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Effectiveness Of Maitland's Mobilization And Conventional Physical Therapy On Synovial Biomarkers In Patients With Knee Osteoarthritis; A Randomized Control Trial

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ABSTRACT

Objectives: To determine the effects of Maitland mobilization and conventional physical therapies on synovial biomarkers, pain, and functional performance in the patients with knee osteoarthritis.

Methods:

A total of 70 eligible patients with knee osteoarthritis, randomly allocated into Group "A" (n=36) undergoing conventional physiotherapy and Group "B" (n=36) implementing Maitland's mobilization for three months. Hyaluronic acid and C-reactive protein levels measured by ELISA method, pain by Numeric pain rating sale and functional performance measured on Western Ontario and McMaster Universities Arthritis Index, instituted at baseline, 6th and 12th weeks of treatment.

Results:

Comparison between group A and B was found non-significant with p-value >0.05 in NPRS, WOMAC and C Reactive Protein at baseline time point. At 18th week assessment, NPRS had

statistically significant differences by p-value=0.026, whereas WOMAC, C Reactive Protein and Hyaluronic Acid were also indicated highly significant difference by p-value <0.001.
For within group comparison at different time points (at base line, 6th, 12th and 18th week) in group A and B, statistically significant difference with p-value <0.001 in NPRS, WOMAC, C Reactive Protein and Hyaluronic Acid for Synovial biomarkers was observed.
Conclusion: Maitland mobilization results in significant reduction in the values of inflammatory biomarkers including hyaluronic acid and C-reactive protein as well as pain and improvements in functional performance as compared to the conventional physical therapy management in subjects with knee osteoarthritis.

Keywords: Synovial Biomarkers, C-reactive protein, Hyaluronic acid, Pain, Physical Functional Performance, knee Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA), a common variety of arthritis, is an inflammatory disease of synovial joints characterized by low level of inflammation. Hence, it has a common etiology of chronic pain as well as physical disability, resulting in financial burden and is characterized by degeneration of articular cartilage resulting in anatomical as well as physiological changes in tissues of the joints. [1] It has a potential to cause wear and tear of the joint structures and is now accepted as an inflammatory and biochemical disease, which is also associated with co-morbidities as well as death.[2] Among the conditions causing disability, Rheumatic and Musculoskeletal diseases (RMDs) are highly prevalent affecting 27.7% population, among which low back pain and osteoarthritis top the list with prevalence range of 12.15 to 13.1% and 11.8% to 12.7% respectively, with osteoarthritis being the main factor, limiting the physical activities.[3] The pathogenesis and progression of OA are influenced by several factors including bone shape and joint dysplasia, synovitis, innate immunity,[4] altered metabolism of lipids**,** adipokines, inflammatory mediators and low-grade inflammation induced by metabolic syndrome.[5] Osteoarthritis of knee is characterized by chronic pain, functional disability and even fatigue, [6] which negatively affects sleep and may lead towards depression.[7] Also, metabolic activity related to synovial tissue and osteophytes may have relation to pain and destruction of articular cartilage.[8]

Biochemical markers are the means to measure a potential change in process of cartilage or bone turnover. Some studies on osteoarthritis, suggest that biochemical markers might be useful in detecting or identifying or measuring high-risk patients.[2] Several biomarkers have been identified in association with osteoarthritis and rheumatoid arthritis including hyaluronic acid and C reactive protein .[6] The effects of exercise have previously been studied however; manual therapy has not been specifically focused. Manual therapy including Maitland mobilization and Mulligan's mobilization with movement (MWM) has shown positive effects in improving pain and function in patients with knee osteoarthritis.[9] A study conducted on the effects of exercise, weight, and diet changes showed that there are positive effects of exercise on the progression of knee osteoarthritis

as well as the inflammatory biomarkers.[10] According to Boffa A et al. synovial fluid biomarkers affect the progression of knee OA. These biomarkers are significant because of their direct contact with the articular cartilage and the synovial membrane.[11] Bricca et al. studied the effects of exercise on biomarkers in osteoarthritis and reported that exercise was harmful in modulating the biomarkers, but there is a lack of current evidence on the impact of exercise on the inflammatory biomarkers. [12] Modulation of these biomarkers can be an important factor in any therapeutic method used to manage the knee osteoarthritis.

There are many synovial fluid biomarkers, however scientific evidence in connection with the effect of biomarkers have gained limited support with lot of conflicting evidences, mandating further research .[11] There is a need to establish the impact of manual therapy on the synovial of biomarkers, pain sensation and functional performance. Hence this study was conducted to determine the effects of Maitland mobilization and conventional physiotherapy on modulation of synovial biomarkers, pain, and functional performance in subjects with knee osteoarthritis. This study has significant importance both for regulating clinical practices as well as research.

MATERIALS AND METHODS

Study Design

Design of this study was parallel group, single blinded, randomized controlled trial with 1:1 for both the groups. The study was approved by Research Ethical Committee, Institutional Review Board and Board of Advanced Studies and Research Isra University, Islamabad Pakistan, on 26/03/2018. The protocol of the study was registered on WHO and ICMJE recognized ISRCTN registry (ISRCTN17691569). The study was conducted according to the consolidated standards of reporting trial (CONSORT) guidelines.

Sample size calculation

Total sample size of study was 76 that were calculated by WHO Geneva software by KC Lun and Peter Chaim, National University of Singapore. In this 95% confidence interval and 80% power of the study was applied. Effect size was used 0.48 and standard deviation was 1 (ref of article). Following formula was used to determine the sample size;

$$n = \frac{2S.D^2\left(Z1-\frac{\alpha}{2}+Z1-\beta\right)^2}{(\mu 1-\mu 2)^2}$$

n=69 + 10% expected dropouts

n=76 total participants were selected

Study Settings

Sample was recruited from Anwar clinic and lab tests were done at Al-Noor diagnostics, Lahore, Punjab, Pakistan, over a period of 6 months from 1st January to 30th June 2018. Lahore is a 2nd biggest city of Pakistan and 1st in Province Punjab.

Participants

All participants were selected after the assessment of inclusion and exclusion criteria

Inclusion Criteria

Sample of N=76 patients with knee osteoarthritis of either genders, aged 50 to 70 years diagnosed on clinical and radiographic basis were recruited, while adhering to principles of the Declaration of Helsinki with written informed consent of the patients. Subjects fulfilling the American College of Rheumatology criteria for Primary osteoarthritis,[13] pain since last 3 months, Grade 2 and 3 of Kellgren-Lawerence classification system for knee osteoarthritis,[14] and BMI between 19 to 28 kg/m^2 were included in the study who were attending the clinic and signed informed consent to be willing to participate in study.

Exclusion Criteria

Patients with trauma within last 6 months, reported uncontrolled diabetes mellitus and hypertensive disease, Associated inflammatory joint disease such as septic arthritis and R.A Patients was taking cover of oral or intra-articular Hyaluronic acid and alendronate and/ or sulfonate compounds of sodium were excluded. Pregnant women and those female who were receiving any treatment that can interfere with bone metabolism such as hormone replacement therapy after menopause, Patients with undiagnosed pathology or impairment, recent surgery, mixed arthritis condition, patients with spinal problems.[(1, 2)]

Randomization and Blinding

Patients with knee osteoarthritis were selected through simple random sampling technique by in step 1 as per inclusion and exclusion criteria. Then, Patients were randomly allocated into 2 equal groups with 1:1 (Group A=35 and Group B=35) with the help of lottery method. Consecutively, 1st selected patients were included in Group A; that was interventional group and 2nd selected patient put into Group B that was controlled group with applying conventional physical therapies. It was a single blinded study in which assessor was blinded. It is not sure that this blindness is maintained throughout the study due to potential disadvantages of feasibility for recruiting independent assessors. Patients and Clinicians are already difficult to blind due to nature of treatment.

Intervention

Manual Therapy based on Maitland's Mobilization was applied on patients of group A, whereas Conventional physical therapies were used on the participants of Group B.

Group A: Maitland's Mobilization Group

Mobilization based on Maitland concept was applied to the participants. Protocol may vary slightly patient to patient, however, general treatment protocol is as following:[(3)] Frequency of exercise is three days a week on alternative day basis. Intensity is Grade I and II based which is progressed to

Grade III of Maitland's Grading, in order to achieve, restore, compensate or prevent from stiffness and flexibility issues. Time of oscillations is 2 or 3 oscillations per second for 1 to 2 minutes.

Patient Position: Patient was lying supine on treatment table with affected knee towards clinician standing side. The knee was in resting position of 25° flexion. A wedge roll may be used to maintain position or support below knee.(3)

Patient Education: Patient was educated regarding the procedure. Precautions of pain provocation were briefed to the patient.(3)

Therapist/ Clinician Position: The therapist is in standing position, facing towards patient on the side of patient's leg under treatment. The therapist holds femur to fix at its distal end, while the tibia is oscillated with other hand as per protocol mentioned above.(3)

Group B: Conventional Physical Therapies Group

This included Ottawa Panel Evidence-Based Clinical Practice Guidelines for Therapeutic Exercises(4), after essential modifications to fit in Pakistan's framework of practice. The hallmark of treatment was covering pain and daily functions. Electrophysiological agents and muscle stabilization exercises were used.(5) Electrical Heating Pads and Pulse Shortwave Diathermy were applied for 15 minutes each. Followed by exercises including knee isometrics, knee pressing, knee squeezing and mid-range straight leg raises were performed.(6) Transcutaneous electrical nerve stimulator was given for 10-15 additional minutes.(7)

Outcome measures

The primary outcome measures were Synovial biomarkers including Hyaluronic acid and C reactive proteins, knee pain, and functional performance. Tools used to collect data of primary outcome measures included ELISA Test (Kits) for synovial biomarkers; Numeric pain rating scale (NPRS) for knee pain with 0 to 10 score, where patients had to mark the pain on a scale of 0 to 10; 0 indicated no pain whereas 10 score showed maximum and unbearable pain and Western Ontario and McMaster Universities Arthritis Index (WOMAC) for the measurement of the functional disability or performance of the patients and consists of 24 items and 3 subscales including pain, stiffness, and physical functions and scored on a 5 point Likert scale. The score ranges for pain, stiffness and physical function are 0-20, 0-8, and 0-68 respectively. A higher score indicates a higher level of impairment. [16]

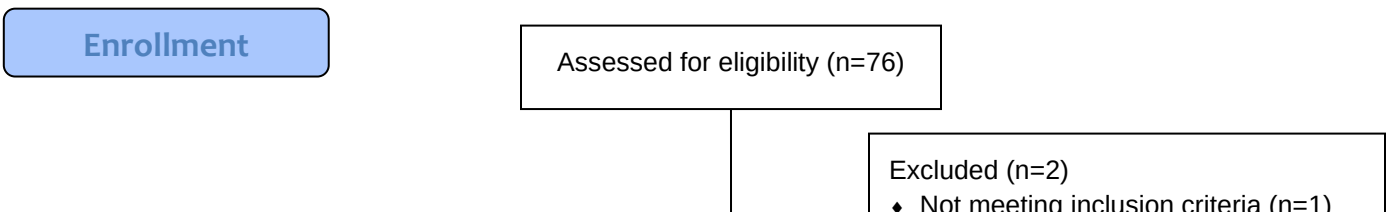

Figure 1: **CONSORT Flow Diagram**

Statistical Analyses

Of the N=76 cases included in the study 3 dropped out from group A and 3 from group B, hence 70 cases with 1:1 were included for data analysis by SPSS version 24. Descriptive analyses of data are displayed in table 1. For qualitative variables, frequencies and percentages are calculated. For quantitative data, first of all normality of data were assessed by Kolmogorov-Smirnov test (K-S test) and data were not found normality distributed. So, for central tendency, median was preferred and Inter quartile range (IQR) was calculated for dispersion. Mean±S.D were also displayed but not preferred. For Inference, it was decided to perform non-parametric tests after Kolmogorov-Smirnov test (p-value<0.05). Mann-Whitney U test was used for between-group comparison and Friedman Test was applied for within group analysis to compare the median at different time points (at base line, 6^{th}, 12^{th} and 18^{th} week). Data were analyzed at 95% confidence interval and p-value ≤0.05 was considered as significant value.

RESULTS OF STUDY

Total participants were 70 with 1:1 ratio, to group A, Mobilization was given whereas Conventional therapy was given to Group B. 20 (57.10%) males and females were treated by Mobilization and Conventional respectively.

Table 1: Descriptive analysis of demographic characteristics of the participants

Characteristics	Response / Units	Group A (Mobilization) , n=35		Group B (Conventional) , n=35	
		Mean ± S.D	Median (IQR)	Mean ± S.D	Median (IQR)
Gender, n (%)	Male	20(57.10)		15(42.90)	
	Female	15(42.90)		20(57.10)	
Age	Years	59.86±3.04	61(5)	61.29±5.33	65(11)
Knee Pain	NPRS	6.71±0.89	6(2)	6.14±0.85	6(2)
Body Mass Index	Kg/m^2	20.86±0.64	21(1)	25±2.10	26(4)
RBG	Value	123.29±14.43	127(28)	127.43±21.46	128(35)
FBG	Value	110.57±6.88	111(9)	113.14±5.98	114(11)
Systolic Blood Pressure	mmHg	129.29±5.71	130(5)	125.71±7.39	120(10)

Diastolic Blood Pressure	mmHg	97.14±7.10	100(10)	90±5.42	90(0)
ESR	Rate	43.29±5.47	44(7)	45.29±9.65	46(21)

The above table shows that, median (IQR) were 61(5) and 65(11) years age of participants in Group A and B respectively. Knee pain that was assessed by NPRS was equal with average 6(2) in both groups. BMI was assessed 21(1) and 26(4) kg/m^2, random blood glucose (RBG) recorded 127(28) and 128(35), fasting blood glucose (FBG) was 111(9) and 114(11), Systolic Blood Pressure recorded 130(5) and 120(10) mmHg, Diastolic Blood Pressure assessed 100(10) and 90(0) mmHg and ESR was found 44(7) and 46 (21) in both groups A and B that were treated by Mobilization and Conventional therapy respectively shown in table 1.

Table 2: Between and within group comparison of pain, disability and Synovial biomarkers

Assessments	Mobilization		Conventional		Mann-Whitney U value	Z-Score	P-value++
	median (IQR)	Mean Rank	median (IQR)	Mean Rank			
NPRS at Baseline	7(1)	33.71	7(2)	37.29	550	-0.8	0.424
NPRS at Week 6th	5(1)	29.79	5(1)	41.21	412.5	-2.56	0.010*
NPRS at Week 12th	2(1)	20.14	4(2)	50.86	75	-6.54	<0.001*
NPRS at 18th	2(0)	31.21	2(1)	39.79	462.5	-2.22	0.026*
Chi -Square Test	99.27		102.13				
P-Value$	<0.001*		<0.001*				
WOMAC at Baseline	83(3)	31.36	84.85(1)	39.64	467.5	-1.71	0.086
WOMAC at 6th Week	59.10(8.33)	21.93	63.64(3.03)	49.07	137.5	-5.61	<0.001*
WOMAC at 12th Week	46.21(6.06)	18	58.33(2.13)	53	0	-7.25	<0.001*
WOMAC at 18th Week	55.30(6.82)	23.36	57.58(2.27)	47.64	187.5	-5.04	<0.001*
Chi -Square Test	94.71		96.43				
P-Value$	<0.001*		<0.001*				
C Reactive Protein at Baseline	9(2)	33.71	9(2)	37.29	550	-0.78	0.435

C Reactive Protein at 6th Week	8(2)	29.79	8(1)	41.21	412.5	-2.47	0.014*
C Reactive Protein at 12th Week	7(1)	34.43	7(1)	36.57	575	-0.47	0.637
C Reactive Protein at 18th Week	5(1)	27.64	6(2)	43.36	337.5	-3.45	<0.001*
Chi -Square Test	91.52		105				
P-Value$	<0.001*		<0.001*				
Hyaluronic Acid at Baseline	100(20)	43	90(20)	28	350	-3.21	<0.001*
Hyaluronic Acid 6th Week	95(15)	44.07	80(20)	26.93	312.5	-3.6	<0.001*
Hyaluronic Acid 12th Week	90(10)	42.64	75(20)	28.36	362.5	-3.03	0.002*
Hyaluronic Acid Follow Up	82(5)	44.07	76(7)	26.93	312.5	-3.58	<0.001*
Chi -Square Test	94.32		87.54				
P-Value$	<0.001*		<0.001*				

"*" indicate the statistically significant difference
"++" indicate that P-Value was calculated by Non-parametric Mann-Whitney U Test which was applied to assess the comparison between two treatments or groups
"$"indicate that P-Value was calculated by Non-parametric Friedman Test which was applied to compare the median at different time points (at base line, 6th , 12th and 18th week) for Within group comparison

For between groups comparison, non-parametric Mann-Whitney U Test whereas for within group comparison non-parametric Friedman Test was applied to compare the median at different time points (at base line, 6th, 12th and 18th week) or for within group comparison

Comparison between group A with mobilization and B with conventional therapy in **table 2** was found non-significant with p-value >0.05 in NPRS, WOMAC and C Reactive Protein whereas Hyaluronic Acid was significant with p-value ≤ 0.05 at baseline time point. At 6th week, in NPRS, WOMAC, C Reactive Protein and Hyaluronic Acid were statistically significant with p-value =0.010, <0.001, 0.014 and <0.001 respectively. NPRS and WOMAC was highly significant with p-value <0.001, and Hyaluronic Acid was also significant with p-value = 0.002, whereas C Reactive Protein was non-significant with p-value =0.637 at 12th week. At 18th week assessment, NPRS had statistically significant difference by p-value=0.026, whereas WOMAC, C Reactive Protein and Hyaluronic Acid were also indicated highly significant difference by p-value <0.001.

For within group comparison at different time points (at base line, 6th, 12th and 18th week) in group A with mobilization and B with conventional therapy was observed statistically significant

difference with p-value <0.001 in NPRS for pain , WOMAC for functional disability, C Reactive Protein and Hyaluronic Acid for Synovial biomarkers that are also shown in **table 2.**
Pair wise comparison was also done by Wilcoxon rank test. Significance difference was observed with p-value <0.001 for all pairs of different time point baseline, 6^{th}, 12^{th} and 18^{th} week in NPRS, WOMAC , C Reactive Protein and Hyaluronic Acid at different time point that is shown in table 3.

Table: 3 Pair wise comparison through multiple comparison test

Pair wise comparison in within group	Mobilization, n=35			Conventional, n=35		
	Mean Rank	Z	P-value	Mean Rank	Z	P-value
NPRS at Week 6 - NPRS at Baseline	18.00	-5.6	<0.001*	18.00	-5.6	<0.001*
NPRS at Week 12 - NPRS at Baseline	18.00	-5.3	<0.001*	18.00	-5.4	0.001*
NPRS at Follow Up - NPRS at Baseline	18.00	-5.4	<0.001*	18.00	-5.23	<0.001*
NPRS at Week 12 - NPRS at Week 6	18.00	-5.23	<0.001*	15.50	-4.98	<0.001*
NPRS at Follow Up - NPRS at Week 6	18.00	-5.3	<0.001*	18.00	-5.24	<0.001*
NPRS at Follow Up - NPRS at Week 12	13.00	-3	0.003	15.50	-5.15	<0.001*
WOMAC at 6th Week - WOMAC at Baseline	18.00	-5.16	<0.001*	18.00	-5.16	<0.001*
WOMAC at 12th Week - WOMAC at Baseline	18.00	-5.16	<0.001*	18.00	-5.16	<0.001*
WOMAC at Follow Week (18th Week) - WOMAC at Baseline	18.00	-5.18	<0.001*	18.00	-5.16	<0.001*
WOMAC at 12th Week - WOMAC at 6th Week	18.00	-5.18	<0.001*	18.00	-5.23	<0.001*
WOMAC at Follow Week (18th Week) - WOMAC at 6th Week	25.50	-3.2	<0.001*	18.00	-5.19	<0.001*
WOMAC at Follow Week (18th Week) - WOMAC at 12th Week	0.00	-5.18	<0.001*	19.00	-2.64	0.008*
C Reactive Protein Week 6 - C Reactive Protein at Baseline	18.00	-5.6	<0.001*	13.00	-5	<0.001*
C Reactive Protein Week 12 - C Reactive Protein at Baseline	18.00	-5.41	<0.001*	18.00	-5.42	<0.001*

C Reactive Protein at Follow - C Reactive Protein at Baseline	18.00	-5.26	<0.001*	18.00	-5.19	<0.001*
C Reactive Protein Week 12 - C Reactive Protein Week 6	10.50	-4.47	<0.001*	18.00	-5.92	<0.001*
C Reactive Protein at Follow- C Reactive Protein Week 6	18.00	-5.23	<0.001*	15.50	-4.86	<0.001*
C Reactive Protein at Follow- C Reactive Protein Week 12	18.00	-5.4	<0.001*	17.50	-4.3	<0.001*
Hyaluronic Acid Week 6 - Hyaluronic Acid at Baseline	17.50	-4.3	<0.001	15.50	-4.93	<0.001*
Hyaluronic Acid Week 12 - Hyaluronic Acid at Baseline	18.00	-5.21	<0.001	18.00	-5.23	<0.001*
Hyaluronic Acid at Follow Week (18th Week) - Hyaluronic Acid at Baseline	18.00	-5.18	<0.001	18.00	-5.19	<0.001*
Hyaluronic Acid Week 12 - Hyaluronic Acid Week 6	15.50	-4.98	<0.001	18.00	-5.6	<0.001*
Hyaluronic Acid at Follow Week (18th Week) - Hyaluronic Acid Week 6	18.00	-5.19	<0.001	20.50	-4.94	<0.001*
Hyaluronic Acid at Follow Week (18th Week) - Hyaluronic Acid Week 12	13.00	-4.5	<0.001	13.00	-2.64	0.008*
“*” indicate the statistically significant difference "+" indicate that P-Value was calculated by Non-parametric Wilcoxon rank test						

DISCUSSION:

The goal of this study was to find how Maitland mobilization and traditional therapy affects synovial biomarkers, pain, and functional performance in patients with knee osteoarthritis. When compared to the outcomes of standard physical therapy management of knee osteoarthritis, Maitland mobilization demonstrated a substantial reduction in the levels of inflammatory biomarkers such as hyaluronic acid and C-reactive protein, as well as pain and functional performance.

In 2008, SD Chua Jr et al reported Arthritis, Diet and Activity Promotion Trial. This was an 18-month single-blind trial with participants randomized to four groups: diet (D), healthy-lifestyle (HL), exercise (E) and diet plus exercise (D + E). Serum levels of cartilage hyaluronan (HA), oligomeric matrix protein (COMP), transforming growth factor-β1 (TGF-β1) and antigenic keratan sulfate (AgKS) were measured by ELIZA(8). In combined results for all four study groups, the HA levels were found to be positively correlated with Kellgren Lawrence scores (K-L scores) while TGF-β1 levels negatively correlated with K-L scores. Weak associations were noted between change in the biomarkers at 18-months and change in outcome measures that included change in weight with AgKS and COMP and change in WOMAC pain with AgKS. When compared to our study, there were differences in sample size, recruited population in terms of

racial and geographic distribution, time of intervention application with subsequent follow up and outcome measurement tools. They compared the outcomes at 6 and 18 months, while we compared on 6 and 18 week while ELIZA testing was used in both the studies. When they measured biomarker levels at 6 and 18-months with adjustments for baseline values, age, gender, and body mass index (BMI), weak but significant differences between intervention groups were found for mean levels of COMP and TGF-β1. Furthermore, AgKS levels averaged over all groups tended to decrease over time. There were no significant associations of baseline biomarkers and the followup outcomes. While in our study, between group comparison was found non-significant with p-value >0.05 in NPRS, WOMAC and C Reactive Protein at baseline. NPRS, WOMAC, C Reactive Protein and Hyaluronic Acid were statistically significant with p-value =0.010, <0.001, 0.014 and <0.001 respectively at 6^{th} week. At 18^{th} week assessment, NPRS had statistically significant differences by p-value=0.026, whereas WOMAC, C Reactive Protein and Hyaluronic Acid were also indicated highly significant difference by p-value <0.001. For within group comparison at different time points (at base line, 6, 12 and 18 week) in both group was observed statistically significant difference with p-value <0.001 in NPRS, WOMAC, C Reactive Protein and Hyaluronic Acid for Synovial biomarkers.

Alessio Bricca et al. published a systematic review and meta-analysis in 2018, which reviewed the changes in cartilage biomarkers as a result of exercise treatment in individuals who were at risk for or had already acquired knee osteoarthritis. According to the findings of this study, exercise treatment has no effect on the amount of molecular biomarkers linked to inflammation or cartilage degradation when cartilage deteriorates. The results of this investigation backed with the conclusions of the primary and sensitivity analyses, which indicated no change or reduction in biomarker levels there was non-significant decrease in CRP. The quality of evidence was found low as less number of RT's were found on the subject (9). In the current study, it was discovered that NPRS had a statistically significant difference with a p-value of 0.026 in the Maitland mobilization group, whereas WOMAC, C Reactive Protein, and Hyaluronic Acid had a highly significant difference with a p-value of 0.001 in the Maitland mobilization group.

In 2019, Harry M. Roberts and o authors conducted an invited review to determine the basic mechanism of changes in joint biomarkers as a result of acute and chronic exercise. In physiologic and pathological illnesses, the time course and mechanisms of change in biomarkers of joint metabolism exists. Biomarkers for bone metabolism, synovium, and inflammation, for example, are less well characterized. Multiple biomarkers that offer information on the numerous components associated to joint health, as shown in osteoarthritis research, and which include indicators of synthesis, degradation, and inflammation, still need to be investigated further. The suggested to define normal and abnormal change in biomarkers in response to exercise therapy According to the findings of this study, exercising for a long time may result in a greater reaction in serum cartilage oligomeric matrix protein (COMP), which can last for many days.(10) They studied effects of acute loading on COMP while we evaluated changes in CRP with Maitland mobilizations. Levels of CRP in the Maitland mobilization group were considerably lowered in the current trial, with a p value of 0.435 at baseline and 0.001 at the 18th week, which is consistent

with the previous study. In addition, at the 18th week of therapy, the value of Hyaluronic Acid was less than 0.05, which is consistent with the previous study.

Another study published in 2011 found a link between the effects of aerobic exercise and the amount of systemic inflammation in various disorders. The study also found that persons who completed prolonged weight-bearing workouts had higher levels of COMP.(11) This study differs with the findings of the current study in terms of different parameters of measurement. We found a significant difference in p values of NPRS, WOMAC, and inflammatory biomarker values from baseline P Values more than 0.005 to P Values less than 0.05. When compared to patients who underwent standard treatment, the Maitland mobilization group demonstrated greater results.

Ramya V. Rao and colleagues conducted a Randomized Crossover study to observe distinguished effects of Maitland mobilization against Mulligan MWM. They compared two techniques to find which mobilization approach will be more helpful in reducing pain, enhancing mobility, and improving function in the knee OA immediately after the intervention. They discovered no significant differences between Maitland Mobilization and Mulligan MWM in terms of NPRS, TUG, and Pain free Squat Angle (p=0.18, p=0.27, p=0.17), however all outcome measures within the treatments showed significant improvements (p=0.001). Both Maitland mobilization and Mulligan MWM are found equally effective in reducing pain, improving functional mobility and pain-free squat angle in knee osteoarthritis immediately after the treatment.(12) In our study Significant difference was observed in p-value <0.001 for all pairs of different time points including baseline, 6^{th}, 12^{th} and 18^{th} week in NPRS, WOMAC , C Reactive Protein and Hyaluronic Acid at different time point.

Madhura Bhagat et al. published findings of their research in 2019. They compared the effects of Mulligan techniques with sham on a sample of 30 subjects with knee OA. Post-intervention median (interquartile range) NPRS (I group: 4.00 [2.00–5.00]; S group: 6.00 [4.00–7.00]) and TUG scores (I group: 10.9 [9.43–10.45]; S group: 13.18 [10.38–16.00]) showed statistically significant differences between the groups, with the intervention group showing better outcomes (p=0.05). Within the intervention group, the post-intervention NPRS and TUG scores were considerably lower (p=0.05) than the pre-intervention levels. Only the NPRS scores in the sham group showed a statistically significant pre–post shift, but not the TUG scores. Mulligan's approaches were found to be successful in relieving pain and functional mobility in those with knee osteoarthritis. Participants reported pain reduction after sham mobilization, therefore the underlying mechanisms for observed benefits need to be investigated further.(13) The similarity with our study is the same outcome measurement tool for pain i.e NPRS but they expressed in terms of median (interquartile range) and we presented as mean±std.dev; while other differences included a larger sample size and testing of synovial biomarkers. Synovial biomarkers investigation gives a more insight towards the mechanism affecting the changes within the joint.

Stephen Cornish and Jason Peeler published a pilot stud in 2021, which investigated at the effects of a treadmill training regimen with lower body positive pressure support on inflammatory biomarkers and cartilage degeneration in patients with knee osteoarthritis. The findings of this study revealed that individuals could complete a 12-week treadmill training programme with lower

body positive pressure support without experiencing an increase in pro-inflammatory biomarkers, cartilage deterioration, or joint discomfort. Knee pain was decreased in their intervention group (14). The differences with our stud were a smaller sample size and different intervention under investigation. I our stud, at the baseline time point, non-significant outcomes with p-value >0.05 in NPRS, WOMAC, and C Reactive Protein were seen in the Maitland mobilization group and conventional treatment group, however Hyaluronic Acid was significant with p-value 0.05 in both groups. WOMAC, C Reactive Protein, and Hyaluronic Acid were statistically significant in the NPRS at the 6th week, with p-values of 0.010, 0.001, 0.014, and 0.001 correspondingly. NPRS and WOMAC were very significant (p-value 0.001), as was Hyaluronic Acid (p-value = 0.002), but C Reactive Protein was non-significant (p-value =0.637).

CONCLUSION: Maitland mobilization results in significant reduction in the values of inflammatory biomarkers including hyaluronic acid and C-reactive protein as well as pain and improvements in functional performance as compared to the conventional physical therapy management in subjects with knee osteoarthritis.

Supporting Information

S1 Checklist: Consolidated Standards of Reporting Trials checklist.
(PDF)
S2 Protocol: Study protocol.
(PDF)
S3 Data: (study data)
Authors' Contribution:
AB, CD: Collected data, analysis and its interpretation.
EF: Conception & study design.
GH: Revising it critically and final approval of manuscript.
IJ, KL: Drafting and data interpretation.
All authors have read and approved the manuscript.
The corresponding author XXXXXXXX is responsible and accountable for the accuracy or integrity of the work.

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