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Effect of resistance exercises and nano-curcumin supplementation on matrix metallopeptidase 13 and cartilage oligomeric matrix protein in women with knee osteoarthritis: a clinical controlled study

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ABSTRACT

Introduction: This study aimed to investigate the effect of resistance training and nano-curcumin supplementation on matrix metallopeptidase 13 (MMP13) and cartilage oligomeric matrix protein (COMP) in patients with knee osteoarthritis.

Materials and Methods: In this open-label parallel randomized trial study 40 women aged between 45-60 years with knee osteoarthritis (OA) were randomly divided into the control, resistance training, nano-curcumin supplementation, and resistance training + nano curcumin supplementation groups. Socio-demographic characteristics, anthropometric and clinical parameters of the patients (WOMAC test) were collected at the beginning and end of the study. The levels of MMP 13 and COMP in the synovial fluid were measured with a human-specific ELISA kit.

Results: Resistance training, supplement intake, and training/supplementation did not significantly change the synovial levels of COMP and MMP 13. Compared with the control group, WOMAC scores were significantly higher in the intervention groups (P = 0.038) .

Conclusion: Resistance training and nano-curcumin by changing the WOMAC scores of patients with osteoarthritis can have a beneficial effect on improving the condition of these patients.

Keywords: Nano-curcumin, MMP13, Resistance exercises, Cartilage oligomeric matrix protein

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Introduction

Osteoarthritis (OA) is a prevalent joint disease in the elderly (1). It causes inflammation of the synovial membrane, thick joint capsule, muscle weakness, and new bone formation (2). Initial damage up-regulates the inflammatory cytokine that results in deregulation of cartilage catabolism and OA progression (3). Proteolytic activities lead to increased release of proteins and protein fragments into the synovial fluid, and ultimately into the bloodstream (4). Biomarkers have the potential role in determining the extent of the different pathological stages associated with OA (5). Significant changes can be occurred in the levels of matrix-degrading enzymes expressions following the cartilage damage (6). Matrix metalloproteinases (MMPs) are considered as a proteases family that breaks down extracellular matrix proteins (7).

MMP-13 or collagenase 3 also belongs to this family of proteases (8). Cartilage degradation is of the main features of OA which is mainly due to an elevated level of matrix-degrading enzymes such as MMP-13 (9). Although there is a low level of MMPs expression in most of the normal tissues, they increase significantly during inflammation (10). During joint inflammation, chondrocytes increase the level of MMPs (11). There are high levels of MMPs concentrations in synovial fluid and cartilage in OA patients which are positively associated with OA severity (12). Cartilage oligomeric matrix protein (COMP) is another biomarker that mainly interacts with collagens and proteoglycans to facilitate the collagen fibrillogenesis and chondrocyte proliferation (3, 13, 14). The highest level of COMP is detectable in the synovial fluid of OA patients that can be suggested as an early diagnostic marker of articular cartilage degeneration in OA (4, 15).

Exercise affects joint homeostasis which shows the dynamic balance of catabolic and anabolic processes within and between joint compositions (16). Systematic training improves physical capacity and has beneficial effects on the metabolism of type II collagen, especially in people with OA with no radiological symptoms (17).

Herbal compounds that stimulate cartilage healing have been recently studied as ideal drugs for OA due to their lower side effects and anti-inflammatory properties compared with chemical drugs (18). The prophylactic and therapeutic effects of curcumin on joint cartilage degeneration have been rarely studied (19). It has been shown that curcumin suppresses MMP-13 expression in IL-1β-induced chondrocytes. Therefore, curcumin prevents articular cartilage destruction (20).

The motivation for the current study comes from two facts. Firstly, there is an increase in the number of women with OA, particularly in younger postmenopausal women. Secondly, the literature review points to the lack of studies on the effect of exercise and nano-curcumin supplementation on the levels of MMP-13 and COMP in the synovial fluid and function and pain of postmenopausal women with knee OA. The current study aimed to find appropriate non-invasive strategies (exercise and nano-curcumin supplementation) for prevention, early diagnosis, and treatment of OA to improve the quality of life in these patients.

Materials and Methods

Study Design

This study was an open-label parallel randomized trial conducted between October 2018 and November 2018. Forty women with knee OA referred to Imam Ali hospital Clinic (Bojnurd, Iran) were selected to participate in this study. Socio-demographic characteristics, anthropometric and clinical parameters of the patients were collected ate the beginning of the study. All subjects completed the informed consent forms to participate in the research.

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Participants

Inclusion criteria were female, 45 to 60 years old, diagnosed with grade II to III OA based on the Kellgren–Lawrence grading scale and X-ray (21) in one or both knees, and lacking regular physical activity. The following patients were also excluded from the study: those with nano curcumin (turmeric) allergy, smokers, those with fractures in lower extremities, drug abusers, and those with neoplasm, epilepsy, mental illness, anemia and cardiovascular disease.

Ethical Issues

This study was approved by the ethics committee of North Khorasan University of Medical Sciences (#IR.NKUMS.REC.1396.77) and obtained clinical registry code (http://www.irct.ir: IRCT20161208031300N1) and considered the Declaration of Helsinki in all steps.

Randomization, Interventions and Follow-Up

Eligible patients were randomly divided into four groups including control group, resistance exercise group, nano-curcumin supplementation group, or resistance exercise and nano curcumin supplementation. We used permuted block method for randomization. The sample size (40 individuals) allowed the production of five blocks using www.sealedenvelope.com. The blocks were non-stratified and had equal sizes. The resistance exercise group performed exercises for 16 weeks three sessions per week. Every exercise session had warming up by an indoor bicycle for 10 minutes prior to the main resistance exercise program. Exercise groups performed knee and thigh resistance exercises including knee extension, hip abduction, and plantar flexion in three sets with an intensity of 50–75% 1RM 3 times a week (22). Afterward, the cooling down was performed for 5 to 10 min. The 1RM values of different movements were measured every 2 weeks, based on which the intensity of the exercises increased. The supplement group took one Nano-curcumin capsule (1000 mg) per day for 16 weeks. Participants of the control group received one daily soft gel capsule as a placebo to attenuate the psychiatric effects of Nano-curcumin supplementation.

Outcome Measures

The primary outcome was the change in the synovial fluid levels of MMP 13 and COMP between the baseline and week 16. Synovial fluid samples were obtained 24h before and 48h after the exercises and supplementation. The volume of aspirated synovial fluid in samples was not equal depended on the disease grade and its progression. The samples were kept at − 70 °C. The levels of MMP 13 and COMP in the synovial fluid were measured through a human-specific ELISA kit (collagenase II, Zelbio, Germany and nitric oxide, Sib-zist, Iran) suggested by the manufactures' protocol. The secondary outcome in this trial was changes in knee pain assessed by McMaster Universities Osteoarthritis Index scale (WOMAC), Western Ontario and changes in BMI. Persian version of WOMAC index was validated in Iran as well (23).

Statistical Analysis

Mean and standard deviation were used to describe quantitative variables. One-way ANOVA test (for normal data) and Kruskal Wallis test (for non-normal data) were used. Paired t-test and nonparametric Wilcoxon ranked sign test were applied to evaluate within-group differences in normal and non-normal data, respectively. The data were analyzed through SPSS version 22. P value less than of 0.05 was considered significant.

Results

As presented in Figure 1, sixty women were selected to participate in the study and finally 40 women received the intervention. The patients were randomly divided into

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four groups. Mean age of the participants was 59.90 ± 4.60 years in the control group, 55.20 ± 4.96 years in the exercise group, 57.30 ± 4.57 years in the supplementation group, and 57.70 ± 5.12 years in the exercise-supplementation group. There were no statistically significant differences in respect of basic characteristics across groups (Table 1).

Table 1. Physical Characteristics of Subjects at the Start of the Study.

Groups (in each group, n=10)	Age (year)	Weight (kg)	BMI (kg/m^2)
Control	59.90 ± 4.60	73.20 ± 9.32	29.95 ± 5.36
Exercise	55.20 ± 4.96	73.10 ± 6.19	30.50 ± 2.37
Supplementation	57.30 ± 4.57	80.20 ± 18.51	31.20 ± 6.96
Exercise-supplementation	57.70 ± 5.12	71.70 ± 9.58	29.80 ± 5.59

The values are presented as Mean ± SD.

Table 2. Within and between-group comparative analysis of synovial fluid values of MMP 13 and COMP before and after the interventions.

		Groups (in each group, n=10)				
Variable		Control	Exercise	Supplementation	Exercise-supplementation	P value
MMP13	Baseline	0.89 ± 0.72	0.99 ± 0.86	0.87 ± 0.68	0.72 ± 0.18	0.963$^{\#\#}$
	16 weeks	0.63 ± 0.27	0.60 ± 0.10	0.58 ± 0.19	0.72 ± 0.23	0.482$^{\#}$
	Changes	-0.26 ± 0.8	-0.39 ± 0.88	-0.29 ± 0.72	-0.001 ± 0.31	0.560$^{\#\#}$
	P value	0.594**	0.114**	0.333**	0.999*	
COMP	Baseline	1.17 ± 0.89	1.15 ± 0.84	0.79 ± 0.60	0.80 ± 0.16	0.297$^{\#\#}$
	16 weeks	0.72 ± 0.58	0.99 ± 0.96	0.68 ± 0.23	0.79 ± 0.58	0.750$^{\#\#}$
	Changes	-0.45 ± 1.16	-0.15 ± 1.45	-0.12 ± 0.60	-0.014 ± 0.56	0.409$^{\#\#}$
	P value	0.203**	0.285**	0.760**	0.575**	

MMP13: Matrix metalloproteinase 13, COMP: Cartilage oligomeric matrix protein.
*P value for within-group comparison of parametric quantitative data using paired sample t-test.
**P value for within-group comparison of nonparametric quantitative data using Wilcoxon signed-rank test.
$^{\#}$ANOVA P value for between-group comparison of parametric quantitative data using one-way ANOVA test.
$^{\#\#}$ANOVA P value for between-group comparison of nonparametric quantitative data using Kruskal–Wallis test.

Table 3. Comparative within and between groups analysis of BMI, WOMAC index, and WOMAC subscales.

		Groups (in each group, n=10)				
Variable		Control	Exercise	Supplementation	Exercise-supplementation	P value
BMI	Baseline	29.95 ± 5.36	30.5 ± 2.37	31.20 ± 6.96	29.80 ± 5.59	0.82$^{\#\#}$
	16 weeks	29.26 ± 5.37	30.46 ± 2.19	29.53 ± 6.36	29.38 ± 5.84	0.54$^{\#\#}$
	Changes	-0.69 ± 1.14	-0.04 ± 0.82	-1.67 ± 3.02	-0.42 ± 1.26	0.114$^{\#\#}$
	P value	0.090*	0.999**	0.027**	0.180**	
WOMAC Pain	Baseline	56.7 ± 14.20	51.30 ± 11.15	43.90 ± 20.39	54.10 ± 10.24	0.25$^{\#}$
	16 weeks	55.90 ± 15.57	41 ± 14.93	32 ± 18.36	41.80 ± 11.10	0.01$^{\#}$
	Changes	-0.80 ± 8.80	-10.30 ± 6.32	-11.90 ± 8.25	-12.30 ± 8.74	0.01$^{\#}$
	P value	0.780*	0.001*	0.001*	0.002*	
WOMAC Stiffness	Baseline	5.60 ± 1.50	6.20 ± 1.22	5.1 ± 2.23	5.50 ± 2.27	0.72$^{\#\#}$
	16 weeks	5.80 ± 1.55	5.20 ± 1.22	4 ± 1.7	4.70 ± 2.45	0.16$^{\#}$
	Changes	0.2 ± 1.03	-1 ± 1.05	-1.10 ± 1.28	-0.80 ± 1.40	0.05$^{\#\#}$
	P value	0.555*	0.015*	0.024*	0.104*	
WOMAC Physical Function	Baseline	19 ± 2.82	18.90 ± 1.91	17.30 ± 3.62	15.70 ± 6.36	0.38$^{\#\#}$
	16 weeks	19 ± 2.82	18.60 ± 2.36	17 ± 3.26	16 ± 6.65	0.36$^{\#\#}$
	Changes	0	-0.30 ± 0.67	-0.30 ± 1.06	0.30 ± 0.94	0.335$^{\#\#}$
	P value	1**	0.180**	0.414**	0.317**	
Total WOMAC	Baseline	81.30 ± 15.54	76.40 ± 12.45	66.30 ± 24.27	75.30 ± 17.25	0.32$^{\#}$
	16 weeks	80.70 ± 17.72	64.80 ± 16.50	53 ± 21.09	62.50 ± 17.09	0.01$^{\#}$
	Changes	-0.6 ± 9.61	-11.60 ± 7.23	-13.30 ± 9.21	-12.80 ± 9.21	0.01$^{\#}$
	P value	0.848*	0.001*	0.001*	0.002*	

BMI: Body Mass Index, WOMAC: Western Ontario and McMaster Universities Arthritis Index.
*P value for within-group comparison of parametric quantitative data using paired sample t-test.
**P value for within-group comparison of nonparametric quantitative data using Wilcoxon signed-rank test.
$^{\#}$ANOVA P value for between-group comparison of parametric quantitative data using one-way ANOVA test.
$^{\#\#}$ANOVA P value for between-group comparison of nonparametric quantitative data using Kruskal–Wallis test.

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According to the results, resistance exercise, supplement intake, and exercise/supplementation were not significantly correlated with the synovial levels of COMP and MMP 13 (Table 2).
As shown in table 3, regarding BMI score, there was no significant different across groups at the beginning and the end of the study. However, according to the within-group tests, there was significant reduced BMI in the supplementation group. Within-group changes in the mean values of WOMAC showed significant improvement of patients' pain in the intervention groups. Compared with the control group, WOMAC scores were significantly higher in the intervention groups (P = 0.038). There were no significant differences between the study groups in respect of physical function (P = 0.358) and stiffness (P = 0.161) categories of WOMAC. No side effects dealing with nano curcumin supplementation was reported in women with knee OA.

Discussion

The results of this study showed that resistance training and nano curcumin supplementation for 16 weeks had no significant effect on the MMP-13 and COMP's synovial levels but has a significant effect on the function and pain in women suffered from knee OA. In line with these findings, a large-scale study (24) found that 10 weeks of resistance and aerobic training have not any significant effect on the levels of TNF-α, IL-1 β, and IL-6 in inactive overweight men but led to a significant increase of 1RM in the resistance training group. Although, the inflammatory biomarkers in plasma, the duration of exercise, and the type of biomarkers were different from those of the current study, it can be argued that the two studies are consistent in terms of the effect of resistance training on synovial levels of inflammatory biomarkers and 1RM. In contrast with our results, it has been reported that 8 weeks of high-volume resistance training reduced MMP2 and MMP9 plasma activities (25). Different results can be related to the different duration of the study and targeted biomarkers. In respect of the effect of exercise on serum levels of MMP, our study was also inconsistent with that of Qi and Changlin (26). They found that intense training in dogs reduced the levels of MMP-1, MMP- 3and 1 / TIMP-3 MMP- compared with normal training. Such inconsistency could be due to differences in the subjects (human vs dog) and the synovial fluid aspiration time (12 hours vs. 24 hours after training). Also, a longer training period in the present study (sixteen weeks) could have been effective in further reducing MMP biomarker in synovial fluid, which could be due to cartilage adaptation to exercise and regeneration and improvement of cartilage. Another study has been shown that the squat exercise and whole-body vibration significantly reduced the plasma concentration of TNF-α in middle-aged people with knee OA (27).
In contrast with the present study, it has been reported that there was reduced COMP level in women with knee OA after acute resistance training (25 sets of 10 repetitions in 60% of 1RM) compared to the non-training group (28). One of the reasons for the different results is the difference in the type of resistance exercise (acute training vs regular training) and type of sample (plasma vs synovial fluid) between the two studies. The results of the present study on the effect of exercise on COMP level are also inconsistent with the results of Qi & Changlin (26). They found that the normal and intense trainings in dogs (2 hours a day for 10 weeks) caused COMP to reach the highest serum level (at week 4) and synovial fluid (at week 6) in both training groups and then followed a declining trend. However, the rate of decline was slow and the total level was still higher than the baseline level. Additionally, aspiration time in Qi and Changlin's study was 12 hours after the training period (10 weeks) while we did the aspiration 24 hours after the training period (16 weeks).

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Consistent with our results, it has been reported that the treatment of OA patients with curcumin and its derivatives such as flexofytol for six weeks, significantly reduced the pain, and improved quality of life and joint flexibility. Flexofytol reduced the markers of collagen degradation, oxidative stress, and inflammation. Curcumin has also anti-inflammatory and antioxidant properties that are effective in treating OA (29).

Li et al. investigated the effect of curcumin on the type II collagen expression in IL-1β-induced chondrocyte in mice which showed that the type II collagen expression was reversed following curcumin use (30). This reveals protective effect of curcumin on IL-1β-induced cartilage degeneration. IL-1β promotes the protein-degrading enzymes production such as collagenase Type II and inflammation. Cartilage destruction is linked with a reduction in type II collagen. Researchers found that the MMPs expressions is increased in the chondrocytes of patients suffered from OA. IL-1β is considered as a major diagnostic cytokine stimulating the IL-1 receptors. Previous studies found that inhibition of NF-κB induced by curcumin can inhibit the cyclooxygenase 2 (COX-2) expressions and reduce the destruction of MMP-induced cartilage. Other studies have shown the protective role of curcumin on the cartilage cells by type II collagen up regulation (20).

Zhang et al. (31), studied the effects of curcumin and curcumin nanoparticles on mice undergoing medial meniscus surgery for 8 weeks. They showed that curcumin significantly prevented the initiation and advancement of OA in mice. Curcumin in both topical and orally encapsulated forms reduced collagen II degradation and down regulated the IL-1β, TNF-α, and MMP13 and. These findings are inconsistent with the results of the present study which showed a non-significant decrease in MMP13 due to nano-curcumin supplementation. It is important to note that our study was performed on humans over a 16-week period with different doses of nano-curcumin, which may be the reason for such inconsistencies. Moon et al. (32) also reported that mice treated with curcumin had lower arthritis scores, lower levels of TNF-α and IL-1β, and inhibited COX-2 and MMP13. Although, the present study showed insignificant findings regarding COMP and MMP13 levels, the result of WOMAC and patients' reports point to the high efficiency of curcumin in reducing inflammation and improving the physical status of the OA patients.

Aborehab et al. (33) assessed the effects of curcumin in thirty-five albino mice. Serum levels of COMP and IL-1β were significantly decreased in the OA group of mice. Curcumin had anti-inflammatory and antioxidant effects in the OA model by reducing oxidative stress and inflammation. Curcumin was also shown to have a protective effect against rheumatoid arthritis in the mice, which was inconsistent with our results. Li et al. (30) performed a study entitled curcumin's effect on the type II collagen expression in IL-1β-induced inflammation in mice's chondrocytes and revealed that type II collagen expression was reversed by curcumin. Therefore, curcumin shows protective role on IL-1β-induced cartilage degeneration. Additionally, IL-1β enhances productizing protein-degrading enzymes such as collagenase-2 and inflammation.

Improvement in pain, stiffness, and performance of the knee in the current study was in line with the study by Bragin et al. (34). In their study, people with knee OA performed a physical exercise protocol for 50 to 60 minutes twice a week for 8 weeks. The exercise protocol included hip flexion, extension, adduction, and abduction that led to improvement in pain and function. Ho et al. (35) investigated the effect of a six-months exercise program on physical, cognitive, and hemodynamic parameters of OA patients with normal blood pressure (NTS) and hypertension (HTS). The program improved standing and walking in patients with OA, regardless

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of blood pressure, which is consistent with the results of our study. Simão et al. (27) reported similar findings about the role of training in the patients who had knee OA. Elderly patients suffered from knee OA that performed squat exercises with vibration twice a week for 12 weeks showed improvement in static and dynamic balance, walking, and pain. Similarly, Foroughi et al. (36) investigated the effect of a six-month resistance training in women over 40 years with knee OA in which resistance training had a positive effect on the health parameters and OA symptoms measured by WOMAC.

Limitations

One of the limitations of this study was the lack of strict control on the patients' diet during the research period.

Conclusion

Resistance training and nano curcumin supplementation could not change the synovial fluid biomarkers of patients with osteoarthritis, but it caused improvements in the physical and functional conditions of these patients. Therefore, performing these exercises and taking nanocurcumin are recommended to improve the condition of these patients. It also seems necessary to conduct more studies in this field.

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Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sadegh Cheragh-Birjandi, Maryam Baghernezhad, Farideh Haghighi, Reza Ganji, Hassan Saadati, and Mohammad Reza Jaafari.

Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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