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ORIGINAL ARTICLE

Clinical and biochemical study of the comparative efficacy of topical versus oral glucosamine/ chondroitin sulfate on osteoarthritis of the knee

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Structure modifying drug

Abstract *Aim of the work:* The aim of this study was to detect and compare the efficacy of topical and oral glucosamine/chondroitin sulfate on knee OA (OAK), and to prove their efficacy on sparing the articular cartilage among the Egyptian patients.

Patients and methods: 180 patients with OAK were included and randomly divided into 2 groups, each of 90 patients. One group took 1500 mg oral glucosamine/chondroitin sulfate and the other group used topical glucosamine/chondroitin sulfate for 3 months. The diagnosis was based on the American College of Rheumatology (ACR) criteria for OAK. Age, duration of OA, and body mass index (BMI) of the patients were recorded. Knee radiographs were assessed with the Kellgren–Lawrence scale. The severity of knee pain, stiffness, and disability were measured using the visual analog scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The serum C-reactive protein (CRP) and Cartilage oligomeric matrix protein changes (COMP) were measured.

Results: No statistical difference was found between the 2 groups regarding age, sex, duration of OA, and Kellgren–Lawrence grading scale. Both VAS and WOMAC subscores showed significant equal relief of pain and joint function between the 2 groups regardless of the severity or duration of knee OA. Topical glucosamine was superior to the oral route in improving stiffness and function.

Conclusion: Topical and oral glucosamine/chondroitin sulfate are safe and equally effective on improving knee pain, stiffness and function. Glucosamine/chondroitin sulfate is beneficial as a symptomatic treatment and not as a cartilage sparing drug in the treatment of OAK.

1. Introduction

Osteoarthritis (OA) is the most common musculoskeletal problem in individuals above 50 years of age. It is a progressive disease that can worsen physical function over time. Worldwide

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estimates indicate that 9.6% of men and 18% of women ⩾60 years have symptomatic OA. In 1990, OA was estimated to be the eighth leading non-fatal burden of disease, accounting for 2.8% of total individuals living with disability [1]. OA can affect the quality of life; mainly walking and climbing stairs [2]. Osteoarthritis has a significant negative impact on the economy, with its total cost estimated as equivalent of 1% of the gross national product (GNP) per year in the UK [2]. Over a 1-year period in the UK, there were 114,500 hospital admissions, in 2000, there were over 35,000 knee replacements performed at a cost of £405 million and also, 36 million working days were lost due to OA alone, at an estimated cost of £3.2 billion in lost production. At the same time £215 million was spent on social services for OA [3].

OA is often associated with the knee, hip, spine, and fingers [4,5]. It involves all tissues of the diarthrodial joints including the bone, cartilage and supporting elements. OA is characterized by focal degeneration of joint cartilage and formation of new bone in the form of osteophytes at the base of the cartilage lesion in the subchondral bone and at the joint margins [6].

Our joints are cushioned by cartilages and lubricated with synovial fluid such that we can move and twist any joint freely without pain. The principal lubricating substances in our cartilage, tendons, ligaments, synovial fluid and mucous membranes are proteoglycans and glycosaminoglycans (GAGs). Glucosamine which is naturally produced by the body is the main ingredient needed to produce GAGs. Glucosamine stimulates the chondrocytes to produce proteoglycans and increase the production of hyaluronic acid resupply of synovial fluid to act as a lubricant, while chondroitin sulfate attracts water into the cartilage and acts as a shock absorber. The proteoglycans are subjected to continuous metabolic turnover, undergoing constant breakdown and resynthesis. The imbalances in these processes that occur with aging or with other medical conditions are partially responsible for the development of arthritis. In old men, the body loses the capacity to produce sufficient glucosamine causing thinning of the cartilage and leads to joint degeneration [7].

In OA, the rate of synthesis and secretion of matrix-degrading metalloproteinases by the chondrocyte are greatly increased leading to a loss of the proteoglycans from the extracellular matrix. Also, lysosomal enzymes can cleave both hyaluronic acid and chondroitin 6-sulfate. It is to be noted that proteoglycan and collagen synthesis continue to rise in proportion to the severity of the lesion [8]. It is tempting to believe that ingestion of these agents would somehow provide beneficial help to the cartilage [9].

An important biomarker of cartilage degradation is termed cartilage oligomeric matrix protein (COMP). The serum levels were found to reflect the extent of cartilage matrix turnover in patients with OA [7,10–12]. COMP is a pentameric glycoprotein which is highly expressed in the cartilage. It binds collagens I, II and IX accordingly, this abundant cartilage matrix protein might have several roles in cartilage tissue homeostasis, including regulation of collagen fibril formation and maintenance of the integrity and properties of collagen network [13]. The rate of synthesis of COMP is enhanced in the human cartilage with early OA lesions and rising levels of COMP have been found to correlate with progression of the disease [14]. COMP was initially thought to be cartilage specific, over the past few years it has been identified in all structures of the joint, including ligaments, meniscus, tendons, and synovium. Serum level of COMP was found also to be increased after physiological cyclic loading [15].

Previous studies have demonstrated an association between OA progression and inflammation as measured by systemic C-reactive protein (CRP) levels. The more aggressive disease seen in OA patients with elevated CRP levels may be linked to a more inflammatory synovial response in the diseased joint [16].

For decades, the traditional pharmacologic management of OA has been mainly symptomatic without well-documented influence on the duration of the disease and its progression. Dietary supplements have become mainstream products in the management of OA like glucosamine sulfate [17]. Glucosamine sulfate, the pharmaceutical derivative of the naturally occurring aminomonosaccharide glucosamine, a constituent of glycosaminoglycan in the cartilage matrix and synovial fluid, has been used orally for the treatment of OA since the early 1980s. After oral administration, glucosamine sulfate is bioavailable and reaches the articular cartilage. It is preferentially incorporated by the chondrocytes into the components of the glycosaminoglycan chains in the intact cartilage, stimulates the synthesis of physiological proteoglycans, and decreases the activity of catabolic enzymes, including metalloproteases [18].

In addition, the compound may reverse some of the negative effects of interleukin-1 on cartilage metabolism [19]. Also, there is a mild anti-inflammatory effect exerted by the suppression of superoxide radical generation or the inhibition of inducible nitric oxide synthesis and selectively, of the cyclooxygenase-2 pathway.

Contradictory researches were published regarding the efficacy of glucosamine and chondroitin sulfate in OA. Some researchers found that glucosamine has no value in the management of OA [20,21]. Others found that oral glucosamine and chondroitin sulfate may relieve the pain and joint stiffness, physical function, overall questionnaire score, and analgesic use associated with OA [22]. Moreover; they may act as a disease-modifying agent in patients with mild to moderate OA showing delayed radiographic progression of OA of the knee [23–28]. Most currently available glucosamine-based drugs and supplements are taken orally at a dosage (1500 mg daily). The dose reaching the articular cartilage is a fraction of a percentage of the oral dose (10–20%) [29]. Lately; an emulsion matrix [obalin] was available. It can hold up to 20% glucosamine compounds in a stable emulsion which can deliver glucosamine transdermally to the joints [19]. Chondroitin sulfate acts as a carrier substance to enhance dermal penetration [30]. Unfortunately, no data are available comparing the efficacy of the two products in managing OA of the knee [31].

The aim of this study was to detect, compare the efficacy of topical and oral glucosamine/chondroitin sulfate on knee OA and to prove their efficacy on sparing the articular cartilage among the Egyptian patients.

2. Patients and methods

One hundred eighty outpatient females aged 32 to 62 years, diagnosed as OA of the knee based on the criteria of the American College of Rheumatology [31] were included. The following predetermined exclusion criteria were considered on enrollment: Pregnant females; other rheumatologic disorders causing erosive arthritis of the knee; cases with severe osteoarthritis or with moderate or marked knee effusion; regular

requirement for analgesia for conditions unrelated to OA; use of oral or topical glucosamine in the previous 6 weeks; use of intra-articular injection of steroids or hyaluronic acid during the previous 6 months. Diabetic patients were informed that glucosamine sulfate causes an increase in blood glucose level and that blood glucose level should be monitored [29].

2.1. Study design

A follow up study was conducted according to a randomized design in the department of Rehabilitation and Rheumatology, Alexandria University Hospitals-Alexandria-Egypt, between December 2007 and November 2011. The protocol was approved by the college of Medicine, Alexandria review board, and patients provided written informed consent. Patients were screened at a baseline visit that included a physical examination, knee examination, knee radiographs, and symptom questionnaire and serum samples were taken for the biochemical analysis of human cartilage oligomeric matrix protein (COMP) and C reactive protein (CRP) before and after the treatment period.

2.2. Biochemical methods

1- Estimation of human COMP by ELISA [32]: [Wielisa COMP assay] IDEON Research Park S-223 70 Lund Sweden. The assay utilizes native human articular cartilage COMP coated to well microtitre plates, and a rabbit polycolonal antiserum directed to human COMP. An overnight preincubation step of sample with primary antiserum, after which the solution is transferred to the COMP coated plate. Bound antibodies are detected after wash using alkaline phosphatase labeled antirabbit IgG conjugate.
2- Estimation of CRP by the turbidimetric method [33]. It assesses agglutination of latex particles coated with antibody against CRP by quantifying the absorbed light.

2.3. Treatment protocol

After enrollment in the study, the patients were randomly divided into 2 groups of ninety patients each. The first group used topical glucosamine chondroitin sulfate preparation and the second group took 1500 mg of oral glucosamine chondroitin sulfate daily. The 2 groups were followed up until completion of the 3 month treatment course. At the end of the treatment period, a second clinic visit was made and included the same previous examination and laboratory investigations. Acetaminophen [500 mg/tablet] was allowed when needed, while no other treatment for osteoarthritis was allowed during the study period [25]. Patients under physiotherapy (infrared and/or TENS) program were allowed to continue their scheduled program.

2.4. Assessment of the knee joints

Clinical and radiological examinations of the knee joint were done for each patient before and after the treatment period. Weight-bearing anteroposterior and lateral semiflexed radiographs were recorded for both knees in each patient. They were radiologically graded according to the Kellgren–Lawrence [34]. All the films were assessed by a specialized reader.

2.5. Assessment of symptom change

Symptoms of knee osteoarthritis were evaluated at the first visit and at the end of the treatment period by using the Visual analog scale (VAS) [35] and Western Ontario and McMaster Universities (WOMAC) osteoarthritis index [6].

Statistical analysis: Study data were statistically analyzed using the Statistical Package for Social version program (SPSS program-version 18). Data were expressed as mean ± standard deviation (SD) or proportions (%). Statistical analysis was carried out using the paired *t*-test, Wilcoxon Signed Ranks Test, proportion hypothesis test and Mann–Whitney test ($P \leqslant 0.05$ was considered as statistically significant).

3. Results

All the included OA patients had completed the 3 month treatment duration. Table 1 gives the baseline characteristics of the 2 groups. No significant differences were found between the 2 groups as regards the age, body mass index (BMI) and duration of knee OA.

Clinical assessment proved that all the included patients were suffering from knee pain. The mean duration of knee pain was 32.8 ± 27.8 and 35.4 ± 20.9 months (among the local and oral groups respectively). The mean visual analog scale for pain assessment was 48.8 ± 4.3% and 62.2 ± 10.1% of the local and oral groups of patients respectively. Also, the mean pain severity score was less than 14 points on the WOMAC index subscale among the 2 groups of patients. The mean stiffness and knee joint function using WOMAC subscales were less than 5 and 23 points respectively among the 2 groups. On radiological assessment, the score of severity among the included patients ranged between 2 and 3 Kellgren and Lawrence grading.

3.1. Knee pain change after glucosamine/chondroitin sulfate treatment

Pain and stiffness decreased markedly in both treatment groups after the 3 month treatment duration with glucosamine sulfate according to the VAS ($P = 0.000$) for the local and oral groups respectively, and according to the WOMAC index score points ($P = 0.000$) for the local and oral groups (Table 2).

3.2. Stiffness and function changes

Joint stiffness decreased markedly in both treatment groups according to the WOMAC index score points ($P = 0.000$) and also regarding joint function ($P = 0.001$) (Table 2).

Improvement of pain, stiffness and joint function in knee osteoarthritis patients of local and oral groups, after treatment is presented in Table 3.

All patients were complaining of pain and joint stiffness prior to the study. According to VAS, pain was decreased by

Table 1 Baseline demographic and clinical characteristics of the knee osteoarthritis patients according to the treatment received (Local and Oral).

Characteristic	Knee OA patients according to treatment	
mean ± SD	Local (n = 90)	Oral (n = 90)
Age (years)	48.6 ± 8.2	50 ± 6.2
Duration of knee pain (months)	32.8 ± 27.8	35.4 ± 20.9
BMI (kg/m^2)	28.3 ± 2.3	29.9 ± 2.3
VAS (%)	48.8 ± 14.3	62.2 ± 10.1
WOMAC index score		
Pain	13.2 ± 4.96	13.4 ± 2.5
Stiffness	4.8 ± 1.9	4.5 ± 1.7
Function	22.5 ± 6.6	23 ± 4.8

OA: osteoarthritis, BMI: body mass index, VAS: visual analog scale, WOMAC: Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.

about 50% in 36% of the treated patients. No improvement was detected among 25% of the orally treated group compared to 16% of the locally treated patients. Decrease of joint stiffness by more than 50% was recorded in 66% of the patients of the locally treated group compared to 46% of the oral group. 25% decrease in joint stiffness was present among 33% of the patients. Regarding joint function; significant improvement was found among the 2 groups. Improvement (> 50%) was recorded among 54% of the local group compared to 35% of the oral group patients. Nearly, no improvement was found in about 40% of the treated patients. The degree of improvement of the joint function to treatment was negatively correlated with the duration of knee pain.

Radiological assessment of the treated groups: Ninety percent of the included patients of the local treated group were classified as grade 2, while 10% were classified as grade 3 Kellgren and Lawrence severity score. Radiological reassessment at the end of the study revealed no change of radiological severity for all the patients and among the two groups (Table 4).

Table 4 Radiological assessment of the knee osteoarthritis patient treated groups according to Kellgren-Lawrence grade (before and after treatment).

Knee OA patients (n = 90 in each group)		
N (%)	Kellgren–Lawrence grade	
	Grade 2	Grade 3
Local group		
Before	81 (90)	9 (10)
After	81 (90)	9 (10)
Oral group		
Before	76 (84)	14 (16)
After	76 (84)	14 (16)

OA: osteoarthritis.

Table 2 Clinical characteristics of patients with knee osteoarthritis before and after local and oral treatment.

Characteristic	Knee OA patients according to treatment groups					
Mean ± SD	Local (n = 90)			Oral (n = 90)		
	Before	After	P	Before	After	P
VAS (%)	48.8 ± 14.3	32.5 ± 21.4	0.000	62.2 ± 10.1	39.6 ± 18.8	0.000
WOMAC score						
Pain	13.2 ± 4.96	7.5 ± 3.5	0.000	13.4 ± 2.5	8.3 ± 2.4	0.000
Stiffness	4.8 ± 1.9	2.3 ± 1.4	0.000	4.5 ± 1.7	2.7 ± 0.7	0.000
Function	22.5 ± 6.6	11.9 ± 7.1	0.000	23 ± 4.8	15.4 ± 3.4	0.000

Table 3 Improvement of pain, stiffness and joint function in knee osteoarthritis patients of local and oral groups, after treatment.

Improvement N (%)	Knee OA patients (n = 90 in each group)			
	⩾75%	50–75%	25–50%	< 25%
Local group				
Pain	7 (8)	33 (37)	36 (40)	14 (15)
Stiffness	0 (0)	59 (66)	30 (33)	1 (1)
Function	0 (0)	49 (54)	5 (6)	36 (40)
Oral group				
Pain	7 (8)	33 (37)	27 (30)	23 (25)
Stiffness	0 (0)	42 (46)	30 (34)	18 (20)
Function	0 (0)	32 (35)	22 (25)	36 (40)

OA: osteoarthritis.

Table 5 Biochemical characteristics of patients with knee osteoarthritis before and after local and oral treatment.

Biochemical Characteristic	Knee OA patients in treatment group (n = 90 each)					
	Local	*P*	Sig	Oral	*P*	Sig
CRP *(mg/L)*						
Before	5.7 ± 7.1	0.16	NS	4.7 ± 2.2	0.13	NS
After	5.6 ± 6.8			4.4 ± 1.96		
COMP *(μg/ml)*						
Before	37.4 ± 7.4	0.11	NS	67.9 ± 24.9	0.68	NS
After	37.3 ± 7.3			67.6 ± 24.8		

OA: osteoarthritis, CRP: C-reactive protein, COMP: cartilage oligomeric matrix protein.

Table 6 Knee osteoarthritis patients need analgesia (acetaminophen) and physiotherapy before and after local and oral treatment.

N (%)	Knee OA patients (n = 90 in each group)		
	Acetaminophen	Physiotherapy	*P*
Local group			
Before	72 (80)	36 (40)	0.000
After	20 (18)	9 (10)	0.000
Oral group			
Before	81 (90)	45 (50)	0.000
After	30 (27)	6 (16)	0.000

Acute phase reactant changes: CRP was measured in the patient sera before and after treatment where, no significant changes were found among the 2 groups (Table 5).

Cartilage oligomeric matrix protein (COMP) changes: The COMP was measured in the sera of both groups before and after the 3 month treatment duration. No significant changes were detected among the 2 groups after treatment (Table 5).

From Table 2 on comparing the results of oral treatment versus local treatment, it is evident that both are equal as regards symptomatic improvement of pain, joint stiffness and joint function. Meanwhile, there was no significant change in levels of the human COMP and C-RP after treatment (Table 5).

There was no statistical difference between the two treated groups regarding the patient need of physiotherapy (infrared and/or TENS) and analgesic tablets (acetaminophen) either before or after the study period (Table 6).

4. Discussion

OA of the knee joint is a disorder characterized by a multiplex of symptoms. This study was designed to detect the effect of glucosamine/chondroitin sulfate on knee OA, their efficacy to stop or improve the degradation of the articular cartilage and to compare the efficacy of the topical versus the oral preparations among the Egyptian patients. The included patients were randomly divided into 2 groups, each of 90 patients. One group took oral and the 2nd group took topical glucosamine/chondroitin sulfate preparations for 3 months. The 2 groups were of matched age, sex, BMI and duration of knee pain. Knee examination, radiological assessment and biological investigations were carried out for all the patients before and after treatment. Joint pain and stiffness were the main symptoms in this study, where VAS ranged between 30 and 85%. Also, WOMAC pain subscale ranged between 7 and 20 points. Knee stiffness measured by WOMAC subscale ranged between 1 and 5 points. Daily activity and knee joint function were affected in most of the patients where WOMAC subscale for joint function ranged between 13 and 31 points. Moreover, all the included patients were suffering from knee cartilage degradation on radiological assessment, ranged between 2 and 3 Kellgren and Lawrence severity scale. No changes in the severity score and joint space width were noticed after completion of the treatment duration. In this study, all the patients completed the treatment duration which reflects the safety of the compound.

The study revealed that the two groups of patients showed marked relief of pain after treatment with a subsequent significant decrease of the need for analgesic tablets and physiotherapy. There was no significant difference between the 2 groups regarding pain relief after treatment. The percentage of patients showed that pain improvement is comparable with other studies [19].

Joint pain measured by VAS was improved in all the included patients. However, there was no significant difference found between the locally and orally treated patients. Decrease of joint stiffness was better in the locally treated group. Rubbing of the joint during application of the glucosamine cream may have an additional value in relieving the joint stiffness. Regarding joint function, significant improvement after treatment was found among the 2 groups. However, better response was recorded among the locally treated patients. The degree of response of the joint function to treatment was negatively correlated with the duration of knee pain (bad response to the drug was recorded in OA patients with more than 24 month duration).

4.1. Joint cartilage turnover

1- The CRP is recognized as one of the most sensitive measures of inflammation. It is highly associated with OAK. However, its high correlation with obesity limits its utility as an exclusive marker for OAK [36]. In this study, there was a statistically insignificant decrease of the mean CRP after treatment among the 2 groups.
2- The COMP is considered as a marker of joint cartilage turnover. Its level increases in the synovial fluid of patients suffering from OA [37]. In this study, there was no significant difference of the mean serum COMP level after treatment among the 2 groups.

In conclusion, this study showed that glucosamine sulfate is effective as pain, stiffness and function improving drug. The local application is slightly more effective than the oral route of administration with nearly no side effects during the 3 month duration of treatment. This study revealed that glucosamine sulfate is beneficial as symptomatic relief of pain, stiffness and improving the joint function rather than a cartilage restoring or sparing drug in the treatment of knee osteoarthritis.

Conflict of interest

None.

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