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Review Article

Role of S-Adenosylmethionine (SAMe) in the Treatment of Osteoarthritis

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Abstract
Osteoarthritis (OA) is a chronic degenerative disorder of multi factorial etiology characterized by the loss of articular cartilage, hypertrophy of bone at the margins, sub-chondral sclerosis, and range of biochemical and morphological alterations of the synovial membrane and joint capsule. Pathological changes in the late stage of OA include softening, ulceration, and focal disintegration of the articular cartilage. Synovial inflammation also may occur. Most arthritis sufferers take acetaminophen to relieve the pain, but it does not reduce the inflammation which could be accelerating the disease process. Doctors often recommend non-steroidal anti-inflammatory drugs (NSAIDs) to reduce the pain and inflammation associated with osteoarthritis. NSAIDs act by reducing the activity of COX enzymes, thus inhibiting the production of inflammatory prostaglandins.
Due to unsatisfactory traditional treatment options, there has been growing interest in the use of natural health supplements for the treatment of osteoarthritis. One such dietary supplement is SAMe which has been prescribed in Europe for the treatment of osteoarthritis, depression and liver disease since the 1970s.
SAMe as a potential safe treatment for osteoarthritis, that may actually regenerate cartilage. Future studies will provide further evidence of SAMe's effectiveness and reveal the mechanism by which SAMe increases cartilage synthesis, which is critical to eliminate the suffering of patients with osteoarthritis.

Introduction

S-Adenosylmethionine [SAMe] also known as Ademetionine or SAMe derived from two materials: methionine, a sulfur-containing amino acid; & adenosine triphosphate (ATP), the body's main energy molecule. SAMe functions primarily as a methyl donor. SAMe is a naturally occurring compound that is involved in many biochemical processes in the body. Numerous scientific studies indicate that SAMe may be useful in the improvement of osteoarthritis, osteoarthritis associated depression, and other disorders. SAMe is the most effective facilitator of youthful methylation. S-Adenosyl-L-methionine (SAMe), a metabolite present in all living cells, plays a central role in cellular biochemistry as a precursor

to methylation, aminopropylation, and transsulfur-ation pathways.[1] (Figure-1)

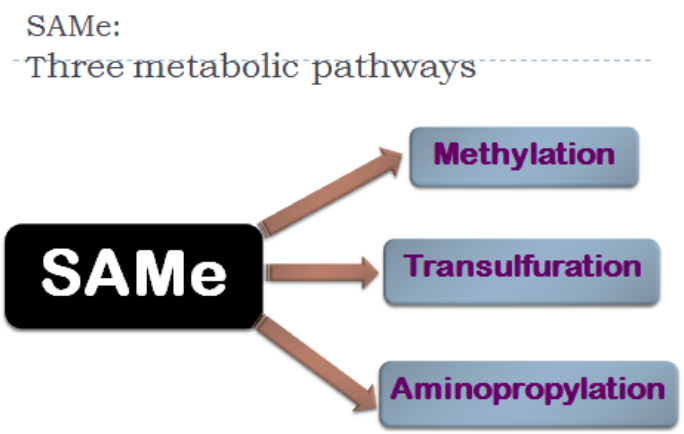

Figure-1 Three metabolic pathways of SAMe

S-adenosylmethionine (SAMe) is a dietary supplement used in the management of osteoarthritis (OA) symptoms. SAMe has a slower onset of action but is as effective as celecoxib in the management of symptoms of knee osteoarthritis.[2] The administration of SAMe to patients with osteoarthritis (OA) seems to have a protective effect, SAMe restores basal conditions after cell damage elicited by TNF alpha stimulation.[3] The therapeutic potency of ademetionine in experimental osteoarthritis and confirm the positive clinical observations as well as in-vitro results with this new drug by other researchers.[4] The therapeutic responses of the two drugs (Indomethacin & SAMe) proved exactly alike, whereas the side-effects following indomethacin administration were not present after SAMe.[5](Figure-2)

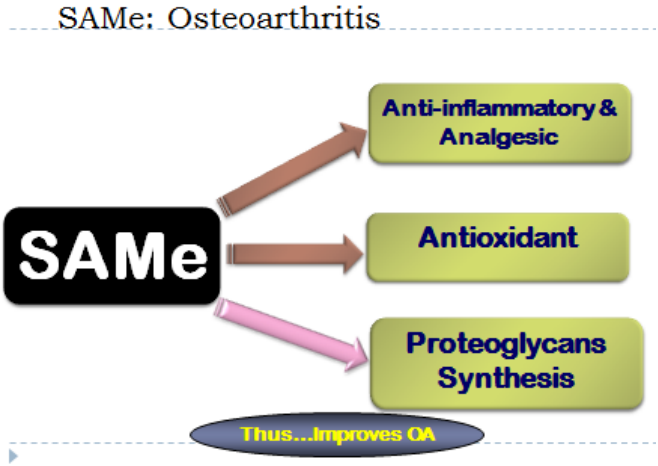

Figure-2 Role of SAMe in Osteoarthritis

Osteoarthritis is a chronic joint disease characterized by pain and immobility due to a gradual loss of cartilage. Current treatments are palliative; there is no cure. With a growing interest in alternative therapies, due in part to safety issues regarding pharmacological treatments like NSAID's, safe dietary compounds that help the body regenerate cartilage tissue are of great clinical importance. The dietary supplement S-adenosylmethionine (SAMe) shows such potential. Clinical trials have shown reduced pain and stiffness while in vitro and animal studies have shown SAMe can stimulate the production of cartilage which is critical in reversing the disease process. The author examines many potential mechanisms of action including: reduction of inflammatory mediators; increasing levels of glutathione; direct or indirect signaling of cartilage synthesis or survival; maintenance of DNA methylation.[6](Figure-3)

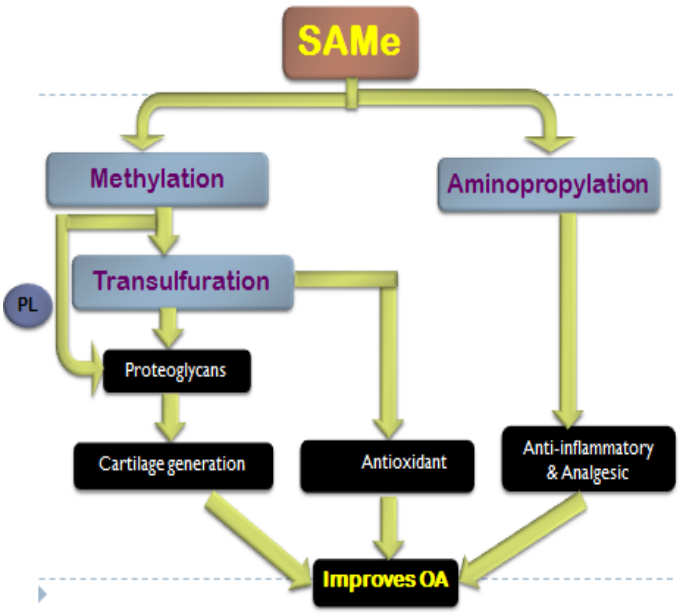

Figure-3 Thebiological role of SAMe in the cell

SAMe appears to be as effective as NSAIDs in reducing pain and improving functional limitation in patients with OA without the adverse effects often associated with NSAID therapies.[7](Figure-4)

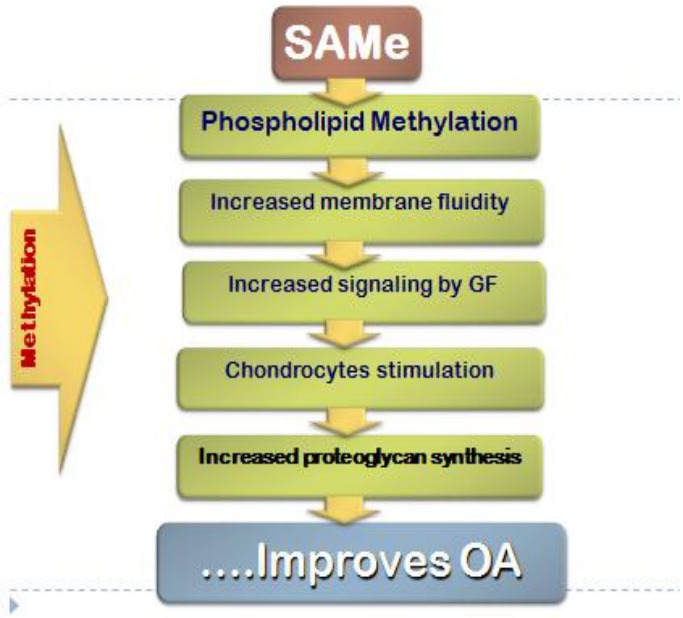

Figure-4 Theprocess of Methylation leads to improvement in Osteoarthritis

The administration of SAMe exerts analgesic and antiphlogistic activities and stimulates the synthesis of proteoglycans by articular chondrocytes with minimal or absent side effects on the gastrointestinal tract and other organs.[8] The results of extensive clinical trials, which have enrolled about 22,000 patients with osteoarthritis in the last five years, support the clinical effectiveness and the optimal tolerability of SAMe administration. The intensity of therapeutic activity of SAMe against osteoarthritis is similar to that exerted by nonsteroidal anti-inflammatory drugs, but its tolerability is higher. Based on thesefindings, SAMe is proposed as the prototype of a new class of safe drugs for the treatment of osteoarthritis.8 SAMe increases chondrocyte proteoglycan synthesis and proliferation rate.[9,10] Oral administration of SAMe (400 mg for 7 d) to 4 subjects significantly increased SAMe concentrations in synovial fluid by 3–4-fold compared with pretreatment values. (Figure-5)

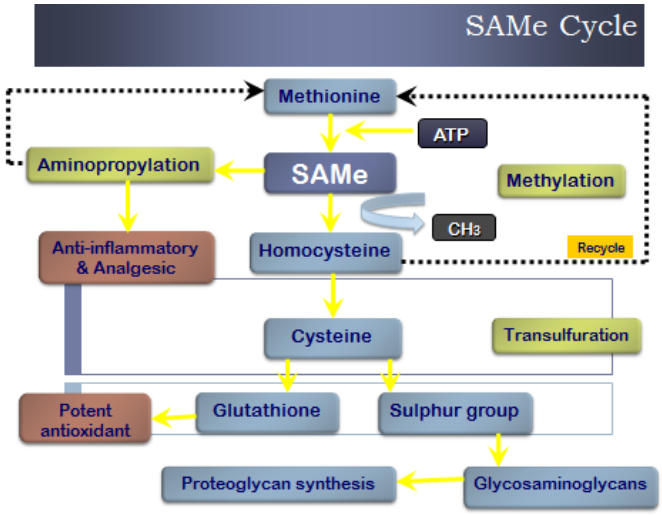

Figure-5 The metabolite S-adenosyl-L-methionine (SAMe)

The recent introduction of an orally administered form of SAMe for use in the treatment of osteoarthritis promises to stimulate further study of SAMe in disease-associated depression, major depressive disorder, and other neuropsychiatric conditions. The metabolite S-adenosyl-L-methionine (SAMe), when prepared as the stable p-toluene-sulfonate complex of its sulfate salt and given in high doses, appears to have mood-elevating effects in depressed adults. The material is remarkably well tolerated when given for this purpose, even in elderly or demented patients. SAMe appears to have central neuropharma-cologic effects and SAMe has effects on monoamine metabolism.[11] SAMe-mediated transmethylation is also critical for the formation of neurotransmitters in the central nervous system.[12] There appears to be a role for SAMe in the treatment of major depression in adults. Oral dosages of 1600 mg/day of SAMe appear to be significantly bioavailable and nontoxic.[13]

As many as 29% to 46% of patients with major depressive disorder (MDD) show only partial or no response to an adequate course of an antidepressant. The current practice is to increase the dose, switch to another antidepressant, or to combine the initial antidepressant with an antidepressant of a different class or a non-antidepressant agent. A growing number of studies have also been directed toward exploring

the potential use of augmenting traditional antidepressants with non pharmaceutic supplements, or even using such supplements as monotherapy for depression. S-adenosyl-methionine (SAMe) is one such compound. Compared with many other non-pharmaceutic supplements, SAMe has been extensively studied, and impressive literature extending back three decades suggests the antidepressant efficacy of SAMe.[14] SAMe reflects a good tolerability of the drug in elderly subjects.[15]

S-adenosyl-L-methionine (SAMe) is one of the better studied of the natural remedies. SAMe is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. SAMe may have a faster onset of action and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer disease. SAMe is well tolerated and relatively free of adverse effects, SAMe appears to be safe and effective in the treatment of depression.[16] (Figure-6)

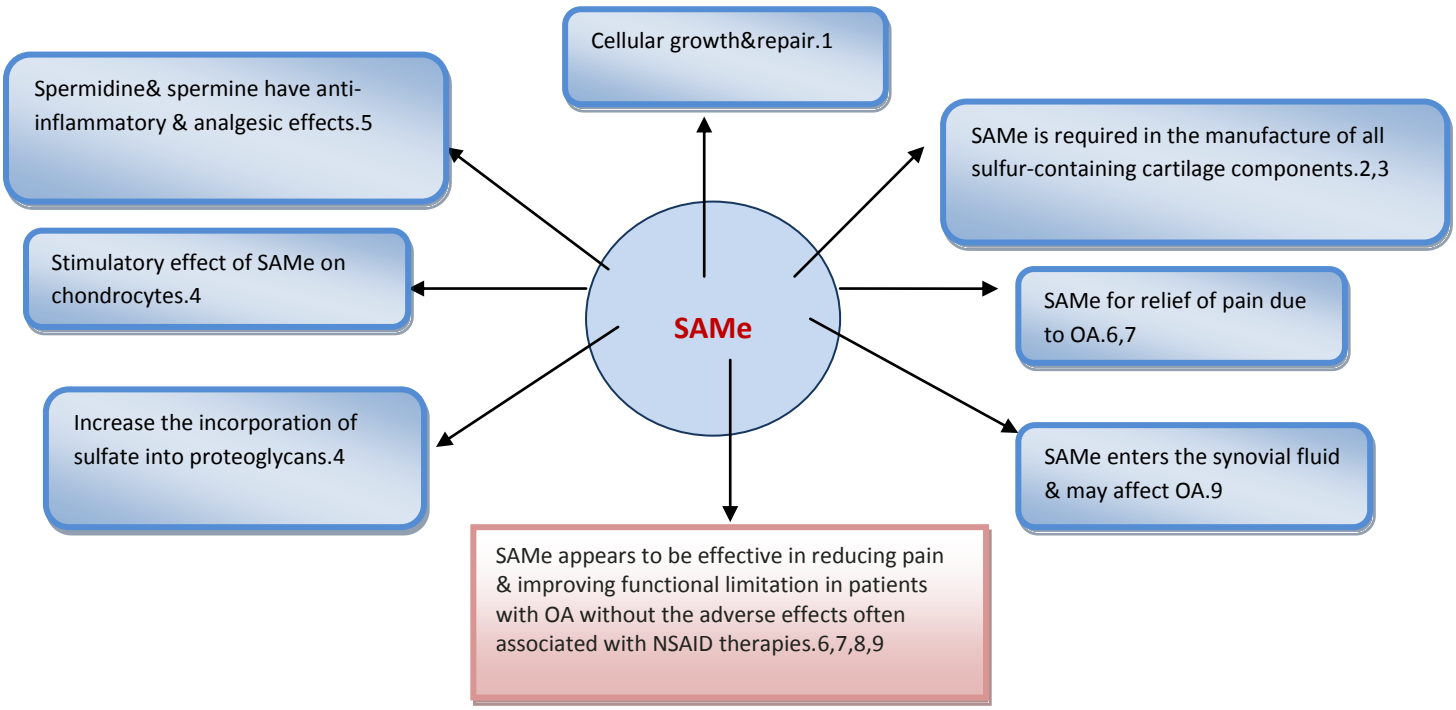

Figure-6 SAMe: Mechanism of action and biological effects in Osteoarthritis

The significant correlation between plasma SAMe levels and the degree of clinical improvement in depressed patients regardless of the type of treatment suggests that SAMe may play an important role in regulating mood.[17] SAMe has been shown to significantly increase cerebrospinal fluid levels of HVA and 5HIAA, the chief metabolites of dopamine and serotonin, two key biogenic amine antidepressant neurotransmitters. This is evidence of SAMe's enhancing brain biogenic amine metabolism and activity.

Lessen arthritis-related pain and Inflammation. The eventual breakdown of SAMe in the body yields substances that help to keep the gel-like Cartilage that cushions joints intact. In the common degenerative joint disease osteoarthritis, cartilage wears down over time. Studies in thousands of osteoarthritis sufferers have demonstrated that SAMe can be as effective at increasing joint mobility and reducing swelling and pain as such NSAIDs (non steroidal anti-inflammatory) as ibuprofen and aspirin. Moreover, SAMe doesn't pose the risk of stomach bleeding or kidney damage that are serious risks with NSAIDs. Recent studies also show that SAMe is also as effective as COX-2 inhibitors such as Celecoxib, for the management of osteoarthritis. It also doesn't wear down joints,

damage cartilage, or block the pain signals that could signal a worsening condition. Although it's not exactly clear how SAMe works for arthritis, very preliminary but intriguing animal studies actually point to a role in repairing cartilage and lubricating joints, properties that may well extend to humans. Clearly more research is needed.

Cartilage Care and Re-growth

Although studies are preliminary, evidence strongly suggests that SAM-e not only protects cartilage from further destruction. Animal studies have shown that SAM-e increases the production of chrondrocytes, the cartilage-producing cells in joints. The theory is, the greater the number of chondrocytes, the greater the amount of cartilage your body can produce. A study in Germany found that 14 patients with osteoarthritis of the finger were given 400mg of SAM-e daily for three months. At the end of the study, those taking SAM-e (compared to placebo) showed a small but significant cartilage increase.

Aerobic conditioning has been shown to improve such things as the overall level of physical activity, reduce pain scores, and reduce levels of anxiety and depression associated with osteoarthritis.[18] SAMe administration also improved the depressive feelings often associated with osteoarthritis.[19]

Conflict of interest (COI): "Abdul Faheem Khan, Khaneta Parveen and Abdul Salim Khan declare that they have no conflict of interest.

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