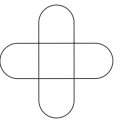
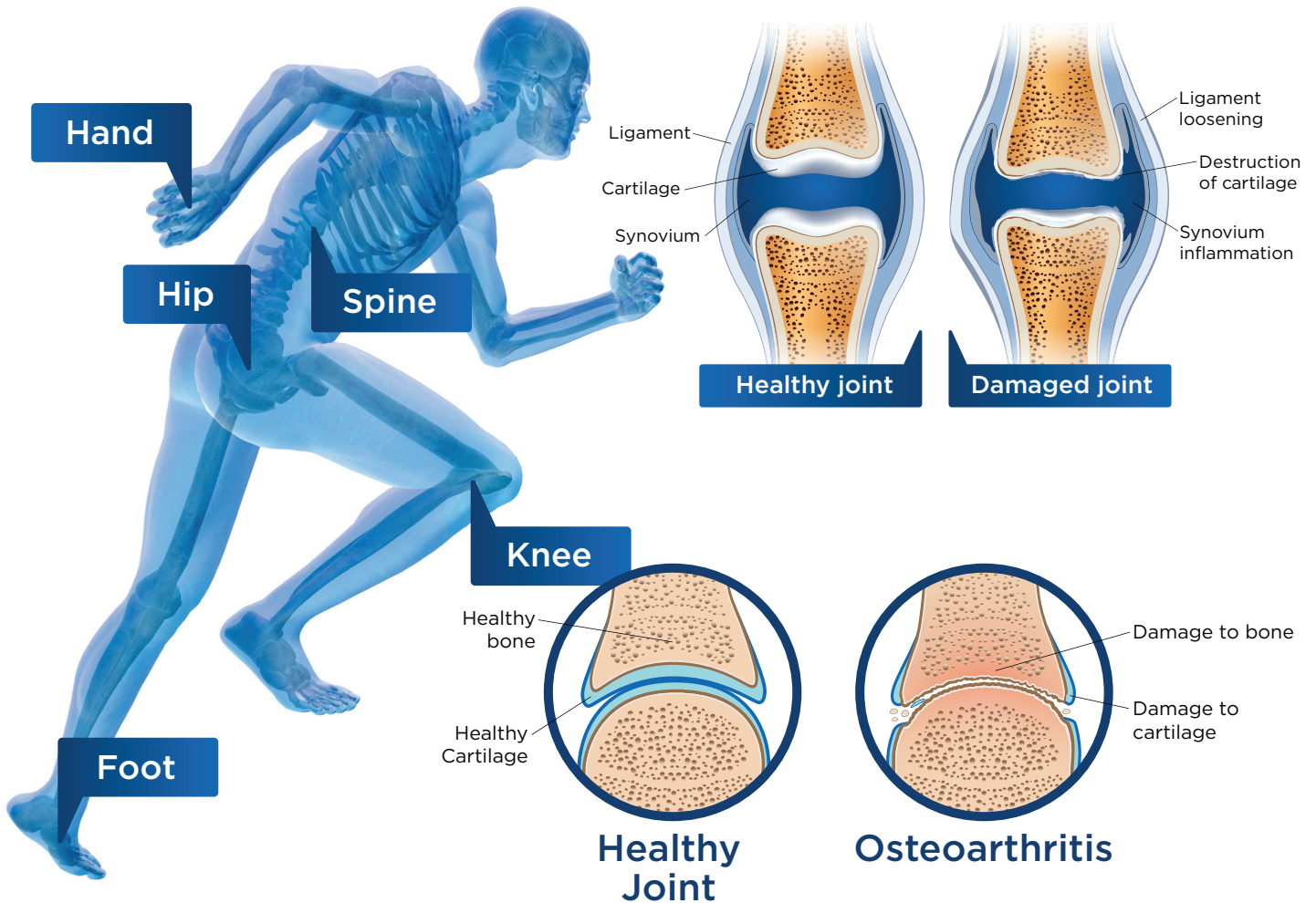




MSM Joint Health Science Brief

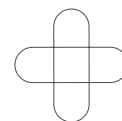


Introduction to joint health

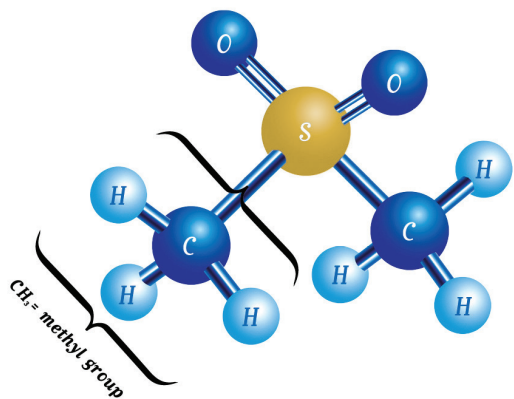


Healthy joints are fortified with structural components such as cartilage and synovium (synovial fluid and membrane) which provide a buffer between bones to reduce friction. Joint tissues adapt to imposed demands by altering structural components within cartilage (mostly type II collagen) providing enough space to allow for the normal biomechanics of the joint, e.g. fluid extension and flexion. When joint biomechanics are not normal, joints do not properly adapt to changing conditions and cartilage is not replenished. Swelling, stiffness and arthritis are the common symptoms. This involves localized inflammation whereby inflammatory cells gather at the site of injury and

release chemicals destructive to cartilage tissue. The cause of injury varies greatly but age-related cartilage degradation and previous injury are commonly cited factors.



MSM and joint health

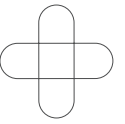


Methylsulfonylmethane (MSM; dimethyl sulfone; DMSO₂) is an organic sulfur-containing compound which naturally occurs in various fruits, vegetables, animals, and humans, with the most abundant natural source occurring in cow's milk (Williams, 1966; Pearson 1981). It is an oxidative metabolite product of dimethyl sulfoxide (DMSO) with about 15% of DMSO being converted to MSM. Research has shown MSM provides multiple health benefits including anti-inflammatory effects, anti-atherosclerotic and antioxidant activity, sports-performance benefits and possible mitigation of seasonal allergies (Barrager, 2002). In the area of joint health extensive clinical (human) research has demonstrated the utility of MSM in alleviating joint pain and stiffness while improving mobility and quality of life in persons suffering from joint ailments.

The physiological role and action of MSM remains to be fully explored. Because of MSM's sulfur content (roughly 34% elemental sulfur) it is used by the body to maintain normal connective tissues. Sulfur is the third most abundant mineral in the body based on percentage of body weight. In arthritic cartilage, the concentration of sulfur has been shown to be one-third the level of normal cartilage in similar conditions (Rizzo, 1995). MSM may also be a donor to the sulfur-containing amino acids (SAA) including methionine, cysteine, cystine, homocysteine, homocystine, and taurine (Parcell, 2002). Endogenous release of sulfur from SAA's is used to synthesize the chondroitin matrix of cartilage (Baker, 1986). Therefore it is hypothetical that some sulfur compounds, sulfur-containing amino acids or collagen supplementation can have a beneficial effect on joints by acting as a sulfur resource to any compounds that are involved with protection and development of cartilage of the joints (Ezaki, 2013).

MSM has also demonstrated favorable effects upon homocysteine and urinary malondialdehyde (MDA) (a marker of oxidative stress), indicating the compound could potentially exert favorable effects on oxidative stress (Kim, 2006). The correlation between oxidative damage and cartilage degeneration in osteoarthritis has been recently shown (Yudoh, 2005). MSM has also demonstrated an effect on hypercoagulation. Pro-coagulant factors have been shown to compromise subchondral vasculature and may thus accelerate joint damage (Ghosh, 2001).

Several in-vivo studies have demonstrated that MSM possesses selective anti-inflammatory activity. In a study examining the effect of MSM on murine macrophages, MSM demonstrated the ability to inhibit the expression of inflammatory markers through the suppression of iNOS and Cox-2 genes. MSM was also shown to strongly inhibit the inflammatory cytokines IL-6 and TNF α , both key in producing an inflammatory response to acute injury. MSM's inhibition of NF-kB, a nuclear transcription factor regulating many of the inflammatory mediators, was identified as a possible mechanism. MSM was able to block the degradation of a key protein, essentially disabling the expression of various inflammatory response mediators (Kim, 06). In another in-vitro study examining the effect of MSM on human chondrocyte cells, MSM again demonstrated powerful IL-6 (and IL-8) suppression by deactivating the protein kinase that would allow for the production of these inflammatory cytokines (Kloesch, 2011). In an in-vitro study evaluating the effect of OptiMSM on tissue components from the knee joint results demonstrated that OptiMSM reduced the expression of inflammatory markers TNF-alpha and IL-1 by 33% and 29% respectively, but did not increase the synthesis of proteoglycans or the cartilage matrix in chondrocytes (Oshima, 2007). Another recent in-vitro study also demonstrated MSM to be a selective inhibitor of NLRP3 inflammasome activation, a multi-protein complex operating as a platform for the inflammatory response mediator interleukin (IL)-1 β (Ahn, 2014). These research studies help clarify several potential mechanisms of MSM in suppressing the inflammatory response.



OptiMSM® research on joint health

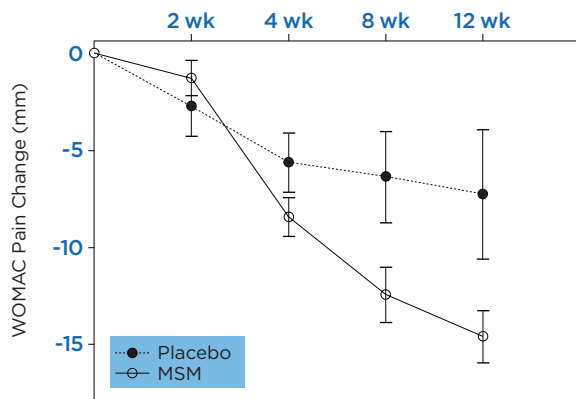


Fig. 2. WOMAC pain changes from baseline to 2, 4, 8 and 12 weeks

OptiMSM has been used extensively in both clinical and pre-clinical research studies. In a study investigating the pharmacokinetics and distribution of OptiMSM following oral administration in Sprague-Dawley rats, OptiMSM was shown to be rapidly absorbed and distributed evenly throughout the body, reaching maximum blood concentrations within two hours after dosing. The radiolabeled OptiMSM was mostly eliminated within 24 hours; this lack of detection may indicate incorporation of sulfur from MSM into N-terminal proteins (methionine, serine, alanine, threonine, valine or glycine) which have a half-life >20 hours. Radioactivity (presence) of MSM was undetectable at 120 hours post-dose, suggesting complete elimination when given in a single dose (Magnuson, 2007). Animal research corroborates this strong trend in reducing inflammatory markers (Ezaki, 2013; Hasegawa, 2004; Alam, 1983). In a study with NZW rabbits experiencing the development of OA, OptiMSM preserved the articular cartilage surface while expression of TNF-alpha in both cartilage and synovial tissue was also decreased, reinforcing the anti-inflammatory properties of the thiol (Amiel, 2008).

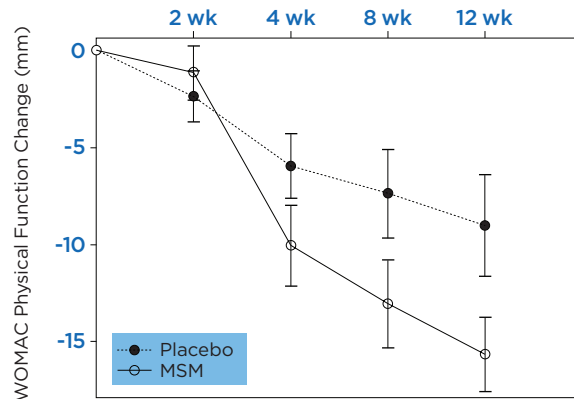


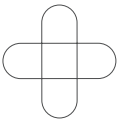
Fig. 3. WOMAC physical function changes from baseline to 2, 4, 8 and 12 weeks

A randomized, double-blind, placebo-controlled trial conducted by Kim et al. corroborates many of the findings of pre-clinical investigation (Kim et al, 2006). Three grams of OptiMSM was consumed twice daily over 12 weeks: based on WOMAC pain and physical function scores OptiMSM improved symptoms of pain and physical function as assessed in 50 men and women with osteoarthritic knee pain.* (See chart) OptiMSM also produced improvements in performing activities of daily living when compared to placebo based on SF-36 assessment. The authors noted in their conclusions, "Another noteworthy finding is that the WOMAC subset continued to decline at 12 weeks, suggesting that the full effects of MSM were not captured during the relatively short intervention." This suggests the duration of three months was effective but not optimal at observing the joint health benefits produced with OptiMSM supplementation.


Studies in support of OptiMSM® research




Subsequent clinical trial research has corroborated the findings of Kim et al. and extended the duration for active treatment of MSM. In a recent randomized, double-blind, placebo-controlled trial with 100 subjects taking three grams (2x/daily) of MSM for 26 weeks the control group experienced significant decreases in all subscales of WOMAC pain and physical index as well as improved performance of daily living as measured on the SF-36. The WOMAC subscales continued to decline at 26 weeks suggesting, according to the authors

"the full effects of MSM were not entirely expressed during the planned intervention timeframe." As in the Kim et al. study MSM benefits in OA sufferers may continue to increase well beyond the time periods studied. Further research is needed in this area (Pagonis, 2014). Other clinical research including combination supplements (e.g. glucosamine, chondroitin, MSM) provide support for the reduction of pain and improvement in physical function observed in clinical research studies with MSM.



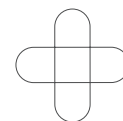
Published studies on the role of MSM in joint health

Study	Design	Study Population	Dosage/Duration	Result
Pagonis et al, 2014	Randomized, double-blind, placebo-controlled trial	100 Subjects with hip and/or knee OA	3g/day MSM (2x/day); 26 weeks	Significant improvement in all WOMAC and SF36 scales for pain, stiffness, physical function and total symptoms. WOMAC subscales continued to decline at 26 weeks.
Debbi et al, 2011	Prospective, randomized, double-blind, controlled trial	49 men and women with knee OA	1.125g MSM (3x/day); 12 weeks	WOMAC pain and stiffness decreased in the MSM group. Moreover, there were significant differences between MSM and control group for WOMAC physical function and WOMAC total score and VAS pain.
Debi et al, 2007	Prospective, randomized, double-blind, controlled trial	60 men and women with knee OA	1.125g MSM (3x/day); 12 weeks	Significant improvements in pain, stiffness and physical function on WOMAC and SF36; significant improvement in physical function as assessed by aggregated locomotor function (ALF)
Kim et al, 2006 	Randomized, double-blind, placebo-controlled trial	50 men and women with mild to moderate knee OA pain	3g MSM (2x/day); 12 weeks	OptiMSM produced significant decreases in WOMAC pain and physical function impairment; significant improvement in performing activities of daily living on the SF-36. Significant reductions in serum homocysteine and urinary malondialdehyde (a marker of oxidative stress).
Usha et al, 2004	Randomized, double-blind, placebo-controlled trial	118 men and women with mild to moderate osteoarthritis	500mg Glucosamine, 500 mg MSM, alone and combo; 12 weeks	Significant decrease in pain, pain intensity and welling indexes for both treatments according to VAS pain index and Lequesne index. Combination provided even better index scores.

Study	Design	Study Population	Dosage/Duration	Result
Pre-clinical				
Ezaki 2013	Animal Study	Cartilage formation in growing rats (G) and cartilage degradation in STR/Ort Mice (A)	0.06g/kg body weight/day; 4/13 weeks	Intake for 13 weeks decreased degeneration of the cartilage at the joint surface in the knee joints in STR/Ort mice in a dose-dependent manner.
Amiel 2008 	Animal study	Mature NZW rabbits transected with right knee ACL		OptiMSM® decreased TNF-α expression in both cartilage and synovial tissue (p<0.01). OptiMSM® has preserved the articular cartilage surface during development of OA & relieved the inflammation level in both cartilage and synovium.
Oshima 2007 	In vitro study	Human (cadaver-derived) osteoarthritic chondrocytes with different grades of OA	0, 1, 3, 6, 12, and 60µg/ml	In Grade II OA chondrocytes, there was a strong trend for 12µg/ml OptiMSM® to reduce mRNA expression of inflammatory markers: TNF-α (-33%) and IL-1 (-29%) when compared to lower concentrations of MSM and control. Results suggest protection of cartilage.
Hasegawa 2004 	Animal study	DBA/1J mice with type II collagen induced arthritis	2.5% MSM in drinking water; 1 week	Arthritic deformation and swelling induced by type II collagen injections were significantly diminished in mice drinking MSM compared to controls. Abnormal white blood cell proliferation in lymph nodes was also reduced in mice drinking MSM.



Study using OptiMSM™



Published studies con't

Study	Design	Study Population	Dosage/Duration	Result
Combination dosages				
Nakasone 2011	Randomized, double-blind, placebo-controlled trial	32 subjects with symptomatic knee OA	2300mg tablet containing 300mg MSM; 16 weeks	Pain significantly improved at all time points in the active group; VAS significantly improved for all three pain subscales; Serum C2C and HA decreased by 10% and 25%, respectively.
Magran-Courtney 2011	Randomized, double-blind trial	30 sedentary women clinically diagnosed knee OA	1,500/1,200/900 glucosamine/chondroitin/MSM; 14 weeks	Significant reduction in WOMAC perceptions of pain, joint stiffness and limitations in physical function; VAS pain decreased; Improvements in QOL measures of physical functioning, vitality, and social function. No significant differences were observed between groups.
Vidyasagar 2004	Open-label study	32 patients from medicine and orthopedic out patient departments	500/400/250 glu/chond/MSM, 2x/day; 12 weeks	Combo useful in decreasing pain, and Lequesne's index, improving functional ability and improving joint mobility.

MSM (methylsulfonylmethane) safety data

Author/Year	Design/Title	Result
1958	LD-50	LD-50 not reached; highest tested dose, 20 grams/kg body weight not toxic; toxicity threshold too high to observe.
1968	Acute Oral Toxicity	Acute Oral LD50 > 17,020 mg/kg BW
1999	Ocular and Dermal Irritation Assay	MSM tested non-irritant to eyes and skin
2003	Subchronic 90-Day Oral Toxicity-organs/tissues	No treatment related histopathological lesions found in the organs and tissues of male and female rats treated with 1,500 mg/kg MSM daily for 90 days.
2005	Ames Test (salmonella typhimurium reverse mutation assay)	In this biological assay for mutagenicity, the five strains tested did not meet the criteria for a potential mutagen.
2013	Patch Test (dermal irritation and sensitization potential)	MSM did not demonstrate a potential for eliciting dermal irritation or sensitization in test population of 50 human subjects.
Takiyama, 2010 ¹	Single and 13-week repeated oral tox study in Mice	NOAEL for MSM at 3% drinking water (8.1 and 8.8g/kg BW - 100x recommended dosage in humans). No toxicity observed at 13 weeks.
Magnuson, 2007 ²	Oral Developmental Toxicity Study in Rats	NOAEL for maternal and developmental toxicity of MSM intake a 1g/kg; no evidence of maternal or fetal toxicity over gestation days 6-20.
Magnuson, 2007 ³	Pharmacokinetics and Distribution of MSM	MSM rapidly absorbed, well distributed and completely excreted from the body after dosage of 500 mg/kg.
Lee, 2006 ⁴	Evaluation of Genotoxicity	MSM not genotoxic in reverse mutation test, in vitro chromosome aberration test, in vivo micronucleus test.
Horvath, 2002 ⁵	Acute & Chronic Toxicity Assessments in Rats	Daily doses of 1.5g/kg and a single dose of 2g/kg for 90 days showed no toxicity in rats.

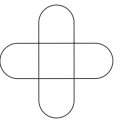
1. Pharmacometrics 2010;79(1/2):23-30

2. Food and Chemical Toxicology 2007;45:977-984

3. Journal of Agricultural and Food Chemistry 2007;55:1033-1038.

4. J. Microbiol biotechnol 2006;16(5):817-820

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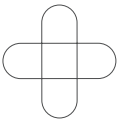
About OptiMSM®

OptiMSM is the world's premier MSM and the only GRAS-affirmed source available in the world. Manufactured exclusively by Bergstrom Nutrition at a dedicated facility in Vancouver, Washington, OptiMSM is the result of a proprietary distillation process that guarantees an ultra-pure product. Bergstrom's stringent quality control ensures batch-to-batch consistency, a fully traceable production process, and includes independent third-party validation of identity and purity.

OptiMSM is:

- The only U.S. made MSM
- GRAS-affirmed with FDA Notification and Letter of "No Objection"
- Kosher and Halal certified, Non-GMO, Non-BSE, gluten-free, allergen free, non-shellfish derived, and vegan
- Backed by extensive toxicology data and ongoing research
- Extremely safe; LD-50 > 17,000mg/kg BW
- Distributed internationally
- Backed by unmatched technical/manufacturing support

For more information and science updates, visit us at www.bergstromnutrition.com



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