Natural Mineral supplementation provides chondroprotection and hence improvement in moderate osteoarthritis of knee

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ABSTRACT

Objective of the study : The primary objective of the study was to determine if natural mineral supplements (Concentrate Trace Mineral Drops CTMD®) can act as chondroprotective agent by determining the WOMAC score, 6 minutes pain free walking distance (MWD) and need for rescue pain medication.

Methodology : A double blind, placebo controlled randomized study in 100 patients with moderate Osteoarthritis of the knee joint was carried out. 40 drops of naturally occurring mineral supplement (CTMD®) was administered per day to the test group. Efficacy was objectively confirmed by evaluating changes in the thickness of articular cartilage, joint space width and synovial fluid composition.

Results : Significant differences in WOMAC scores (reduction of 16.2 vs 7.1) and 6 MWD (122 feet vs 46 feet) in the CTMD group as compared to the placebo group was observed at 24 weeks. Ultrasonography and synovial fluid examination revealed improvement in cartilage structure. The treatment was well tolerated and the adverse event profiles were not significantly different between the two groups.

Conclusion : This preliminary study suggests that CTMD improves joint health and hence increases walking distances and allows partial withdrawal of NSAIDs in subjects with Osteoarthritis of the knee.

INTRODUCTION

Minerals are of vital importance for most body functions and even small departures from the normal mineral composition of the interior of the cell may have profound physiological consequences (1). There is fast growing evidence that minerals and trace elements like Boron, Zinc, Copper, Selenium, Magnesium, Manganese, Vitamins A, E and C, Niacin, Pantothenic Acid, Omega 3 fatty acids, Chondroitins, Glucosamine, Collagen, Hyaluronic Acid and Sulphur containing amino acids play a significant role in the production of cartilage matrix (2,3).

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 (4). Furthermore, increased Magnesium in the diet may influence inflammation through reducing the serum level of the pro-inflammatory protein C - reactive protein (5).

Also, naturally occurring minerals are known to play a major role as cofactors. Copper is one such essential cofactor of the Collagen cross-linker lysyl oxidase. Recent evidence has suggested an excess of reactive oxygen species arising from an imbalance in the antioxidant status of the joint may result in cartilage degradation and joint remodelling (6). 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-1â, as well as Nitric Oxide production secondary to the induction of inducible Nitric Oxide Synthase (7,8).

Selenium, an essential co-factor for Glutathione Peroxidase also has a role in reducing the incidence of osteoarthritic lesion [9,10]. Boron, Manganese and Selenium have been reported to slow down pathogenesis and hence reduction in appearance of Osteoarthritic lesions and severity of symptoms in Osteoarthritis (2).

Studies with mineral products from the Sierra Mountains (Sierrasil), seaweed derived multi mineral supplement (Aquamin), Phytalgic, showed significant improvements over time on WOMAC pain, activity, composite and stiffness scores as well as the 6 MWD and partial withdrawal of NSAIDs over 12 weeks of treatment (11, 12,13,14).

Studies pertaining to the efficacy of Glucosamine and Chondroitin alone have produced variable results suggesting that the benefits of this approach may have limitations. The probable reason could be inadequate intake of cofactors, especially minerals or trace elements (15).

Based on previous studies that showed beneficial effect of minerals in patients with joint pains and without intending a therapeutic claim, we decided to subjectively as well as objectively assess this mineral food supplement for having possible beneficial effects in Osteoarthritis of knee.

MATERIALS AND METHODS

The food supplement which is the subject of this clinical investigation is the Concentrate Trace Mineral Drops (CTMD) which contains over 72 natural minerals in ionic form, concentrated from the Great Salt Lake in Utah. It is 100 % natural with no other ingredients added. Half tsf (approx 40 drops) serving of CTMD 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, carbonate, 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 CTMD.

The criteria for selection were patients who present with symptomatic primary Osteoarthritis of the knee (16), above 50 years of age, defined by daily pain for the previous 3 months irrespective of NSAIDs or analgesics at least once a week, with history of less then 30 minutes of morning stiffness and a WOMAC score of d" 75 in the target knee.

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 one was taken into account.

The main exclusion criterias were evidence of secondary knee Osteoarthritis, severe Osteoarthritis (JSW < 2 mm), prior intra articular injections and corticosteroids within the previous 3 months, treatment with Diacerin in the 3 months prior to inclusion and patients with clinically significant systemic disease.

A total of 100 patients were enrolled in a double blinded manner into either the Concentrated Mineral Drops treatment group or placebo group and were administered CTMD and placebo respectively for 24 weeks. Patients were advised to take CTMD twice daily for 6 months, on an empty stomach. The dose was gradually increased to 40 drops (½ tsf) from 5-10 drops a day in a weeks time.

At the baseline visit, vital signs were checked for and laboratory tests carried out. The subjects were assessed for WOMAC score, 6 MWD, joint space width, articular cartilage thickness and cellularity of synovial fluid. Patients were evaluated weekly for any adverse events and need for any rescue medication (NSAIDS) in the first month. This was followed by monthly follow ups upto the 6th month.

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

The Western Ontario and McMaster Universities Osteoarthritis Index WOMAC (17, 18), 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. Pain scale designed by Andrea Mankoski (Refer Table 5) was used as it described severity very precisely.

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. (19)

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 > 0.50 mm during the study, as previously reported (19,20)

Ultrasonographically, articular cartilage on weight bearing condyle appears as hypoechoic 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) (21,22).

Cellularity of synovial fluid was compared by aspirating 2 ml of fluid under aseptic conditions. Normal synovial fluid have cell count of less then 2000/microlitre with a predominance of mononuclear cells . Increased counts upto 5000 with predominance of polymorphonuclear leucocytes are seen in osteoarthritis. (1)

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 CTMD 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

Table 6 shows that all four groups were comparable for number of subjects, gender, weight, age, WOMAC scores, 6 MWD, mean joint space width, average articular cartilage thickness and cell count indicating that the randomization was effective for those parameters.

4 patients in CTMD and 3 in placebo group did not complete the study. Reasons for withdrawal were personal or inefficacy. One of these patients had nausea in CTMD group but returned to normal after withdrawal. Both groups displayed an improvement from baseline for WOMAC values over the course of 24 weeks of treatment (table 6). The magnitude of these benefits was significantly greater in CTMD group ($p < 0.005$). It is of note that after 4, 8 and 12 weeks of treatment, CTMD group had marked improvement over baseline but not significant ($p > 0.05$) when compared to placebo.

The composite WOMAC score of the test group significantly improved by 7.1 and 16.2 as compared to 4.3 and 7.1 for Placebo at 12 and 24 weeks respectively. 16 patients (34 %) reported reduction by a score of 5 versus 4 patients (8%) in placebo by 12 weeks. It improved further to 52% (n=24) as against 21% (n=10) at 24 weeks. (fig 1a)

Within group analysis showed that the pain, stiffness and activity scores, were improved by 1.5, 0.6, 5 and 4 ,1.2, 11 points in test group as compared to non significant changes of 1, 0.3, 3 and 1.8, 0.4, 5 points for Placebo at 12 and 24 weeks.(fig 1b,1c,1d) Pain, stiffness and activity scores were reduced by atleast one point in 15, 4 and 20 patients versus 5, 2 and 6 patients in placebo at 12 weeks. It improved further to 28, 10, 30 patients (60%, 21%, 65%) versus 10, 4, 18 patients (21%, 8%, 38%) at 24 weeks.

The pain free distance covered during a 6 minute walk was significantly improved by 80 and 122 feet over time on treatment within the mineral supplement group. The placebo group also demonstrated improvement of 30 and 46 feet in 6 MWD over time on treatment but was not significant. 12(26%) and 15 (32%) patients showed improvement of 100 feet in 12 and 24 weeks in treatment group as compared to 5(10%) and 8(17%) patients for placebo group.

Rescue medication atleast once a week (Paracetamol with dosing limited to 4 × 500 mg per day) was required by 18 patients in CTMD versus 30 patients in placebo group. Further, there was a 23% reduction in use of Paracetamol in CTMD as compared to placebo group.

We could not observe any significant changes in X - Ray. No increase in JSW was observed in any group. However joint space width was maintained better in CTMD group as only 4 patients (8%) in CTMD showed decrease in joint space width by atleast 0.01 mm as compared to 10 patients (21%) of placebo.Ultrasonologicaly, cartilage thickness improved by at least 0.01 mm in 6 (13%) patients of CTMD group as against 4 patients (8%) who lost thickness at least by 0.01 mm. In placebo, only 2 patients (4%) had improved thickness whereas 10 patients (21%) lost thickness by at least 0.01mm.

25 (54%) patients had synovial fluid cell counts below 500 by 24 weeks compared to 10 (21%) patients before the treatment in CTMD group. In placebo, 16 (34%) patients had cell count below 500 compared to 11(23%) before treatment. Average cell count reduced to 240 for CTMD and 430 for placebo.

Adverse events were distributed somewhat evenly across 14 in test group and 10 patients in the control groups. In 4 (8%) patients, adverse events were considered at least possibly related to the mineral as supplement. 1 subject reported a poor tolerance for one week and left the trial . The adversities were related to upper GI discomfort. All complaints completely resolved by 8 weeks for both groups. A summary of hematological and biochemical safety variables is depicted in Table 7 shows that CTMD is absolutely safe.

No significant change in blood pressure, respiration rate and pulse rate were noted at the 5 intermediate evaluation points till the study's conclusion. Pulse rate increased in 4 patients from a screening value of 76.2 ± 1.2 to 81.4 ± 1.5 beats for initial one week only in CTMD group. Similarly transient increase blood pressure was noted in 6 patients for the first week only in the test group.

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.

Table 1. Mineral composition of CTMD

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

Table 2. Kellgren – Lawrence Grading Scale

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

Table 3. Brandt Radiographic Grading Scale of Osteoarthritis of the Tibiofemoral Joint.

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 4. Ahlback Radiographic Grading Scale of Osteoarthritis of the Tibiofemoral Joint.

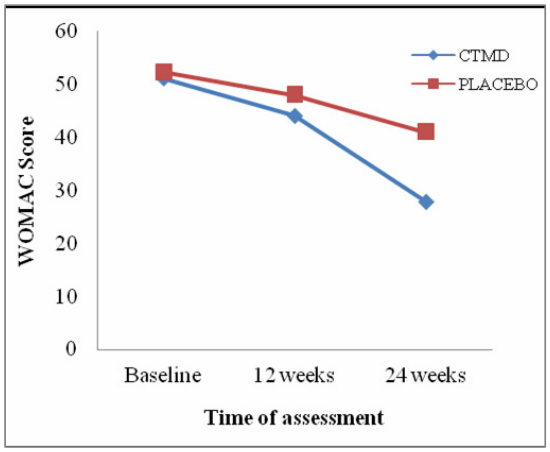
0	Pain free
1	Very minor annoyance - occasional minor twinges.
2	Minor annoyance - occasional strong twinges.
3	Annoying enough to be distracting.
4	Can be ignored if you are really involved in your work, but still distracting.
5	Can't be ignored for more than 30 minutes.
6	Can't be ignored for any length of time, but you can still go to work and participate in social activities.
7	Makes it difficult to concentrate, interferes with sleep You can still function with effort.
8	Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.
9	Unable to speak. Crying out or moaning uncontrollably - near delirium.
10	Unconscious. Pain makes you pass out.

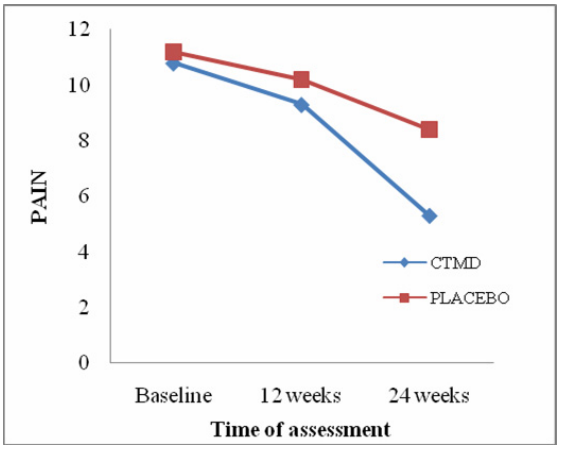
Table 5. Pain scoring scale by Andrea Mankoski

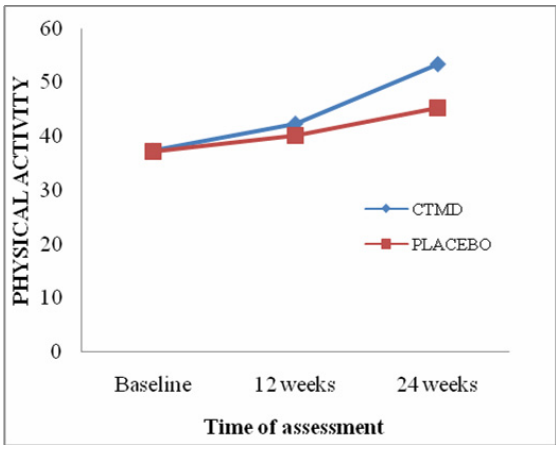
		CTMD	PLACEBO
N		46	47
No. of men (%)		24	22
Mean Age(years)		56	57
Mean Weight		74	72
Height		166	167
Severity	Mild	16	13
	Moderate	34	37
Duration of symptoms (months)		17	18
WOMAC Score	Total(96)	50 – 64 (51.2)	52 – 63 (52.4)
	Pain(20)	10 – 12 (10.8)	11 – 12(11.2)
	Stiffness(8)	4 – 4(4)	4 – 4 (4)
	Physical activity (68)	36 – 48 (37.4)	37 – 47(37.2)
6 MWD (feet)		1126 – 1448 (1260)	1089 – 1527 (1286)
Cartilage thickness(mm)		4.48 – 4.52(4.50)	4.48 – 4.56(4.49)
Joint space (mm)		4.58 – 4.63(4.6)	4.57 – 4.72(4.62)
Cell counts(no./ml)		240 – 1800 (480)	210 – 1900 (500)

Table 6. Demographic and osteoarthritic characterstics of 100 patients randomized to receive CTMD or placebo

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







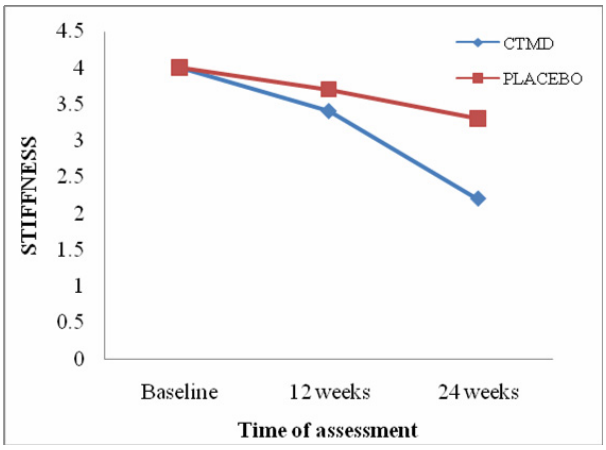


Figure 2 displays the significant reduction in need of rescue medication

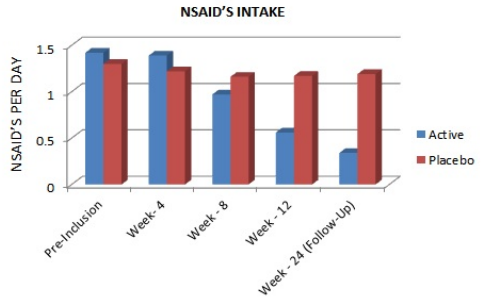
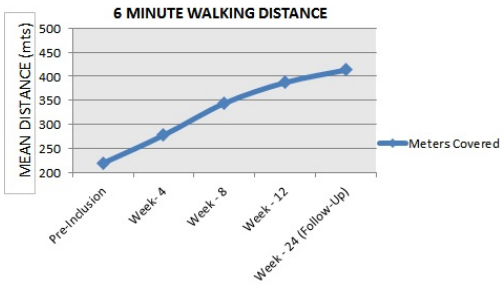
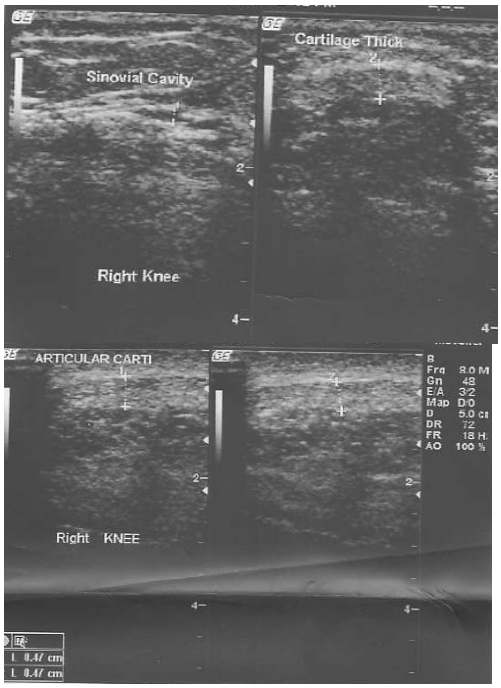


Fig 3 displays the improvement in six minutes pain free walking distance

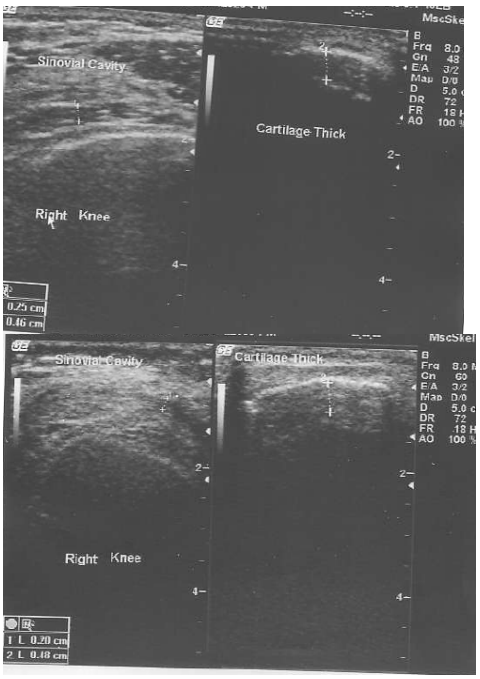


Pt 1 Right knee



pre 0.46 cm1
post -0.47cm

Pt -2



pre 0.46cm
post 0.48cm

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 (23), along with the appreciation that the NSAID class provides symptomatic relief rather that abrogating the disease process, there is a great need for alternatives.

Natural mineral supplement CTMD was selected because of easy availability in market, being a derivative from natural sources and already being consumed by masses. These minerals can be of most benefit if they 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.

The dose of the mineral supplement was determined based on available literature about daily dietary allowance of various minerals (1). 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.

In all CTMD treated patients, there was a significantly faster onset of benefits, which is evident from week 3 or 4 onwards compared to placebo, where it is evident at week 6 onwards and at the conclusion of the study differences between groups were significant. This was an improvement of 9.6% and 3.5% respectively over their 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 36 % (18 patients in CTMD versus 30 patients in placebo group).

Synovial fluid examination suggested that CTMD helped in restoring synovial fluid rheological properties and synovial metabolism and in reducing cartilage pathology .by decreasing Average cell count significantly to 240 for CTMD and 430 for placebo.

The placebo group also showed improvements over time on treatment for the pain, activities and composite scores but these improvements were not significant and possibly because of the following. Since healthy habits contribute to improvement, patients in placebo group also showed improvement in primary and secondary assessments. As subjects may have had expectations that all potential treatments in the randomized protocol would provide benefits, it may have resulted in a placebo response. Additionally, the ingestion of supplemental minerals may alter the basal nutritional status of the subjects. Rescue medication use was greater in placebo than CTMD groups, and this may have masked differences between the positive benefits related to treatment and placebo groups.

Our extensive literature search did not yield any study that present objective clinical data showing beneficial effect of mineral supplementation in joint health. We compared 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 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.

The mechanism by which this natural mineral supplement achieves these actions and benefits is unclear. The literature does not provide a clear link between a nutrition-based action of minerals and an effective anti-arthritic therapy. CTMD is composed of multiple minerals and the 'active ingredient' for the complex is difficult to determine. A number of the minerals, Manganese and Selenium in it may have anti-inflammatory and anti-oxidant properties which might directly and/or indirectly influence the efficacy of this unique complex.

CTMD slows cartilage damage progression thus conforming its validity as 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.

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-1â. However, the present study does not directly assess whether protection against cartilage degradation was associated with the therapies, nor is it likely that a substantial change in joint architecture would occur in this timeframe (24).

MRI reveals the entire spectrum of OA related abnormalities in knee. It also allows assessment of soft tissue structures, cartilage and bone lesions. It is a better alternative but expensive. Ultrasonography is however 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.(21,22)

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 main limitations of this study were its short duration (24 weeks), lack of assessment for remnant effects after treatment stoppage and limited sample size (50 subjects per treatment arm). Additional study of longer treatments in a greater numbers of subjects would be helpful to verify the treatment effect for CTMD and to explore the lack of significant treatment effect and its efficacy may have been under demonstrated within this 24 week study period.

CONCLUSION

As alternative approaches to the management of Osteoarthritis are desirable, natural mineral supplement (CTMD) alone or in combination with other nutraceuticals improves joint health and hence provide a significant relief of osteoarthritis symptoms. The benefits were evident within 4 weeks and associated with an excellent safety profile.

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