

## Original Research Article

# Study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis of the knee

**Shashikala Eda\***

Department of Pharmacology, Mallareddy Institute of Medical Sciences, Hyderabad, Telangana, India

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**\*Correspondence:**

Dr. Shashikala Eda,

E-mail: [drvijayragava@gmail.com](mailto:drvijayragava@gmail.com)

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### ABSTRACT

**Background:** Osteoarthritis (OA) of the knee is the most common degenerative joint disorder that results in disability and increased morbidity. Conventional treatment of OA with non-steroidal anti-inflammatory drugs (NSAIDs) often leads to serious adverse side effects that may increase morbidity and mortality. Glucosamine and Methylsulfonylmethane (MSM) have anti-inflammatory and analgesic properties which may supplement NSAIDs. Hence this study was aimed to determine the effectiveness and safety of these drugs in the management of knee OA

**Methods:** 76 (63.33%) female and 44 (36.67%) male patients of OA of the knees were divided equally into four groups depending upon the therapy with Glucosamine or MSM or their combination (study groups) or none of them (control group) for 12 weeks. After the written consent, a detail Clinical History & Examination, Biochemical investigations, X-rays of chest and knees and ECG were done. The outcome of the treatment was assessed by Western Ontario and McMaster University Osteoarthritis (WOMAC) Index and for any adverse drug effects.

**Results:** After 12 weeks of study there was significant decrease in mean WOMAC pain scores (27.29-39.13) and total aggregate scores (23.53-37.14%) in study groups ( $p < 0.01$ - $p < 0.001$ ) as compared to control group (14.28 % and 8.82% respectively). Besides the relief of pain and improvement in physical functions were superior in patients treated with combination therapy.

**Conclusions:** This study showed Glucosamine & MSM are effective in the management of OA of knee and are safe health supplement to NSAIDs while their combination was more superior and effective.

**Keywords:** Joint pains, Physical function, Efficacy, Adverse effects

### INTRODUCTION

Osteoarthritis (OA) is one of the most common degenerative joint disorders of multifactorial etiology affecting the mankind. Knee osteoarthritis is the most common type of OA, which is primarily a disorder of cartilage with secondary changes in the bone in which progressive destruction of articular cartilage, hypertrophy of bone at the margins, subchondral sclerosis, and biochemical and morphological alterations of the

synovial membrane and joint capsule occur, that results in swelling, pain, disability and increased morbidity.<sup>1-3</sup>

45% of women over the age of 65 years have symptoms while radiological evidence was found in 70%.<sup>4-6</sup> OA was estimated to be the 10th leading cause of nonfatal burden.<sup>4,5</sup> In India OA is the most frequent joint disease with a prevalence of 22% to 39% more predominant in women.<sup>1,7,8</sup> By 2025 India may become the osteoarthritis capital of the world with over 60 million cases.

The reasons for such a high incidence of osteoarthritis are obesity, lack of balanced diet and regular exercise, not getting enough exposure to sunlight and increase in smoking due to life style changes.

Conventional treatment of OA with non-steroidal anti-inflammatory drugs (NSAIDs) do not improve the underlying pathology of the disease, but are often associated with adverse effects including serious gastrointestinal (GI) side effects that may lead to frequent hospitalization and increased mortality.

In view of the recent withdrawal of some cyclo-oxygenase-2 inhibitors (Rofecoxib due to serious GI side effects), identifying a safer alternative treatment options which are effective and well-tolerated with minimal or no side effects is needed. The Complementary and Alternative Medicines (CAM) such as Glucosamine and Methylsulfonylmethane (MSM) are frequently used to reduce the swelling and pain of OA; and to slow or prevent further joint degeneration, besides they found to be well tolerated by OA patients.

Glucosamine an amino monosaccharide, is an intermediate substrate used in the synthesis of glycosaminoglycan and proteoglycans by the articular cartilage. It also acts as the provider of sulfate ions for the synthesis of chondroitin sulfate and keratin sulfate.<sup>9</sup> It is one of the most effective chondroprotective agent, which also has mild anti-inflammatory activity.<sup>10,11</sup>

Methylsulfonylmethane (MSM) is the oxidized form of dimethyl-sulfoxide a natural organic form of sulphur, which is needed for the formation of connective tissue. It also blocks the inflammatory process by (OH-) free radicals and enhances the activity of cortisol, a natural anti-inflammatory hormone produced in the body.<sup>12</sup> Because of these natural properties of anti-inflammatory and effective natural analgesic, it has been found to be effective in the treatment of pain, inflammation in arthritis.<sup>13</sup> Hence the present study was designed with the aim of determining and comparing the efficacy and safety profile of oral Glucosamine, MSM and their combination in the management of osteoarthritis of the knee.

## METHODS

This is a prospective comparative study of osteoarthritis patients conducted in the Departments of Pharmacology and Orthopedics, Mallareddy Institute of Medical Sciences and Hospital, Suraram, Hyderabad, Telanagana, from November 2020 to November 2021, after the Institutional Ethical Committee approval.

### Inclusion criteria

Patients with symptomatic knee OA of minimum six months duration confirmed by antero-posterior knee X-ray as per Kellgren and Lawrence grading criteria, and who not received any NSAIDs over previous two weeks

were included in this study as per American Collage of Rheumatology.<sup>14,15</sup>

### Exclusion criteria

Patients with inflammatory arthritis and other types of arthritis, history of recent knee injury or who had intra-articular treatment with any product or arthroscopic procedures within 6 months, patients with gastrointestinal disorders like peptic ulcer; and patients who lack ability to perform or comply with treatment procedure were excluded from the study. Similarly, patients with Diabetes mellitus, Coronary Artery Disease (CAD) and Chronic Kidney Disease (CKD) were also excluded from this study.

After a written consent from each patient, a detailed clinical history, clinical examination, routine biochemical investigations (fasting plasma sugar (FPS), serum creatinine, serum electrolytes) chest X-ray PA view, knee x-ray antero-posterior view and electrocardiogram (ECG) were done.

Patients were categorized into four groups: each comprising 30 patients (19 females (63.33%) and 11 males (36.67)).

#### Group (Gr) 1

Control Gr: OA patients received conventional treatment (NSAIDs) and No Glucosamine or MSM.

#### Group (Gr) 2

Study Gr 1: OA patients received Glucosamine 500 mg 3 times /day.

#### Group (Gr) 3

Study Gr 2: OA patients received MSM 1000 mg 3 times/day.

#### Group (Gr) 4

Study Gr 3: OA patients received Combination of Glucosamine 500 mg 3 times/day and MSM 1000 mg 3 times/day.

The clinical outcome of the study was assessed by modified Western Ontario and McMaster University Osteoarthritis (WOMAC) Index and for any Adverse Effects.<sup>16</sup> WOMAC Index is a questionnaire to assess joint pain (for a score of 20), joint stiffness (for a score of 8), physical function (for a score of 68) in OA patients with a total aggregate score of 96 (Appendix I).

In this study pain scores for joint pains and Total aggregate scores were evaluated separately at the beginning of the study, then at the 4th, 8th, and 12th week of treatment.

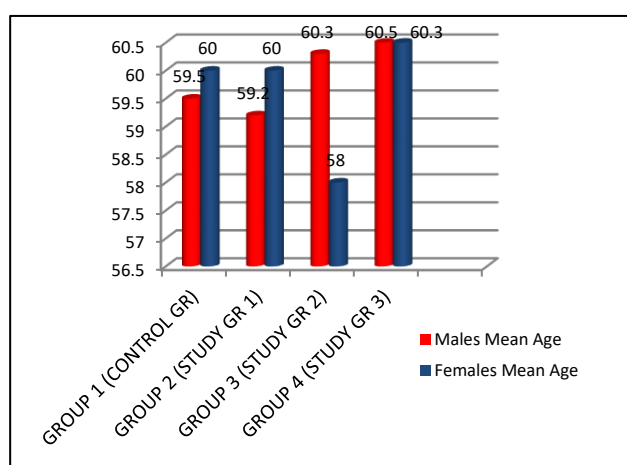
**Statistical analysis**

The data obtained from the study are presented as mean with standard deviation and percentage and results are assessed by using Student’s t test; p<0.05 values are considered as statistical significance

**RESULTS**

**Clinical characteristics**

This study consisted of 120 OA patients with 76 females (63.33%) and 44 males (36.67%) with age ranging from 55 to 67 years with a mean of 59.73 years ±7.3. In males age was between 56-67 years with mean of 59.88±6.2 years, while in female patients it ranged between 55-65 years with a mean of 59.58±5.4 years.



**Figure 1: Mean age of patients in years.**

**Table 1: Age of the patients and duration of OA of the knee.**

Parameters		Group 1 (Control Gr)	Group 2-Study Gr 1 (Glucosamine)	Group 3-Study Gr 2 (Methylsulfonyl methane)	Group 4-Study Gr 3 (Glucosamine and Methylsulfonyl methane)
Age (years)	Range	55-65	57-65	56-66	55-67
	Mean	58 ±3.5	59.5±6.5	59±5.5	60 ±7
Osteoarthritis duration (years)	Range	1-5	1-4	1-5	2-6
	Mean	2.61±1.2	2.63±1.3	2.58±1.7	2.67±1.5

**Table 2: Grading of OA of the knee.**

Kellgren and Lawrence grades		Group 1 (Control Gr)	Group 2 –Study G1 1 (Glucosamine)	Group 3-Study Gr 2 (Methylsulfonyl methane)	Group 4-Study Gr 3 (Glucosamine and Methylsulfonyl methane)
Grade 1	No.	12	11	10	10
	%	40%	36.67%	33.33%	33.335%
Grade 2	No	18	19	20	20
		60%	63.33%	66.67%	66.67%

Each group consisted of 30 patients with 19 females (63.33%) and 11 males (36.675%). (Table 1, Figure 1)

The duration of OA in this study ranged from 1 to 6 years with a mean of 2.62±1.4 years with no difference of statistical significance among the four groups. (Table 1)

In this study all the OA patients were either Kellgren and Lawrence grade 1 or 2. Grade 1 osteoarthritis was present in 43 (35.83%) patients and grade 2 osteoarthritis in 77 (64.17%) patients with no difference of statistical significance among the groups. (Table 2)

**Initial baseline scores**

In this Study the Initial baseline WOMAC pain scores in study groups ranged between 10-12 with a mean of 11 while in control Gr it was between 10-11 with a mean of 10.5. (Table 3). Similarly the WOMAC total aggregate scores in study groups ranged between 33-37 with a mean of 34.66 and in Control Gr it ranged between 33-35 with a mean of 34 with no difference of statistical significance. (Table 4)

**After 4 weeks of therapy**

The mean WOMAC pain scores decreased to 10 (9.09%), 9.5 (9.52%) and 10 (13.05%) in study Grs 1, 2, 3 respectively and in control Gr it decreased to 10 (4.76%) (Tables 3, 5) while the mean WOMAC total aggregate scores decreased to 32.0 (5.88%), 30.0 (14.28%) and 29.0 (17.14%) in study Grs 1, 2, 3 respectively and in control Gr it decreased to 33 (2.94%) (Tables 4, 6).

**Table 3: WOMAC pain scores.**

Joint Pain Scores		Group 1 (Control Gr)	Group 2--Study Gr 1 (Glucosamine)	Group 2--Study Gr 2 (Methylsulfonyl methane)	Group 4--Study Gr 3 (Glucosamine and Methylsulfonyl methane)
<b>Initial Baseline</b>	Range	10-11	10-12	10-11	11-12
	Mean	10.5±1.04	11±1.01	10.5±1.03	11.5±1.04
<b>After 4 weeks</b>	Range	10-11	9-12	9-10	8-12
	Mean	10 ±1.03	10±1.1	9.5±1.02	10±1.01
<b>After 8 weeks</b>	Range	9-10	9-10	8-9	7-9
	Mean	9.5±1.02	9±0.71	8.5±1.04	9±0.612
<b>After 12 weeks</b>	Range	8-9	7-8	6-8	6-7
	Mean	9±1.03	8±1.02	7±1.04	7±1.02

**Table 4: WOMAC total aggregate scores.**

Total Aggregate Scores		Group 1 (Control Gr )	Group 2--Study Gr 1 (Glucosamine)	Group 3--Study G 2 (Methylsulfonyl methane)	Group 4--Study Gr 3 (Glucosamine and Methylsulfonyl methane)
<b>Initial Baseline</b>	Range	33-35	33-35	34-36	33-37
	Mean	34±11.02	34±15.02	35±16.03	35±12.03
<b>After 4 weeks</b>	Range	32-34	31-33	31-32	30-31
	Mean	33±12.04	32±14.01	30±15.01	29±15.01
<b>After 8 weeks</b>	Range	31-33	30-31	27-29	26-28
	Mean	32±11.04	30±0.72	28±14.04	26±14.44
<b>After 12 weeks</b>	Range	30-32	26-28	24-26	21-23
	Mean	31±12.05	26±12.13	25±13.12	22±17.02

**Table 5: Effect of therapy on WOMAC pain scores.**

Joint Pain Scores	Group 1 (Control Gr )	Group 2--Study Gr 1 (Glucosamine)	Group 3--Study Gr 2 Methylsulfonyl methane)	Group 4--Study Gr 3 (Glucosamine and Methylsulfonyl methane)
<b>Initial Basal line mean</b>	10.5	11	10.5	11.5
<b>After 4 wks</b>	10	10	9.5	10
<b>% of ↓</b>	-0.5;4.76%	-1;9.09 %	-1;9.52%	-1.5;13.05%
<b>After 8wks</b>	9.5	9	8.5	9
<b>% of ↓</b>	-1;9.52%	-2;18.18% (p<0.05)	-2;19.05% (p<0.05)	-2.5;21.74% (p<0.01)
<b>After 12 wks</b>	9	8	7	7
<b>% of ↓</b>	-1.5;14.28% (p<0.05)	-3;27.27% (p<0.01)	-3.5;33.33% (p<0.01)	-4.5;39.13% (p<0.01)

**After 8 weeks of therapy**

Similarly, the mean WOMAC pain scores decreased to 9.0 (18.18%), 8.5 (19.05%), 9.0 (21.74%) in Study groups 1, 2, 3 respectively while in Control Gr it decreased to 9.5 (9.52%). (Tables 3, 5).

So also the mean WOMAC Total aggregate scores decreased to 30.0 (11.76%), 28.0 (20.0%), 26.0 (25.71%) in Study groups 1, 2, 3 respectively while in Control Gr it decreased to 32 (5.88%). The relief of pain and physical function was statistically significant in all Study groups.

**After 12 weeks of therapy**

The mean WOMAC Pain scores decreased to 8 (27.27%), 7.0 (33.33%) and 7.0 (39.13%) respectively in Study groups 1, 2, 3 and in Control Gr it decreased to 9.0(14.28%) while the mean WOMAC Total aggregate scores decreased to 26.0 (23.53%), 25.0 (28.57%), 22.0

(37.14%) in study groups 1, 2, 3 respectively and it decreased to 31 (8.82%) in Control Gr.

The joint pains decreased in all groups but more significant in Study groups with improvement in physical functions as compared to Control Gr. Besides this was statistically more significant in Study Gr 3.

**Table 6: Effects of therapy on WOMAC total aggregate scores.**

Total Aggregate Scores)	Group 1 (Control Gr)	Group 2--Study Gr 1 (Glucosamine)	Group 3--Study Gr 2 Methylsulfonyl methane)	Group 4--Study Gr 3 (Glucosamine & Methylsulfonyl methane)
<b>Initial basal line mean</b>	34	34	35	35
<b>After 4 wks</b>	33	32	30	29
<b>% of ↓</b>	-1;2.96%	-2;5.88 %	-5;14.28%	-6;17.14%
<b>After 8wks</b>	32	30	28	26
<b>% of ↓</b>	-2;5.88%	-4;11.76%	-7;20.0% (p<0.05)	-9;25.71% (p<0.01)
<b>After 12 wks</b>	31	26	25	22
<b>% of ↓</b>	-3;8.82%	-8;23.53% (p<0.05)	-10;28.57% (p<0.01)	-13;37.14% (p<0.01)

**Table 7: Adverse side effects.**

Adverse side effects	Group 1 (Control Gr)	Group 2 –Study G1 1 (Glucosamine)	Group 3-Study Gr 2 (Methylsulfonyl methane)	Group 4-Study Gr 3 ( Glucosamine & Methylsulfonyl methane)
<b>Gastrointestinal</b>	No. 8	1	2	2
	% 26.67%	3.33%	6.67%	6.67%

**Adverse effects of the drugs**

In Study Grs 5.56% of patients (one in study Gr 1, two each in Study Gr 2, 3) had mild gastrointestinal (nausea, vomiting, epigastric pain) side effects which was not statistically significant; while in Control Gr gastrointestinal adverse side effects occurred in 26.67% patients (Table 7).

**DISCUSSION**

In this study after 12 weeks of therapy there was very significant decrease of mean WOMAC pain scores (27.27-39.13%) and mean WOMAC Total aggregate scores (23.53-37.14%) in all Study groups of patients (p<0.05-p<0.001) treated with Glucosamine or MSM or in combination as compared to 14.28% decrease of mean WOMAC pain scores and 8.82% decrease of mean WOMAC total aggregate scores in control Gr of patients treated with conventional therapy.

The relief of pain and improvement in the physical functions including stiffness of knee joints were better and superior in patients treated with combination of Glucosamine and MSM.

Lubis et al similarly found significant decrease of WOMAC scores and clinical improvement in OA patients treated with combination of Glucosamine, MSM and chondroitin sulfate after 12 weeks as compared to Glucosamine and chondroitin sulfate and Placebo group. However they also found that glucosamine-chondroitin sulfate was not effective in reducing joint pain in OA compared to placebo.<sup>17</sup>

Similarly, Usha et al reported efficacy of Glucosamine as well as MSM as compared to placebo in the treatment of knee OA, but concluded that the combination of Glucosamine and MSM was more effective in reducing pain and swelling, walking time and joint mobility as compared to individual treatments.<sup>18</sup>

Pujalte et al in a small number of patients showed that oral Glucosamine resulted in substantial improvement in patients with osteoarthritis.<sup>19</sup> So also Reichelt et al have reported that with intramuscular Glucosamine 400 mg twice weekly, an impressive decrease in pain and functional limitation was achieved between the fourth and fifth weeks of treatment.<sup>20</sup> However Hochberg MC et al did not reported any efficacy and decrease of WOMAC scores with Glucosamine in their study as compared to

Placebo.<sup>21</sup> So also Messier et al did not find any difference in the physical function, mobility, and pain between control and the Glucosamine group in their study.<sup>22</sup>

Pagonis et al concluded that the decrease of pain in OA patients was due to analgesic effect of MSM in their study, while Kim et al with high and variable dosage of oral MSM for 12 weeks found a 25.1% decrease in WOMAC pain scores.<sup>23,24</sup> So also Debbi et al found that patients with OA of the knee treated with 3.375 g/d of MSM for 12 weeks showed a significant improvement in the function and total score scales of the WOMAC (21.1% decrease) compared to a placebo-controlled group.<sup>25</sup>

The results of the present study also indicate that all treatments in all Study groups were well tolerated and the adverse effects observed were predominantly minor gastrointestinal symptoms that did not necessitate withdrawal of treatment.

Similarly Lubis et al, Usha et al, Kim et al and Debbi et al reported minor adverse events mainly GI related in their studies.<sup>17,18,24,25</sup>

The long-term treatment and follow up (for at least 6 months for each patient) for more number of OA patients with these Complementary and Alternative Medicines (CAM) in this study was not possible due to covid-19 pandemic and was restricted to 12 weeks of duration. A long-term treatment and follow up with these CAM may halt the progress of the disease due to their natural anti-inflammatory, analgesic and chondroprotective properties which will be more beneficial than conventional treatment with NSAIDs.

## CONCLUSION

In India OA is the most frequent joint disease progressing to become the osteoarthritis capital of the world, similar to Diabetes mellitus. High incidence of osteoarthritis is due to ever increasing numbers of obesity, lack of balanced diet and regular exercise, not getting enough exposure to sunlight and increase in smoking due to life style changes. Conventional treatment of OA with NSAIDs do not improve the underlying pathology of the disease, but instead are often associated with serious adverse effects; hence the need for safe alternative treatment options which are effective and well-tolerated with minimal or no side effects. This study showed Glucosamine and MSM are effective in the management of OA of knee with minimal and minor adverse effects and are safe health supplement to NSAIDs. The combination therapy of Glucosamine and MSM achieves superior clinical efficacy as compared to monotherapy of either of them as compared to Control Gr. The combination therapy may halt the progress of the disease due to their natural anti-inflammatory, analgesic and

chondroprotective properties in long term treatment and follow up.

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**APPENDIX**

**Western Ontario and McMaster university Osteoarthritis (WOMAC) Index osteoarthritis index**

SCORES	None=0	Mild=1	Moderate=2	Severe=3	Extreme=4
<b>1. PAIN SCORES (20):</b>					
<b>a) Indicate the amount of pain experienced in your knees in the past 48hrs with the following activities</b>					
1. Walking on a Flat surface 2. Going Up or Down Stairs 3. At night while in Bed 4. Sitting of Lying 5. Standing upright					
<b>b) Describe Level of Pain in the past 48hrs</b>					
1. Right Knee 2. Left Knee					
<b>2. STIFFNESS SCORES (8): Indicate the degree of stiffness of knees with the following activities</b>					
1. Stiffness of knee s after first awakening in the Morning 2. Stiffness of knee s after Sitting, Lying or Resting later in the day					
<b>3. PHYSICAL FUNCTION SCORES (68): Indicate the degree of difficulty with following activities</b>					
1. Descending Stairs 2. Ascending Stairs 3. Rising from sitting 4. Standing 5. Sittning 6. Bending to the floor 7. Walking on a Flat surface 8. Getting in or out of car 9. Going shopping 10. Putting on socks/stockings 11. Taking off socks/ stockings 12. Rising from bed 13. Lying in bed 14. Getting on/out of bath 15. Getting on/off toilet 16. Heavy Domestic duties(mowing the lawn, lifting heavy grocery bags) 17. Light Domestic duties (tidying a room, dusting, cooking)					