ORIGINAL ARTICLE

Effects of glucosamine and chondroitin sulfate supplementation in addition to resistance exercise training and manual therapy in patients with knee osteoarthritis: A randomized controlled trial

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Abstract

Objective: To determine the added benefits of short-term glucosamine and chondroitin sulfate supplementation in combination with manual therapy and resistance exercise training in the management of knee osteoarthritis.

Method: A parallel-design, double-blind randomised controlled trial was conducted from January to September 2020 at the Foundation University Institute of Rehabilitation Sciences and Fauji Foundation Hospital, Rawalpindi, Pakistan, and comprised of knee osteoarthritis patients of either gender having radiological evidence of grade III or less on Kellgren classification. The subjects were randomly allocated to active comparator group A and experimental group B. Both the groups received manual therapy and resistance exercise training, while group B additionally received glucosamine and chondroitin sulfate supplementation for 4 weeks. Study outcomes included pain, function, quality of life, range of motion, strength, fall risk, skeletal muscle mass, visceral fat area, body fat, intracellular water ratio, and segmental lean and fat mass. Data was analysed using SPSS 21.

Results: Of the 24 subjects, there were 12(50%) in each of the two groups. Each group had 9(75%) males and 3(25%) females. In terms knee osteoarthritis grade, there was no significant difference between the groups (p=1.00). No significant differences were observed in any of the outcome measures neither at 2 weeks, nor at 4 weeks post-intervention between the groups (p>0.05) except for percentage change in segmental lean mass of the right leg at 2nd week and of the left leg at 4th week (p<0.05).

Conclusion: Manual therapy and resistance exercise training are effective in the management of knee osteoarthritis, however, glucosamine and chondroitin sulfate supplementation for 4 weeks showed no additional benefits.

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Keywords: Chondroitin sulfate, Glucosamine, Knee osteoarthritis, Physiotherapy, Resistance exercise, Manual therapy.

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Introduction

Half of the world's population over the age of 65 years suffers from osteoarthritis,[1,2] making it the most common cause of joint pain and disability.[3-6] Knee joint is the most common site of osteoarthritis, comprising 80% of the total disease burden,[4] being the 4th and 8th leading cause of disability in females and males respectively.[6] The prevalence of knee osteoarthritis (KOA) has been shown to continually increase in the elderly population[3,4] and a 2.1 fold increase has been observed in its prevalence since the mid 20th century.[4] This is perhaps in accordance with the general trend of increase in non-communicable diseases related to advancements in medical field and increase in life expectancy, as well as sedentary lifestyle contributing to obesity and eventually KOA.[3,4] Unfortunately, there is no known cure for KOA and symptom management is the mainstay of the treatment.[3] Prolonged use of pharmacological treatments is associated with numerous side-effects[3] and for this reason there is an increasing interest in the use of non-pharmacological alternatives for the management of KOA, including dietary supplements, exercise and manual therapy.[3,5,7] The most commonly used supplements for the management of KOA include glucosamine and chondroitin sulfate[3,8-15] and some studies have shown the two to be slightly more effective when administered in combination.[10-12] However, it is imperative to point out that the evidence regarding the effectiveness of glucosamine and chondroitin sulfate is contradictory, with some studies supporting, and others negating their effectiveness in KOA management.[3] On the other hand, in terms of therapeutic exercises for the management of KOA, progressive resistance training has been found to exert positive effects.[16,17] Literature has shown muscular atrophy,[18] especially weakness of quadriceps femoris being a significant contributor in terms of knee pain and related disability in persons with KOA,[16,19] advocating the importance of resistance exercise training in KOA management.

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The current study was planned to determine the additional benefits of short-term supplementation of glucosamine and chondroitin sulfate in combination with resistance exercise and manual therapy in the management of KOA.

Patients and Methods

A parallel-design, double-blind randomised controlled trial (RCT) was conducted at the Foundation University Institute of Rehabilitation Sciences (FUIRS), Islamabad, and Fauji Foundation Hospital (FFH), Rawalpindi, Pakistan, from January to September 2020. After approval from the FUIRS ethics review committee, the sample was acquired using purposive sampling technique. Those included were individuals of either gender aged 40-70 years, having KOA history of no less than 3 months, with knee pain no more than 8/10 cm on the visual analogue scale (VAS)[20] and radiological evidence of grade III or less on Kellgren classification.[23,24] Those with signs of serious pathology, such as malignancy, inflammatory disorder or infection, history of trauma or fractures in lower extremity, signs of lumbar radiculopathy or myelopathy, history of knee surgery or replacement and/or receiving intra-articular steroid therapy in the preceding two months were excluded. Those meeting the inclusion criteria were assessed and diagnosed by a physiatrist and then referred to FUIRS research lab for final inclusion.

After taking consent from the subjects, they were randomly allocated to active comparator group A and experimental group B using the lottery method. Both the groups received manual therapy and resistance exercise training, including interferential therapy and heat therapy using a hot pack for 20 minutes prior to manual therapy, followed by joint mobilisation, consisting of tibio-femoral anterior and posterior glide and patello-femoral joint mobilisation, 3 times a week. Resistance exercise training was carried out as supervised exercise training 3 times a week and as home exercise programme for the remaining 4 days. The exercise session was started with 5-10 minutes of pain-free self-paced walking, followed by resistance exercise training, including leg press, concentric and isometric knee extension and flexion in sitting, isometric terminal knee extension in lying and mini-squats.[16] Three sets of 8 repetitions were carried out for each individual exercise, allowing 1-2 minute rest between the sets.[18,25] For equipment-based supervised resistance training 80% of 8 repetition maximum was used as training intensity, which was reassessed every week.[16,23] The participants in the experimental group also received film-coated tablets of glucosamine 500mg and chondroitin sulfate sodium 400mg, thrice a day for 4 weeks. The active comparator group received empty capsules during the research process to ensure blinding. The physical therapist responsible for delivering the treatment was different from the one responsible for outcome assessment. Participants and the outcome assessor were both blinded, and were not aware of the treatment group allocation to minimise bias.

Outcome measurement tools included VAS for pain (intraclass correlation ICC=0.97)[22] and the Knee Injury and Osteoarthritis Outcome Score (KOOS) (ICC=0.83-0.89),[26] modified sphygmomanometer test for isometric muscle strength in knee flexion and extension (ICC>0.83),[27] 5 repetition sit to stand test (5XRSS) (ICC=0.982-0.998),[26] knee range of motion (ROM) in flexion and extension (ICC=0.96),[27] fall risk score via Biodex balance system (ICC=0.80)[28] and body composition analysis using multi-frequency direct segmental bio-electrical impedance analysis (In-Body 720) (ICC>0.8).[31,32]

Data was analysed using SPSS 21 at a confidence interval (CI) of 95%. Normality was assessed using Shapiro Wilk test of normality. Since all data was not normally distributed, Mann Whitney U and Friedman tests were used for inter- and intra-group comparison. The sample size was calculated to be 8 using the Harvard sample size calculator,[33] considering VAS as the primary outcome variable with a minimal detectable change of 2.8 cm,[32] power of 0.8 and a two-sided significance level of 0.05. The sample was inflated to cover up for potential dropouts.

Results

Of the 50 individuals assessed, 24(48%) were included; 12(50%) in each of the two groups (Figure). Both groups had 9(75%) males and 3(25%) females. In terms KOA grade,

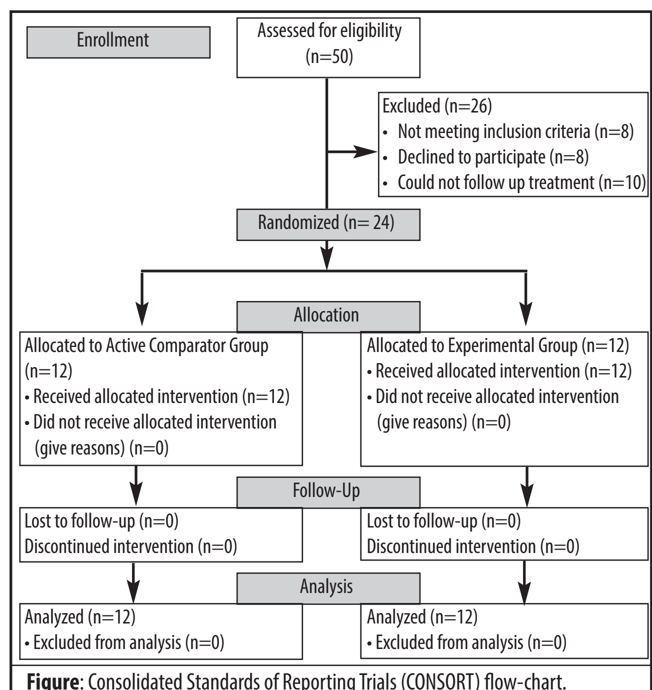

Figure: Consolidated Standards of Reporting Trials (CONSORT) flow-chart.

Table-1: Comparison of participant characteristics, visual analogue scale (VAS), knee osteoarthritis and outcome score (KOOS), range of motion (ROM), isometric muscle strength, 5 repetition sit to stand test (5XSST) and fall risk scores between the two groups at baseline, 2-week and 4-week post-intervention follow-up.

Variable			Median (IQR)		p-value
			Active Comparator Group	Experimental Group	
Age (years)			57.00 (9.00)	57 (11.00)	0.932
Weight (kg)			72.00 (13.25)	72.00 (10.50)	0.932
Height (cm)			162.00 (14.75)	162.50 (9.25)	0.843
BMI (kg/m2)			27.39 (3.95)	27.37 (1.89)	0.887
Visual Analogue Scale (cm)		Baseline	6.00 (1.50)	6.00 (1.00)	0.630
		2nd Week	3.5 (1.00)	3.5 (1.00)	0.887
		4th Week	3.00 (1.00)	2.50 (1.00)	0.443
Knee Osteoarthritis & Outcome Score (KOOS)	Total	Baseline	38.00 (3.00)	38.00 (4.00)	0.799
		2nd Week	50.00 (6.00)	53.00 (6.00)	0.755
		4th Week	60.50 (15.00)	68.00 (15.00)	0.630
	Symptoms	Baseline	50.00 (8.25)	50.00 (8.25)	1.000
		2nd Week	69.50 (3.00)	71.00 (3.00)	0.755
		4th Week	78.50 (15.00)	86.00 (15.00)	0.630
	Pain	Baseline	42.00 (0.00)	42.00 (0.00)	1.000
		2nd Week	57.00 (8.00)	61.00 (8.00)	0.755
		4th Week	71.00 (20.00)	81.00 (20.00)	0.630
	ADL	Baseline	51.00 (0.75)	51.00 (0.75)	1.000
		2nd Week	62.00 (6.00)	65.00 (6.00)	0.755
		4th Week	73.00 (16.00)	81.00 (16.00)	0.630
	Sports	Baseline	10.00 (0.00)	10.00 (0.00)	1.000
		2nd Week	10.00 (0.00)	10.00 (0.00)	1.000
		4th Week	25.00 (0.00)	25.00 (0.00)	1.000
	QOL	Baseline	38.00 (5.25)	38.00 (5.25)	1.000
		2nd Week	50.00 (12.00)	56.00 (12.00)	0.755
		4th Week	69.00 (0.00)	69.00 (0.00)	0.755
Range of Motion (°)	Flexion (Symptomatic Side)	Baseline	88.00 (8.75)	90.50 (8.75)	0.799
		2nd Week	113.00 (8.75)	115.50 (8.75)	0.799
		4th Week	128.00 (8.75)	133.00 (8.75)	0.410
	Flexion (Asymptomatic Side)	Baseline	125.00 (8.75)	130.00 (8.75)	0.410
		2nd Week	128.00 (8.75)	133.00 (8.75)	0.410
		4th Week	132.50 (4.50)	135.00 (4.50)	0.410
	Extension (Symptomatic Side)	Baseline	-10.00 (3.75)	-10.00 (3.35)	1.000
		2nd Week	-5.00 (3.75)	-5.00 (3.75)	0.932
		4th Week	0.00 (4.00)	0.00 (3.75)	0.630
	Extension (Asymptomatic Side)	Baseline	-3.00 (1.5)	-3.00 (1.5)	1.000
		2nd Week	-1.00 (1.50)	-1.00 (1.50)	1.000
		4th Week	0.00 (1.75)	0.00 (1.50)	1.000
Isometric Muscle Strength (mmHg)	Flexion (Symptomatic Side)	Baseline	85.00 (7.50)	85.00 (10.00)	0.671
		2nd Week	95.00 (7.75)	95.00 (11.50)	0.514
		4th Week	120.00 (7.50)	120.00 (10.00)	0.887
	Flexion (Asymptomatic Side)	Baseline	105.00 (3.75)	105.00 (9.00)	0.887
		2nd Week	125.00 (8.75)	125.00 (7.50)	0.551
		4th Week	145 (10.00)	145 (7.50)	0.443
	Extension (Symptomatic Side)	Baseline	92.5 (8.75)	90.00 (10.00)	0.932
		2nd Week	100.00 (12.50)	102.50 (10.00)	0.630
		4th Week	126.50 (8.75)	127.50 (10.00)	0.843
	Extension (Asymptomatic Side)	Baseline	114.50 (10.00)	111.0 (13.75)	0.887
		2nd Week	133.50 (10.00)	131.75 (13.75)	0.977
		4th Week	157.00 (10.00)	155.00 (10.00)	0.843
5 repetition sit to stand test (seconds)		Baseline	50.00 (6.36)	50.00 (6.11)	0.887
		2nd Week	21.21 (1.86)	21.00 (1.48)	0.755
		4th Week	18.50 (2.01)	18.00 (1.75)	0.843
Fall Risk Score	(Eyes Open)	Baseline	3.3 (0.73)	3.25 (0.73)	0.843
		2nd Week	3.29 (0.60)	3.23 (0.56)	0.887
		4th Week	3.30 (0.75)	3.24 (0.72)	0.755
	(Eyes Closed)	Baseline	4.28 (0.52)	4.23 (0.41)	0.843
		2nd Week	4.30 (0.54)	4.25 (0.71)	0.977
		4th Week	4.21 (0.63)	4.26 (0.64)	0.755

$p<0.05$ is considered significant. IQR: Interquartile range, BMI: Body mass index, ADL: Activities of daily living, QOL: Quality of life.

there was no significant difference between the groups (p=1.00). There were no significant intergroup differences at baseline ($p<0.05$) in terms individual factors or outcome variables either (Table 1).

No significant differences were observed in any of the outcome measures neither at 2 weeks, nor at 4 weeks post-intervention between the two groups ($p>0.05$) except for percentage change in segmental lean mass of the right leg at the 2nd week and of the left leg at the 4th week ($p<0.05$) (Table 2).

Discussion

The current study looked into the effects of resistance exercise training and manual therapy with and without short-term glucosamine and chondroitin sulfate supplementation on pain, KOOS, ROM, 5XSST, fall risk, phase angle, impedance, intracellular water (ICW) ratio, visceral fat area, percentage body fat, skeletal muscle mass, segmental lean mass and segmental fat mass in KOA patients, with positive effects of treatment on all outcomes in both groups, except for fall risk. In vitro and in vivo studies have shown beneficial effects of both glucosamine and chondroitin sulfate on injured cartilage, and are found to reduce pain and inflammation.[3] Because both the supplements produce similar effects, they are commonly used in combination in KOA management[3] and are among the highest-selling dietary supplements.[14] However, conflicting and inconclusive results have been reported regarding the therapeutic effectiveness of glucosamine and chondroitin sulfate in the management of KOA, and thus their treatments effects need to be clarified.[3,10] For this reason, the current study determined the additive benefits of glucosamine and chondroitin sulfate supplementation in the management of KOA in addition to resistance exercise and manual therapy, both of which are found to be effective in the management of KOA.[5,16,33]

A systematic review in 2018 suggested that

Table-2: Comparison of body composition parameters between the two groups at baseline, 2-week follow-up and post-intervention at 4th week.

Variable		Median (IQR)		*p*-value
		Active Comparator Group	Experimental Group	
Phase angle (°)	Baseline	5.6 (0.63)	5.6 (0.59)	0.799
	2nd Week	5.8 (0.62)	5.8 (0.60)	0.443
	4th Week	5.9 (0.63)	5.9 (0.60)	0.443
Impedance (Rt.) (Ω)	Baseline	308.12 (51.11)	308.10 (78.18)	0.410
	2nd Week	303.11 (51.13)	302.90 (78.20)	0.319
	4th Week	300.67 (51.09)	300.50 (78.19)	0.319
Impedance (Lt.) (Ω)	Baseline	307.37 (45.28)	307.38 (63.34)	0.977
	2nd Week	306.16 (45.27)	306.18 (63.36)	0.755
	4th Week	305.05 (45.28)	305.08 (63.35)	0.977
Visceral fat area (cm^2)	Baseline	147.48 (18.51)	147.48 (18.44)	1.000
	2nd Week	144.18 (18.52)	144.18 (18.48)	0.887
	4th Week	142.98 (18.50)	142.98 (18.45)	0.977
Percentage body fat (%)	Baseline	40.20 (7.33)	40.20 (9.33)	0.755
	2nd Week	39.80 (7.33)	39.80 (9.18)	0.887
	4th Week	39.45 (6.55)	39.50 (9.33)	0.932
ICW ratio (%)	Baseline	61.80 (0.10)	61.90 (0.175)	0.630
	2nd Week	62.65 (0.10)	62.75 (0.075)	0.128
	4th Week	63.05 (0.175)	63.10 (0.175)	0.478
ICW ratio (Rt. Leg) (%)	Baseline	61.90 (0.10)	61.90 (0.175)	0.799
	2nd Week	62.80 (0.038)	62.80 (0.080)	0.932
	4th Week	63.20 (0.075)	63.20 (0.183)	0.843
ICW ratio (Lt. leg) (%)	Baseline	61.66 (0.0825)	61.64 (0.14)	0.713
	2nd Week	62.54 (0.06)	62.54 (0.1175)	0.887
	4th Week	62.93 (0.1325)	62.93 (0.2025)	0.887
Skeletal Muscle Mass (kg)	Baseline	17.60 (4.24)	17.60 (5.75)	0.977
	2nd Week	18.06 (4.35)	18.06 (5.84)	0.887
	4th Week	18.10 (4.03)	18.10 (5.48)	0.799
Segmental Lean (Rt. leg) (kg)	Baseline	6.25 (1.18)	6.20 (1.15)	0.671
	2nd Week	6.41 (1.22)	6.48 (1.65)	0.266
	4th Week	6.64 (1.26)	6.66 (1.64)	0.378
Segmental Lean	2nd Week	3.35 (0.63)	3.66 (0.69)	0.010
% change (Rt. leg)	4th Week	6.41 (0.18)	6.45 (1.08)	0.068
Segmental Lean (Lt. leg) (kg	Baseline	6.13 (1.17)	6.13 (1.20)	0.551
	2nd Week	6.34 (1.16)	6.34 (1.16)	0.266
	4th Week	6.52 (1.14)	6.53 (1.15)	0.114
Segmental Lean	2nd Week	3.43 (0.10)	3.43 (1.10)	0.514
% change (Lt. leg) (kg)	4th Week	6.36 (0.15)	6.52 (2.56)	0.010
Segmental fat (Rt. Leg) (kg)	Baseline	4.10 (0.54)	4.10 (0.51)	0.713
	2nd Week	3.81 (0.50)	3.81 (0.48)	0.932
	4th Week	3.69 (0.49)	3.69 (0.46)	0.713
Segmental fat (Lt. Leg) (kg)	Baseline	4.10 (0.54)	4.10 (0.62)	0.977
	2nd Week	3.82 (0.48)	3.82 (0.59)	0.932
	4th Week	3.69 (0.49)	3.69 (0.46)	0.799

$p<0.05$ is considered significant; IQR: Interquartile range, ICW: Intracellular water.

glucosamine and chondroitin sulfate in combination are found to reduce KOA pain,[3] which is in accordance with the findings of the current study showing that glucosamine and chondroitin sulfate group demonstrated lower levels of pain after 4 weeks of treatment compared to physical therapy and exercise only group even though the differences were not significant. Furthermore, in terms of KOOS scores, manual therapy and exercise was found to be effective, but no added benefit of glucosamine and chondroitin sulfate supplementation was observed neither in the overall KOOS scores nor in the pain, symptoms, activities of daily living (ADLs), quality of life (QOL) or sports and recreation subscales. These findings are in accordance with earlier findings.[8,10,34] Another systematic review in 2018 also reported no additional benefits of glucosamine and chondroitin sulfate supplementation on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and its subscales, based on the summary of 29 RCTs.[35] However, a study has shown beneficial effects of glucosamine and chondroitin sulfate supplementation on pain, but only in the moderate to severe subgroup when observed after 6 months.[8]

Another study showed glucosamine supplementation in combination with strength training to be more effective than exercise only in terms of pain and concentric work, but no significant differences were observed in terms of muscle cross-sectional area, eccentric work, muscle strength, muscle power or 5XSST after 12 weeks of training.[17] These findings are comparable to the current study.

It is also imperative to point out that glucosamine and chondroitin sulfate are considered dietary supplements, and are thus exempted from the United States Food and Drug Administration (FDA) rigorous regulations required for prescription and non-prescription drugs, and are generally recognised as safe.[38.39] For this reason the duration of supplementation has not been established by FDA. However, reported improvements have been observed as early as three weeks, with a steady state achieved in 3-4 days and 50% of maximal efficacy (Emax) accomplished in 35 days.[37,38] Previous studies have administered glucosamine and chondroitin sulfate supplementation ranging from 42 days to 3 years[35] but due to increased risk of participant dropout in long-term follow-up and lack of funding, the treatment was administered for 4 weeks only in the current study. Even though, the findings of the current study showed no statistically significant additional benefit of glucosamine and chondroitin sulfate on disability and function when combined with manual therapy and exercise, which is in accordance with the findings of the previous studies concluding that there is no significant effect of glucosamine and chondroitin sulfate on WOMAC and its subscales,[35] careful interpretation of the findings is essential as the treatment duration was only 4 weeks. Furthermore, greater improvement was noted in terms of pain in the supplementation group, which is also in accordance with the findings of the previous studies[35] but the difference was not significant, and it is suggested that future studies with a longer treatment duration should be carried out to determine if the difference is statistically significant.

The biggest threat to the internal and external validity of

the current study was the coronovirus disease 2019 (COVID-19) pandemic and recurring lockdowns, because of which the current study was done at a single centre with a small sample size and short treatment duration with a short-term follow-up. Another limitation was a wide age range. Multi-centre studies with larger samples and longer treatment durations along with longer follow-up periods are recommended.

Conclusion

Physical therapy and resistance exercise training is effective in KOA management, short-term supplementation of glucosamine and chondroitin sulfate showed no additional benefits after 4 weeks of treatment.

Limitation: The current study was retrospectively registered at clinicaltrials.gov (NCT04654871).

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