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ConcenTrace® Clinical Trial

Natural mineral supplementation provides chondro-protection, hence improvement in moderate osteoarthritis of knee.

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ConcenTrace® (CTMD) Clinical Trial

NATURAL MINERAL SUPPLEMENTATION PROVIDES CHONDRO-PROTECTION 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 ConcenTrace® Trace Mineral Drops (CTMD) can act as chondroprotective agent by determining the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, 6 minutes pain free walking distance (6 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 (JSW) and synovial fluid composition.

Results: Significant differences in WOMAC scores and 6 MWD 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 groups.

Conclusion: This preliminary study suggests that CTMD improves joint health and increased walking distances and allows partial withdrawal of nonsteroidal anti-inflammatory drugs (NSAIDs) in subjects with osteoarthritis of the knee.

INTRODUCTION

Minerals are crucial for many body functions and even small departures from the normal mineral composition of the interior of the cell may have profound physiological consequences (8). There is fast growing evidence suggesting that minerals and trace elements like boron, zinc, copper, selenium, magnesium and manganese including vitamins A, E, and C, niacin, pantothenic acid, omega-3 fatty acids, chondroitin, glucosamine, collagen, hyaluronic acid and sulphur-containing amino acids play a significant role in the production of cartilage matrix(6,23).

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 (12). Furthermore, increased magnesium in the diet may influence inflammation through reducing the serum level of the pro-inflammatory C-reactive protein (22). The trace element copper is an essential cofactor in enzymes such as 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 remodeling (9). Antioxidant enzyme superoxide 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 (4, 18).

Selenium, an essential co-factor for glutathione peroxidase also has a role in reducing the incidence of osteoarthritic lesion [13, 21]. 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 (6).

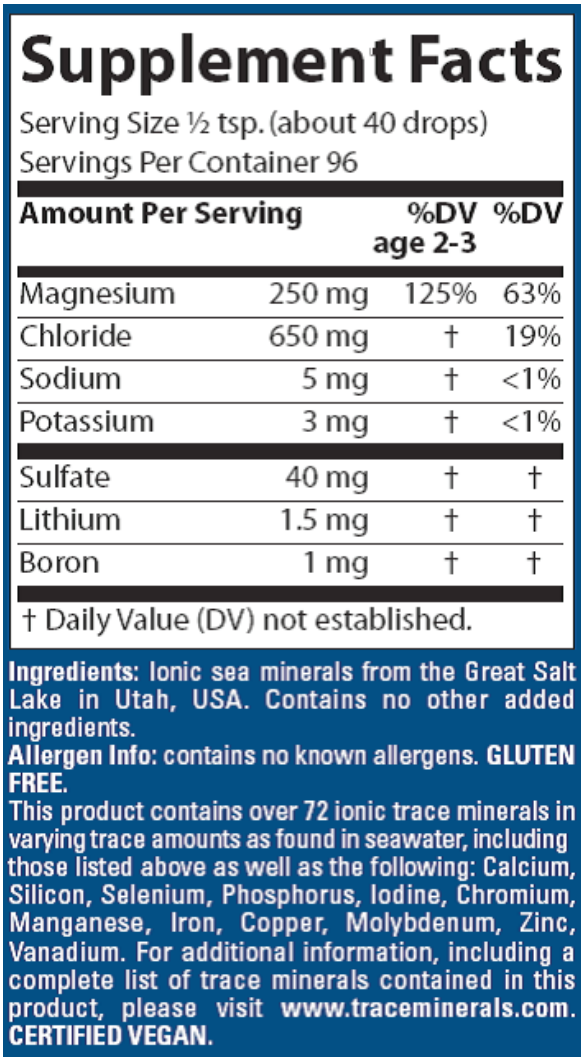
Studies with mineral products from the Sierra Mountains (Sierrasil), seaweed-derived multi -mineral supplement (Aquamin) and Phytalgic showed significant improvements over time on WOMAC pain, activity, composite and stiffness scores as well as the 6 MWD and partial withdrawal of NSAIDs over 12 weeks of treatment (5, 10, 11, 19).

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 (16).

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 ConcenTrace® 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. Refer to Table 1 for typical Mineral Composition of CTMD.



Supplement Facts

Serving Size ½ tsp. (about 40 drops)
Servings Per Container 96

Amount Per Serving		%DV age 2-3	%DV
Magnesium	250 mg	125%	63%
Chloride	650 mg	†	19%
Sodium	5 mg	†	<1%
Potassium	3 mg	†	<1%
Sulfate	40 mg	†	†
Lithium	1.5 mg	†	†
Boron	1 mg	†	†

† Daily Value (DV) not established.

Ingredients: Ionic sea minerals from the Great Salt Lake in Utah, USA. Contains no other added ingredients.
Allergen Info: contains no known allergens. **GLUTEN FREE.**
This product contains over 72 ionic trace minerals in varying trace amounts as found in seawater, including those listed above as well as the following: Calcium, Silicon, Selenium, Phosphorus, Iodine, Chromium, Manganese, Iron, Copper, Molybdenum, Zinc, Vanadium. For additional information, including a complete list of trace minerals contained in this product, please visit **www.traceminerals.com.**
CERTIFIED VEGAN.

Table 1. Mineral composition of CTMD

The 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 3 months, irrespective of NSAIDs or analgesics at least once a week, with history of less than 30 minutes of morning stiffness and a WOMAC score of ≤ 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 criteria 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.

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.

A total of 100 patients were enrolled in a double blinded manner into either the CTMD 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 tsp.) from 5-10 drops a day in a week's 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, up to 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 Arthritis Index (WOMAC) (2, 14) is a widely used measure of patient's subjective assessment of pain joint mobility and physical disability. It evaluates 3 dimensions: 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.

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

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. (15)

Anterior & posterior 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 (15).

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) (3, 24).

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 determined.

The study was approved by the 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 7). 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 average WOMAC score of the CTMD group significantly decreased by 7.1 and 16.2 as compared to 4.3 and 7.1 for placebo at 12 and 24 weeks, respectively (see Graph 1). 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.

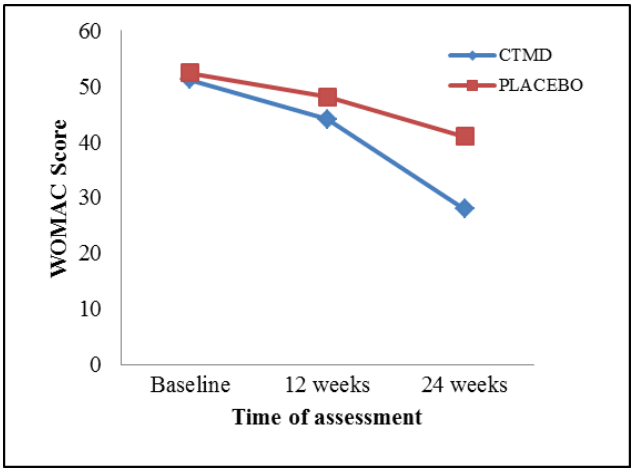
Analysis within the group showed that the pain, stiffness and activity scores after 12 weeks had decreased by 1.5, 0.6, 5 in the CTMD group as compared to a non-significant decrease of 1, 0.3, 3 in placebo (see Graph 2, 3, 4). After 24 weeks pain, stiffness, and activity scores had decreased 4, 1.2, and 11 points in CTMD group as compared to non-significant changes of 1.8, 0.4, 5 points for placebo. Pain, stiffness and activity scores decreased by at least one point in 15, 4 and 20 patients versus 5, 2 and 6 patients in placebo

		CTMD	PLACEBO
Number of Participants		46	47
Number 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		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 [4.5]	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]

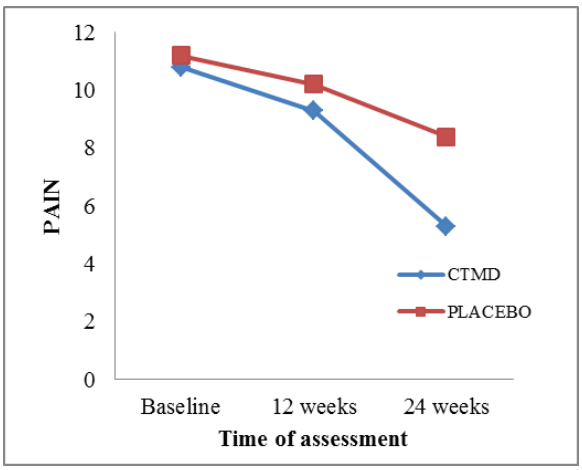
Table 6. Demographic and osteoarthritic characteristics of 100 patients randomized to receive CTMD or placebo.
Note: Numbers in brackets "[ ]" = average.

		CTMD (n = 46)			Placebo (n = 47)		
		Baseline	12 weeks	24 weeks	Baseline	12 weeks	24 weeks
WOMAC Score	Score Range	50-64	40-59	29-54	52-63	44-60	38-59
	Average	52.2	45.1 (14%)	36 (31%)	52.4	48.1 (8%)	45.3 (15%)
Pain Score	Score Range	10-12	8-11	6-10	11-12	10-11	6-10
	Average	10.8	9.3 (14%)	6.8 (37%)	11.2	10.2 (9%)	9.4 (16%)
Stiffness Score	Score Range	4-4	3-4	2-4	4-4	3-4	3-4
	Average	4	3.4 (15%)	2.8 (30%)	4	3.7 (7.5%)	3.6 (10%)
Physical Limitation	Score Range	36-48	30-40	22-36	37-47	32-40	28-38
	Average	37.4	32.4 (13%)	26.4 (30%)	37.2	34.2 (8%)	32.2 (13%)

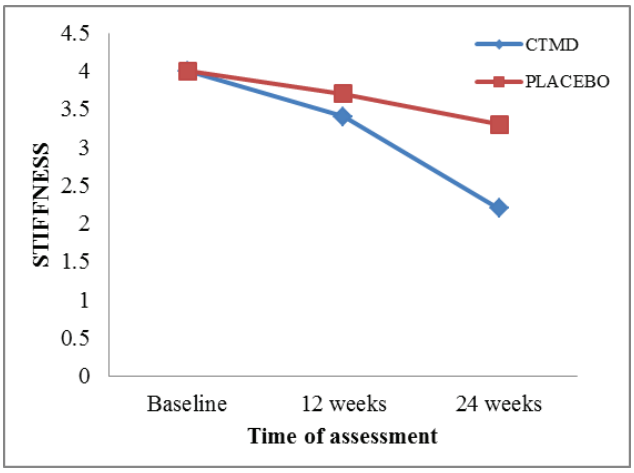
Table 7. WOMAC scores of the CTMD and Placebo groups.
Note: Higher scores on the WOMAC indicate worse pain, stiffness, and functional limitations.



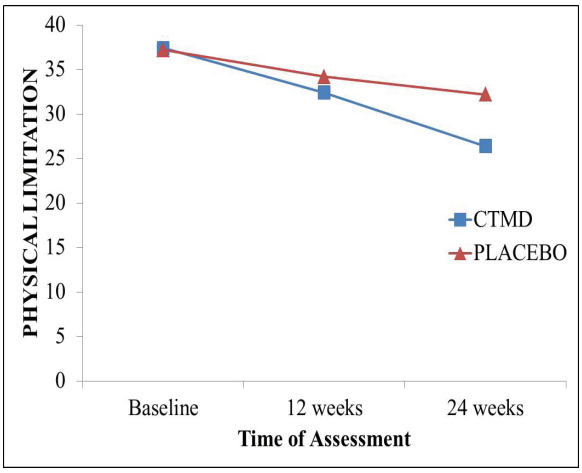
Graph 1: WOMAC scores



Graph 2: PAIN scores



Graph 3: STIFFNESS scores



Graph 4: PHYSICAL LIMITATION scores

at 12 weeks. It decreased 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 at least 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. Furthermore, 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 joint space width 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 at least 0.01 mm as compared to 10 patients (21%) of placebo.

Ultrasonologically, 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.

Synovial fluid examination suggested that CTMD helped in restoring synovial fluid rheological properties and synovial metabolism and in reducing cartilage pathology. 25 (54%) patients had 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 500s 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 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 8 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 to 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.

Laboratory Tests		
Hematology	Initiation	Completion
CBC: Hemoglobin	11.4	11.6
PCV	38 4	0
Platelet Count thous/mm3	200- 400	210-400
TLC thous/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 million/mm3 4	.0-4.4	4-4.2
SGPT	16- 18	16-18
SGOT	18-20 1	6-20
Serum Creatinine	0.8- 0.9 0	.8-0.9
Glucose (F)	80 8	0-100

Table 8: Safety Assessments - Hematological and biochemical parameters observed at the time of initiation and completion of trial at 24 weeks.

Discussion

Recent documentation of an increased risk for cardiovascular disease and stroke with cyclooxygenase-2 (COX-2) inhibitors and significant gastrointestinal, renal complications and premature deaths associated with non-selective COX inhibitors, 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 ionic 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. (8) 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.

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; the ingestion of supplemental minerals may alter the basal nutritional status of the subjects; rescue medication use was greater in placebo and 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 presented 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 (5, 10, 11, 19) 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 antioxidant properties which might directly and/or indirectly influence the efficacy of this unique complex.

CTMD slows cartilage damage progression thus confirming 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-1β. However, the present study does not directly as-

sess 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. (17)

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 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.

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 alone or in combination with other nutraceuticals improves joint health and provides a significant relief of osteoarthritis symptoms. The benefits were evident within 4 weeks and associated with an excellent safety profile.

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