



## **Concentrace Trace Mineral Drops A Natural Food Supplement Provides Early Relief From Osteoarthritis of Knee Symptoms: A Randomized, Placebo Controlled Clinical Trial**

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### **Abstract**

**Objective:** This study was conducted to evaluate the impact and therapeutic potential of natural food supplement CTMD<sup>®</sup>- Concentrace Trace Mineral Drops on walking distance, pain and joint mobility in subjects with moderate to severe osteoarthritis of the knee.

**Methods:** The study was a double-blinded, parallel-group, where 100 patients with mild to moderate osteoarthritis of knee were randomly assigned to receive either CTMD<sup>®</sup> or an identical placebo. The data regarding the demography, OA of Knee using X-Ray and ultrasound were recorded at the baseline and at 8, 12 and 24 weeks. The primary efficacy was measured by WOMAC and Visual Analog Scale (VAS) for pain, consumption of rescue medication (NSAIDs or analgesics), and tolerability; secondary efficacy was measured by improvement in the radiological changes, ultrasound and synovial fluid assessments. Safety measures included vital signs and laboratory based assays. **Results:** Ninety three (93) out of 100 subjects successfully completed the study. Seven subjects did not complete the study, reasons of withdrawal were adverse events, personal or lack of efficacy, and few were drop-outs as did not meet the selection criteria at base line. One of these subjects had nausea as adverse event in CTMD<sup>®</sup> group. The active group that received CTMD<sup>®</sup> showed improvements in WOMAC and VAS after 8 weeks ( $p < 0.001$ ) as compared to placebo, but the improvement was not statistically significant. In reference to base line values CTMD<sup>®</sup> treated group had considerably faster onset of benefit while placebo-treated individuals failed to show significant benefits. Ultrasonography and synovial fluid examination revealed improvement in cartilage structure, rescue medication intake was 18-23% lower in CTMD<sup>®</sup> as compared to placebo group. Tolerability was good in both the groups, no serious adverse events were noted and safety parameters remained unchanged.

**Conclusion:** This preliminary study suggested that the natural food supplement CTMD<sup>®</sup> may increase range of motion and walking distances in subjects with OA of the knee and reduced use of NSAIDs over 12 weeks of treatment. This clinical study brings forth CTMD<sup>®</sup>, a food supplement as a new line of treatment, which is both safe and effective, for patients of Osteoarthritis. Further evaluation in larger study samples will confirm its utility in the management of osteoarthritis.

**Key words:** Osteoarthritis (OA) of Knee, Concentrace Trace Mineral Drops-(CTMD<sup>®</sup>), WOMAC, VAS of Osteoarthritis, Clinical Trials on Osteoarthritis, Food Supplements in Osteoarthritis

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### **INTRODUCTION**

Osteoarthritis (OA) is a painful and debilitating joint condition that affects hundreds of millions worldwide (Murray CJL et al 1996). It is characterized by breakdown of

the cartilage present in the joints although the exact biochemical cause of OA remains unknown, the process usually begins when the joint structures are abnormal or the

stress placed on the joint surfaces is unusually high.

Much of the disease progression is due to mechanical stress on the joint and over time the excessive stress can induce metabolic and structural changes in the cartilage, bone and articular surfaces. In addition, bone and joint abnormalities have been documented in the developing countries and may be associated with nutritional and developmental problems.

In Asian countries like India, primarily older people suffer from this disease which is aggravated by increasing weight with age, increasingly sedentary lifestyles and the lack of adequate exercise regimes. Pharmaceutical approaches to disease management include the popular non-steroidal anti-inflammatory class (NSAIDs), but NSAID use is accompanied by side-effects including gastrointestinal distress, ulcer formation and cardiovascular problems (Kraan et al 2000; Dickman et al 2004). As a result, glucosamine and other new anti-inflammatory compounds with fewer adverse effects are being explored as possible treatments for OA (Graham et al 2005; Kimmel et al 2005; Berman et al 2004). Growing evidence suggests that several minerals play an important role in joint health. 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 increased cartilage damage (Noack et al 1994). Trace minerals such as boron and manganese have been shown to reduce the symptoms and may slow the pathogenesis of OA (Walter et al 2003; Miler et al 2005).

Concentrace Trace Mineral Drops (CTMD<sup>®</sup>) is extracted from Great Salt Lake and is the most powerful and natural health supplement for trace minerals in the world. Utah's Great Salt Lake harvests low sodium concentrace for Trace Minerals Research. Trace Mineral Drops is the largest body of concentrated sea water in the world and is particularly rich in certain minerals and trace minerals like magnesium, selenium, lithium, and boron which are vitally important to human health.

It's highly concentrated and contains over 72 ionically charged trace minerals, 100 % natural with no other added ingredients. CTMD<sup>®</sup> contains a full spectrum of all the minerals which are naturally present in the body. It has been extracted using a completely natural process that removes the sodium and gives a formula about 78 times more concentrated than the sea water. No other health supplement is as naturally powerful. Many other trace mineral products are high in aluminum but CTMD<sup>®</sup> is extremely low in heavy metals and contains no other contaminants (Table 1).

This study was designed to determine the efficacy of a food supplement, CTMD<sup>®</sup> on pain and function in subjects with osteoarthritis using VAS, WOMAC & Ultrasound along

with the use of rescue medication (analgesic & NSAIDs), and was compared with placebo.

**Table 1** Composition of CTMD<sup>®</sup>

Typical mineral composition of CTMD <sup>®</sup>		
Serving size: 1/2 tsp. (about 40 drops)		
Amount Per Serving		% DV*
Magnesium	250 mg	63%
Chloride	690 mg	21%
Sodium	6 mg	0%
Potassium	3 mg	0%
Sulfate	37 mg	**
Boron	370 mcg	**

\*Daily Values (DV) are based on a 2,000 calorie diet.  
\*\*Daily Value not established.

## MATERIALS AND METHODS

### Study design and participants

This was a double-blind, randomized, placebo-controlled, parallel-group clinical study. It was approved by the Clinicom Independent Ethics Committee for the Protection of Subjects, and was registered with CTRI (CTRI/2010/091/001105).

A total of 100 subjects were enrolled based on the eligibility criteria. All subjects had provided signed written informed consent before being randomized to either study drug or placebo. This study was performed according to all national laws and regulations governing the conduct of Clinical Trials. It conformed to the revised declaration of Helsinki, and to current Good Clinical Practice (GCP).

Subjects were considered eligible if they were aged between 50 and 75 years, had chronic osteoarthritis of the knee (as evidenced from clinical history and X-ray documentation) with no other rheumatologic condition, experienced pain and/or stiffness requiring the regular use of NSAIDs, and could demonstrate their capacity to fill subject diary relating their daily treatment (King DE et al 2005; Kurz

et al 2002; Frestedt JL et al 1999 and 2009; Jacquet A et al 2009)

Subjects with inflammatory arthritis with osteoarthritis other than knees, with known allergy to any of the constituents of the study drug, with any other co-morbidity affecting the evaluation of the study, or who were not fit to participate in such a study were excluded.

The primary objective of the study was to evaluate the effectiveness of CTMD<sup>®</sup> in improving the signs & symptoms of subjects with osteoarthritis of knee by assessing decrease in pain, stiffness & physical functions from baseline to the completion of therapy using WOMAC scale, assessment of Range of Motion (ROM) along with 6 Minute Walking Distance (MWD), improvement in radiological features and reduction in the use of analgesics and NSAIDs by at least 20% from initial usage (Gaby AR 1999; Stephn H 1998; Altman, R, et al 1986; Chaojeannie 2008).

The secondary objective of the study was to evaluate the role of Trace Minerals CTMD<sup>®</sup> and their effectiveness in improving the Quality of Life (QoL) of subjects with OA knee, and assessing improvement by Ultrasonography and Synovial fluid.

#### Equipment

Ultrasound was delivered by a Chattanooga intellect 200 ultrasound unit that was calibrated by an equipment specialist. The unit operated at 1.00 MHz and had a 10 cm<sup>2</sup> sound head. The effective radiating surface was 8.5 ± 1.5 cm<sup>2</sup>. The output meter reading accuracy was ± 20%. ROM was measured with a large, clear, plastic, 360o goniometer.

#### Study procedures

After the subjects provided written informed consent, the eligible subject's were randomized using Random Number Table and received the study drug or identical placebo for 12 weeks. Unblinding was performed after database lock.

At the baseline visit complete medical and physical examination was performed, BMI and fasting blood sample were measured, concomitant medications were noted and the WOMAC symptom assessment questionnaire was filled. VAS Pain Scale at 0hr and 1, 2 & 4hrs after dosing were recorded by the subject and Six-Minute Walk test for effectiveness, Articular cartilage thickness & synovial fluid thickness using ultrasound was measured by the Investigator.

The assessments were performed at 4<sup>th</sup>, 12<sup>th</sup> and 24<sup>th</sup> week. The subjects were instructed to fill subject diary daily to record all medication used (study drug and other medication).

Subjects in the study were advised not to modify the nature of their treatment for pain and stiffness control and to keep using their usual analgesic and NSAID medications as

often as needed during the treatment period. The study drug was used in addition to these medications. Subjects could reduce the use of their pain and inflammation medications, if they did not feel the need for them, but they had to note all medications taken every day in their diary.

The study drug is a commercially prepared food supplement, CTMD<sup>®</sup>, marketed preparation which consisted of over 72 natural minerals in ionic form, concentrated from the Great Salt Lake in Utah. Half tsf (approx 40 drops) serving of CTMD<sup>®</sup> contained magnesium 250 mg, chloride 690 mg, sodium 5 mg, potassium 3 mg, sulfate 37 mg lithium 295 mcg, boron 370 mcg. In addition, it also contained naturally occurring varying trace amounts of bromide, carbonate, calcium, silicon, nitrogen, selenium, phosphorus, iodide, chromium, Manganese, titanium, rubidium, cobalt, copper, antimony, molybdenum, strontium, zinc, Nickel, tungsten, etc plus other elements in sea water.

This preparation was administered orally, as 20 Drops in the morning & 20 Drops in the evening, half an hour before food. Each patient was given treatment for 4 weeks at the beginning of each study period, and all used containers and unused capsules were returned at the next visit. Patient withdrawals were noted with reasons. Any adverse events or side effects in the course of the trial were noted and classified as either mild, moderate, severe or life threatening. They were also judged to be associated or not associated with the trial drug therapy.

#### Statistical Analysis

All analyses were done as intention to treat (ITT), using all available data at each time point. The statistical analysis was performed by an independent statistician using the following tests – ANOVA, paired and unpaired t tests, Bonferroni, Chi Square, Friedman and Wilcoxon tests as appropriate. The following software will be used: SPSS 11.5, SAS 9.1 and MS Excel. Statistical significance was taken at the 95% level (p <0.05). Results will be expressed as the Mean ± SEM.

## RESULTS

#### Demography

A total of 100 were enrolled in the study, of which 93 subjects were considered for analysis. In Group-1 subjects received CTMD<sup>®</sup> and in Group-2 subjects received identical Placebo. In group-1, the total numbers of male patients were 26 and female patients were 21. Similarly, the total numbers of male patient's in group-2 were 23 and female patients were 23 (figure 1).

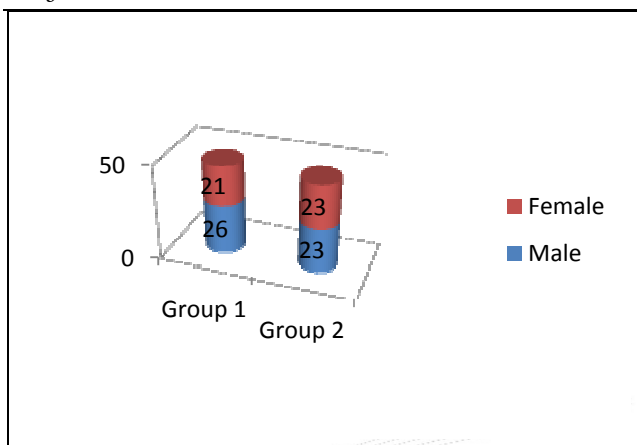


Figure 1 Demographic characteristics: Sex-wise distribution of subjects in each group

The baseline characteristics were in table below.

Table 2 Baseline Characteristics

Characteristics at Base Line	
Parameters	Values
Total number of subjects	100
Male/Female	49/44
Mean Age (range), years	55.2 ±5.2
Mean Height (range), cms	158.8±8.5
Mean Weight, (range), Kg	63±7.8
BMI(range), (kg/m2)	22.6±4.5
Osteoarthritis (n)	
One knee	52
Two knees	41
WOMAC scores at inclusion (mean ± SD)	
Pain score	282.7 ± 75.0
Stiffness score	93.6 ± 45.6
Function score	688.8 ± 281.0
Total score	1000.5 ± 388.7
Active Range of motion	94.7±3.8
VAS of pain score	7.8±2.2
Gait Velocity	55.2±3.3

The Western Ontario and McMaster Universities Osteoarthritis Index

Friedman test was performed to compute the individual variation in each visit and the baseline values. The Figure 2

showed the variation in the WOMAC scores, which decreased significantly week 4 onwards, for all the three parameters Pain (P<0.002), Stiffness (P=0.0017) and Physical disability (P=0.003). The difference got more significant as the trial progressed from week 4, week 8, week 12 and the follow up period of week-24. The results demonstrated that the CTMD® led to symptomatic relief for the patients on a long term basis and that the benefits were additive or accumulative over a longer course of time.

Visual Analogue Scale

The Visual analogue test was performed to observe the reduction in symptoms of pain. The Friedman test was applied to the complete data at each visit to test for significance. As illustrated in Figure 3, there was significant reduction in the VAS on a scale of 10 from the baseline to the post treatment and follow up.

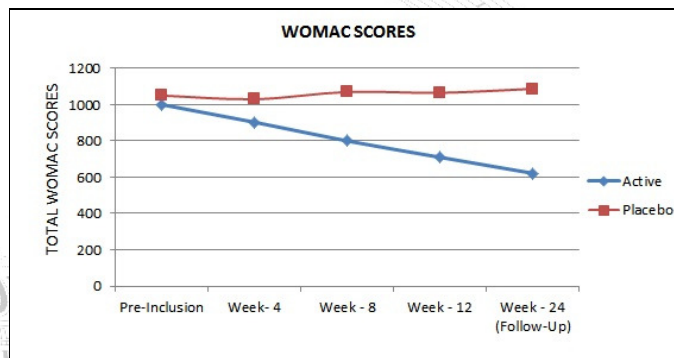


Figure 2 Change from baseline in WOMAC Scores

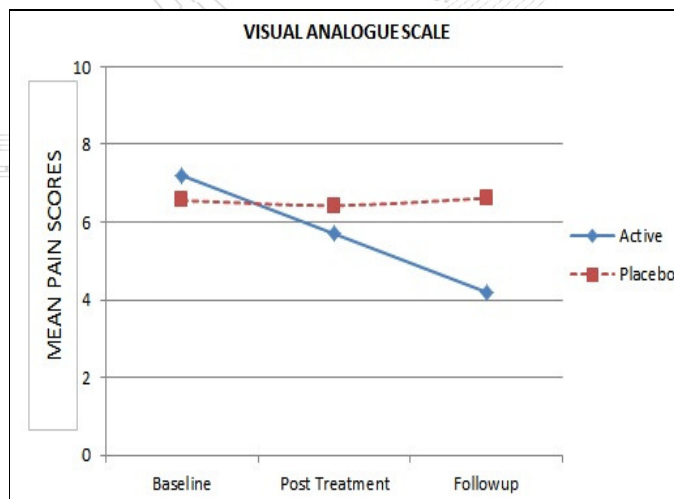


Figure 3 VAS scores- change from baseline

**Distance Walked in 6 Minutes**

The paired t Test was applied to measure the change in the vital parameters in both the groups. These vital parameters (heart rate, respiratory rate, Systolic and diastolic BP) were measured at the commencement and at the culmination of the trial. Figure 4 showed significant change in the distance walked in 6 minutes ( $P < 0.05$ ). This was consistent as after continuous exercise (continuous walking for 6 minutes), increase in the vital parameters was natural and physiological.

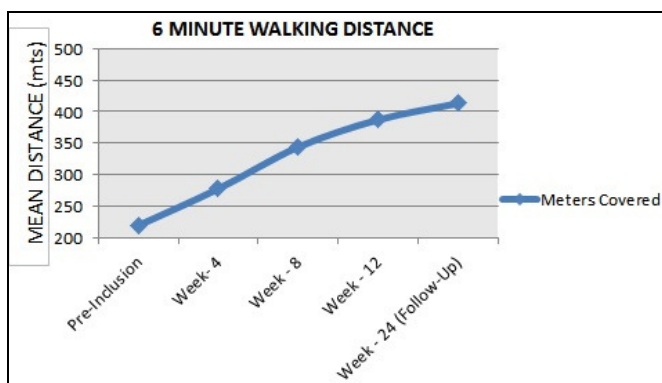


Figure 4 Change from baseline in Distance Walked In 6 Minutes

**Use of Analgesics and NSAIDS**

Overall 72 of the 100 patients used common analgesics (mostly paracetamol alone or combined, less frequently opiates, low-dose NSAIDs or aspirin).

**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, along with the appreciation that the NSAID class provided symptomatic relief rather than abrogating the disease process, and thus there was a great need for alternatives (Frestedt JL et al 2008 and 2009; Jacquet A et al 2009).

Natural mineral supplement CTMD<sup>®</sup> 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 with which they interact. 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.

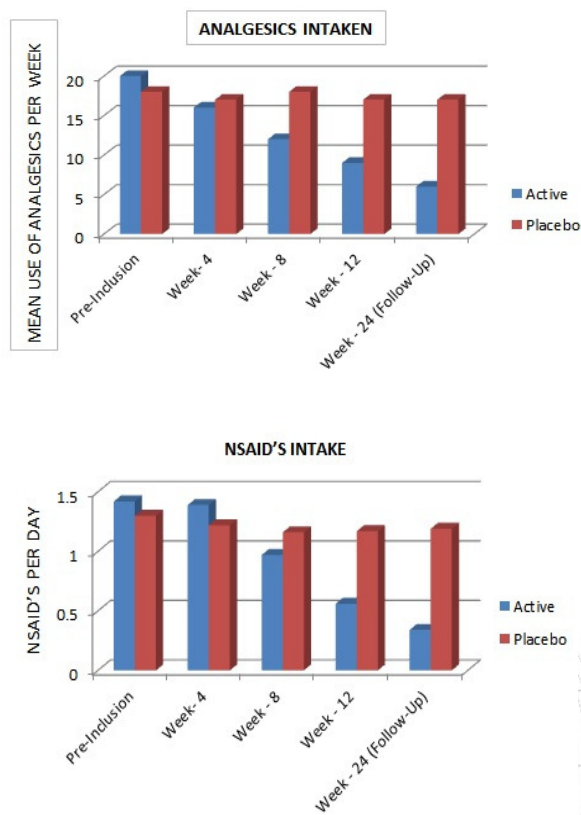


Figure 5 Analgesic Used

The dose of the mineral supplement was determined based on the literature about daily dietary allowance of various minerals (Frestedt JL 2009; Gaby AR 1999). Patients with severe osteoarthritis were excluded as they had severely damaged cartilage, and did not benefit from conservative treatment including dietary and viscosupplementation.

In all the CTMD<sup>®</sup> treated patients, there was a significantly faster onset of benefits, which was evident from week 3 or 4 onwards compared to placebo, where it was evident at week 6 onwards and at the conclusion of the study differences between groups were significant.

There 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, the subjects indicated that the ability to walk even a little bit further was important to them. Need of rescue medication reduced by 36 % (18) patients in CTMD<sup>®</sup> as compared to patients in placebo group.

Synovial fluid examination suggested that CTMD<sup>®</sup> helped in restoring synovial fluid rheological properties and synovial metabolism and in reducing cartilage pathology by

decreasing the Average cell count significantly to 240 for CTMD<sup>®</sup> 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 the healthy habits contributed to improvement, this showed improvement in primary and secondary assessments. As subjects 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 might have altered the basal nutritional status of the subjects. Rescue medication use was greater in placebo and CTMD<sup>®</sup> groups, and this may have masked differences between the positive benefits related to treatment and placebo groups.

Since there are no similar studies, we compared our results with subjective data of other double blind placebo controlled studies 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 achieved these actions and benefits was unclear. The literature did not provide a clear link between a nutrition based action of minerals and an effective anti-arthritis therapy. CTMD<sup>®</sup> is composed of multiple minerals and the 'active ingredient' for the complex was difficult to determine. A number of the minerals, Manganese and Selenium in it might have anti-inflammatory and anti-oxidant properties which might directly and/or indirectly influence the efficacy of this unique complex.

CTMD<sup>®</sup> slowed cartilage damage progression thus confirming its validity as supplement. As there were no changes in various clinical and laboratory measures of safety in this 6 month study, it was considered safe for use. 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.

These early onsets of benefits (as early as one week) in some patients were consistent with those in-vitro studies, which demonstrated the protection of human cartilage degradation was induced by IL-1 $\beta$ . However, the present

study did not directly assess whether protection against cartilage degradation was associated with the therapies, and that a substantial change in joint architecture occurred in this timeframe.

MRI revealed the entire spectrum of OA related abnormalities in knee, and though expensive was a better alternative. 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. Conventional radiograms were 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 limitation of this study was its short duration (24 weeks including follow up), 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<sup>®</sup> and to explore the lack of significant treatment effect and its efficacy may have been under demonstrated within this 24 week study period.

## CONCLUSION

The above study was conducted to determine the efficacy on pain and function in subjects with osteoarthritis of knee, of a food supplement, CTMD<sup>®</sup> when compared with placebo.

The following conclusions were drawn from the study:

The WOMAC scores demonstrated significant improvement in pain, stiffness and physical disability for patients with knee osteoarthritis. The scores reduced significantly in all the parameters under consideration, hence substantiating the efficacy of CTMD<sup>®</sup> similarly dramatic improvement was seen on application of the visual analogue scale pain score.

The mean distance covered in 6 minutes too increased noticeably and was consistently more than that seen at the baseline. Furthermore, no adverse effects were noted in the trial.

There was a statistically significant difference in the use of rescue medication between the two groups i.e. CTMD<sup>®</sup> and Placebo at visit 3. These findings helped to conclude that the need of rescue medication was further decreased by 24 weeks in CTMD<sup>®</sup> group.

However there were no observable significant changes in X-ray, no increase in joint space width in any group.

Ultrasonography of Cartilage thickness- improved insignificantly in CTMD<sup>®</sup> group by 0.02 mm as compared to 0.04 mm in the placebo.

Synovial fluid examination suggested that it helped in restoring synovial fluid rheological properties, synovial metabolism and in reducing cartilage pathology.

This clinical trial conducted in 93 subjects over time duration of 12 weeks and follow-up at 24<sup>th</sup> week demonstrated short term as well as long term benefits of CTMD<sup>®</sup> in improving the clinical condition of patients with osteoarthritis. A multitude of disadvantages were incurred with the standard line of treatment so far followed by clinicians worldwide for osteoarthritis, and hence safer and naturally active agents are the need of the hour.

This clinical study brings forth CTMD<sup>®</sup>, a food supplement as a new line of treatment, which is both safe and effective, for patients of Osteoarthritis. Further evaluation in larger study samples will confirm its utility in the management of osteoarthritis.

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