Methyl-sulphonyl-methane (MSM) and Musculo-skeletal health – a review for clinicians

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Introduction and background

Methylsulphonylmethane (MSM) is an organo-sulphur compound, $(CH_3)_2SO_2$ and a metabolite of its parent compound, dimethyl sulfoxide commonly known as DMSO, $(CH_3)_2SO$. Both are naturally occurring substances of low molecular weight consisting of two hydrocarbon units (methyl groups) attached to one sulphur, and in the case of MSM, two double-bonded oxygen atoms ($DMSO_2$) (DMSO comprising just one oxygen atom).[1-3]

The presence of these organosulphur compounds within the atmosphere, soil and all living organisms including humans, is described by the Earth's sulphur cycle. The sulphur cycle commences with the uptake of sulphate by marine algae and phytoplankton and the subsequent formation of dimethyl sulphide (DMS) gas which is released into the atmosphere and responsible for the distinctive oceanic odour experienced at the seaside. Atmospheric DMS gas, through interaction with ultraviolet light, ozone and nitrate undergoes a process called 'photochemical oxidation' resulting in the production of DMSO and MSM.[1, 2] Both DMSO and MSM subsequently return to Earth through precipitation, entering the soil where it is absorbed and incorporated into plants ('bioaccumulation') or processed by bacteria in soil, thus improving soil quality. Absorbed MSM is utilised and excreted by plants as sulphide through the process of plant respiration or released into the soil when plant material subsequently decays., Once oxidised into sulphate and incorporated into minerals, sulphate reaches the ocean through surface runoff and erosion and the sulphur cycle is completed. [1, 2]

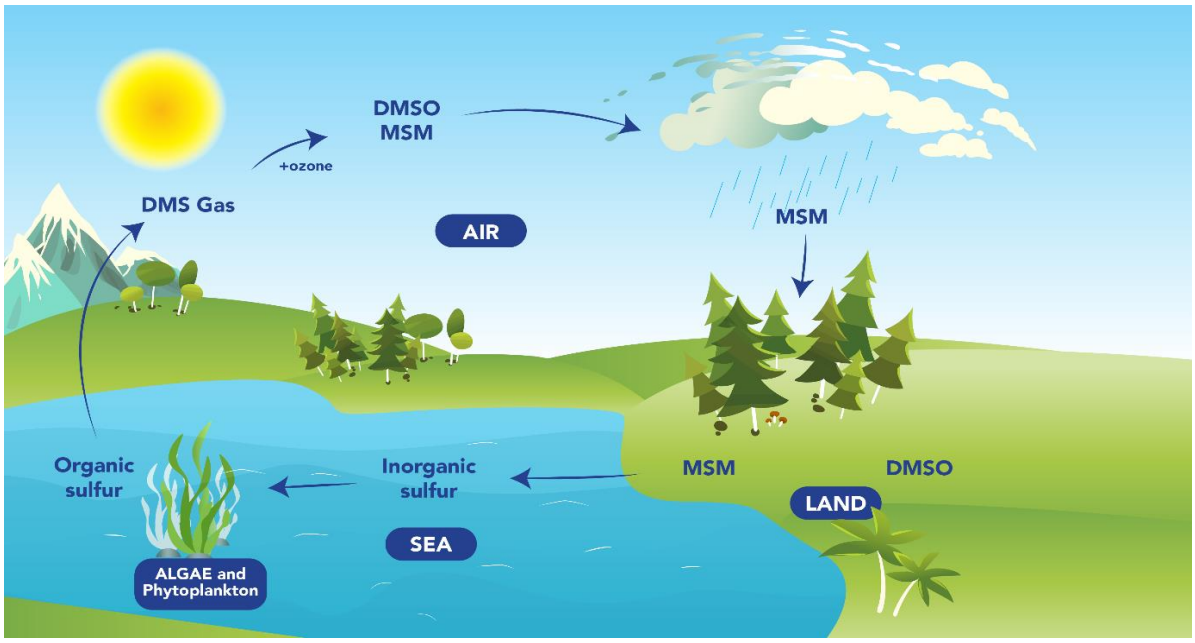

Figure 1 - The sulphur cycle

MSM in Humans

Small amounts of MSM are thus found in various human food sources including fruit, vegetables, grains and cow's milk, [1-4] although some of which is lost in the process of cooking and processing of food. [4] In addition, around 15% of ingested DMSO is metabolised to MSM in humans.[5-7] The healthy human microbiome further plays an important role in enhancing MSM levels with the ability to further produce some MSM from ingested precursors such as DMS, DMSO and methionine. [2]

Pharmacokinetic research indicates that exogenous MSM is rapidly absorbed in humans, Krieger *et al.* reporting detectable increases after a 3-gram dose thereof within 90 minutes of ingestion. [4, 8] Bloomer *et al.* have subsequently confirmed that 3g daily of supplemental MSM results in a significant increase in serum MSM levels after two weeks [4], plasma levels peaking after 4 weeks (at ≈1900µM) and then remaining steady thereafter (up to 16 weeks) concluding that higher doses lead to greater plasma concentrations of MSM but prolonged supplementation beyond 4 weeks did not lead to continued elevation thereof.[9] Butawan *et al.* (2017) reports on numerous pharmacokinetic studies concurring that MSM is mostly excreted via urine in various mammals and humans with smaller amounts also detectable in stool. Rat studies also reveal that exogenous MSM is evenly distributed in soft tissue, [10] a finding supported by existing data on DMSO's and MSMs unique ability to penetrate cell membranes and tissue due to their respective low molecular weights. [1] This, together with data confirming MSMs distribution to cerebrospinal fluid and brain tissue in humans, suggests a similar even distribution thereof in human tissue as well.[2]

Mode of Action

MSM is utilised within the body to maintain and repair normal connective tissue [6, 7, 11] probably due to its sulphur content - sulphur being the eighth most abundant element in living organisms[1] and the third most abundant element in terms of percentage of total human body weight.[12] In connective tissue such as tendons and ligaments, sulphur is necessary for cross-linking of extracellular matrix proteins such as glycosaminoglycans (GAGs) and hyaluronic acid.[13] The protein rich extracellular matrix is rich in sulphur and provides vital properties such as cushioning and strength and disulphide bonds found in connective tissue provide strength, but importantly, also necessary flexibility.[13] Supplemental sulphur may also contribute to improved cartilage formation where deficiency exists [12, 14, 15].

In addition to directly being a source of sulphur, extensive research into the mode of action of MSM has been conducted. Butawan *et al.* eloquently summarises the complex mechanism of action of MSM based on numerous *in vitro* and *in vivo* studies which largely place its mode of action '*at the crosstalk of inflammation and oxidative stress at a transcriptional and subcellular level'.*[2] The general consensus amongst researchers is that MSM's primary action is both that of anti-inflammatory and anti-oxidant [2, 4, 7, 9] via various mechanisms and pathways. Such opinion largely stems from the data summarised below:

Anti-inflammatory	Inhibition of transcriptional activity of NF-κβ and preventing degradation of its respective inhibitor [16-18]
	Consequent downregulation of mRNA for IL-1, IL-6 and TNF-α [18-20]
	Reduces expression of iNOS and COX-2 (through inhibition of NF-κβ)[17]
	Inhibition of expression of NLRP3[19]
Antioxidant	Regulation of the balance between reactive oxygen species (ROS) and antioxidant enzymes by influencing NF-κβ, STAT, p53 & NRF2 transcription factors.[2]

NF-κβ *(nuclear factor kappa-light-chain-enhancer) a pro-inflammatory signalling pathway for transcription of cytokines.*
iNOS *(inducible nitric oxide synthase) – a family of enzymes necessary for production of nitric oxide which modulates vascular tone and regulates mast cell activation.*
NLRP3 *(nucleotide-binding domain (NOD)-like receptor protein 3) inflammasome - assists with maturing of inflammation markers in response to cellular stress.*
STAT *(signal transducer and activator of transcription) are transcription factors necessary for cytokine signalling.*
P53 *(tumour suppressor protein 53) a transcription factor with both oxidative and anti-oxidative action.*
Nrf2 *(nuclear factor erythroid 2-related factor 2) is a regulator of cellular resistance to oxidants.*

MSM thus is thought to exert an anti-inflammatory action by reducing inflammatory cytokines, inhibiting vasodilatory mediators and the attraction of immune cells to sites of inflammation with possible indirect inhibition of mast cell inflammatory mediation. This is achieved primarily through the inhibition of NF-κβ.[2] Such action is further complemented by the further regulation of various transcription factors involved with innate antioxidant mechanisms.

Commercial manufacture and production of MSM

Since the yield of MSM from plant material is very limited, to produce sufficient quantities for pharmaceutical use, MSM is preferably manufactured from its parent compound DMSO by oxidising it with food grade hydrogen peroxide[21], yielding MSM and water. Researchers have subsequently confirmed that MSM produced in this manner had a similar anti-inflammatory action *in vitro* to that of MSM extracted from onions, garlic or chives in terms of inhibition of NLRP3 inflammasome. [19, 21]

Once the DMSO is converted to MSM, removal of excess water is done preferably by distillation in multiple stages, capable of producing MSM that is 99.9% pure as opposed to the alternative crystallisation method. [22]

Clinical application of MSM

1. Osteoarthritis (OA)

Pain, stiffness & swelling

Various human OA trials confirm MSM's ability to significantly improve *pain* [6, 7, 23-25] in terms of the Visual Analogue Scale (VAS) pain scale[23, 24], Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain subscale[6, 7, 23, 25], 36-Item Short Form Survey (SF36) pain subscale[6, 23] and Lequesne Index[24], as well as *stiffness*[6, 23, 25], and *swelling.* [24]

MSM has also proven effective in improving pain in OA when combined with glucosamine and chondroitin[26, 27] however, subsequently, a double-blind, randomised, controlled trial determined that the addition of MSM to glucosamine and chondroitin led to significantly superior outcomes in

terms of pain reduction (WOMAC and VAS scores) in knee OA (Kellgren-Lawrence grade I-II) compared to glucosamine and chondroitin alone with no significant effect on pain over placebo.[28]

Range of motion

MSM treatment has also resulted in significant improvements in physical function and range of motion in various OA trials as determined by the WOMAC [6, 7, 23, 25], SF36 [6, 7, 25] as well as Aggregated Locomotor Function (ALF).[25]

Trials on various other MSM combination products have also reported significantly improved physical function in knee OA[26, 27, 29], interestingly, when a combination of MSM and boswellic acids was compared with glucosamine sulphate for the treatment of knee OA, the MSM/boswellic acid combination led to greater improvements in terms of the Lequesne Index sub-category III measuring function.[29]

2. Preservation of joint integrity

MSM has displayed a variety of joint protective effects in various arthritic animal models.

Cartilage

Using an accepted human OA model i.e. STR/Ort mice spontaneous arthritis model, MSM administration over 13 weeks resulted in decreased degeneration of joint surface cartilage of the knee in a dose dependent manner.[30] Oshima *et al.* (2007) also reported that MSM at concentrations equivalent to those in human studies led to reduced mRNA expression of inflammatory mediators TNF-α (-33%, p=0.08), IL-1 (-29%, p=0.08) in human Grade II OA chondrocytes suggesting its potential cartilage preservation effect in early stage OA.[20]

Other protective effects

Both MSM and DMSO were found to lessen the destructive changes in the joints of mice with spontaneous arthritis.[31] In an animal model of rheumatoid arthritis (RA) MSM supplementation resulted in significantly lower arthritic (deformation) scores, demonstrating a protective action against type II collagen-induced murine arthritis. [32] Most recently, in adjuvant-induced arthritis in rats, MSM (alone and in combination with thiocolchicoside) significantly reduced joint swelling, moderated infiltration of inflammatory cells and synovial proliferation as well as demonstrated a cartilage protective effect and significantly reduced IL-17 and malondialdehyde (MDA – a marker of oxidative stress) at levels comparable with diclofenac.[33]

3. Exercise recovery

The established anti-inflammatory and antioxidant action of MSM has led to various trials investigating such action in the sport and exercise context, research confirming that pre-treatment with MSM leads to reduced post-exercise muscle soreness[3, 34-36] and joint pain[3] as well as resulting in improved recovery.[34, 35, 37]

Such clinical effects are attributed to MSMs anti-oxidant action which was shown to dampen the inflammatory response from strenuous exercise [38] and exercise induced oxidative stress[39, 40] by causing sustained increases in total anti-oxidant capacity of plasma (TAC)[39, 40] as well as lowering uric acid and bilirubin levels post exercise. [39] Such action was also confirmed with concurrent lower markers of muscle damage (CK).[40] MSM was also shown to improve markers of exercise recovery with statistically significant increases of Trolox-equivalent antioxidant capacity (TEAC) assay

immediately post exercise, [37] glutathione levels were also shown to be elevated after endurance exercise when MSM was consumed for 10 days prior to the event.[41]

Dosing and Posology

According to MSM pioneer, Professor Stanley Jacob (Jacob *et al.* 1999), patients experience benefits from taking 2-8 grams of MSM per day, with higher doses warranted in more severe inflammatory conditions but a daily dose of 2 grams being sufficient for general health maintenance. In his experience where higher doses are necessary one should commence treatment with 2 grams daily and gradually increase the total daily intake using divided doses throughout the day.[1]

Arthritis and degenerative joint disease

When applied as a standalone therapy in human OA trials with clinically significant outcomes, the MSM dosages applied range from 3.3 - 6 grams/day as split doses. [6, 7, 23] Where applied as an active ingredient in combination products, trials with clinically significant outcomes in this context applied between 0.5 and 5.0 grams of MSM per day.

Exercise recovery

In the majority of exercise recovery trials MSM was applied preventatively i.e. pre-exercise for a period of 10-30 days (average ≈20days).[3, 36-38, 40-42] This is supported by pharmacokinetic research which confirmed that serum MSM levels peak after 2-4 weeks of supplementation at a dose of 3 grams daily [4] with dose dependent steady stages achieved after 4 weeks.[9]

Most exercise recovery studies applied a dosage of 3 grams/day[3, 36-38, 42] with two studies dosing at 50mg/kg body weight [40, 41] equivalent to 3 grams in a 60kg participant. In a dose comparative trial, Kalman *et al.* (2012) reported that a lower daily dose of 1.5 grams/day did not achieve significant improvements in terms of muscle soreness and TEAC in contrast with that of 3 grams/day.[37]

Contrastingly, in one study, a single 100mg/kg body weight (6 grams in a 60kg adult) dose of MSM immediately before exhaustive exercise reduced post-exercise oxidative stress in healthy, untrained men.[39]

Safety & Tolerability

The consensus within the available literature is that MSM is generally well tolerated and safe. [1, 2] A number of animal toxicity studies have been completed with Horvath *et al.* reporting only minor adverse events when applying dosages of 1.5g/kg for a period of 90 days to rats i.e. an equivalent human dose of 105 grams per day in a 70kg human,[14, 43] further the LD50 of MSM is reported to be in excess of 20 grams/kg,[1] accordingly, the US FDA has endorsed MSM with a GRAS (generally recognised as safe) certification.[2, 9, 44]

Jacob *et al.* (1999), based on extensive clinical experience, reports that MSM is safe for use in pregnancy in consultation with the respective physician. Animal trials also found no toxic effects on pregnant rats or their foetuses given high dosages of 1g/kg for 21 days.[45] Although limited formal data exists on the topic of potential drug interactions, it is also the experience of Jacob *et al.* (1999) that there are no confirmed drug interactions with MSM. DMSO however, was shown to inhibit

platelet aggregation and, although not confirmed for MSM, concurrent use with blood thinning drugs should thus be done with caution.[1]

Debbi *et. al.* (2011) applied 3.3g daily for 12 weeks to 49 patients with knee OA and encountered no adverse events or side effects. Kim *et al.* (2006) implemented extensive safety monitoring mechanisms in their trial applying 6g of MSM daily to 50 patients with knee OA for 12 weeks. No significant changes were recorded in terms of full blood counts, kidney and liver function, lipid profile, BMI, vital signs or stool occult blood tests. Adverse events encountered were minor, without complication or negative impact on daily functioning and occurred equally in both MSM and placebo groups. Jacob *et al.* (1999) reports possible temporary, mild gastrointestinal discomfort, increase in stool frequency and headaches in patients taking high doses of MSM without gradually increasing the daily dose or without using split doses but, also claims MSM is safe for long term at doses exceeding 2g/day without serious side effects.

Conclusion

The naturally occurring organo-sulphur compound known as MSM with a similar structure to its parent compound DMSO, has been confirmed to have both anti-inflammatory and antioxidant properties. Although applied in this manner in various clinical contexts, the majority of data from human trials is centred around its use in osteoarthritis where 3-6 grams daily has been shown to improve pain, stiffness, swelling, range of motion and physical function. There is also data suggesting MSMs joint preservation action including that of cartilage in models of RA and OA. The other significant body of clinical evidence for MSM is its ability to support recovery from exercise. MSM used preventatively for approximately 20 days at a dosage of 3 grams daily pre-exercise, is reported to reduce post exercise muscle soreness and joint pain, improve recovery, and favourably influence the physiological markers thereof. Available data suggests MSM is safe for long term use, tolerable at recommended doses, and with the possible exception of blood thinning drugs, has no known drug interactions.

(Full, corresponding reference list available for download as separate file)