The use of methylsulfonylmethane (MSM) in the treatment of osteoarthritis

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Dedication

I would like to thank God for helping me through this program and through life. I would really like to thank my husband, Russell, for being so supportive as I go through school. He has truly been an inspiration to me and helped my get through hard weeks when I really needed him most.

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Introduction

Osteoarthritis (OA) is among the most frequent and symptomatic health problems presented by middle aged and older adults, and it is a major cause of morbidity and disability (Buckwalter & Martin, 2006). According to recent data published by the Centers for Disease Control and Prevention, approximately 46.4 million U.S. citizens suffer from doctor-diagnosed OA. As the population ages, OA numbers are expected to increase to 67 million affected Americans by 2030 (Centers for Disease Control and Prevention 2006). OA has a profound effect on the economy, costing more than $60 billion per year in the U.S. These costs do not take into account pain and suffering, decreases in job related productivity, decreased ability to participate in regular exercise to prevent other morbidities, and the cost to family members who must care for the patients with OA. OA is second to ischemic heart disease as a cause of work disability in men over 50 years (Buckwalter, Saltzman, & Brown, 2004). OA can affect any joint, but most commonly it occurs in the knee, hip, hand, and spine. Less frequently OA occurs in the foot, wrists, shoulders, and ankles (Arden & Nevitt, 2006).

OA is a degenerative joint disease that involves progressive loss of articular cartilage, followed by attempted repair of the damaged articular cartilage, leading to remodeling and sclerosis of bone, and osteophyte formation. Though there are theories regarding the cause of this joint degeneration, the actual disease of the bone that causes the symptoms of OA is not well understood. Current treatments for OA cannot prevent or cure the disease and symptomatic treatments often do not provide adequate pain relief. There seems to be no one superior treatment for OA when all options are compared. Once the diagnosis of OA has been made, patients may suffer with repercussions, such as limited mobility and pain, for the rest of their lives (Buckwalter & Martin, 2006).

The demand for arthritis pain control has lead to the use of a variety of medical therapies in search of the most effective drug with analgesic and anti-inflammatory properties (Kim, Axelrod, Howard, Buratovich, & Waters, 2006). Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the most widely used medication in the treatment of OA, though there is limited evidence that they improve the course of the disease. There are several adverse effects associated with the use of NSAIDs and this limits their use as a long-term therapy (Usha & Naidu, 2004). Cyclooxygenase 2 (COX-2) selective agents are preferred drugs for moderate to severe pain, but have recently shown adverse side effects and many have been removed from the market (Ge et al., 2006). The use of the combination dietary supplement glucosamine and chondroitin sulfate has been used for the treatment of OA since the 1960s (Felson et al., 2000). These compounds occur naturally in the body and may be involved in the repair and maintenance of normal cartilage (Felson et al.). These compounds have been through numerous clinical trials and have shown to have beneficial effects regarding the patient's condition. However, it should be known that several of these studies were performed by the manufacturer of the product (Felson et al.). Intraarticular injections are considered as a treatment only after oral and intramuscular intake of other options has failed (Ge et al.). Glucosamine, chondroitin, sodium hyaluronate, and NSAIDs are the most common treatments used in as intraarticular injection (Ge et al.).

In the vast majority of cases, surgical treatment is considered only after the failure of other non-surgical treatments. Total joint arthroplasty is a successful procedure that can eliminate disability from end-stage osteoarthritis and restore patients to their normal functioning (Felson et al., 2000). Good short-term results are achieved by the procedure but steady

deterioration occurs over the following 10-15 years resulting in the need for a repeat total joint arthroplasty (Ge et al., 2006).

Exercise is also an effective intervention for OA. Growing evidence shows that inadequate motion, deconditioned muscle, and joint stiffness may contribute to signs and symptoms of OA (Felson et al., 2000). Muscle conditioning and aerobic exercise have proven to lessen the symptoms in people with knee OA (Felson et al.). Goals of an exercise program should include increasing joint range of motion, increasing strength and endurance of muscles surrounding the joint, assisting in weight loss, increasing aerobic capacity, and improving functional capacity (Domenica et al., 2005).

Methylsulfonylmethane (MSM) is a dietary supplement that may be beneficial in the treatment for OA. MSM also known as methyl sulfone or dimethylsulfone (DMSO2) is the first oxidized metabolite of dimelthylsulfoxide (DMSO). Robert M. Herschler, who first discovered this compound, registered eleven patents on the odorless substance between 1981 and 1996. (Lang, 2001). MSM is a form of complementary and alternative medicine (CAM) that is used by a wide variety of patients. In a study done by the CDC in 2004, of the six hundred twelve participants from ages eighteen to eighty-four surveyed with rheumatoid arthritis, osteoarthritis, or fibromyalgia, 89.4% had tried some form of CAM for arthritis. At the time of the survey 4.6% of those surveyed were currently on MSM (Herman, Allen, Hunt, Prasad, & Brady, 2004). MSM is believed to have anti-inflammatory and antioxidant mechanisms (Beilke, Collins-Lech, & Sohnle, 1987). MSM has also been shown to improve upper and lower respiratory symptoms in individuals suffering from seasonal allergic rhinitis. Because chronic allergy is an inflammatory response to allergens, it is believed that these symptoms were relieved by the anti-inflammatory properties of MSM (Barrager, Veltmann, Schauss, & Schiller, 2002). A

combination of MSM and aspirin is thought to induce some chemoprevention though the mechanism is unknown (Ebisuzaki, 2003).

Origin of MSM and its relationship to DMSO

Methylsulfonylmethane (MSM) is an organic containing compound also known as methyl sulfone and dimethyl sulfone (DMSO2). MSM is a normal oxidative metabolite product of dimethyl sulfoxide (DMSO), a pungent solvent used for the treatment of interstitial cystitis (Childs, 1994). The cycle of DMSO and MSM begins in the ocean where algae and phytoplankton release dimethyl sulfonium salts. These salts are transformed into a volatile compound, dimethyl sulfide, then leave the ocean as a gas and rise to the upper atmosphere. When dimethyl sulfide is exposed to ultra-violet light and ozone the result is DMSO and DMSO2. Both DMSO and DMSO2 are water soluble compounds that return to the surface of the earth via rainwater. The compounds are soaked up by plants and concentrated in the matrix of the plant. MSM is found in a variety of fruits, vegetables, grains and animals. MSM has been used with a clinical benefit in diseases. DMSO, its parent compound, has yielded positive results in clinical trials (Jacob & Appleton, 2003; "Methylsulfonylmethane (MSM). Monograph," 2003). MSM is a more stable organic compound with pharmacotherapeutic properties than DMSO, and has the advantage of being odorless and only slightly bitter tasting (Usha & Naidu, 2004). DMSO2, like its parent compound DMSO is a scavenger of intracellular hydroxyl [OH-] free radicals, which are primary triggers of the inflammatory process (Childs). DMSO is readily absorbed through the skin and could possibly be a "carrier" of other substances. It readily passes through tissues and takes other compounds with it. DMSO2 does not share this quality with

DMSO, in that it does not take compounds through tissue layers into circulation when it is used dermally (Childs). Because DMSO has the advantage of great permeability, it can penetrate cell membranes that are impermeable to other antioxidants (Fox & Fox, 1983). Since these two compounds are so similar, in the body 15% of DMSO is converted to DMSO2 (Hucker et al., 1967).

Pharmacokinetics of MSM

It is thought that the primary mechanism of action of MSM is donation of sulfur. Sulfur is a trace element found in our bodies that is depleted by low protein diets and the use of acetaminophen, one of the most commonly prescribed drugs for OA. Sulfur is a major component of connective tissue. Sulfur strengthens connective tissue by forming cross-linkages called disulfide bonds that are the links in chains of glucosaminoglycans that build cartilage (Jacob & Appleton, 2003).

Evidence of this mechanism is visible in a study by Richmond in 1986, where MSM with a radioactive tracer on the sulfur portion was fed to growing guinea pigs. Twenty-four hours after ingestion the guinea pigs were sacrificed and tests were completed to measure the incorporation of the radioactive sulfur from MSM into essential amino acids methionine and cysteine. This study confirmed that sulfur from MSM was incorporated into serum proteins through donation of the sulfur molecule. The methionine seemed to have a higher specific activity, which lead researchers to believe it was synthesized before cysteine.

In a study by Layman and Jacob in 1985 involving Rhesus monkeys, 3 grams of DMSO was given for every kilogram of body weight to three primates for fourteen days. To determine

the absorption, metabolism, and excretion of the compound, urine and fecal output was collected and blood samples were taken from each monkey at one, two, four, six, eight, and twenty-four hours after the first dose of DMSO. A peak serum concentration of DMSO was observed four hours after ingestion. The serum levels declined rapidly after twenty-four hours. The serum half-life was found to be sixteen hours with an elimination constant rate of 4%. With continued treatment, a steady state of DMSO in the blood was reached within four days. When DMSO was stopped on day 14, the mean DMSO2 serum concentration declined for the next 96 hours and only traces were detected after 120 hours. The study found no excretion of DMSO or DMSO2 in fecal matter. DMSO and DMSO2 were found to be excreted in the urine in monkeys. This accounted for 60% and 21% of ingested compound that was found unchanged in the urine. Once DMSO treatment stopped DMSO and DMSO2 continued to be excreted in the urine for 5 days. When these results were compared to the excretion of DMSO and DMSO2 in man there were marked differences (Layman & Jacob, 1985). While DMSO2 was completely cleared from the urine in monkeys in 120 hours, it took 400 hours for the complete clearing in man (Hucker et al., 1967). This showed that DMSO2 is cleared faster in monkeys than in man and that DMSO2 binds to tissues more readily in man than in monkeys. This study helped to further explain the pharmacokinetics of DMSO and MSM.

Another study by Hucker et al. in 1967 involving human subjects, DMSO was given to two patients in a 70% DMSO solution dermal swab, and given orally to one patient and the two routes of administration were then compared. When administered dermally, which involved applying DMSO in a water solution to the entire body surface with a gauze pad, peak serum levels were achieved in 4 to 8 hours. When given orally, the drug was more readily absorbed reaching serum peak levels in 4 hours. Both the unchanged drug and its metabolite DMSO2

were detected in the urine in both patient groups. DMSO2 did not appear in the serum until after 48 hours of administering DMSO in both study groups, and persisted in the serum for 400 hours.

Urinary excretion of DMSO given dermally began shortly after administration of the drug. Total DMSO excreted was 13% of original dose. Urinary excretion of DMSO2 was apparent 8 hours after the administration of the drug, and continued for 456 hours, adding up to 17.8% of the dose of DMSO. The results for oral DMSO administration were slightly different. DMSO was detected in the serum within 4 hours of oral administration. DMSO2 was recognized in the serum after 72 to 96 hours and could be detected for up to 400 hours after. Urinary excretion of orally administered DMSO was detected almost immediately after drug administration and continued for 120 hours. The results of this study explained that when DMSO is administered it is excreted partly as the parent unchanged drug and partly converted to DMSO2 (Hucker et al., 1967).

The fact that serum levels were lower when the drug was administered dermally compared to oral administration suggests that absorption in the gastroinstestinal tract is more complete than absorption through the skin. According to Hucker et al. the explanation for DMSO clearing faster than DMSO2 may be due to the lower renal clearing of DMSO2 or possibly more extensive tissue binding of DMSO2. It is also possible that DMSO is irreversibly bound at a site from which it is slowly converted to DMSO2 and then excreted (1967).

In addition to its ability to absorb through the skin with its parent compound DMSO, MSM has shown the ability to cross the blood brain barrier; without causing neurological damage (Lin, Nguy, Shic, & Ross, 2001). Magnetic Resonance Spectroscopy demonstrated this phenomenon in three normal volunteers on the daily recommended dose of 1-3g daily (Lin et al.). Another study by Rose et al. in 2000, involving a 62-year-old man also showed MSM

crossing the blood brain barrier. One possible explanation for the presence of MSM in the brain is that the compound in the localized spectrum is a contribution from dimethyl sulfone in cerebral spinal fluid. It was also determined by this study that the half-life of MSM in the brain is about 8 days. The interaction of this compound on cognitive performance was not measured, though future studies on this method of absorption are needed.

Clinical Trials Performed on MSM

MSM was first researched in a clinical trial (Kim et al., 2006) as a potential treatment for osteoarthritis. In the Phoenix, AZ metropolitan area patients in this study were over 40 years old, and diagnosed with knee OA according to modified criteria of the American College of Rheumatology (ACR), which includes functional classes I, II, and III, mild to moderate osteophytes and joint space narrowing, regular arthritis pain for 3 or more months, greater than 40 out of 100 on visual analogue scale, and rating more than 2 on patient global assessment of overall arthritis disease status (Kim et al.). A washout period of 7 days was required for all NSAID users prior to beginning the study. This was a double-blind study with 25 patients in the control group and 25 patients in the MSM group. All patients were given rescue analgesics, 325 milligrams of acetaminophen, to be used when pain was intolerable and were not to exceed 2.6 g/day. A dose of 6g/day of MSM was administered to the patients based on common clinical and over-the-counter recommendations for the use of MSM. Primary endpoints were a total of the subscales in the Western Ontario McMaster University Osteoarthritis Index (WOMAC version 3.1), which includes questions on pain, stiffness, physical function, and aggregated symptoms total symptoms, and were taken at baseline after the washout period, 2, 4, 8, and 12 weeks.

Global Assessment, or overall arthritis disease status measured don a 5-point Likert scale, was taken for both the physician and the patient at baseline and again at 12 weeks. Another questionnaire included was an SF-36 used to assess quality of life, which is a 36 item questionnaire broken into 9 categories including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health and reported health transition, because it was previously applied in other studies pertaining to osteoarthritis. Blood was drawn for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and urine malondialdehyde (MDA) on these patients to monitor the potential activity, both adverse and beneficial, of MSM in the body (Kim et al.). These levels were measured in the blood at baseline and 12 weeks. CRP and ESR were measured to monitor the potential anti-inflammatory activities of MSM. MDA was tested to measure the potential antioxidant activities of the supplement that have been previously suggested in other studies (Beilke et al., 1987). Forty of the fifty individuals enrolled completed the study. Adverse effects included: bloating, constipation, indigestion, fatigue, concentration issues, insomnia, and headache. All of these symptoms were minor and did not interfere with activities of daily living for the patient. The treatment group showed improvement in both decreasing pain and increasing physical function on the WOMAC subscales. There were no significant changes in the areas of joint stiffness and aggregated total symptoms. There was an overall decrease in arthritis pain by 25.1%. There were similar changes in the placebo group which showed that the effect of MSM was modest. There was a significant change in two of the three WOMAC subscales, pain and physical function, ($p < 0.05$). Pain and physical function were still continuing to decline at 12 weeks. This may show that MSM was just starting to have its effect and a longer study may provide more information on its benefit (Kim et al.). Because a plateau was never reached, it lead to the

suspicion that MSM might have had an even greater effect and just took longer to reach a steady state than was expected (Kim et al.). Though this study showed that MSM does have a statistically significant effect on pain and physical function, it showed no significant changes in the anti-inflammatory activities of MSM, ($p < 0.05$). There was a small change from baseline, but were not significant. MDA levels decreased in the MSM group significantly to the placebo group suggesting changes in oxidative stress with MSM (Kim et al.). This decrease may be due to the methyl donation from MSM. This decrease suggests a potential role of MSM in supporting metabolic processes like antioxidant capacities (Kim et al.).

Another study involving MSM and its efficacy, performed by Usha et al. in 2004, looked at the safety and efficacy of glucosamine sulfate, MSM, and the combination of the two versus a placebo in OA of the knee. MSM is an effective natural analgesic that blocks the inflammatory process and increases the activity of cortisol, a natural anti-inflammatory hormone produced by the adrenal cortex (Jacob & Appleton, 2003). One hundred and eighteen patients were enrolled through an outpatient facility in Hyderabad, India after fulfilling inclusion and exclusion criteria. Included were male and females between the ages of 40 and 70, with radiological evidence of OA of the knee, symptoms for a minimum of 6 months, not taking NSAIDs for previous 2 weeks, and having a Lesquesne index, used to assess clinical functional status, score between 8 and 18. Upon enrollment, patients underwent a full medical exam. Radiographs were taken of the knee in the anterior-posterior and lateral positions. In this randomized, double-blind, placebo-controlled study the patients were separated into four different groups. Group 1 ingested 500mg of glucosamine with a placebo MSM. Group 2 ingested 500mg of MSM and a glucosamine placebo. Group 3 ingested 500mg of glucosamine and 500mg of MSM. Group 4 ingested glucosamine placebo and MSM placebo capsules. Treatment continued for 12 weeks

and patients were evaluated at 0, 2, 4, 8, and 12 weeks. Efficacy was evaluated by description of pain and swelling on a four-point scale with 0 = no pain or swelling and 3 = severe pain and swelling, and this was accomplished using a VAS 0-100mm scale with 0 = no pain and 100 = most severe pain. Joint mobility was assessed in the same format as pain and swelling but in a category by itself. Walk time was also measured for a 15m distance. All of these parameters were used to assess efficacy of MSM and glucosamine (Usha & Naidu, 2004). Safety was monitored by medical history, physical exam, and vital signs at each visit. Biochemical laboratory tests, liver function tests, and renal function tests were performed before the trial and every 4 weeks of the clinical trial. Compliance to the regimen was monitored by pill counting at every visit. Patients who had not taken >80% of their medications were considered "noncompliant." Compliance was measured using a 4-point scale with 3 being excellent compliance (drug consumption >90%), 2 being good compliance (drug consumption 81-90%), 1 being fair compliance (drug consumption 65-80%), and 0 being poor compliance (drug consumption <65%). These scores were added to the global evaluations at the end of the study. Four patients in the placebo group and two patients in the combination group were lost to follow-up. The last recorded data was carried forward for analysis on these patients. Of the 118, 28 were in the placebo group, 30 in the glucosamine group, 30 in the MSM group, and 30 in the combination group. The results of the study included significant ($p<0.05$) decreases in pain and swelling in the group using MSM, in patients using glucosamine, and a very significant decrease in patients using the combination. There was no significant decrease in pain and swelling in the placebo group. This suggested that combination therapy was more effective than single therapy alone. Treatment with glucosamine, MSM, and the combination of the two also favorably altered walking time and joint mobility compared to placebo. Rescue analgesics, with a

maximum of 2 grams of Paracetamol per day, were significantly decreased in patients on combination when compared to individuals on glucosamine and MSM alone and placebo. The use of rescue analgesics increased on average from fifteen to twenty-four capsules per person in 12 weeks in the Glucosamine and MSM alone and placebo groups. The combination group had an average decrease from thirteen to eight rescue analgesic capsules taken in 12 weeks of treatment. The results of this study helped to support the use of MSM, but more strongly supported the used of MSM in combination with other supplements like glucosamine sulfate (Usha & Naidu).

Discussion

Osteoarthritis is the leading cause of disability in the older population. Eighty percent of individuals with OA have limited mobility (Ge et al., 2006). With such a large portion of the population affected, there will be consequent increased spending on diagnosis, side-effect prevention, and loss of productivity due to OA (Ge et al.). With this disease process affecting so many individuals, it is important to widen the area of research and look for more possible treatments for OA. Stephen Parcell, a research associate from Bastyr University Botanical Medicine Department, completed a review discussing the importance of sulfur in diets and the benefit derived from this element (2002). Thirty-four percent of the MSM is made up of elemental sulfur. Sulfur is needed for the formulation of connective tissues, and this is why MSM has been studied as a potential treatment for arthritis. The concentration of sulfur in arthritis cartilage has shown to be one third the concentration level when compared to normal cartilage. The two studies mentioned above both showed that MSM was associated with some

relief from arthritic pain (Kim et al., 2006; Usha & Naidu, 2004). DMSO, the parent compound to MSM, has shown to have analgesic properties and it penetrates the skin quickly. It is not approved by the Food and Drug Administration for analgesic use in patients with arthritis, though it has shown promise as a topical agent (Evans, Reid, & Sharp, 1993). DMSO also inhibits prostacyclin by interfering with the release of arachidonic acid from cellular phospholipids, thus preventing the inflammatory process (Alam & Layman, 1983). With DMSO having analgesic and anti-inflammatory properties, it is believed that MSM also has these same properties. MSM in combination with aspirin showed to change cell type or differentiate and terminate cell proliferation, showing it to be an alternative mechanism for chemopreventive action. The mechanism of aspirin is known to affect arachidonic acid, but it is still unknown if MSM inhibits prostaglandin synthesis (Ebisuzaki, 2003) though it did affect fifty-percent of arachidonic acid release in aortic endothelial cells (Alam & Layman). The LD50 (Lethal Dose, 50%) of MSM has not been set though the typical dose take by humans is between one and six grams per day. In rats, a dose of 2g/kg of body weight was given to 10 rats to observe the acute and subchronic toxicity of MSM. This dose is proportionately five to seven times the maximum dose given to humans. There were no adverse effects or mortality observed. Renal histology was normal and there were no lesions present. It was concluded that MSM is a well tolerated substance in rats (Horvath et al., 2002; Magnuson, Appleton, Ryan, & Matulka, 2006). Adverse effects noted in Usha et al. study were mild gastrointestinal discomfort and were not considered serious side effects (Usha & Naidu). With this evidence, MSM is considered to be a well tolerated supplement in any individual or animal.

Though MSM has shown to be an efficacious supplement in relieving pain and inflammation induced by osteoarthritis, and has shown to be a safe supplement for use, it still

lacks results of a long-term meta-analysis clinical trial. There have not been any studies done longer than 12 weeks on MSM supplements. The long-term effect of the supplement is unknown. Another possibility would be to explore the use of MSM in combination with other treatments for palliative control of arthritis pain. MSM does appear to be less effective than COX-2 inhibitor drugs (Kim et al., 2006) and has no effect on COX-1 (Ebisuzaki, 2003), but its use as an additive to other treatment for OA should be considered (Kim et al.).

A few clinical trials have been performed using mehtylsulfonylmethane (MSM) as an anti-inflammatory and analgesic agent to treat the pain caused by inflammation in OA. Although these studies have shown MSM to be beneficial, further studies must be performed in order to consider the supplement to be a proven treatment for OA. The purpose of this review is to evaluate the supplement methylsulfonylmethane, its proposed mechanisms of action, and its efficacy in treating the inflammation and pain associated with osteoarthritis. Through this review there is no conclusive proof that MSM is beneficial for patients with OA. More in depth clinical trials should be performed before a conclusion is made.

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Abstract

Objective. Osteoarthritis (OA) is on of the most common symptomatic health problems of middle aged and older adults. The demand for arthritis pain control has lead to the use of many different medical therapies in search for the most effective drug with analgesic and anti-inflammatory properties. Methylsulfonylmethane (MSM) is a dietary supplement that may be beneficial in the treatment for OA. **Methods.** Information searches for MSM were performed and information was used from the following search engines: MEDLINE, PubMed, CINAHL, Google Scholar. **Results.** Though MSM has shown to be an efficacious supplement in relieving pain and inflammation induced by OA, and has shown to be a safe supplement for use, it still lacks results of long-term clinical trials. **Conclusion.** Although studies have shown MSM to be beneficial as a treatment for OA, further studies must be performed in order to consider the supplement to be a proven treatment for OA.