

## An Update on Pharmacological and Clinical Aspects of S-adenosylmethionine in Metabolic Syndrome

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### Abstract

S-adenosylmethionine (SAME), recognized as the principal methyl donor in metabolic reactions, has recently attracted growing research interest. It has been investigated as a potential biomarker for cardiovascular diseases and various malignancies. Although SAME supplements have been available for more than five decades, evidence supporting their clinical efficacy across most proposed indications remains limited. Given the global impact of metabolic syndrome, this study aims to review current evidence regarding the role of SAME in its pathophysiology. Relevant studies assessing the association between SAME and metabolic syndrome in humans or animal models were identified through searches of Scopus, PubMed, and Google Scholar databases from beginning to 2025, following standard narrative review methodology. Approximately 50 relevant publications were identified, addressing the relationship between SAME levels and coronary artery disease, besides the effect of SAME supplementation and hypertension, ischemia, aortic dissection, obesity, diabetes, heart failure, myocardial infarction, and liver disorders such as metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, cholestasis, jaundice, and viral hepatitis. Findings on the therapeutic role of SAME supplementation remain limited and often contradictory. As both SAME deficiency and excess appear to contribute to the development of metabolic syndrome, further research exploring its dose-dependent effects is essential.

**Keywords:** S-adenosylmethionine, Metabolic Syndrome, Cardiovascular, MASH, Diabetes.

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### 1. Introduction

Metabolic syndrome, with its spectrum of hyperlipidemia, impaired glucose regulation, obesity, and cardiovascular dysfunction, represents an intricate challenge for modern healthcare (1).

The search for molecular mediators that bridge metabolic pathways has placed methionine and its metabolites at the cross-

roads of cellular homeostasis (2).

As an essential amino acid, methionine and its metabolites have recently attracted increasing scientific interest. Methionine adenosyl transferase (MAT), encoded by the MAT1A and MAT2A genes, catalyzes the conversion of methionine into S-adenosylmethionine (SAME), which serves as the methyl donor for methyltransferase reactions, producing S-adenosylhomocysteine (SAH). The buildup of SAH serves as a strong inhibitor of methyltransferases, consequently interfering with normal cellular methylation reactions.

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Subsequently, SAH hydrolase reversibly converts SAH into homocysteine and adenosine. Homocysteine can then be remethylated to regenerate methionine through a process dependent on folate and vitamin B<sub>12</sub>, or it may enter the transsulfuration pathway, which requires vitamin B<sub>6</sub> (3, 4).

SAMe is the second-most used enzyme substrate, after ATP (5). SAMe is the principal methyl donor in one-carbon metabolism, fueling hundreds of millions of methylation, transsulfuration, and aminopropylation reactions daily and participating in the biosynthesis of nucleotides, polyamines, glutathione, phospholipids, gene expression, and the maintenance of redox status (2).

SAMe acts as an allosteric inhibitor of MTHFR and as an activator of cystathionine  $\beta$ -synthase, thereby controlling homocysteine metabolism (6). Since dietary methionine supply is often insufficient to fulfill the body's requirement for SAMe, new methionine molecules are synthesized endogenously through the re-methylation of homocysteine (7). SAMe/SAH ratio is considered the methylation potential or capacity index. A low ratio was associated with increased risks of metabolic diseases (8).

The effectiveness of SAMe supplementation is still controversial in all indications in both animal and human studies. The role of SAMe supplementation in depression has long been studied (9). However, a recent systematic review reports ineffectiveness of SAMe in reducing depression symptoms (10). Similar results were obtained in a meta-analysis in 2023 regarding SAMe effectiveness in cognitive impairment (11).

In contrast, reports exist regarding the role of SAMe supplementation in rheumatic diseases, with similar effectiveness as NSAIDs in relieving pain in osteoarthritis (12).

Moreover, it has been reported that SAMe exerts a gastroprotective effect comparable to that of sulfasalazine in an animal model of chronic colitis (13).

SAMe has also been investigated as a cancer biomarker and in the treatment of gastric, colorectal, breast, head and neck, osteosarcoma, lung, prostate, and retinoblastoma cancers, both as monotherapy or as a chemo-

sensitizing agent (14). Moreover, studies exist regarding the effectiveness of SAMe for cancer-related fatigue (15).

While considering the role of SAMe in metabolic syndrome, it should be noted that tight regulation of SAMe synthesis and catabolism is essential, as alterations in these processes are increasingly linked to liver lipid accumulation, insulin resistance, and the pathogenesis of Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) and related cardiovascular complications (16).

Mechanistically, SAMe balances hepatic lipid metabolism through pathways that control the ratio of key phospholipids and triglyceride synthesis, operating via enzymes such as phosphatidylethanolamine N-methyltransferase and glycine N-methyltransferase (17). A deficiency or excess of SAMe disrupts this delicate equilibrium, predisposing individuals to steatosis, chronic inflammation, and fibrosis (18). Furthermore, SAMe modulates glucose flux and insulin sensitivity by influencing transsulfuration and methylation of metabolic regulatory genes (19). Through its role in glutathione synthesis, SAMe also fortifies antioxidant defenses, which are pivotal for preventing oxidative stress-induced vascular injury and for maintaining myocardial function (20). Understanding how SAMe orchestrates these interconnected metabolic processes offers new avenues for managing obesity, improving lipid and glucose profiles, and reducing cardiovascular risk in patients with metabolic syndrome. This study aimed to review the latest evidence regarding the effect of SAMe on metabolic syndrome.

## 2. Review Methodology

Databases including Scopus, PubMed, and Google Scholar were searched for relevant English language literature from the beginning up to 2025. Based on common strategies for narrative reviews, the search was guided by a combination of keywords and related MeSH terms such as “S-adenosylmethionine”, “Metabolic Syndrome”, “Cardiovascular”, “Coronary”, “NAFLD”, “Diabetes”, “Liver”, “Myocardial Infarction”, “Obesity”, and “Dyslipidemia”. The initial search was supplemented by scanning reference lists of key

articles and relevant reviews to identify additional pertinent studies. Two reviewers then independently screened titles and abstracts to select potentially relevant publications. In the next phase, the full texts of these articles were examined by the same reviewers, focusing on their relevance to the review's main themes (e.g., role of SAME in metabolic, cardiovascular, and hepatic disorders). Data extraction was performed flexibly, with the reviewers recording key findings, study designs, and conceptual frameworks that were judged important for the narrative synthesis. The reviewers discussed the selected evidence iteratively to ensure consistency in interpretation and to highlight major patterns, controversies, and knowledge gaps. Duplicate entries, conference abstracts, non English publications, and studies without full text access were excluded. Through this process, approximately fifty papers were retained and formed the basis for the thematic discussion in this narrative review.

### 3. Results

#### 3.1. SAME Supplements

SAME was first discovered in 1951 by Giulio Cantoni (14). It was first marketed in Europe in 1975 for the treatment of depression and arthritis, and later introduced in the United States in 1999 as a dietary supplement aimed at supporting joint function, liver health, and emotional well-being (5). SAME is available as an over-the-counter supplement in tablet or capsule dosage form, usually at a dose of 200 or 400 mg per pill. Most of the available formulations are a combination of SAME with vitamins, minerals, and herbal ingredients, including zinc, riboflavin, pyridoxine, cyanocobalamin, manganese, selenium, glucosamine, curcumin, quercetin, etc. (7).

Although the exact daily dose of SAME supplements is not well defined, most formulations are administered once daily, with total daily doses ranging from 157.8 mg to 1600 mg; the median and most frequently used dose is 400 mg, while the mean dose is approximately 472.2 mg (5, 7).

SAME is available in our region, Iran, under the brand name of ADOMEDS®, containing 400 mg of SAME with a recommended dose of 800-1600 mg/day for boosting mood

and protecting the liver and joints.

Although SAME exhibits limited oral bioavailability and poor direct cellular uptake, extracellular SAME is enzymatically degraded to 5' methylthioadenosine (MTA), which readily permeates cell membranes and is subsequently recycled within cells to regenerate methionine and SAME. This recycling pathway explains SAME's sustained therapeutic actions despite its low direct cellular uptake (21).

SAME has an excellent safety profile, with gastrointestinal side effects occurring in a minority of subjects (22).

Although SAME is sold in many regions without definite effectiveness in any of its proposed indications, the detrimental effects of excess methylation should also be noted (5). Excess SAME is catabolized to adenine and methylthioadenosine, toxic inhibitors of methylation (5). Moreover, there are reports regarding the use of SAME as monotherapy in various cancers, indicating that SAME may potentially be toxic (5).

#### 3.2. SAME level and CAD

Several studies have explored the association between methionine metabolite levels and both the risk and outcomes of CAD. Earlier research primarily focused on SAH or homocysteine as biomarkers for CAD, though findings have been somewhat inconsistent. More recently, attention has shifted toward SAME and the SAME/SAH ratio, as evidence suggests that an imbalance in this ratio can lead to abnormal DNA methylation patterns—such as those involving FABP4, EC-SOD, and MCP-1—that are characteristic of atherosclerosis. These methylation alterations contribute to vascular and endothelial dysfunction, impairing vasodilation and increasing carotid intima-media thickness (4, 23, 24).

Si Liu *et al.* investigated the relationship between plasma SAME levels and mortality risk of 1,553 patients with CAD. It was found that patients in the lowest quartile of SAME concentrations had a significantly higher risk of all-cause mortality (HR 1.59, 95% CI: 1.14–2.21) and cardiovascular mortality (HR 2.14, 95% CI: 1.41–3.27) compared to those in the highest quartile. Furthermore,

each 1-SD decrease in SAME levels was associated with a 42% increase in total mortality risk and a 66% rise in cardiovascular mortality risk. These findings suggest that low plasma SAME levels are independently associated with increased mortality risk in CAD patients, even after adjusting for other cardiovascular risk factors (3).

Results of another study with the participation of 70 patients with a history of prior angioplasty and a healthy control group suggest higher plasma total homocysteine and lower 5-methyltetrahydrofolate and SAME levels in patients as compared with a control group, even after adjustment for age and BMI (6).

Results of a study on 30 patients with proven cardiovascular disease and 29 age- and sex-matched controls suggest that homocysteine, SAH ( $P=0.0021$ ), and SAME ( $P=0.0493$ ) differed statistically between groups (25).

In contrast to the previous studies reporting a lower level of SAME in patients with CAD, results of a case-control study with the participation of 72 atherosclerotic patients with  $\leq 50\%$  stenosis, and 88 patients with coronary artery disease with  $>50\%$  stenosis, showed statistically higher SAH, and lower SAME/SAH ratio in patients with  $>50\%$  stenosis, while SAME, homocysteine, folate, or vitamin B12 levels represent no changes between groups (4).

On the other hand, some studies suggest that SAME is not an independent predictor of cardiovascular outcomes. Results of a study on 297 CKD patients with a mean SAME concentration level of 183.4 nmol/L suggest that during a 4-year follow-up period, higher SAME levels were associated with an increased risk of MACE in univariate analysis. However, after adjusting for age, sex, and renal function markers, the association was lost (26).

It seems that among all methionine metabolites, SAH and the SAME/SAH ratio might be more sensitive biomarkers for CAD. Results of a multivariable adjusted analysis study on 1553 patients with CAD showed that those in the highest quartile of plasma SAH levels had a higher risk of all-cause death (adjusted Hazard Ratio [HR], 2.15; 95% CI, 1.54-

3.01;  $P<0.001$ ) and cardiovascular death (adjusted HR, 2.20; 95% CI, 1.49-3.25;  $P=0.001$ ), after adjusting for the age and sex. It has been demonstrated that each 1 SD increase in the SAH level was associated with a 25% higher risk of total death and a 29% greater risk of cardiovascular death (27).

Another study on the middle-aged Chinese population suggests that increased SAH and decreased SAME/SAH ratios are associated with atherosclerosis risk, with higher pernicious than homocysteine (24).

On the other hand, there is still controversy for the predicting role of SAH while considering other variables as a results of a case-control analysis in China suggest that among females, SAH levels were higher in stroke cases than controls, while in males under 60, higher SAH was associated with increased total stroke risk, and no significant association was observed in males aged 60 or older (28).

Recent studies on urine SAME levels have received more attention, as a result of a study on 62 patients with stage II–V of CKD showed decreased urine levels and SAME/SAH ratio and also cysteine/homocysteine ratio in blood plasma ( $P<0.05$ ), compared with patients with stage II CKD, suggesting urine SAME as a noninvasive biomarker to categorize the severity of the CKD (29).

The role of methionine or methionine-derived metabolite supplementation in reducing the risk of CAD is still controversial, and more studies are required in the field. Results of a study on 10 healthy volunteers receiving methionine (0.1 g/kg body weight, orally) suggest that SAME, SAH, and the SAME/SAH ratio levels remarkably increased 8 hours after methionine administration, although the plasma asymmetric dimethylarginine (ADMA) levels and endothelial function (evaluated by flow-mediated dilation) remained unchanged. This suggests that alterations in methylation status, as reflected by SAME and SAH levels, may not directly influence endothelial nitric oxide production or vascular function in healthy individuals. Therefore, the mechanism by which methionine impairs endothelial function appears to be independent of SAME-mediated methylation pathways (30).

Similarly, results of an animal study on 48 male apolipoprotein E-deficient mice, receiving a high-methionine diet for 15 weeks, suggest significantly higher SAME, SAH, and SAME/SAH ratio, besides increased atherosclerotic lesion size and alteration in atherosclerosis-related genes methylation pattern (23).

### 3.3 SAME in Hypertension, Ischemia, and Heart Failure

SAME plays a crucial role in both the central and autonomic nervous systems, participating in the metabolism of neurotransmitters such as norepinephrine and serotonin, processes that can influence blood pressure regulation. Additionally, SAME exerts an activating effect on cystathionine  $\beta$  synthase and hydrogen sulfide production. This, in turn, modulates K<sub>ATP</sub> channel-dependent mechanisms that contribute to reduced sympathetic outflow and vascular relaxation.

Moreover, the activatory effect of SAME on cystathionine beta-synthase and hydrogen sulfide affects KATP channel-mediated pathways involved in diminishing sympathetic outflow (31).

Results of a study suggest that higher levels of Hcy and SAH, and lower levels of SAME/SAH, plasma folate, and vitamin B12, were observed in patients with essential hypertension as compared with a control group (32).

The study, led by Mariusz Sikora, investigated the hypotensive effects of SAME in hypertensive rats. Using intracerebroventricular infusions, researchers measured mean arterial blood pressure and heart rate in male normotensive Wistar Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). While WKY rats exhibited a biphasic response, SHR showed a dose-dependent hypotensive effect when infused with SAME at concentrations of 10  $\mu$ M, 100  $\mu$ M, and 1 mM. Pretreatment with hexamethonium (a ganglionic blocker) and glibenclamide (a KATP channel blocker) significantly reduced SAME's hypotensive effects, suggesting its role in the autonomic nervous system and KATP channel-dependent mechanisms (31).

On the other hand, within the context

of the methionine cycle, elevated SAH levels may result from disturbances in folate and vitamin B<sub>12</sub> metabolism, which impair the normal functioning of this pathway. Indeed, it has been reported that folic acid supplementation at a dose of 2.4 mg per day for eight weeks significantly increased SAH concentrations ( $p = 0.027$ ) in a cohort of Chinese patients with hypertension (33).

Another study investigated the effects of SAME on ischemic brain metabolism in SHR using an incomplete cerebral ischemia model induced by bilateral common carotid artery occlusion. SHRs were administered 100 mg/kg SAME intraperitoneally six times at 30-minute intervals post-occlusion. Results suggest that SAME significantly mitigated ischemia-induced reductions in creatine phosphate, ATP, and glucose while reducing elevated GABA levels. Additionally, SAME significantly suppressed brain edema, lowering water content in the cortex (78.7% vs. control: 80.3%) and subcortex (76.4% vs. control: 77.8%). These findings suggest SAME exerts a protective effect on energy metabolism and neurotransmitter balance in ischemic SHR brains (34).

Although limited evidence exist regarding the role of SAME in heart failure (HF), results of a study suggest that SAME supplementation (100-200 mg/kg for two weeks) in a group of rats with chronic heart failure, induced by isoproterenol, leads to a remarkable decrease in the heart-to-body weight ratio, besides normalizing TNF- $\alpha$  and GSH levels ( $P < 0.001$ ) (35).

### 3.4 SAME in Aortic Dissection and Myocardial Infarction

It has been proposed that SAME possesses anti-inflammatory properties mediated through modulation of the immune response, including suppression of CD45<sup>+</sup> leukocytes, neutrophils, and macrophages within the aortic wall. Additionally, SAME reduces pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$  while enhancing the anti-inflammatory cytokine IL-10. Together, these effects help preserve myocardial structure and vascular integrity, thereby preventing adverse cardiac remodeling.

In this study, four-week-old male C57BL/6N mice were used to investigate the effects of SAME on thoracic aortic dissection (TAD). The mice were administered SAME orally at a dosage of 500 mg/kg (effective concentration 50 mg/kg) for one week before TAD induction and continued daily throughout the 28-day modeling period using  $\beta$ -aminopropionitrilemonofumarate (BAPN). SAME supplementation significantly improved survival rates, reduced aortic rupture and dissection incidence, and alleviated extracellular matrix degradation. It also suppressed inflammatory cell infiltration, blunted M1 macrophage polarization, and reduced CD4<sup>+</sup> and CD8<sup>+</sup> T cell activation, demonstrating a protective role against BAPN-induced aortic inflammation and TAD progression (36).

Findings from an animal study on angiotensin II-induced aortic dissection indicated that SAME supplementation markedly decreased the incidence of aortic dissection, extended survival time, and mitigated vascular elastic fiber degradation. Furthermore, SAME inhibited the cellular phenotypic switch by up-regulating the expression of contractile marker proteins while downregulating the expression of synthetic marker proteins such as osteoblast protein, matrix metalloproteinase 2, and matrix metalloproteinase 9. The protective effects of SAME in this model appear to be mediated, at least in part, through activation of the PI3K/AKT/mTOR signaling pathway (37).

It has been suggested that supplementation with SAME (15 mg/kg, intraperitoneally) in a group of rats after inducing MI by blocking the coronary arteries remarkably improved the survival rate, contractile and diastolic heart function, ventricular pressure change, LVEF, and LVFS, besides increasing VEGF, bFGF, and HIF1- $\alpha$  expression in myocardium, and decreasing markers of fibrosis, including collagen I, collagen III. Moreover, activating the Jagged1/Notch1 signaling pathway, which is involved in angiogenesis, might be involved in this process (38).

### 3.5. SAME in Dyslipidemia, Diabetes, and Obesity

SAME-dependent methylation plays a key role at the intersection of sulfur amino

acid and lipid metabolism, particularly in the synthesis of phosphatidylcholine, a major component of very low-density lipoproteins (VLDL). When hepatic SAME levels are low, the assembly of VLDL is impaired, resulting in the production and secretion of lipid-poor VLDL particles (39).

Plasma SAME levels, rather than methionine concentrations, show an independent association with fat mass and truncal adiposity, implying that obese individuals may exhibit enhanced conversion of methionine to SAME (39).

On the other hand, chronic hyperglycemia triggers reactive oxygen species overproduction. Normalizing SAME levels has been associated with improving insulin sensitivity through enhanced IRS-1 and Akt phosphorylation, as well as suppressed IKK- $\beta$ /NF- $\kappa$ B signaling pathway. SAME may improve glucose intake and increase mitochondrial DNA density in skeletal muscle. Neutralizing oxidative stress through restoration of GSH level and production of polyamines (spermidine and spermine) might be other mechanisms involved in the antidiabetic effects of SAME (40, 41). Results of a study involving 610 patients suggest that positive associations exist between plasma and erythrocyte SAME levels and BMI, fat mass, and trunk fat, regardless of age and gender. Moreover, it has been suggested that overtake of methionine-containing proteins is associated with obesity through conversion to the SAME. On the other hand, Plasma SAME was not associated with LDL-cholesterol (39).

Results of an experimental study by Bratoeva *et al.* evaluated the effects of SAME on oxidative stress and obesity in male Wistar rats fed a high-fructose diet. Rats receiving SAME (20 mg/kg) showed reduced lipid peroxidation (MDA) and inflammation (TNF- $\alpha$ ), along with increased glutathione levels compared to untreated high-fructose diet rats. The findings suggest that SAME may attenuate oxidative damage and fat accumulation through antioxidant and anti-inflammatory mechanisms (42).

The role of SAME in controlling weight might be dose-dependent, as evidence suggests that supplementation with SAME might

be effective in reducing serum leptin and food intake in an animal model, although the dosing should be considered (43).

Results of a study on a diabetic rat treated with 10 mg/kg/day of SAME intraperitoneally for 4 weeks suggest a remarkable reduction in malondialdehyde and protein carbonyl levels in both kidney and liver tissues compared to the diabetic control group ( $P < 0.05$ ), besides lowering tissue pathological changes, and insignificant reduction in fasting blood glucose, urea, creatinine, ALT, and AST levels (44). A study by Jin *et al.* investigated the effects of short- and long-term SAME treatment in a type 2 diabetes mouse model. SAME administration (15 mg/kg/day) increased mitochondrial DNA density in skeletal muscle, improved insulin sensitivity, and prevented weight gain. These findings suggest a potential role for SAME in managing diabetes and obesity through mitochondrial and metabolic regulation (45). In addition, an experimental study showed the effects of SAME supplementation in male C57BL/6 mice under control and high-fat diets. SAME reduced fasting glucose increased hepatic glutathione, and improved hippocampal microglial morphology, particularly in control mice, with weaker effects observed in obese mice. The findings suggest that SAME may mitigate aging-related metabolic and neuroinflammatory changes, although its benefits are diminished in the presence of obesity (46).

Another study indicates the effects of SAME (23.7 mg/kg body weight per day) on reducing blood glucose, cholesterol, and triglycerides, as well as improving leptin sensitivity and insulin resistance in an animal model of mice (43).

### 3.6. SAME in Liver disease

#### 3.6.1. Metabolic dysfunction-associated steatohepatitis (MASH)

It has been proposed that SAME deficiency triggers hyperphosphorylation of hepatic proteins—particularly  $\alpha$  catenin (Ser641) and AKT1—through activation of casein kinase 2 $\alpha$  (CK2 $\alpha$ ) and AKT1. This cascade promotes lipogenesis, inflammation, and fibrosis, while also contributing to mitochondrial and peroxisomal dysfunction, disrupted lipid

metabolism, and impaired protein translation pathways. More specifically, lowered SAME levels reduce protein methyltransferase 1 activity, resulting in upregulation of glycolytic enzymes (glucokinase, phosphofructokinase, and pyruvate kinase) and downregulation of gluconeogenic enzymes (phosphoenolpyruvate carboxykinase, fructose 1,6 bisphosphatase, and glucose 6 phosphatase). These alterations inhibit dihydroxyacetone phosphate (DHAP) formation, mammalian target of rapamycin complex 1 (mTORC1) activity, and the activation of sterol regulatory element-binding protein 1 (SREBP-1), ultimately leading to defective VLDL secretion (10, 47, 48). In other words, diminished phosphatidylcholine/phosphoethanolamine ratio reduces VLDL secretion, leading to triglyceride accumulation and increased membrane permeability to proinflammatory cytokines (49).

Maintaining physiologic hepatic methylation (responsible for 85% of all body methylation) and liver antioxidant capacity through the synthesis of glutathione, and augmentation in the expression of the AT1R-associated protein (ATRAP), an inhibition of AT1R, besides stabilizing hepatocyte membranes, would minimize the risk of MASH (10, 49, 50).

It should be noted that excessive SAME accumulation—as observed in glycine N-methyltransferase deficiency—can also promote hepatic steatosis by increasing phosphatidylethanolamine N-methyltransferase activity and redirecting phosphatidylcholine toward triglyceride synthesis (10).

In addition to these potential pathways, the precise mechanism through which SAME influences NAFLD is still not fully understood (51).

It has been proposed that supplementation with SAME (30 mg/kg five days a week for eight weeks) normalized up to 90.0% of the biochemical dysfunction associated with MASH in an animal model of mice (47).

Findings from a systematic review encompassing 15 studies indicate that the most frequently used doses of SAME for liver-related conditions range between 1000 and 1200 mg per day (52).

Results of a study in guinea pigs with MASH, administered SAME (50 mg/kg, i.p.

for 4 weeks), showed significantly reduced insulin resistance, triglyceride, lipogenesis, reactive oxygen species, inflammation, and liver fibrosis scores (49). Results of a similar study on guinea pigs suggest that supplementation with SAME (50 mg/kg) diminishes total cholesterol, triglycerides, hydroxyproline,  $\alpha$ -smooth muscle actin, and TGF- $\beta$ , while administered concurrently with a high-fat/high-cholesterol diet, or post NAFLD induction (53).

As described, methionine metabolites have been linked to metabolic syndrome and its related diseases. It has been reported that SAME, SAH, Hcy, and the SAME/SAH ratio are remarkably (all  $P < 0.001$ ) higher in NAFLD patients than normal population, with significant correlation with the degree of hepatic steatosis (all  $P$  for trend  $< 0.001$ ) (8).

The results of a study suggest that SAME supplementation in both 19 patients with NAFLD and male C57BL/6 rats remarkably restored SAME concentration, reduced hepatic steatosis, and upregulated ATRAP protein expression. Mechanistically, SAME maintained ATRAP mRNA nucleocytoplasmic shuttling by preserving HuR methylation, suggesting a protective role of SAME in NAFLD progression (51).

Results of a randomized clinical trial on patients with MASLD (FIB-4 score  $< 1.30$ ) supplemented with a formulation containing 200 mg SAME three times a day for three months suggest that the intervention group represents a significant reduction in triglycerides, VLDL-c, total cholesterol, LDL-c, and glucose levels, along with an increase in HDL-c, besides insignificant reduction in AST, and ALT levels (50).

Results of a study on 40 patients with comorbid metabolic-associated steatohepatitis and arterial hypertension suggest that after 5 months of SAME + antihypertensive therapy, remarkable improvement was observed in the clinical signs/symptoms, systolic and diastolic blood pressure, BMI, waist-to-hip ratio, AST, ALT, and ALP levels (54).

### 3.6.2. Alcoholic Liver Cirrhosis

In patients with alcoholic liver disease, SAME supplementation reduces lipid

peroxidation and serum transaminase concentrations, while prolonged administration may enhance survival or postpone the requirement for liver transplantation in cases of early-stage cirrhosis (10).

Results of a study on 123 patients with alcoholic cirrhosis suggest that supplementation with AdoMet (1200 mg/day for 2 years) leads to a 30% reduction in mortality or transplantation rates among treated patients, which was statistically significant in patients during the early stages (55).

### 3.6.3. Hepatic Cholestasis

SAME represents a pivotal role in maintaining normal bile acid synthesis, secretion, and flow (10).

Results of a study on 115 patients with cholestatic liver disease randomized to receive a similar dose of ursodeoxycholic acid + 1000 or 2000 mg/day of SAME suggest that the itching score, serum IL-12 and IL-18, ALT, AST, total bilirubin, total bile acid, and total effective rate showed more improvement in the group that received higher doses of the SAME. Moreover, no difference was observed between groups in terms of adverse reactions (56).

There is a report regarding the partial effectiveness of SAME (400 mg twice daily) in intrahepatic cholestasis of pregnancy with improvement in bilirubin, ALT, AST, and ALP levels, although the parallel group receiving ursodeoxycholic acid showed more efficacy (57).

Another study investigated the effect of combined ursodeoxycholic acid (10 mg/kg/day, PO) or SAME (50 mg/kg/day, IV) for 10 days on 102 neonates with cholestasis. Results suggest more than 20.0 % improvement in the treatment rate ( $p=0.005$ ), besides more decrease in endotoxin, matrix metalloproteinase-9, and IL-18 levels in the combined therapy group (58).

While evaluating the cost-effectiveness of SAME supplementation in hepatic cholestasis, a comprehensive economic analysis conducted in the United Arab Emirates confirmed the cost-effectiveness of SAME compared to UDCA in chronic Intrahepatic Cholestasis, as cost-utility analyses suggest SAME had an in-

cremental cost-utility ratio of 44,448 AED per quality-adjusted life year compared to UDCA. Moreover, SAME demonstrated cost-effectiveness in reducing alkaline phosphatase but was less cost-effective for other biomarkers compared to UDCA (59).

Results of a similar study in China confirmed the cost-effectiveness of the SAME in this setting, as treatment with SAME resulted in 1.25 quality-adjusted life years at a cost of CNY 55,239 vs 1.05 quality-adjusted life years and CNY 44,119 for no treatment (60).

#### 3.6.4. Hepatic Jaundice

There is a report regarding the effectiveness of the SAME in infants with neonatal jaundice, with the effective rate of treatment more than 70.0% (61).

#### 3.6.5. Viral Hepatitis

It has been suggested that supplementation with SAME, besides routine protection in 76 cases of viral hepatitis, leads to remarkable improvement in the total response rate, liver function tests, and liver fibrosis indicators (62). Contrastingly, results of a prospective, randomized, placebo-controlled, double-blind trial among 87 patients with hepatitis C cirrhosis suggest that supplementation with 2.4 g/d of oral SAME for 8 months did not remarkably change  $\alpha$ -fetoprotein, viral count, liver function test, oxidative stress, or serum glutathione level (22).

#### 3.6.6. Hepatic Carcinoma

Aberrant SAME concentrations leading to disturbances in histone methylation processes may play a crucial role in tumorigenesis, especially in the development of hepatocellular carcinoma (HCC).

The effect of SAME supplementation on hepatocellular carcinoma progression was also investigated in vitro and in liver-specific PCK1 knockout mice, and the results suggest an inhibitory effect on tumor growth through inhibiting the PI3K/AKT signaling pathway and enhancing histone H3K9 trimethylation (63).

#### 3.6.7. Hepatic Ischemia

It has been reported that SAME (20

mg/kg) remarkably reduced bacterial translocation, lipid peroxidation, endotoxin, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, caspase-1, -3, and -9 levels, and increased IL-10, glutathione, and phosphatidylcholine levels in a model of hepatic ischemia–reperfusion injury in male Wistar rats. Moreover, the survival rate increased by more than 60.0% (64).

## 4. Discussion and Conclusion

Although several potential pharmacological effects of SAME have been described (Table 1), there is currently no robust evidence from large clinical trials to support them.

Both SAME deficiency and excess may disrupt normal methylation processes, thereby increasing the risk of cardiovascular and hepatic complications, as well as metabolic disorders such as diabetes, dyslipidemia, and obesity. This effect might be dose-dependent, although current evidence on this relationship remains limited. Furthermore, findings regarding the efficacy of SAME supplementation and its association with serum levels across various diseases are inconsistent. Therefore, well-designed animal studies and large-scale clinical trials are warranted to clarify these associations. In addition, cost-effectiveness analyses are necessary to determine the true clinical value of SAME supplementation.

In conclusion, dysregulation of SAME—manifesting as either deficiency or excess—represents a critical, modifiable nexus in the pathophysiology of metabolic syndrome, linking aberrant one-carbon metabolism to multi-organ dysfunction, including hepatic steatosis, insulin resistance, dyslipidemia, obesity, coronary artery disease, and heart failure. While preclinical and small clinical evidence support physiological SAME restoration (typically 400–1200 mg/day) as an adjunctive strategy to mitigate inflammation, oxidative stress, and methylation imbalances—particularly in MASH and early cardiovascular risk—current human data remain preliminary and heterogeneous. Clinicians may judiciously consider SAME supplementation in high-risk MetS patients with confirmed low SAME/SAH ratios, prioritizing it alongside lifestyle interventions and standard pharmacotherapy, while awaiting robust RCTs

**Table 1.** Summary of Putative Mechanisms of SAdMe in Metabolic Syndrome Components.

| Indication                  | Probable SAdMe Mechanisms                                                                                                                                                              | SAdMe Deficiency Effects                  | References          |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------|
| Coronary Artery Disease     | ↓ SAdMe/SAH ratio → DNA hypermethylation (FABP4, MCP-1) → endothelial dysfunction                                                                                                      | ↑ All-cause & CV mortality (HR 1.59-2.14) | (3,4,6,23-30)       |
| Hypertension                | ↑ Cystathionine-β-synthase → H <sub>2</sub> S → KATP activation → ↓ sympathetic outflow                                                                                                | ↑ SAH, homocysteine levels                | (32,33)             |
| MASH/NAFLD                  | ↓ PEMT activity → ↓ VLDL secretion → triglyceride accumulation<br>↓ Protein methyltransferase-1 → ↑ lipogenesis (AKT1/SREBP-1 hyperphosphorylation) ↓ GSH synthesis → oxidative stress | Hepatic steatosis, fibrosis               | (10,47,49,50,53)    |
| Diabetes/Insulin Resistance | ↑ IRS-1/Akt phosphorylation<br>↑ Skeletal muscle mtDNA density<br>↓ IKK-NF-κB signaling<br>↑ GSH, polyamines (spermidine/spermine)                                                     | Insulin resistance                        | (40-43)             |
| Obesity                     | ↑ Leptin sensitivity<br>↓ Oxidative stress (↑ GSH)<br>↓ TNF-α, MDA                                                                                                                     | BMI, truncal fat mass                     | (39, 40-42, 45, 46) |
| Aortic Dissection           | ↓ M1 macrophage polarization<br>↓ CD4 <sup>+</sup> /CD8 <sup>+</sup> T-cell activation<br>↑ IL-10, ↓ IL-1/TNF-α<br>PI3K/Akt/mTOR activation                                            | Aortic rupture, matrix degradation        | (36,37)             |
| Myocardial Infarction       | ↑ VEGF, bFGF, HIF1-α<br>Jagged1/Notch1 → angiogenesis<br>↓ Collagen I/III                                                                                                              | Adverse cardiac remodeling                | (36,38)             |
| Cholestasis                 | Bile acid synthesis/secretion regulation<br>↑ Phosphatidylcholine stabilization                                                                                                        | Pruritus, ↑ liver enzymes                 | (56-59)             |

to establish optimal dosing, long-term safety, and personalized biomarkers for therapeutic response. This targeted approach could transform SAdMe from a controversial supplement into a precision tool for MetS management, addressing a major global health burden.

**Ethics approval and consent to participate**  
Not applicable.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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