The Role of Glucosamine Chondrotin Sulfate in the Treatment of Osteoarthritis of Knee

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Abstract

Background: Osteoarthritis (OA) currently seems inevitable and unavoidable for a large swath of the population .its etiology relates to a strong ,but complex ,non mendelian genetic basis ,combined with mechanical and metabolic factors that cause molecular alterations the end results of which affect the whole joint .Glucosamine and chondrotin sulfate alone or in combination may be of benefit to a subgroup of individuals who have knee pain due to OA.

Glucosamine has been shown to alter cartiage turn over in patients with OA undergoing physical training

Aim of the study: To find the validity of glucosamine chondrotin sulfate in treatment of grade 1 and 2 OA.

Methods: the sample of 280 patients (418 knee) were divided in to two groups , group A (132 patient) treated by classical methods by glucosamine chondrotin sulfate for one year. For both groups different parameters were used including pain stiffness effusion crepitus and genu varum and different radiological findings and we used MRI for evaluation pre and post treatment

Result: Female/ male ratio was 2.89 the highest age group was (60-69) year regarding the clinical presentation of patients the commonest clinical presentation were pain and stiffness and the MRI finding including bone marrow edema shows good indicator for response to treatment .

Conclusion: Pain ,stiffness and crepitus were common presentation of OARelief of pain andstiffness were related to decrease of effusion and bone marrow edema which is the result of using nonsteroidal anti-inflammatory drugs with glucosamine chondroitin sulfate more than when non steroidal anti- inflammatory drugs alone.

Keyword: Osteoarthritis- glucosamine chondroitin sulfate

Al – Kindy Col Med J 2013; Vol. 9 No. 1 P:100

Introduction

Osteoarthritis afflicts 13.9% of all people 25 years old and older and 33.6% of all people 65 years old and older. In 2005, a conservative estimate of U.S adult with OA numbered 26.9 million. Knee OA accounts for 1 of 5 primary factors of disability in non-institutionalized adults. The estimated annual U.S., expenditure for OA treatment and lost work is more than $33 billion[1]

Osteoarthritis is a condition that represents a pathological imbalance of degradative and reparative involving the whole joint and its component parts, with secondary inflammatory changes, particular but also in the articular cartilage itself. Idiopathic.primary OA may involve one particular generalized or involve multiple joints in erosive inflammatory form[2].

A cartilage is a tissue with compressive and viscoelastic properties which are conveyed by extracellular matrix, which is composed largely of proteoglycans and type 11 collagen[3]. Normally, this matrix goes through an active remodeling process wherein synthetic and low levels of degradation enzyme activities are kept well balanced by constant breakdown and repair, so that the cartilage's volume is maintained[4]. Glucosamine-Chondrotin sulfate reduces long-standing pain, reverse cartilage damage.

The central features in OA is loss of articular cartilage and reduced capacity for repair; the chondrocytes themselves appear to be the driving force behind these deficiencies[5]. A focal lesion in the cartilage might lead to abnormal loading of the surrounding chondrocytes, which, in turn, respond by promoting a cascade of slow but persistent degradation of cartilage, ultimately leading to loss of joint function.Biomechanical and biochemical forces are involved in cartilage destruction which is at the core of OA(6).

Glucosamine sulfate is an aminosuger molecule needed to form glycosaminoglycan and hyaluronic acid molecules that are major constituents of joint cartilage, or the tissue that lines the joints. Chondrotin sulfate is a

glycosaminoglycan molecule. Because glucosamine sulfate is a smaller molecule than chondrotin sulfate, it is more easily absorbed across GIT, making it more available for tissue such as cartilage to use. Chondrotin sulfate helps draw water into the cartilage and making it more elastic(7).

MRI can provide semi-quantitative assessment in OA because it can detail articular cartilage integrity; subchondral bone-marrow pathology; edema or cysts; subchondral bone attrition; marginally, centrally, and posteriorly positioned osteophytes; meniscal and ligament integrity; synovitis and effusion; and loose bodies(3).

Methods:

A randomized clinicaltrial was done in Al-KindyTeachingHospital, and Al-Jarah Private Hospital in the period between February 2008 and February2011.A total number of 450 patients (628knees) with osteoarthritis of knee joint were recruited in this study.

Participants:

Following the approval of ethical and scientific committee in Al Kindy College of Medicine and the scientific committee in al Kindy Teaching Hospital, patients presented with OA of the knee clinically (pain and stiffness in the knee) and radio logically(plain X-Ray in standing position) were included in this study. Informed consent was taken from each patient before obtaining any information.

All study samples were assessed for inclusion criteria that list any patient with stage II primary, chronic OA and more; unilateral or bilateral is eligible for this study.

Those patients presented with rheumatologic problems other than OA or have history of drug sensitivity were excluded.

Of these, only two hundred and eighty (80.0%) of the patient (360 patients and 534 knees) met the inclusion criteria and adhered to the study instructions in completing the one year period of the follow up.

Measurements: complete history, rheumatologic examination, and MRI investigation were performed for each patient before giving the intervention and one year later, Other data as age, gender, duration of disease, type of standard OA treatment were also obtained.

Follow up: All patients were followed in a monthly visit to assess their adherence to the instructions and only those who adhered to the instructions at the end of the study (280 patients and 418 knees) period were included in the analysis.

The patients were divided randomly into two groups:

Group A included 132 patients(197 knee) treatment with classical (standard) method (The protocol of the treatment, include a modification from ESCISIT (Task Force of Standing Committee for International Clinical Studies including Therapeutic Trails) published at 2008 inRheumaticDiseases Clinics of North America) (1,4).

1- Treatment tailored according to risk factors, such as obesity and activity, age, level of pain, sign of inflammation, and location and extent of structural damage.

2- Education, exercise, use of appliances, and weight reduction.

3- Paracetamol as the first analgesic used.

4- Topical NSAIDs is efficacious and safe.

5- NSAIDs can be considered in patients for whom paracetamol is not helpful. Nonselective NSAIDs or COX-2 inhibitors play a role for a subset of patients for whom NSAIDs are contraindicated or do not work(8).

While group B included 148 patients (221 knee) treated, in addition to above standard methods, with Glucosamine chondrotin sulfate tablets (1500 mg) for one year.

For both groups data were collectedin the same way in the whole period of the study.

Both groups were evaluated according to MRI findings before starting treatment, six months, and one year after treatment.Patients in whom symptomatic OA at multiple joint sites was diagnosed.

MR images were PA and interpreted by radiologist.

Cartilaginous defects, osteophytes, subchondral cysts, and bone marrow edema were assigned to one or more of the following anatomic locations:

Cartilaginous defects were classified as diffuse or focal. The surface extent of a diffuse or focal cartilaginous defect was estimated and classified as follows: grade 0, absent; grade 1, minimal (<5 mm); grade 2, moderate (5–10 mm); or grade 3, severe (>10 mm). The depth of a cartilaginous defect was classified by using a modification of the classification of Yulish et al (10): grade 0, absent (no abnormality in signal intensity or morphology); grade 1, less than 50% reduction of thickness of cartilage; grade 2, 50% or greater reduction of thickness of cartilage; or grade 3, full-thickness or near full-thickness cartilaginous defect.

Osteophytes were defined as focal bony excrescences that were seen on transverse, sagittal, or coronal images and that extended from a cortical surface.. Osteophytes were classified with the following scale: grade 0, absent; grade 1, minimal (<3 mm); grade 2, moderate (3–5 mm); or grade 3, severe (>5 mm). The size of the osteophyte was a measurement from the base to the tip (11.

Subchondral cysts were characterized as well-defined foci of high signal intensity on T2-weighted images in the cancellers' bone underlying the joint cartilage. Their greatest dimension was measured, and they were classified as follows: grade 0, absent; grade 1, minimal (<3 mm); grade 2, moderate (3–5 mm); or grade 3, severe (>5 mm).

Bone marrow edema was characterized as an ill-defined area of increased signal intensity on T2-weighted gradient-echo images in the subchondral cancellers bone that extended away from the articular surface over a variable distance (12). The lesions were classified as follows: grade 0, absent; grade 1, minimal (diameter of <5 mm); grade 2, moderate (diameter of 5 mm to 2 cm); or grade 3, severe (diameter of >2 cm).

Meniscus subluxation was defined as protrusion over the edge of the tibial plateau on coronal intermediate-weighted images and was classified as follows: grade 0, absent; grade 1, minimal (less than one-third width of the meniscus bulging); grade 2, moderate (one- to two-thirds of the meniscus width was involved); or grade 3, severe (more than two-thirds of the meniscus width was involved).

Presence of a knee joint effusion was evaluated on T2-weighted coronal, sagittal, and transverse images. A small effusion was present when a small amount of fluid distended one or two of the joint recesses, a moderate effusion was present when more than two joint recesses were partially distended, and a massive effusion was present when there was full distension of all the joint recesses. The lateral, medial, and suprapatellar joint recesses were evaluated.

Statistical analysis was done by using MINI TAB version 17 software. Descriptive statistics was addressed my measuring the frequency and percentage. Chi square test was used in finding the association, and if it not applicable, Fisher Exact test was used instead. P value less than 0.05 considered statistically significant.

Results:-

After analysis of data of 280 patients (418 knee): Group A including 132 patients (197 knee) and group B including 148 patients(221 knee). Age and sex distribution were studied and the finding: Female/ male ratio was 2.89 (table 1). The highest age group was (60-69), was 46.8%, then the age group (50-59), was 29.3%. Table (2).

Regarding the clinical presentation of patients, we found that all patients in both groups presented with pain, and most of the patients presented with stiffness (95.36%),

joint effusion (91.7%), crepitus(55.36%), genu varum (13.2%). Table (3).

The radiological findings before treatment were, narrow one compartment (76.43%), narrow two compartment(19%), narrow three compartment(4.7%), bony spiking of tibial spine(96.43%), subchondral cysts (12.14%), and subchondral sclerosis(5.7%).

Evaluation of subchondral cysts by MRI before and after the treatment in both group were of no significant (table 5).

Bone marrow edema evaluation by MRI was of significant, in group A, before the treatment, in grade 1, 94% of patient while after the treatment 3 months, 6 months and one year- 91.7% ,89.4%, 87.12% respectively. In group B, before treatment in grade 1, 93.2%, while after treatment, 3 months, 6 months, one year-18.2%, 12.84%, 8.1% respectively,(table 5).

Meniscal subluxation seen by MR, before and after the treatment was of no significant (table 6).

Cartilage defect as seen by MRI, in group A, grade 1, before treatment 88.6% and after treatment 3 months, 6 months, one year was 85.6%, 84.1%, and 83% respectively, while in group B, grade 1, before the treatment was 86.5%, while after treatment, 3 months, 6 months and one year was 81.1%,77.7% and 54.7% respectively (table 7). The depth cartilage defect as seen by MRI, in group A,before treatment 92.4%, while after the treatment, 3 months, 6 months, and one year was 90.2%, 89.3% and 89.3% respectively, while in group B, grade 1, before treatment was 88.5%, after the treatment, 3 months, 6 months, and one year was 82.4%, 68.2% and 66.22% respectively, (table 8). Regarding osteophytes and subchondral cyst as seen by MRI were of no significant (table 9).

Clinical assessment of patients before and after the treatment was seen in (table 12), we found that pain, stiffness, effusion and crepitus were good criteria for evaluation of the effect of treatment , also we found the longer the treatment the better the outcome.

All MRI images were analyzed in consensus by one reader by using a comprehensive score form (13)

Description of the Studied Sample

Table (1) Gender distribution

Groups	No	Female No (%)	Male No %	P value
Group A	132	96 (72.7)	36 (27.3)	0.573
Group B	148	112 (75.7)	36 (24.3)	
Total	280	208 (74.3)	72 (25.7)	
Female – male ratio=2.89				

Table 2 Age and gender distribution

Group	Sex	40-49 No (%)	50-59 No (%)	60-69 No (%)	70-79 No (%)	Total	P value
Group A	Female	9 (9.4)	47 (49)	33 (34.3)	7 (7.3)	96	0.248
	Male	4 (11.2)	10 (27.7)	14 (38.9)	8 (22.27)	36	
Group B	Female	6 (5.4)	52 (46.4)	42 (37.3)	12 (10.7)	112	
	Male	3 (8.3)	16 (44.4)	42 (37.3)	8 (22.3)	36	
Total		22	125	131	35	280	

Clinical findings

Table 3 Clinical finding before and after starting the treatment

	Pain Before	Pain After	Stiffness Before	Stiffness After	Joint effusion Before	Joint effusion After	Crepitus Before	Crepitus After	Genu .Varum Before	Genu .Varum After
Group A No (%)	132 (100)	72 (54.5)	128 (96.9)	107 (59.1)	127 (96.2)	89 (67.4)	`58 (43.9)	35 (28.9)	15 (11.4)	12 (9.1)
Group B No (%)	148 (100)	34 (23)	139 (93.9)	69 (87.2)	133 (89.9)	105 (70.9)	97 (65.5)	32 (21.6)	22 (14.9)	18 (12.2)
P value	0.000		0.008		0.531		0.040		0.964	

MRI findings

Table 4 Subchondral cyst before and after treatment (MRI)

	Grad 1				Grad 2				Grad 3			
	Before	After 3 m	6 m	1 Y	Before	After treat 3M	6 M	1Y	Before	After teat 3M	6M	1Y
Group A No (%)	16 (7.6)	16 (7.6)	16 (7.6)	16 (7.6)	3 (2.3)	3 (2.3)	3 (2.3)	3 (2.3)	1 (0.8)	1 (0.8)	1 (0.8)	1 (0.8)
Group B No (%)	24 (18.2)	24 (18.2)	24 (18.2)	24 (18.2)	4 (3.0)	4 (3.0)	4 (3.0)	4 (3.0)	2 (1.5)	2 (1.5)	2 (1.5)	2 (1.5)
P value	0.942				0.963				0.985			

Table 5 Bone marrow edemabefore and after treatment (MRI)

	Grad 1				Grad 2				Grad 3			
	Before	After 3 m	6 m	1 year	Before	After 3 m	6 m	1 year	Before	After 3 M	6 m	1 year
Group A No (%)	124 (94)	121 (91.7)	118 (89.4)	115 (87.1)	7 (5.3)	6 (4.6)	6 (4.6)	5 (3.8)	1 (0.7)	1 (0.7)	1 (0.7)	1 (0.7)
Group B No (%)	138 (93.2)	27 (18.2)	19 (12.8)	12 (8.1)	8 (5.4)	4 (2.7)	3 (2)	2 (1.4)	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)
P value	0.00				0.048				0.245			

Table 6 Meniscal subluxation before and after 1 Year treatment (MRI)

	Grad 1		Grad 2		Grad 3	
	Before	After	Before	After	Before	After
Group A No (%)	13 (9.8)	13 (9.8)	4 (3)	4 (3)	1 (0.76)	1 (0.76)
Group B No (%)	17 (11.5)	17 (11.5)	5 (3.4)	5 (3.4)	1 (0.65)	1 (0.65)
P value	1.00		1.00		1.00	

Table 7 Cartilage defect before and after treatment (MRI)

	Grad 1				Grad 2				Grad 3			
	Before	After 3 m	6 m	1 year	Before	After 3 m	6 m	1 year	Before	After 3 M	6 m	1 year
Group A No (%)	117 (88.6)	113 (85.6)	111 (84.3)	110 (83.8)	11 (8.3)	11 (8.3)	11 (8.3)	11 (8.3)	6 (4.6)	6 (4.6)	6 (4.6)	6 (4.6)
Group B No (%)	128 (86.5)	120 (81.1)	115 (77.7)	81 (54.7)	14 (9.5)	13 (8.9)	12 (7.8)	10 (6.8)	4 (2.7)	4 (2.7)	4 (2.7)	4 (2.7)
P value	0.041				0.824				1.00			

Table 8 Depth of defect before and after treatment (MRI)

	Grad 1				Grad 2				Grad 3			
	Before	After 3 m	6 m	1 year	Before	After 3 m	6 m	1 year	Before	After 3 M	6 m	1 year
Group A No (%)	122 (92.4)	119 (90.2)	118 (89.3)	118 (89.3)	6 (4.5)	6 (4.5)	6 (4.5)	6 (4.5)	2 (1.5)	2 (1.5)	2 (1.5)	2 (1.5)
Group B No (%)	131 (88.5)	122 (82.4)	101 (68.2)	98 (66.2)	14 (9.5)	14 (9.5)	13 (8.9)	12 (7.8)	3 (2)	3 (2)	3 (2)	3 (2)
P value	0.166				0.856				1.00			

Table 9 Osteophyltes before and after treatment (MRI)

	Grad 1				Grad 2				Grad 3			
	Before	After 3 m	6 m	1 year	Before	After 3 m	6 m	1 year	Before	After 3 M	6 m	1 year
Group A No (%)	123 (93.3)	122 (92.4)	122 (92.4)	122 (92.4)	7 (4.9)	6 (4.5)	6 (4.5)	6 (4.5)	2 (1.5)	2 (1.5)	2 (1.5)	2 (1.5)
Group B No (%)	137 (92.8)	135 (91.3)	134 (90.5)	134 (90.5)	8 (5.4)	7 (4.9)	7 (4.9)	7 (4.9)	3 (2)	3 (2)	3 (2)	3 (2)
P value	0.648				0.864				1.00			

Discussion:-

and most of these studies concluded thatthis association is poor). Magnetic resonance (MR) imaging allows another perspective of the structural abnormalities associated with OA, and MR imaging findings have been associated with clinical features, which include knee pain. A major hallmark of OA is loss of cartilage. The exact cause of knee pain in patients with OA remains enigmatic because hyaline cartilage does not contain pain fibers and, as such, cannot be the direct cause of pain in OA. Pain fibers are present in other structures in the knee, such as the joint capsule, periosteum, insertional sites of ligaments and muscles, outer third of the menisci, and, possibly, the synovium), but their role is uncertain. A large joint effusion was associated with pain and stiffness. Another association found between structural abnormalities seen on MR images of the knee and clinical features was that between grade 2 and 3 (moderate and massive) joint effusion and knee pain or knee stiffness. In the literature, a controversy exists about the association between joint effusion and knee pain. Hill et al (13) found that moderate and severe effusions (grade 2 and 3) were substantially more common among patients with knee pain compared with those without having OA of the knee. Link et al (14) reported no significant association between the presence or the amount of joint effusion and clinical features. They did, however, find a trend toward higher pain scores in patients with joint effusion. In some studies (13,15,16), an explanation for the association between pain and joint effusion has been given in that the researchers suggested that capsular distention is the cause of knee pain. The presence of an osteophyte in the patellofemoralcompartment was associated with pain. All other imaging findings, including focal or diffuse cartilaginous abnormalities, subchondral cysts, bone marrow edema, subluxation of the meniscus, meniscus tears, or Baker cysts, were not associated with symptoms, We used MRI in this study to evaluate the role of Glucosamine Chondrotin sulfate drug in treatment of knee OA depending on only four parameters : pain, effusion(clinically and on MRI) , bone marrow edema(MRI), regeneration of cartilage(decrease the defect and increases the thickness). In a study done by Peter R. Kornaat, MDtheyconcluded that there were only two associations between structural abnormalities found on MR images and clinical features in patients with OA of the knee. Moderate and massive joint effusion was associated with both knee pain and knee stiffness. The presence of a patellofemoral osteophyte and the presence of more than four osteophytes in the entire knee were associated with knee pain only. Focal or diffuse cartilaginous abnormalities, subchondral cysts, bone marrow edema, subluxation of the meniscus, meniscus tears, or Baker cysts were not associated with pain and stiffness in our study we found that these parameters were important in evaluation of the patients before and after treatment with Glucosamine chondrotin sulfate regarding pain and stiffness. In our study, depending on some other parameters in evaluation of patients, in addition to pain and stiffness, the effusion and bone marrow edema were important factors, in addition to regeneration of articular cartilage which was seen after about six months of treatment with Glucosamine Chondrotins ulfate, while the relief of pain and stiffness and decrease of effusion and bone marrow appears earlier during the period of treatment, we concluded that Glucosamine Chondrotin has in addition to its role in cartilage regeneration, some anti-inflammatory effects which causes relief of pain, stiffness, edema, and effusion. The effect of Glucosamine Chondrotin Sulfate is likely the result of reactions including its anti-inflammatory activity, the stimulation of the synthesis of proteoglycans and hyaluronic acid, and the decrease in catabolic activity of chondrocytes inhibiting the synthesis of proteolytic enzymes, nitric oxidem and other substances that contribute to damage cartilage matrix and cause death of articular

chondrocytes(17). The bioavailability of chondrotin sulfate range from 15% to 24% of the orally administered dose. More particularly, on articular tissue, Ronca et al.(18) reported that chondrotin sulfate is not rapidly absorbed in the gastrointestinal tract and a high content of labeled chondrotin sulfate is found in the synovial fluid and cartilage.

Conclusion:

Comparing the results of clinical and MRI finding we conclude the followings:

1-Pain and stiffness and crepitus which are caused by OA of the knee are the most common presentation.

2- Relief of pain and stiffness were related to decrease of effusion and bone marrow edema which is caused by non steroidalanti inflammatory drugs with Glucosamine Chondrotin sulfate, more than when we use non steroidalanti-inflammatory drugs alone.

3- To get good result from using glucosamine chondrotin sulfate, treatment must be continue for 9-12 months.

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