

Effect of Combined Garlic Therapy and Comprehensive Rehabilitation Program versus Comprehensive Rehabilitation Program Alone on Control of Clinical Manifestations and Quality of Life of Knee Osteoarthritis Patients

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Abstract

Objective: To compare the effect of comprehensive rehabilitation program versus combined garlic therapy and comprehensive rehabilitation program in controlling the clinical manifestations and quality of life in patients with knee osteoarthritis

Design: Randomized clinical trial

Setting: Outpatient setting

Participants: 43 patients with knee osteoarthritis randomized to group I (comprehensive rehabilitation) (n=15) and group II (combined garlic therapy and comprehensive rehabilitation) (n=28).

Intervention: All patients had diet modification, electrotherapy, resistance and flexibility exercises for legs 3 times weekly for 8 weeks. Group II received garlic capsules 900mg daily with breakfast for 8 weeks.

Main Outcome measures: knee pain by visual analogue scale (VAS), Stanford health assessment questionnaire (HAQ), one repetition maximum (1RM) for quadriceps, body mass index (BMI), synovial fluid level of interleukin1 β , interleukin 6, tumor necrosis factor α and selenium.

Results: BMI significantly decreased in both groups ($P < .05$) without significant difference between groups. Knee pain significantly decreased in group II mean \pm standard deviation ($-51.77 \pm 11.17\%$) more than in group I ($-22.92 \pm 5.31\%$) ($P = .00001$). 1 RM significantly increased in group II ($105.10 \pm 65.90\%$) more than in group I ($64.78 \pm 54.77\%$) ($P = .01986$). Percent change of HAQ was more in group II (-36.56 ± 12.2) than in group I (-16.42 ± 14.10) ($P = .00004$). Synovial selenium significantly increased only in group II ($213.19 \pm 28.26\%$) ($P = .00001$). Synovial inflammatory mediators significantly reduced only in group II (interleukin1 β ($-89.67\% \pm 3.73$) ($P = .00001$), interleukin 6 ($-92.98\% \pm 5.02$) ($P = .00001$), tumor necrosis factor α ($-83.20\% \pm 8.52$) ($P = .00001$).

Conclusion: Garlic improves rehabilitation outcome of knee osteoarthritis

Key words:

Garlic; Knee; Osteoarthritis; Rehabilitation

Introduction

Management of knee OA includes patient education, proper joint protection and conservation [1], physiotherapy to ameliorate pain, quadriceps strengthening [2-7], stretching of hamstrings and quadriceps to correct flexibility deficits [8] and weight reduction [9]. All these factors are necessarily interconnected [1,10].

Complementary and alternative medicine (CAM) have been commonly used by osteoarthritis patients [11,12]. Zochling et al.

reported 40% prevalence for use of CAM among osteoarthritis patients. However, further studies were recommended [12].

Garlic (*Allium sativum*) has been used by various cultures, as antibiotic and immune booster [13-15]. Garlic has strong antioxidant properties [16]. It has been suggested that garlic can prevent cardiovascular diseases [16-18], inhibit platelet aggregation, thrombus formation, prevent cancer, diseases associated with cerebral aging, arthritis and cataract formation [16,19]. Garlic is composed of flavonols, selenium and sulphur compounds [13-15,18,20,21]. Some sulphur compounds decomposed into variety of thiosulfinate and polysulfide by the action of enzyme alinase. In addition to diallylsulfide, diallyldisulfide and diallyltrisulfide [18,22,23]. These organo-sulphur compounds have very strong antioxidant properties [18,22,23]. Selenium has 3 major functions; reduction of organic and

inorganic peroxide, metabolism of hydrogen peroxide which is intermediate step in the metabolism of prostaglandin and modulation of respiratory burst through the control of superoxide O_2 and hydrogen peroxide [11,24]. Eicosanoids synthesis is significantly diminished in the absence of selenium. It is likely that both anti-inflammatory and immune modulating effects of selenium are mediated by means of production of eicosanoids and reduction of hydroperoxides [11].

The high content of selenium and sulphur compounds in garlic would suggest its beneficiary effect in treating osteoarthritis. However, the use of garlic as antioxidant in treatment of knee OA has not been extensively studied in the recent literature.

Aim of the study: to compare the effect of comprehensive rehabilitation program versus combined garlic therapy and comprehensive rehabilitation program in controlling the clinical manifestations and quality of life in patients with knee osteoarthritis.

Methods

Study design: This study is a prospective single blind randomized clinical trial. Ethics approval was obtained from research ethics committee at our institution before initiation of the study

Participants: Forty three patients from those attending the outpatient clinic of physical medicine and rehabilitation department at our institution between the period of January 2007 to July 2007 (42 female, 1 male, age range 39-66 y) volunteered in the current study. The inclusion criteria were: primary knee osteoarthritis diagnosed according to American College of Rheumatology criteria [25] and their clinical conditions had been chronic or subacute. Exclusion criteria were: 1-secondary osteoarthritis due to other rheumatologic diseases 2-Any uncontrolled medical problems that precluded resistance exercise such as hypertension, angina, severe cardiomyopathy or diabetes.

Outcome measures: Initial evaluation: All included patients signed informed consent for participation in the study after being informed about its details. All patients were examined by the principal investigator. Medical history, occupational history, and detailed drug history were conducted to all patients. Then, general examination and musculoskeletal examination were carried out. The latter included knee alignment, presence of any knee deformity, bilaterality of the disease, tenderness, and effusion. Visual analogue scale (VAS) for knee pain was done [26]. The Stanford health assessment questionnaire (HAQ) was completed [27]. Assessment of one repetition maximum (1RM) for the quadriceps was performed for all patients [28]. Body weight and height were measured and body mass index (BMI) was calculated [28]. Initial synovial fluid analysis including selenium level, IL1 β , IL6, and TNF α levels were done. Diet session for correction of eating habits as well as session for proper joint conservation techniques were conducted for all patients [29].

Interventions: Patients were randomly assigned into two groups according to their national number endings; those with odd number constituted group I performed rehabilitation program only, and did not receive placebo as the two groups of patients did not know each other. Those with even endings of their number represented group II (garlic group) received garlic in addition. Both groups had the same exercise program, electro-analgesia, diet modification and analgesic medications for 8 weeks.

Exercise program: All patients in both groups performed the following exercise program at our department for 3 sessions per week on alternate days, for 8 weeks.

1-Flexibility exercise: Patients performed static stretching of both hamstrings and quadriceps muscles before the resistance exercise [30].

2- Dynamic resistance exercise for quadriceps, using Cybex weight machine was conducted after electro-analgesia and flexibility exercises. Exercise was carried out at intensity of 40% of 1 RM for 8 repetitions [31,32]. The 1RM measurement was repeated every 2 weeks so that the intensity of resistance exercise was kept at constant level throughout the study.

In addition, all patients were instructed to perform the same flexibility exercise at home on the remaining days of the week.

Electro-analgesia: All patients received interferential current for both knees for analgesia. This was carried out before the exercise program, 10 minutes for each knee [33]. All patients were advised to use ice packs for 15 minutes for each knee at home, on daily basis [29]

Garlic therapy: Group II patients received garlic medication from our institution and instructed to take 900 mg daily (3 capsules, each capsule is equivalent to 3 garlic cloves) with breakfast for 8 weeks. This is the recommended dose for garlic in the previous literature to treat many other conditions such as high blood pressure, high cholesterol, bacterial infections and cancer [15].

Analgesic medications: All patients were instructed to take acetaminophen, 500 mg three times daily as needed in case of severe knee pain. In addition, patients were asked to stop the use of all other non-steroidal anti-inflammatory drugs.

Final evaluation: After 8 weeks all patients had the following measurements: 1-Local knee examination. 2-VAS for knee pain. 3-HAQ 4-1RM for quadriceps. 5-BMI 6- Synovial fluid level of selenium, IL1 β , IL6 and TNF α .

Statistical analysis: Results were expressed as mean and standard deviation as well as percent changes of the variables. Paired T test was used to compare between variables within each group before and after the rehabilitation program. P was considered significant if ≤ 0.05 . Chi square was used for contingency tables. Mann Whitney U test was used to compare between variables in between the two groups at baseline and at the end of the study. P was considered significant if ≤ 0.05 . Pearson's product moment correlation test was done to correlate between clinical and laboratory variables. Significant correlation was considered if $r \geq 0.3044$ which correspond to $p \leq 0.05$. Power of calculation was equal to 80%.

Results

Baseline characteristics of both groups (Table 1) the characteristics of both groups (age, gender, chronic diseases namely diabetes mellitus, hypertension, coronary artery disease) were equivalent without any significant difference.

Variable	Group I (n=15)	Group II (n=28)	Significance
Age (mean \pm SD)	51.9 \pm 6.7	55 \pm 7.91	P=0.09
Gender, n (%)	0(0%)	1(3.57%)	
Male	15(100%)	27(96.42%)	
Female			

Chronic Diseases, n (%)	2(13.3%)	6(21.43%)	P=0.1
Diabetes Mellitus	2(13.3%)	7(25%)	P=0.08
Hypertension	1(6.7%)	1(3.57%)	P=0.31
Coronary artery disease			
*P if significant if <0.05 Abbreviation: SD: Standard Deviation			

Clinical findings of the knee (Table 2) at baseline, both knees were affected in both groups, with deformity present in 3 patients (26%) in group I and in 12 patients (42.86%) in group II, with significant difference between groups (P=0.021). Initially, there was no significant difference between groups regarding knee effusion. After rehabilitation, effusion recovered significantly only group II patients (garlic group) (P=0.00001), with significant difference in between groups (P=0.0025).

Table 1: Baseline characteristics of patients in both groups

Variable	Group I	Group II	Significance
Bilaterality of OA No (%)	15(100%)	28(100%)	Not applicable
Deformity no (%)	3(20%)	12(42.86%)	P=0.021*
Effusion no (%)	13(86.7%)	26(92.86%)	P=0.35
Pre-program	9(60%)	0(0%)	P=0.025*
Post-program			
*P if significant if <0.05 Abbreviation: Non sig:Non Significant			

Table 2: Clinical findings of the knee joints

Knee pain by VAS and quality of life by HAQ (Table 3), there were no significant difference between groups at base line regarding knee pain and quality of life. After rehabilitation, knee pain by VAS decreased significantly in both groups, with significantly higher

percent change in group II. Associated with pain reduction, there were significant decline of HAQ scores in both groups. The decline was more significant in group II (P=0.0019).

Variable	Group	Pre-Program Mean ± SD	Post-Program Mean ± SD	Mean percent change mean% ± SD	Significance within group (Pre & post)	Significance between groups
VAS	Group I	85 ± 8	65.3 ± 5.8	-22.9 ± 5.3	0.00001*	0.1579
	Group II	87.89 ± 10.31	42.5 ± 11.34	-51.7 ± 11	0.00001*	0.00001*
HAQ	Group I	1.6 ± 0.2	1.3 ± 0.3	-6.42 ± 14.1	0.0002*	0.0737
	Group II	1.7 ± 0.29	1.07 ± 0.24	-5.56 ± 12.2	0.000001*	0.0019*
*P if significant if <0.05						

Table 3: Knee pain by VAS and quality of life by HAQ

Changes in BMI and quadriceps strength (Table 4), at baseline, both groups were equivalent regarding BMI and 1RM. After rehabilitation, BMI significantly reduced in both groups without difference in

between groups. 1RM improved significantly in both groups with higher significant improvement in group II.

Variable	Group	Pre-program Mean ± SD	Post-program Mean ± SD	Mean percent change mean% ± SD	Significance within group	Significance between groups
BMI	Group I	34.9 ± 5.9	34.7 ± 5.8	-0.64 ± 1.0	0.0159*	0.0833
	Group II	37.39 ± 4.32	37.03 ± 4.4	-0.97 ± 2.5	0.023*	0.0931
1RM	Group I	15.7 ± 6.4	23.8 ± 6.6	64.78 ± 54.77	0.00001*	0.346
	Group II	16.54 ± 6.16	30.98 ± 7.74	105.1 ± 65.9	0.000001*	0.0015*

*P if significant if <0.05

Table 4: Changes in BMI and quadriceps strength by 1RM

Synovial fluid analysis (Table 5), initially, selenium level was significantly higher in group II patients (P=0.00001). At the end of the study; it significantly increased only in group II.

Variable	Group	Pre-program Mean ± SD	Post-program Mean ± SD	Mean percent change Mean ± SD	Significance Within group	Significance Between groups
Selenium Pg/ml	Group I	60.0 ± 7.2	59.2 ± 6.1	-1.11 ± 14.8	0.279	0.00001*
	Group II	72.5 ± 6.48	226.04 ± 14.9	213.19 ± 28.2	0.000001*	0.00001*
IL1 β Pg/ml	Group I	14.4 ± 3	14.9 ± 3.6	7.77 ± 32.22	0.344	0.00001*
	Group II	20 ± 4.16	1.97 ± 0.45	-89.67 ± 3.73	0.000001*	0.00001*
IL6 Pg/ml	Group I	57.9 ± 8.1	60.2 ± 8	5.05 ± 14.36	0.1641	0.00001*
	Group II	21238.4 ± 3182.04	1448.57 ± 998.41	-92.98 ± 5.02	0.000001*	0.00001*
TNF α Pg/ml	Group I	20.7 ± 3.9	21.6 ± 3.9	10.3 ± 37.72	0.3054	0.00001*
	Group II	29.78 ± 7.06	4.82 ± 2.23	-83.2 ± 8.52	0.000001*	0.00001*

*P if significant if <0.05

Table 5: Synovial fluid analysis

The inflammatory cytokines (IL1β, IL6, TNFα) were found to be significantly higher in group II patients at baseline(P=0.00001). Instead of this, at the end of the study, they declined significantly in synovial fluid of group II patients only

Variable	Knee effusion	VAS	HAQ	1RM
Selenium	r=-0.698** p<0.0001	r=-0.737** p<0.0001	r=-0.407** p=0.007	r=0.413** p=0.006
IL1 β	r=0.707** p<0.0001	r=0.761** p<0.0001	r=0.492** p<0.0001	r=-.423** p=0.005
TNF α	r=0.614** p<0.0001	r=0.707** p<0.0001	r=0.386* p=0.011	r=-0.347* p=0.023

*Significant correlation

Table 6: Correlation between clinical and laboratory parameters

Variable	IL1 β	TNF α
Selenium	r=-0.940** p<0.0001	r=-0.915** p<0.0001

*Significant correlation
**Highly significant correlation

Table 7: Correlation between selenium and cytokines

At the end of the study, selenium inversely correlated with knee pain and effusion and HAQ scores. Positively correlated with 1RM

(Table 6). Selenium was inversely correlated with cytokines IL1β and TNFα. Cytokines IL1β and TNFα. Correlated with knee pain, effusion and HAQ scores and negatively correlated with 1RM (Table 7).

Discussion

In the present study, there was significant decline in synovial cytokines IL1β, IL6 and TNFα in garlic group only. This was accompanied by more control of knee pain and effusion, as well as better muscular strength and quality of life. In addition to high synovial selenium at the end of the study that was positively correlated with improvement of quadriceps strength and negatively correlated with knee pain, effusion, HAQ scores and cytokines level.

These results would suggest the beneficial effect of garlic regarding control of inflammation in those patients.

Garlic has been reported as one of complementary medicine in osteoarthritis [12] however the exact mechanism was not determined. Denisov et al. recommended the use of garlic for the treatment of rheumatoid patients in combined and monotherapy to control clinical manifestations [34]. There is no similar work in recent literature demonstrating the effect of garlic on synovial cytokines in knee osteoarthritis patients. However, garlic suppressed TNFα and IL6 in inflammatory bowel disease [35], and in normal and pre-eclamptic placenta [36]. It suppressed TNFα and IL1β in intestinal epithelial cells [37]. It also reduced all cytokines, nitric oxide and prostaglandin E2 by macrophages [38].

Garlic also has very strong antioxidant action with ability to scavenge reactive oxygen species. It increases intracellular glutathione disulfide reductase and superoxide dismutase activity. This ameliorates oxidative stress. This action of garlic is related to its content of

organosulphur compounds, allixin, selenium and saponin. Although their individual involvement is complex [16,18,22].

The pathophysiology of osteoarthritis is complex network of biochemical factors including proteolytic enzymes that lead to breakdown of cartilage. Cytokines such as IL1 and TNF α produced by synoviocytes, mononuclear cells or by articular cartilage itself upregulate metalloproteinase results in sequestration of trace elements including selenium [39,40]. In addition to excessive production of nitric oxide and prostaglandin E2 that are augmented by cytokine. Oxidative stress and free radical activity have strong contribution to the severity of clinical signs of osteoarthritis [41,42].

Selenium supplementation alone modulated inflammation and immune response at clinical and experimental level [43,44]. Kurz et al. [45] found significant reduction of mice knee osteoarthritis with increased expression of glutathione peroxidase in synovium after intake of diet rich in selenium. Selenium improved indices of inflammation in experimental models such as adjuvant arthritis in rats or in the lupus mice [46]. Selenium intake resulted in reduction of pain, swollen and tender joints numbers in rheumatoid arthritis patients [47]. In the present study, we had similar results after garlic supplementation. In addition, to decline of cytokines in synovial fluids and improvement of muscular strength. This is because garlic is rich in selenium plus organosulphur compounds.

The control group who did not receive garlic had reduction of knee pain but not effusion. This could be explained by many factors including improvement of muscular strength by dynamic resistance exercise, significant reduction of body weight and use of electroanalgesia. Revising the literature, resistance exercise for knee osteoarthritis reduced pain and increased functional ability [48]. Felson et al demonstrated that weight reduction alleviate symptoms of knee osteoarthritis [9].

Study limitation

The sample (43 patients) was not large. Despite randomization only one male patient was included. Larger sample would allow better generalization and documentation of the effect of garlic on inflammatory process associated with knee osteoarthritis. We did not include placebo in those group not receiving garlic based on that both group did not know each other and the target of the the study was more objective evidence through cytokine changes. Placebo effect might have limited effect in the subjective results but not the objective results (cytokines and effusion) in Group II. So, further study with inclusion of placebo might qualify more accurate results and conclusion. We did not record if each individual group utilized acetaminophen as pain killer. This could be considered limitation. But acetaminophen has no effect on inflammation and inflammatory cytokines. The dose of garlic used in this study was similar to that used for control of hypertension as there is no specific dose mentioned in literature for osteoarthritis. Dose dependant effect was not tested. The duration of the study was 8 weeks; we don't know whether longer treatment duration would result in better response. We did not use placebo for the group which did not receive garlic based on patients on each group did not know each other.

Conclusion

This study supports the use of garlic as complementary treatment for knee osteoarthritis since it improves clinical and laboratory indices of inflammation, hence, the rehabilitation outcome. Further studies

are needed for definite documentation about the role of garlic in improving the rehabilitation outcome.

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