pain. However, the long-term detrimental effects of ICS have remained a concern.[12] Intra-articular hyaluronic acid injections have concerns about effect duration, safety, effectiveness, and heterogeneity.[13] Current OA treatment guidelines strongly discourage using glucosamine & chondroitin sulfate and platelet-rich plasma (PRP) therapy because of low-quality evidence.[14,15] Thus, efforts to find a safe and effective therapeutic option for OA are still ongoing.

Metformin is a safe and generally well-tolerated oral biguanide that has been widely used as first-line therapy for type 2 diabetes for more than six decades.[16,17] Recent studies suggest that chronic low-grade inflammation contributes to the pathogenesis of OA.[18] Proteolytic enzymes, such as MMPs and ADAMTS aid in the breakdown of ECM components of articular cartilage in OA e.g. type II Collagen, Aggrecan and others.[19,20] Metformin treatment of IL1β-induced chondrocytes resulted in downregulated MMP3, ADAMTS5, and enhanced production of Collagen II, Aggrecan, and SOX9 in an in vitro study.[20] Metformin promotes chondroprotection by suppressing inflammation through activating AMPKα and increasing SIRT1 expression and, as a result, by inactivating NF-κ B signaling. This reduces pro-inflammatory cytokine (TNF-α and IL-6) production and IL-1β-induced extracellular matrix (ECM) degradation, inhibits RAGE accumulation, increases autophagy & cell proliferation and decreases catabolism & apoptosis levels.[21,22] In OA, Oxidative stress caused by reactive oxygen species (ROS) e.g. superoxide (O2-), hydroxyl radical (-OH), peroxide, hydroxy proline, and malondialdehyde (MDA) can lead to hyaline cartilage degradation directly.[23] Metformin has antioxidant effect and decreases the formation of mitochondria-induced ROS in chondrocytes in OA animals.[24] Metformin therapy also reduced mice's dorsal root ganglion (DRG) pain sensitivity by upregulating AMPKα1 expression and decreased the expression of the pain-related mediator (CGRP) in the DRG.[25,26] This study aimed to evaluate the effect of metformin as add-on therapy to ibuprofen on knee pain, other symptoms, activities of daily living, sport and recreation function, and knee-related quality of life in patients with mild to moderate (grade II-III) knee OA over an 8-weeks period.

Materials and Methods:

This study was a randomized, double-blind, placebo-controlled trial conducted in the Bangladesh Medical University (BMU), Dhaka, Bangladesh in collaboration with the Department of Pharmacology and the Department of Physical Medicine and Rehabilitation. Before the study's conduct, the research protocol was submitted to the Institutional Review Board (IRB) of BMU to review the scientific and ethical issues related to the research to obtain the required approval. The protocol was reviewed and the IRB of BMU issued a Clearance Letter (Memo No. BSMMU/2023/11020). The trial was registered on ClinicalTrials.gov (trial ID number NCT06126029) and conducted in accordance with the International Council for Harmonisation Good Clinical Practice (ICH GCP) guidelines. The intervention phase was executed from October 2023 to February 2024.

Sample size was estimated using the formula: $n=[(Z_\alpha + Z_\beta)^2 \times \{ (p1 (100-p1) + p2 (100-p2))\}]/(p1-p2)^2$; where n=sample size, Z_α=1.96 at 5% level of significance, Z_β

=1.64 at 95% power, p1=89.98% (Treatment group response), p2=50% (Control group response).[27] The desired sample size was 28. Considering 20% dropout rate, sample size was 35 in each group. So, total sample size was 70.

A total number of 70 patients were randomized into two groups; the placebo group (n = 35) and the intervention group (n = 35). Inclusion criteria were patients with knee pain and normal body weight for Asians (BMI: 18.5-22.9 kg/m^2) of both sex, age: 18-65 years old, and patients with radiological evidence of mild and moderate knee OA (grade II & III) in one or both knee joints according to the Kellgren-Lawrence radiographic grading scale.[28] The exclusion criteria were patients with prior history of knee trauma or surgery, history of presence of systemic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, gout or pseudogout, chronic diseases (including diabetes mellitus, cardiovascular, pulmonary, renal or hepatic impairment), those taking immunosuppressant, who had received an intra-articular steroid injection or metformin within 3 months of the study, known allergy to metformin, pregnancy or lactation. All the patients attending the outpatient department of Physical Medicine and Rehabilitation, BSMMU, during the first visit were given X-rays of the affected knee joints (anteroposterior and lateral views) in a standing position and were diagnosed as having mild or moderate (grade II-III) knee OA according to the Kellgren-Lawrence radiographic grading scale by a competent physiatrist with a fellowship degree. Patients with major comorbidities or an inability to cooperate with study requirements were precluded from entry. The study objectives were explained to each participant and they were informed about the potential benefits and risks associated with the intervention. Participants were also informed that they can participate in this study of their free will and also, they had every right to refuse to participate or to withdraw at any time without compromising their medical care. All participants provided written informed consent prior to their involvement in the study. Participants' confidentiality was rigorously protected. The participant's personal information regarding name, age, sex and other information was not disclosed anywhere and were used for research purpose only.

Patients were randomized in a double-blind manner to either the intervention or placebo group in a 1:1 ratio using simple randomization by computer-generated random numbers through online GraphPad software. Here, every patient had an equal chance to be assigned to any one of the groups (Placebo and Intervention). Immediately after randomization, random numbers from the two sets were assigned as patient code numbers. Allocation was concealed using sealed envelopes to prevent selection bias. Thus, all participants and the investigator, who required being blinded for such a study, were effectively blinded and unaware of the group allocation. The whole process of randomization and blinding was conducted by a competent third person who had no relationship with this research.

Medicines and placebo were purchased from the manufacturer at the original market price so that there was no conflict of interest. Metformin tablets (metformin ER 500 mg) and placebo tablets were purchased from Opsonin Pharma Limited, a leading pharmaceutical company in Bangladesh. The placebo tablet had the same size, shape & color and were supplied in an identical container.

Both groups received Ibuprofen tablet 400 mg twice daily for two weeks as standard of care. As add-on therapy to ibuprofen, patients in the Intervention group (n=35) received one tablet of metformin 500 mg ER (extended release) and patients in the placebo group (n=35) received one placebo tablet (similar to metformin ER 500 mg tablet), orally once daily with an evening meal for 8 weeks. At baseline visit (day 0), each participant was evaluated using the Bengali KOOS questionnaire before giving the medicine. Patients were requested to avoid any non-steroidal anti-inflammatory drugs (NSAIDs) for the next six weeks and any dietary supplement during the study period. Instruction for the activities of daily living (avoiding stairs, walking on flat surface, prohibiting weight carrying, using walking aid and kneecap during walking, avoiding kneeling and squatting, avoiding sitting for prolonged periods in with bent knees in one position, measures to reduce weight) was prescribed for all participants (both placebo and intervention group). They were in touch with the investigator over the phone during the study period. Compliance was assessed over the phone and by returned empty strips of tablets at the end of eight weeks (56±4 days) of treatment.

Patient's symptoms were assessed by the translated and validated Bengali version of Knee Injury and Osteoarthritis Outcome Score (B-KOOS) questionnaire

version LK 1.0 at baseline and 8 weeks after treatment. KOOS is a 42–item self-report questionnaire, consisting of 5 subscales that include pain (9 items), other symptoms (7 items), activities of Daily Living (ADL) (17 items), Sport and Recreation Function (Sport/Rec) (5 items) and knee-related Quality of Life (QOL) (4 items). Standardized answer options are given by 5 Likert boxes and each question is assigned a score from 0 to 4. Each subscale score was converted into a normalized score of 0 to 100 for better representation. Finally, they were summed up and averaged for the total KOOS score from 0 to 100. Here, score 100 indicates no symptoms and score 0 indicates extreme symptoms. The total procedure took approximately 20-30 minutes for each patient in each visit.

The primary outcome was the change in the KOOS total scores from baseline to 8 weeks in both groups. The secondary outcomes were the change in the scores of 5 individual subscales- pain, other symptoms, activities of daily living (ADL), sport and recreation function, & knee-related quality of life (QOL) of the KOOS scale.

Statistical analysis was done by Microsoft Office Excel 2016. Quantitative variables were presented as mean ± standard deviation (SD), while qualitative variables were represented as percentages (%). For normally distributed data, an unpaired t-test was done to compare the mean values between the two arms and a paired t-test was done to compare the mean values within the same group before and after the intervention. Chi-squared test was done to compare categorical data between the two groups. Fisher's exact test was used to examine adverse effects reported. A statistically significant p-value is < 0.05.

Results:

Among the 300 patients assessed for eligibility with knee OA, 230 patients were excluded (208 patients who did not meet the inclusion criteria and 22 patients who declined to participate). Consequently, a total of 70 patients were enrolled based on the study's eligibility criteria. They were randomly assigned to allocated interventions (intervention group: n=35; placebo group: n=35). Nine participants (12.85%) from both study groups dropped out due to discontinued intervention (n=1), unable to come to the follow-up for work-family issues (n=8) (intervention group: n=4; placebo group: n=4). Final analysis consisted of a total of 61 patients (intervention group: n=30; placebo group: n=31). The CONSORT flow diagram of the study participants is shown in **Figure 1**.

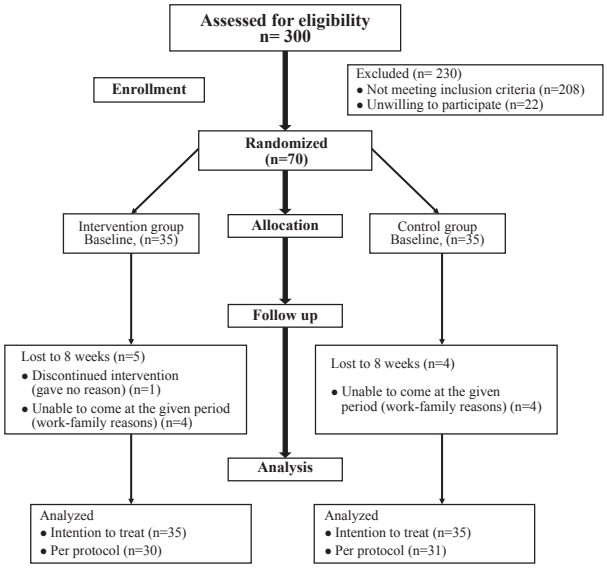

Figure 1: Flowchart of Consolidated Standards of Reporting Trials (CONSORT).

There was a statistically non-significant difference between the two groups concerning age, gender, family history, residence, educational level, social class, smoking, BMI, disease duration, number of symptomatic knees and KL grading at baseline ($p>0.05$) as postulated in **Table 1**.

Table 1: Baseline characteristics of participants at the time of enrollment (N=61)

Variables		Placebo (n=31)	Intervention (n=30)	p value	Method
Age (years)		47.81 ± 10.96	51.10 ± 8.13	0.187	Unpaired t-test
Sex	Male	09 (29.03%)	03 (10.00%)	0.105	Fisher's exact test
	Female	22 (70.97%)	27 (90.00%)		
BMI (kg/m^2)		21.98 ± 1.12	21.88 ± 1.08	0.726	Unpaired t-test
Family History	Yes	10 (32.26%)	08 (26.67%)	0.632	Chi-squared (X^2) test
	No	21 (67.74%)	22 (73.33%)		
Smoking	Yes	03 (9.68%)	02 (06.67%)	1.00	Fisher's exact test
	No	28 (90.32%)	28 (93.33%)		
Residence	Urban	17 (54.84%)	18 (60.00%)	0.684	Chi-squared (X^2) test
	Rural	14 (45.16%)	12 (40.00%)		
Educational level	Primary	9 (29.03%)	10 (33.33%)	0.414	Chi-squared (X^2) test
	Secondary	15 (48.39%)	17 (56.67%)		
	Higher secondary	07 (22.58%)	03 (10%)		
Social class	Upper	13 (41.94%)	14 (46.67%)	0.460	Chi-squared (X^2) test
	Middle	17 (54.84%)	13 (43.33%)		
	Lower	01 (03.33%)	03 (10%)		

K-L Radiological Grading	Grade II (mild)	30 (96.78%)	28 (93.22%)	0.612	Fisher's exact test
	Grade III (moderate)	1 (3.22%)	2 (6.67%)		
Affected Knee	Bilateral	10 (32.26%)	8 (26.67%)	0.351	Chi-squared
	Left	12 (38.70%)	8 (26.67%)		(X^2) test
	Right	9 (29.04%)	14 (46.67%)		
Duration of knee pain	≤5 year	26 (83.88%)	22 (73.33%)	0.518	Chi-squared
	6 - 9 year	3 (9.67%)	6 (20%)		(X^2) test
	≥10 year	2 (6.45%)	2 (6.67%)		

Table 2 shows KOOS knee outcome changes from baseline to after 8 weeks of treatment. There was no significant difference in the mean KOOS scores between the two groups prior to intervention ($P \geq 0.05$). In the intervention group, the mean values for total KOOS scale and all 5 subscales of the KOOS scale were significantly higher after treatment compared to their respective mean values at baseline ($p < 0.05$). Following 8-week treatment period, the intervention group exhibited significantly higher mean values for KOOS total scale and its subscales- knee pain, activity of daily living (ADL), and knee-related quality of life (QOL) in comparison with the placebo group ($p < 0.05$).

Table 2: Comparison of KOOS Score between two groups (between baseline and after 8 weeks of treatment)

		Placebo (n=31) Mean ± SD	Intervention (n=30) Mean ± SD	P value
KOOS	At Baseline	51.87± 11.68	49.88 ± 5.43	0.40
pain	At the end of 8 weeks	52.69 ±10.81	63.88 ± 18.45	0.01*
KOOS other	At Baseline	74.25 ±16.79	70.57 ± 16.96	0.40
symptoms	At the end of 8 weeks	72.56 ±14.78	75.55 ± 10.24	0.36
KOOS	At Baseline	55.56 ±15.25	55.61 ± 15.39	0.858
ADL	At the end of 8 weeks	55.42 ± 13.28	63.82 ± 15.70	0.028*
KOOS	At Baseline	40.88 ± 16.30	36.57 ± 17.32	0.33
Sport/Rec	At the end of 8 weeks	40.46 ± 15.92	48.66 ± 17.76	0.06
KOOS	At Baseline	38.96 ± 12.47	38.81 ± 12.46	0.963
QOL	At the end of 8 weeks	40.23 ± 11.71	49.79 ± 16.78	0.013*
KOOS	At Baseline	52.12 ± 8.96	50.29 ± 12.21	0.51
Total score	At the end of 8 weeks	52.27 ± 13.87	59.99 ± 10.10	0.02*

*; Significant ($p<0.05$). Unpaired t-test was done between placebo and intervention arms.

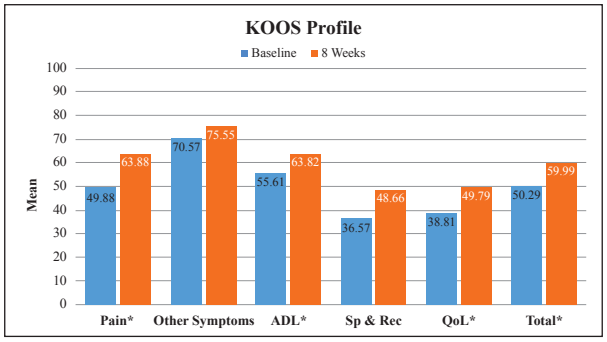

Figure 2: Bar diagram showing the KOOS profile of changes in scores of total and five subscales in the intervention arm, between baseline and after 8 weeks of treatment.

*; Significant change ($p<0.05$)

Table 3 shows the treatment-related adverse events in the placebo and intervention groups that occurred during the treatment period. Only a low frequency of gastrointestinal tract-related side effects was reported, that appeared early in the course of therapy and subsided over time. Adverse events in the placebo group were diarrhea (1), nausea (2), and dyspepsia (1), whereas adverse events in the intervention group were diarrhea (1), nausea (1), and dyspepsia (2). There was no statistically significant difference between adverse events of the placebo and intervention groups after 8 weeks of treatment ($p > 0.05$). All the events were mild in form and did not require discontinuation of treatment. No severe adverse effects were observed in either group.

Table 3: Comparison of adverse events between two groups

Adverse Events	Placebo (n=31)	Intervention (n=30)	p value
Diarrhoea	1(3.22%)	1(3.33%)	1.00
Nausea	2(6.45%)	1(3.33%)	1.00
Dyspepsia	1(3.22%)	2(6.67%)	0.612

Fisher's exact test was done between placebo and intervention groups.

Discussion:

Metformin, an antidiabetic medication, has been demonstrated in preclinical and clinical studies to exhibit anti-inflammatory and chondroprotective properties[29]. The current randomized, double-blind,

placebo-controlled trial aimed to determine the efficacy of metformin as add-on therapy to ibuprofen in mild to moderate (grade II-III) knee OA patients.

KOOS is a valid and reliable questionnaire which is widely used for research purposes in clinical trials including for knee OA, large-scale databases and registries. The inclusion of 'Sport and Recreation function' and 'Quality of Life' increased its validity and sensitivity than WOMAC index[30]. Its improvement is regarded as having greater therapeutic potential. As far as research on Metformin's effects on individuals with mild to moderate (grades II–III) knee OA is concerned, this was one of the few studies done[31].

The findings from our study demonstrated a significant improvement in KOOS total score and its subscales-knee pain, activity of daily living (ADL), and knee-related quality of life (QOL) score in the metformin group when compared to the placebo group after treatment, which is similar to previous studies.[31-33]. Metformin's potential to relieve pain in OA patients as also reported by others, is due to metformin-induced activation of AMP-activated protein kinase (AMPK), and AMPK activation inhibits NF-κB activation and also suppresses mTORC1 that participates in the transmission of pain[34,35]. Pain reduction by metformin is also due to the suppression of pain-related signals, nociceptive neuron sensitivity and by down regulating TRPV1 expression[36,37]. In our study, pain consequences such as an impairment in activity of daily living, knee-related QOL, and KOOS total scores improved in individuals with OA when their pain levels decreased after taking metformin.

The KOOS other symptoms and sports & recreation function score increased but were not statistically significant compared to the placebo arm after 8 weeks of treatment ($p > 0.05$). Use of higher doses of metformin (>500 mg) and for longer durations (>8 weeks) might have caused significant improvement in KOOS, other symptoms, and sports & recreation function in the present study.

This present study observed a very low frequency of gastrointestinal adverse effects such as diarrhoea, nausea and dyspepsia, probably due to the use of extended-release formulation of metformin tablets, as also reported by previous studies[38]. Notably, these adverse effects occurred early in the treatment, were mild and transient in nature, and resolved with continued medication use. Administration of the study medications after a meal helped alleviate these gastrointestinal adverse effects.

As proposed by some authors, metformin administration in patients with early knee osteoarthritis (mild to moderate) in this study was rational and has resulted in a significant reduction of knee pain and other consequences[39]. Because, it is now clear that synovitis may exist before cartilage degeneration that appears on imaging in OA, and synovitis may drive the development of OA[39,40]. Metformin can also be an effective alternative treatment for other mild to moderate inflammatory diseases where long-term treatment is necessary.

According to our results, we found that metformin is tolerable and effective as add-on therapy to ibuprofen in patients with early knee osteoarthritis through significant improvements in clinical outcome (KOOS score), possibly by decreasing synovial inflammation and cartilage degeneration.

Conclusion:

Metformin may be safe and effective as add-on therapy to ibuprofen in patients with early (grade II-III) knee osteoarthritis. Metformin's potential mechanisms of action in lowering the severity of OA symptoms include anti-inflammatory and chondroprotective effects. Additional research is required to validate these results and clarify the precise mechanism of action of metformin in OA. Strengths of the current study are randomization, double-blinding and placebo-control. Also, ibuprofen was fixed as the standard of care for all participants and bought from the same manufacturer. Knee OA patients were diagnosed by a competent physiatrist with a fellowship degree. Limitations include, it was a short-duration study with a relatively small sample size, use of small metformin dose (500 mg) once daily with only one follow-up, wide variation in the duration of knee pain at baseline, ranging from 1 month to 12 years and <5% of the study participants had moderate (grade III) OA.

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