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The potential for structural modification hence benefit in osteoarthritis of knee by mineral supplementation –pilot study

KEYWORDS

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ABSTRACT *The potential for structural modification by natural mineral supplement was evaluated in a pilot prospective, study of six months duration in twenty patients with moderate Osteoarthritis of knee.*

WOMAC values (subsets and total) showed significant improvement from baseline over the course of six months treatment ($p < 0.001$). The pain free distance covered during a Six minute walk (6MWD) also significantly improved by 140 feet ($(p<.001$). Requirement of rescue medication decreased to once a week in 45%. The mean (SD) change for the percentage of painful days were 45.0 (38.7). 25% patients demonstrated improved cartilage thickness by at least 0.01 mm as against 15% who lost thickness at least by 0.01 mm. 55% patients showed improved Cell counts (below 500 microlitre) in Synovial fluid. Hematological and Biochemical safety variables showed that mineral supplement is absolutely safe.

The study suggests that natural mineral supplementation helped in synovial metabolism and in reducing cartilage pathology hence had structural efficacy.

Introduction

Osteoarthritis (OA)is a degenerative disease characterized by focal areas of loss of particular cartilage in synovial joints, subchondral bone changes, osteophyte formation at the joint margins, thickening of the joint capsule and mild synovitis. ACR Guidelines for Medical Management of Osteoarthritis of the knee recommend patient education to reduce weight, quadriceps strengthening exercise, Non-steroidal anti-inflammatory drugs (NSAIDS) and chondroprotection.(1)

NSAIDs are the mainstay of management for pain, but since it may cause serious gastrointestinal and cardiovascular adverse events (2), it has led to search for structure modifying therapeutic solutions that can lead to an enhancement of tissue regeneration and the reduction of degenerative mechanisms.

Inconsistent results for chondroprotection by neutraceuticals like glucosamine, chondroitin, intrarticular hyalran emphasize the associated role of cofactors, vitamins and minerals from diet. (3, 4, 5)

Minerals and trace elements like Boron, Zinc, Copper, Selenium, Magnesium, Manganese, Vitamins A, E and C, Niacin, Pantothenic Acid, Omega 3 fatty acids, chondroitin sulphate, Glucosamine, and Sulphur containing amino acids play a significant role in the production of cartilage matrix. In vitro studies suggested that these trace minerals may favorably affect the synthesis of proteoglycans. The trace element copper is an essential cofactor in enzymes such as the collagen cross-linker lysyl oxidase (6, 7, 8, 9).

Naturally occurring minerals such as magnesium, copper, manganese, selenium and zinc have shown anti-inflammatory effects in both animal and human studies. In a rat model of osteoarthritis, a deficiency of dietary magnesium was demonstrated to enhance the amount of cartilage damage. Furthermore increased magnesium in the diet may influence inflammation through reducing the serum level of the pro-inflammatory protein C-reactive protein [10, 11].

Recent evidence has suggested an excess of reactive oxygen species arising from an imbalance in the antioxidant status of the joint (such as reduced levels of SOD) may result in cartilage degradation and joint remodeling [12].

Anti-oxidant enzyme super oxide dismutase requires copper, zinc and manganese as cofactors. It was demonstrated in the Haqqi model of human cartilage explants that mineral supplementation reduced cartilage degradation in response to IL-1β, as well as nitric oxide production secondary to the induction of inducible nitric oxide synthase. (13, 14)

Several clinical studies have also reported the effectiveness of minerals in the management of osteoarthritis (15,16,17,18), however that the results of the available studies were heterogeneous and did not allow firm objective evidence of structural benefit .

This study was intended to explore whether clinical benefit seen with adequate mineral supplementation in osteoarthritis is because of chondroprotective structural modification.

Materials and methods

The selection criteria for selection were patients who present with symptomatic primary Osteoarthritis of the knee (1), above 50 years of age, defined by daily pain for the previous three months, analgesics usage at least once a week, less than thirty minutes of morning stiffness and a WOMAC score of ≤ 75 in the target knee.

The food supplement selected is Concentrate Trace Mineral Drops (CTMD) it was selected because of easy availability in market, being a derivative from natural sources and already being consumed by masses.

The supplement contains over 72 natural minerals in ionic form, concentrated from the Great Salt Lake in Utah. Half tsf (approx 40 drops) serving of it contains magnesium 250 mg, chloride 690mg, sodium 5mg potassium 3mg, sulfate 37 mg lithium 295mcg, boron 370 mcg. In addition it also contains naturally occurring varying trace amounts of bromide,carbo nate,calcium,silicon,nitrogen,selenium,phosphoros,iodide, chromium, manganese, titanium, rubidium, cobalt, copper, antimony, molybdenum, strontium, zinc, Nickel, tungsten, etc plus other elements in sea water. Refer Table 1 for typical Mineral Composition of supplement used.

The radiographic eligibility criteria included Kellgren Lawrence classification for knee Osteoarthritis grade 0, 1, 2 or 3 (Table 2), Brandt Radiographic Grading Scale of Osteoarthritis grade 1 and 2 (Table 3), Ahlback Radiographic Grading Scale of Osteoarthritis of the Tibiofemoral Joint 0 & 1 (Table 4). If both knees were symptomatic, only the most painful

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one was taken into account.

The main exclusion criteria were evidence of secondary knee Osteoarthritis, severe Osteoarthritis (JSW < 2 mm), prior intra articular injections and corticosteroids, oral Diacerin within the previous three months, prior to inclusion and patients with clinically significant systemic disease.

A total of twenty patients were enrolled & advised to take mineral supplement twice daily for six months (24 weeks), on an empty stomach. The dose was gradually increased to 40 drops (½ tsf) from 5-10 drops a day in a week's time.

At the baseline visit, besides vital signs & laboratory tests the subjects were assessed for WOMAC score, 6 MWD, radiological assessment of joint space width, ultrasonological measurement of articular cartilage thickness and cell counts of synovial fluid.

Patients were evaluated weekly for any adverse events and need for any rescue medication (NSAIDS) in the first month followed by monthly evaluation up to six months.

WOMAC score and 6 MWD assessments were carried out every month. X-Ray, Ultrasonography, Synovial fluid assessment and Laboratory tests were repeated only at the end of 6 months.

The Western Ontario and McMaster Universities Osteoarthritis Index WOMAC (19) is a widely used measure of patient's subjective assessment of pain joint mobility and physical disability. It evaluates 3 dimensions, namely pain, stiffness and physical function with 5, 2, and 17 questions respectively. Total maximum score is 96 and minimum is 0. Each subscale is summated to a maximum score of 20, 8 and 68 respectively.

The six minute walking distance was carried out by marking off a 50 meter distance in an interior hallway and asking subjects to walk as far as they can and as quickly as they can over 6 minutes. The total distance was measured and recorded. (20)

Anteroposterior radiographs of the knee joints were obtained with patients in a weight bearing position, joint fully extended, standing at 1 meter from the X- Ray source, using previously published guidelines. Width was measured of the narrowest point of the JSW (minimal JSW). This progression was defined by a JSW loss of more than 0.50 mm during the study, as previously reported (21, 22)

Ultrasonographically, articular cartilage on weight bearing condyle appears as hypo echoic band with sharp anterior and posterior margins. It is thickest over intercondylar area (8 – 10 mm) and thinnest over femoral condyles (average 4 – 5 mm) (23, 24).

Cellularity of synovial fluid was compared by aspirating 2 ml of fluid under aseptic conditions. Normal synovial fluid has cell count of less then 2000/microlitre with a predominance of mononuclear cell. Increased counts up to 5000/ microlitre with predominance of polymorphonuclear leucocytes are seen in osteoarthritis. (6)

Tolerability and safety assessments included any symptoms and signs referred by patient and also by laboratory based hematological and biochemical assays. Adverse effects were categorized as isolated, intermittent or continuous depending on interference with the subject's daily activities as mild, moderate or severe. Possible causal relationship with the mineral supplement in terms of Definite / Possible / Probable / Non Assessable / None was also arrived at. The study was approved by ethics committee and all the patients were well informed and gave written consent to participate in the study.

Results

Of 32 screened patients, 20 were considered eligible for this pilot study. The most common reason for non-inclusion was either a lack of radiographic evidence of knee OA or severe disease with a JSW <2 mm at the narrowest point. No patients discontinued the treatment till the end of the study. Table 5 summarizes the main baseline characteristics of the 20 patients.

Symptomatic outcome measures showed significant improvement from baseline for WOMAC values (subsets and total) over the course of six months of treatment ($p < 0.001$). It is of note that after 12 weeks of treatment though the WOMAC scores had marked improvement over baseline but were not significant ($p > 0.05$) .The magnitude of Pain reductions appeared at week 4 but were insignificant. Table 6 summarizes the change in WOMAC scores, sub score of pain physical activity, &stiffness, 6MWD from baseline over 24 weeks of treatment. (figure 1)

Percentage of responders i.e. the percentage of patients having an improvement of at least 30% in pain on VAS or reduction in pain by womac sub score of between baseline and final visit were 55%.

The pain free distance covered during a 6 minute walk was significantly improved by 140 feet over 6 months ((p<.001) on treatment with the mineral supplement.(figure 3)

An improvement of 100 feet over 6months was noticed in 5 (25%) patients.

All the patients needed Rescue medication at least twice a week (Nsaid –Lornoxicam 8mg SOS) till initial 2weeks. Requirement of nsaid decreased to once a week in 4patients (20%), 6 (30%) 9 (45%) by 8, 12, 24weeks. Between baseline and final visit, 7 (35%) patients were NSAID free for last 30 days and the mean (SD) change for the percentage of painful days 45.0 (38.7). only 4 patients had no change in the rescue medication requirement. (figure 2)

Radiology did not reveal any increase in joint space width (JSW) in any patient. The study group had insignificant deterioration in the JSW (mean SD =0.05, p=0.82) with only 3 patients (15%) with a reduction in JSW >0.05 mm (p=0.90) hence labeled progress or. Ultrasonologicaly, at six months cartilage thickness improved by at least 0.01 mm in 5 (25%) patients as against 3 patients (15%) who lost thickness at least by 0.01 mm.

Synovial fluid examination suggested that it helped in restoring synovial fluid rheological properties and synovial metabolism and in reducing cartilage pathology. 11(55%) patients had cell counts below 500/ microlitre by 24 weeks compared to n=4 (20%) before the treatment.

Average cell count reduced to 240/ microlitre from a value of 480/ microlitre at the start of study.

No significant change in Blood pressure (systolic and diastolic), respiration rate and pulse rate were noted from screening for the study, at the 5 intermediate evaluation points till the study's conclusion. Only 2 subjects (10%) people experienced side effects with Minerl supplementation at this doses. The adverse effects were related to upper GI discomfort , mild to moderate in intensity and were completely resolved by 8 -12 weeks . A summary of Hematological and Biochemical safety variables is depicted in Table 7 shows that this mineral supplementation was absolutely safe.

DISCUSSION

Recent documentation of an increased risk for cardiovascular disease and stroke with COX-2 inhibitors and significant gastrointestinal, renal complications and premature deaths associated with non-selective COX inhibitors (2), along with

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the appreciation that the NSAID class provides symptomatic relief rather that abrogating the disease process, there is a greater search for alternatives.

In osteoarthritis, the exact mechanism remains controversial. It is suggested that there is a mismatch between regenerative and degenerative forces that govern cartilage formation, partly because of a malfunction in proteoglycan synthesis (6). The rationale for a general therapeutic application of mineral supplementation stems from this hypothesis.

Mineral supplementation can be of most benefit if minerals are in balance with other elements they interact with. Too much of one element can lead to imbalances in others, so it is important that they are derived from natural sources where they are balanced and in ionic form. Trace elements, bound in chelated form, are more readily available to the body and less likely to interact and interfere with each other during absorption.(7,9)

The dose of the mineral supplement was determined based on available literature about daily dietary allowance of various minerals (6). Patients with severe Osteoarthritis were excluded as they have severely damaged cartilage. Obviously the number of healthy synoviocytes in these patients is poor, which eventually means that there are not enough healthy cells to act upon and would not benefit from conservative treatment including dietary and viscosupplemtation.

The onset of benefits is evident from week 3 or 4 onwards there was an improvement of 9.6% over baseline walking distances at 24 weeks. Although, these distances appear to be small, our subjects indicated that the ability to walk even a little bit further was important to them. Need of Rescue medication was reduced by 45 %. This early onset of benefits as early as one week in some patients is not inconsistent with the in vitro studies demonstrating the protection of human cartilage degradation induced by IL-1β. However, the present study does not directly assess whether protection of against cartilage degradation was associated with the therapies, nor is it likely that a substantial change in joint architecture would occur in this timeframe (10, 11, and 12).

Our extensive literature search did not yield any study that present objective clinical data showing beneficial effect of mineral supplementation in joint health. We could compare our results with subjective data of other double blind placebo controlled studies (11, 12, 13, 14) and found them comparable.

Some of the comparable studies (15,16,17,18) included Joy L Frestedt et al (n = 50, improvement in WOMAC P < 0.001, 6 MWD of 7% over 3.5%), Mark JS Miller, (n = 91 improvement in WOMAC Total 38 – 43% versus 27% and VAS scores after 8 weeks (p < 0.001), 28 - 23% lower use of rescue medication, Jacquet A (significant less use of analgesics (P < 0.001) with a group mean difference of -10.0 (95% CI: - 4.9 to - 15.1). Mean WOMAC scores for pain, stiffness and function in the active arm were significantly different (P < 0.001) and showed benefits in Osteoarthritis as noted in a separate the potential to act as disease modifying agents in osteoarthritis.

Synovial fluid examination suggested that mineral supplement helped in restoring synovial fluid rheological properties and synovial metabolism and in reducing cartilage pathology. Joint fluid is not considered an optimal source of biomarkers because of the difficulty in obtaining repeated samples Average cell count significantly decreased to 240/microlitre.

MRI reveals the entire spectrum of Osteoarthritis related abnormalities in knee as it allows assessment of soft tissue structures, cartilage and bone lesions and it can be used to monitor cartilage damage in vivo but reproducibility is expensive. Ultrasonography on the other hand is a simple relatively inexpensive method to depict early changes of synovium and articular cartilage in patients with joint disease. Studies comparing MRI and Ultrasound modalities showed that there was a significant correlation between MRI and Ultrasound techniques for evaluating cartilage changes in patients with Osteoarthritis. (23,24). However some studies suggest that total cartilage volume and mean thickness are relatively insensitive to diseases progression though there are some conflicting results. There is evidence to suggest that Osteoarthritis causes regional changes in cartilage structure with some regions exhibiting thinning or loss of cartilage while swelling may occur elsewhere on articular cartilage. For this reason localized measures of cartilage thickness are likely to provide fuller picture changes in cartilage during disease process (25,26)

Conventional radiograms are commonly used to assess the severity of articular involvement. However alterations appear late. In early disease, structural changes in OA joint are difficult to study because of relative insensitivity of radiographs. The groups had insignificant deterioration in the JSW (mean (SD) (0.05) (p=0.82) as compared to some studies using placebo arm which normally reports significant deterioration in the JSW to a tune upto 0.55mm (mean (SD) −0.09, p=0.01) (3)

By the time patients presents with symptoms and want treatment, it's really no longer just a cartilage disease but all of the other tissues in the joint, including the subchondral bone, synovium, joint capsule, periarticular muscles, sensory nerve endings, and ligaments are affected. Treatment development continues to focus on cartilage and just treating the cartilage alone by throwing new cartilage into the mix or protecting remaining cartilage from being further damaged is not going to solve the problem (27).

Other limitations of this study were its short duration (24 weeks), lack of assessment for remnant effects after treatment stoppage and limited sample size. Additional study of longer treatments in a greater numbers of subjects would be helpful to verify the treatment effect for mineral supplementation and to explore the lack of significant treatment effect and its efficacy may have been under demonstrated within this 24 week study period.

However in this pilot study mineral supplementation slows cartilage damage progression thus conforming its validity for chondroprotection supplement. It is clear that this mineral supplement is indeed safe, as there were no changes in various clinical and laboratory measures of safety in this 6 month study. Supplementation was efficacious, particularly compared to baseline conditions, but there were also clear difficulties in determining a sustained disassociation from placebo which warrants further study.

Conclusion

Therapeutic approaches to cartilage lesions are a new challenge. A number of viable options have been made available over the years to address problems concerning cartilage damage. As alternative approaches to the management of Osteoarthritis are desirable, natural mineral supplement alone or in combination with other nutraceuticals improves joint health and hence provide a significant relief of osteoarthritis symptoms. However, carefully conducted randomized, prospective studies for each of these nutraceuticals should be conducted to validate the safety and efficacy of cartilage regeneration.

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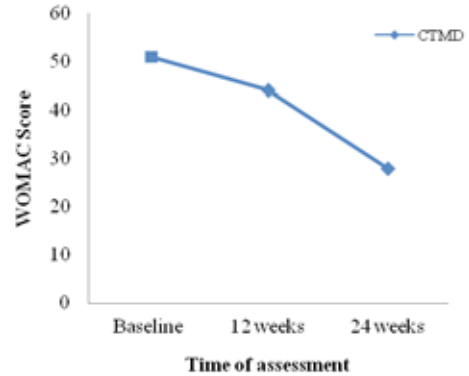
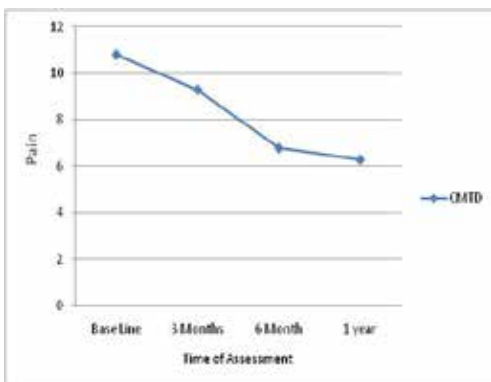
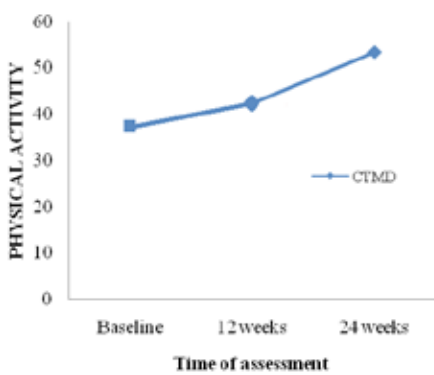






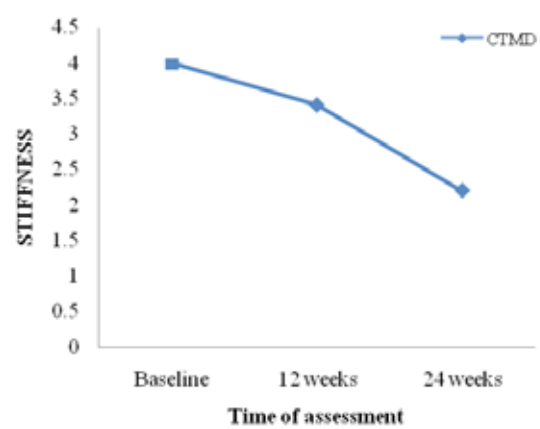
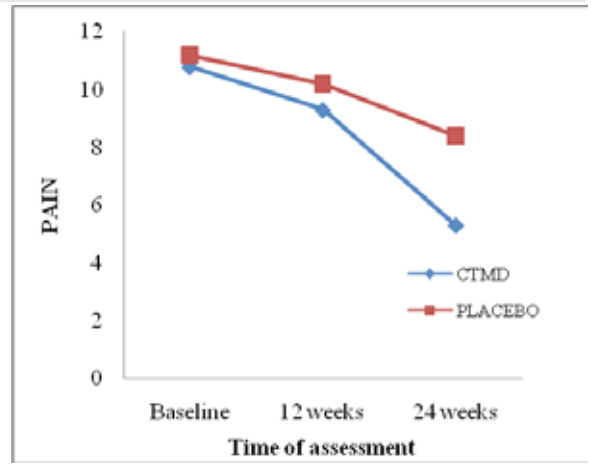


Fig 1 A,B,C,D displays the change in WOMAC scores ,sub-score of pain physical activity,&stiffness from baseline over 24 weeks of treatment



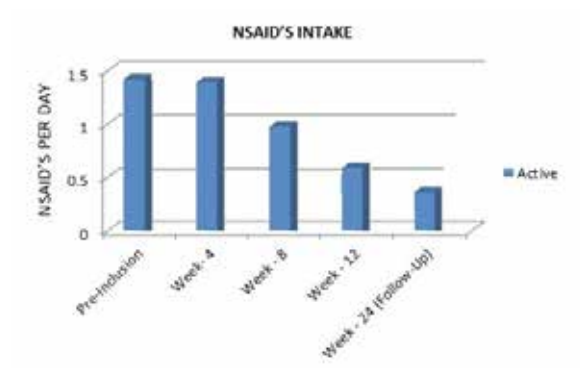


Figure 2 displays the significant reduction in need of rescue medication

Fig 3 displays the improvement in six minutes pain free walking distance

Table 1 mineral composition of supplement

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Supplement Facts

Serving Size ½ teaspoon (about 40 drops)
Servings Per Container 25

Amount Per Serving		%DV
Magnesium	250 mg	63%
Chloride	690 mg	20%
Sodium	5 mg	<1%
Potassium	3 mg	<1%
Sulfate	37 mg	†
Lithium	395 mcg	†
Boron	370mcg	†

† Daily Value not Established.

Ingredients: Ionic Sea minerals. Contains no other added ingredients. In addition to the elements listed above, this product contains the following in naturally occurring, varying trace amounts: Bromide, Carbonate, Calcium, Silicon, Nitrogen, Selenium, Phosphorus, Iodide, Chromium, Manganese, Titanium, Rubidium, Cobalt, Copper, Antimony, Molybdenum, Strontium, Zinc, Nickel, Tungsten, Germanium, Scandium, Vanadium, Tellurium, Tin, Lanthanum, Yttrium, Silver, Gallium, Bismuth, Zirconium, Cerium, Cesium, Gold, Beryllium, Hafnium, Samarium, Terbium, Europium, Gadolinium, Dysprosium, Thorium, Holmium, Lutetium, Erbium, Ytterbium, Neodymium, Praseodymium, Niobium, Tantalum, Thallium, Rhenium, Indium and Palladium, plus the other elements found in seawater.

Grade	Criteria
0	Normal
I	Doubtful narrowing of joint space, possible osteophyte development
II	Definite osteophytes, absent or questionable narrowing of joint space
III	Moderate osteophytes, definite narrowing, some sclerosis, possible joint deformity
IV	Large osteophytes, marked narrowing, severe sclerosis, definite joint deformity

Grade of Osteoarthritis	Description
0	No radiographic findings of osteoarthritis
1	< 25% joint space narrowing with secondary features
2	50–75% joint space narrowing without secondary features
3	50–75% joint space narrowing with secondary features
4	> 75% joint space narrowing with secondary features

Grade of Osteoarthritis	Description
0	No radiographic findings of osteoarthritis
1	Joint space narrowing < 3 mm
2	Joint space obliterated or almost obliterated
3	Minor bone attrition (< 5 mm)
4	Moderate bone attrition (5–15 mm)
5	Severe bone attrition (> 15 mm)

Table 2.(a)Kellgren – Lawrence Grading Scale (b). Brandt Radiographic Grading Scale (c) Ahlback Radiographic Grading Scale of Osteoarthritis of the Tibiofemoral Joint.

Baseline characteristics	(n=20)
Demographic characteristics	
Age (years) mean	54 (7.4)
Sex (n=male)	12
Weight (kg)	70 (12.9)
Height (cm)	162(7.6)
Right knee, No	13
Pain score on 0–100 VAS	58.4 (12)
Womac score total	52-62 (2.4) Mean-51.4
6MWD	1226-1488 Mean 1290
Cartilage thickness (mm)	4.48 -4.52(1.1) Mean 4.50
Joint space width (mm)	4.56-4.64 Mean 4.6
Osteophyte score (4 grades No (%) 0	1
1	10
2	8
3	1
Kellgren and Lawrence score (5 grades), No (%)	
0	0 (0)
1	1
2	1
3	17
4	1

Cell counts no/ microlitre 240-1800 (480)

Table 5 Baseline characteristics of the 20 patients with medial knee OA with regards to the treatment
CTMD (n=20)
Baseline 3months 6m
Total **50- 64 40-** 59 **29- 54**
(51.2) (7.1) (16.2)
Pain 10 - 12 8-11 6-10
(10.8) (1.5) (4)
Stiffness 4 -4 3-4 2-4
(Av 4) (0.6) (1.2)

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(37.4) (5) (11)

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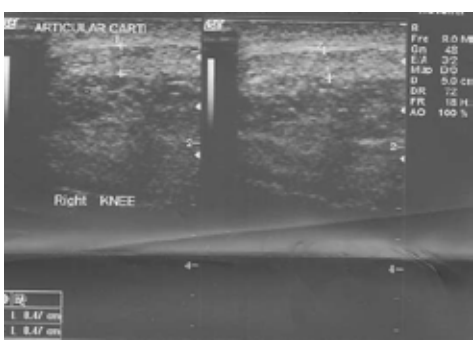
Table 6 change in WOMAC scores ,subscore of pain physical activity,& stiffness from baseline over 24 weeks of treatment

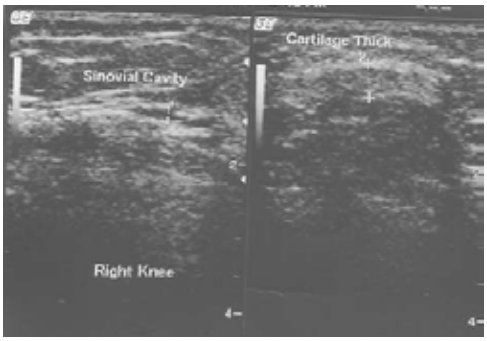
		Screening	Follow-up at 24 week
Laboratory Tests:			
Hematology:			
	CBC: Hemoglobin	11.4	11.6
	PCV	38	40
	Platelet Countthous/mm3	200- 400	210-400
	TLCthous/mm3	4.2-9.4	4-9
	Absolute neutrophil count-thous/mm3	5-7	5-7
	Absolute lymphocyte count-thous/mm3	2-2.	2-2.4
Absolute RBC count millions/mm3		4.0-4.4	4-4.2
	SGPT	16- 18	16-18
	SGOT	18-20	16-20
	Serum Creatinine	0.8- 0.9	0.8-0.9
	Glucose (F)	80-	80-100

Table 7 : safety Assessments-- haematological and biochemical parameters observed at the time of initiation and completion of trial at 24 weeks

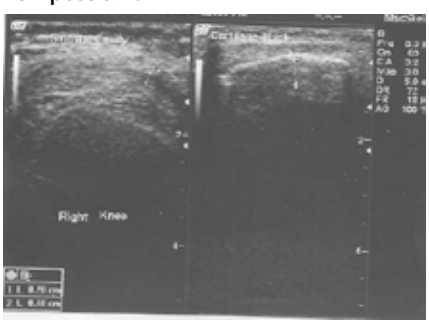
Pt 1 rt knee-0.47cm



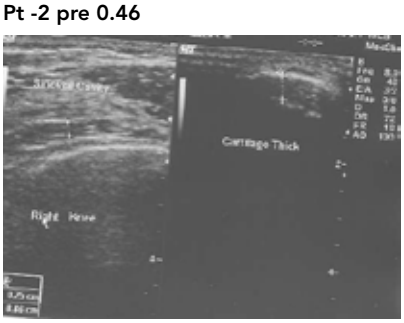
Pt 1 pre 0.46



Pt 2 post 0.48



Pt -2 pre 0.46



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