Dietary Supplement S-Adenosyl-L-Methionine (AdoMet) Effects on Plasma Homocysteine Levels in Healthy Human Subjects: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial

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Abstract

Objectives: To determine if exogenous S-adenosyl-L-methionine (AdoMet), a commonly used nutritional supplement, increases the level of plasma homocysteine (Hcy), a potential cardiovascular risk factor, in healthy human subjects.

Design: Double-blind, placebo-controlled, randomized clinical trial.

Setting: Mayo Clinic, Rochester, Minnesota.

Subjects: Fifty-two (52) healthy human volunteers.

Intervention: Subjects received placebo or AdoMet (800 mg per day) for 4 weeks. Hcy levels were measured before and after administration of AdoMet or placebo.

Outcome Measures: The primary outcome measure was change in Hcy level. Secondary outcome measures included an interim Hcy determination (at 2 weeks) and changes in levels of high-sensitivity C-reactive protein (hsCRP), lipids, and alanine aminotransferase.

Results: There was no statistically significant change in Hcy between groups. Similarly, no statistically significant differences in change in Hcy or hsCRP levels were observed at 2 or 4 weeks. There was a small but statistically significant increase ($p < 0.04$) in alanine aminotransferase at week 2 and a statistically significant decrease ($p < 0.04$) in total cholesterol in the AdoMet group compared with the placebo group.

Conclusions: AdoMet at a daily dose of 800 mg for 4 weeks does not appear to significantly affect Hcy levels in the blood.

Introduction

The Centers for Disease Control and Prevention (CDC) estimated that 30% of adults use dietary supplements regularly1 and spend $1.3 billion to $1.7 billion annually on these supplements.2 In a large population-based survey conducted by the CDC involving more than 31,000 participants, 36% of the adults reported using some form of complementary and alternative medicine (CAM) therapy in the preceding year.3 S-adenosyl-L-methionine (AdoMet or SAM-e) has been available as a dietary supplement in the United States since 1999. AdoMet has been studied for use in the treatment of depression, liver cirrhosis, cholestasis, degenerative joint disease, fibromyalgia, and neurologic disorders.4–6 AdoMet is metabolized to S-adenosyl-L-homocysteine (AdoHcy) in methylation reactions. AdoHcy can then be hydrolyzed by AdoHcy hydrolase to homocysteine (Hcy) and adenine (Fig. 1). This metabolic pathway raises the possibility that

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individuals who take supplemental doses of AdoMet could develop elevated levels of Hcy, a potentially unfavorable outcome. To determine the effect of the dietary supplement AdoMet on plasma Hcy levels, we conducted a double-blind, placebo-controlled, randomized clinical trial.

**Subjects and Methods**

**Study subjects**

Between June 2005 and April 2006, healthy human volunteers were screened for inclusion and exclusion criteria at Mayo Clinic in Rochester, Minnesota. Included as study subjects were volunteers able to provide informed consent and complete the study. Excluded were volunteers younger than 18 years or older than 65 years; pregnant women or women actively trying to conceive; nursing mothers; volunteers with bipolar disorder or panic disorder; and smokers. Exclusion medications that could alter Hcy levels included antilipid medications (e.g., statins, gemfibrozil, ezetimibe, niacin); antidepressant medications; androgens (e.g., testosterone); antiepileptics; azuridine; carbamazepine; cloquinol; cyclosporine; fibrates; hydrochlorothiazide; levodopa; metformin; methotrexate; nicotinic acid; nitrous oxide; phenytoin; omeprazole; estrogen (subjects taking estrogen-containing oral contraceptive pills were not excluded); penicillamine; triamterene; and trimethoprim. Potential volunteers taking any of these medications were excluded from study participation.

**Study design and sample size**

We performed a double-blind, placebo-controlled, randomized clinical trial. Subjects were randomly assigned to receive placebo or AdoMet. The effect size was defined as the expected mean difference divided by the standard deviation.

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**FIG. 1.** (A) The structure of S-adenosyl-l-methionine (AdoMet). (B) Homocysteine (Hcy) and homocystine. Hcy is a monomer, and homocystine is an Hcy dimer. (C) Metabolic pathways of AdoMet and Hcy. The circled numbers correspond to enzymatic reactions: 1, AdoMet decarboxylase; 2, AdoMet-dependent; MT, methyltransferase; 3, Gly-N-MT; 4, S-adenosyl-l-homocysteine (AdoHcy) hydrolase; 5, cystathione β-synthase; 6, betaine Hcy MT; 7, MTHF reductase; 8, AdoMet synthetase; 9, cystathione γ-lase. The AdoMet, AdoHcy, and Hcy pathway is emphasized in bold. ATP, adenosine triphosphate; Cys, cysteine; DMG, dimethyl-glycine; Gly, glycine; Met, methionine; MS, methyltetrahydrofolate-Hcy MT; MTHF, methylenetetrahydrofolate; P, inorganic phosphate; PP, inorganic diphosphate; PLP, pyridoxal phosphate; Sar, sarcosine; THF, tetrahydrofolate.
have more than 90% power to detect a change of 1.83
spray tandem mass spectrometry.14 Inter- and intra-assay
obtained from fasting participants. The Mayo Medical La-
Hcy were evaluated at 2 and 4 weeks. Additionally, lipid
m
10
stearate. An AdoMet dose of 800 mg per day was used. This
riboflavin, 24.4 mg of stearic acid, and 12 mg of magnesium
Technologies, Inc. (Chandler, AZ). Each placebo tablet con-
to AdoMet, were analyzed by Supplement & Nutrition
AdoMet (103.25%). Placebo tablets, identical in appearance
Naturals (Scotts Valley, CA) (manufacturer lot no. 4516,
(St Paul, MN) and was tested independently by Source
study design was approved by the Mayo Clinic Institutional
searchers and was conducted by a centralized pharmacy. The
random number table. Subject allocation was blinded to the re-
seachers and was conducted by a centralized pharmacy. The

AdoMet source

AdoMet was obtained from Pharmacist’s Ultimate Health
St Paul, MN) and was tested independently by Source Naturals (Scotts Valley, CA) (manufacturer lot no. 4516, threshold lot no. B128014). For each tablet with a specified content of 400 mg of AdoMet, the analysis revealed 413 mg of AdoMet (103.25%). Placebo tablets, identical in appearance to AdoMet, were analyzed by Supplement & Nutrition Technologies, Inc. (Chandler, AZ). Each placebo tablet contained 662 mg of cantab (sugar), 400 mg of whey, 1.6 mg of riboflavin, 24.4 mg of stearic acid, and 12 mg of magnesium stearate. An AdoMet dose of 800 mg per day was used. This dose has been well tolerated in previous clinical trials.8–13

Laboratory studies

Data collection included determination of baseline complete blood cell count, creatinine, lipids (total cholesterol, triglycerides, and high-density lipoprotein [HDL]), alanine aminotransferase (ALT), Hcy, high-sensitivity C-reactive protein (hsCRP), folate, vitamin B6, and vitamin B12. ALT and Hcy were evaluated at 2 and 4 weeks. Additionally, lipid levels and hsCRP were rechecked at 4 weeks. Values were obtained from fasting participants. The Mayo Medical Laboratories’ Hcy assay uses liquid chromatography electron spray tandem mass spectrometry.14 Inter- and intra-assay coefficients of variation for this assay were 2.9% to 5.9% and 3.6% to 5.3%, respectively, at mean Hcy concentrations of 3.9, 22.7, and 52.8 μmol/L.14 All the laboratory studies were conducted at the Mayo Clinic.

Statistical analysis

Subjects were followed for 4 weeks with laboratory stud-
ies at baseline and at weeks 2 and 4. We calculated the dif-
fferences for laboratory studies between the baseline and
week 2 or week 4 measurements in the individual patient. If
the subject was unavailable for follow-up, the laboratory test
result remained at whatever the last cycle was. The median
and range values (minimum, maximum) on laboratory
studies were compared between the 2 groups using the 2-
sided Wilcoxon rank sum test because the assumption of
normal distribution might be violated. Mean ± SD was
compared using 2-sample t test, otherwise. To account for
the measurements at baseline, similar analyses were done
using the percent change in measurements from baseline to
week 2 or week 4 in place of actual differences: (baseline –
week 2)/baseline × 100% or (baseline – week 4)/baseline ×
100%. Secondary end points of interest included changes in
hsCRP, lipid, and ALT levels between baseline and week 2
and week 4 measurements. Adverse events and other cate-
gorical subject demographic variables were compared using
the Fisher exact test or the Pearson chi square test. All ana-
lyses were based on the total 52 subjects whom we intended
to treat. Any p values less than 0.05 were considered statisti-
cally significant.

Results

The study group comprised 41 women (78.9%) and 11
men (21.1%). The mean age was 35.3 years (range, 18–60
years) (Fig. 2). There were no statistically significant differ-
ces between baseline subject characteristics or baseline
laboratory studies in the placebo and AdoMet groups (Table
1). Adverse events were minor and were not significantly
different between the placebo and AdoMet groups (Table 2).

The primary endpoint, change in Hcy at 4 weeks, was not
significantly different between the 2 groups. Likewise, there
were no statistically significant differences in change in Hcy
or hsCRP at 2 or 4 weeks (Table 3). This was true for absolute
differences, relative percent changes, and log transforma-
tions of Hcy and HDL, and when the data were analyzed in a
non-intention-to-treat manner, or only on the subjects who
completed the study (23 subjects in the placebo group and 22
subjects in the AdoMet group). There was a small increase in
ALT at 2 weeks in the AdoMet group compared with the placebo
group (p < 0.035). There was a small, but statistically
significant, decrease (p < 0.04) in total cholesterol in the
AdoMet group compared with the placebo group. Interest-
ingly, the subject with the highest baseline Hcy level
(13.1 μmol/L, just above the normal limit) had a decline in
Hcy during AdoMet treatment to 12.3 μmol/L (2 weeks) and
10.7 μmol/L (4 weeks). This individual had a baseline creat-
inine of 1.5 mg/dL. Elevated creatinine is associated with
increased Hcy levels.

Discussion

AdoMet is a frequently used dietary supplement. It is im-
portant to study potential toxicities and cardiovascular risk
factors from supplement use. Our results indicated no change
in Hcy levels. Loehrer and colleagues studied the effect of
oral AdoMet (400 mg) on plasma 5-methyltetrahydrofolate
(5-MTHF), AdoHcy, Hcy, and methionine levels in 14 healthy
human subjects over a 24-hour period.8 They found a transient
increase in AdoMet plasma levels from (mean ± standard er-ror) 38.0 ± 13.4 to 361.8 ± 66.4 nmol/L (p < 0.001), which re-
turned to baseline values with a half-life of 1.7 ± 0.3 hours. AdoHcy and 5-MTHF showed significant transient increases from 29.9 ± 3.7 to 51.7 ± 7.1 nmol/L, and from 25.1 ± 2.5 to 36.2 ± 3.5 nmol/L, respectively (p < 0.001). Hcy and methi-
onine did not change significantly during the 24-hour study
period. AdoMet did not inhibit MTHF reductase, the 5-
MTHF-forming enzyme, but rather caused a transient in-
crease in 5-MTHF, a key cofactor in Hcy metabolism, which
they suggested could result in lower Hcy levels. The au-
thors hypothesized that “lack of change of homocysteine
concentrations after AdoMet administration could be explained by sufficient capacity of homocysteine handling.\textsuperscript{8}

Gören et al. published their results of AdoMet administration on Hcy levels.\textsuperscript{15} In that study, an open-label, single-arm design, 15 healthy subjects were enrolled. Subjects received oral AdoMet for 4 weeks titrated up to 1,600 mg per day. AdoMet levels became significantly elevated from baseline: baseline, 0.75 ± 0.12 nmol/mL; week 2, 0.79 ± 0.13 nmol/mL \((p < 0.01)\); and week 4, 0.78 ± 0.12 nmol/mL \((p = 0.002)\). However, no patients developed increased Hcy levels with AdoMet treatment at week 4 \((7.29 ± 1.91 \mu mol/L; p = 0.11)\). At the week 2 Hcy assessment, there was an increase in Hcy from the baseline level of 6.93 ± 1.52 \(\mu mol/L\) to 7.58 ± 2.10 \(\mu mol/L\), which was of borderline statistical significance \((p = 0.05)\). One subject with a family history of mania developed a manic reaction. No other psychiatric changes were noted. No patients discontinued AdoMet because of adverse reactions, which were primarily mild gastrointestinal tract symptoms.

To our knowledge, our study is the first placebo-controlled, double-blind, randomized trial of the effect of a 4-week administration of AdoMet on Hcy levels in human subjects. AdoMet was well tolerated in this study with adverse effects similar to those of placebo. There was no significant change in ALT levels, consistent with the prior use of AdoMet in the treatment of liver diseases.\textsuperscript{16–19} We found no statistically significant changes in Hcy levels, which suggests that the AdoMet = AdoHcy = Hcy system has the capacity to process increased exogenous AdoMet without a substrate (AdoMet).

### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo ((n = 26))</th>
<th>AdoMet ((n = 26))</th>
<th>Total ((n = 52))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (19.2%)</td>
<td>6 (23.1%)</td>
<td>11 (21.1%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Female</td>
<td>21 (80.8%)</td>
<td>20 (76.9%)</td>
<td>41 (78.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.33</td>
</tr>
<tr>
<td>White</td>
<td>15 (57.7%)</td>
<td>18 (69.2%)</td>
<td>33 (63.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown or did not disclose</td>
<td>11 (42.3%)</td>
<td>7 (26.9%)</td>
<td>18 (34.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, mean ± SD, years</strong></td>
<td>35.0 ± 12.0</td>
<td>35.7 ± 11.7</td>
<td>35.3 ± 11.8</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*p-values: Fisher exact test values (sex), Pearson chi square test values (race), and 2-sample \(t\) test (age).

AdoMet, S-adenosyl-l-methionine; SD, standard deviation.

### Table 2. Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo ((n = 26))</th>
<th>AdoMet ((n = 26))</th>
<th>Total ((n = 52))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloating or flatulence</td>
<td>4 (15.4%)</td>
<td>1 (3.9%)</td>
<td>5 (9.6%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Abdominal cramps/pain</td>
<td>1 (3.9%)</td>
<td>2 (7.7%)</td>
<td>3 (5.8%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (7.7%)</td>
<td>2 (3.9%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Headache/migraine</td>
<td>0</td>
<td>2 (7.7%)</td>
<td>2 (3.9%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (3.9%)</td>
<td>1 (3.9%)</td>
<td>2 (3.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0</td>
<td>1 (3.9%)</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1 (3.9%)</td>
<td>0</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>1 (3.9%)</td>
<td>0</td>
<td>1 (1.9%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

*p-values are Fisher exact test values.

AdoMet, S-adenosyl-l-methionine.
mass action effect increase in product (Hcy level). This observation agrees with the short-term data of Loehrer et al.\(^8\) and the 4-week study by Goren et al.\(^15\) Table 4 compares the effect of exogenous AdoMet administration on Hcy in these 2 studies and in our study (Table 4). AdoMet dosing at 800 mg per day is approximately 2 mmol of AdoMet per day. This is comparable to methionine-loading studies using roughly 50 mmol of methionine. Methionine loading (oral or intravenous bolus of methionine followed by blood or urine testing for Hcy) has been used as a diagnostic tool to evaluate the

### Table 3. Laboratory Study Results Expressed as Median (Minimum, Maximum) Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 26)</th>
<th>AdoMet (n = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hcy, (\mu\text{mol/L})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.5 (4.9, 10.5)</td>
<td>8.3 (4.5, 13.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Week 2</td>
<td>6.9 (5.5, 9.8)</td>
<td>8.8 (4.9, 12.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Week 4</td>
<td>7.5 (5.6, 10.5)</td>
<td>8.2 (4.4, 12.2)</td>
<td>0.32</td>
</tr>
<tr>
<td>Baseline – week 2</td>
<td>0.0 (–2.3, 2.1)</td>
<td>0.1 (–2.5, 3.3)</td>
<td>0.94</td>
</tr>
<tr>
<td>Baseline – week 4</td>
<td>0.0 (–2.3, 2.1)</td>
<td>0.0 (–2.0, 2.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>(Baseline – week 2)/baseline (\times 100%)</td>
<td>0.5 (–30.7, 23.3)</td>
<td>1.3 (–40.4, 29.2)</td>
<td>0.82</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>0.0 (–30.7, 21.4)</td>
<td>0.0 (–28.2, 23.4)</td>
<td>0.39</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>21.0 (13.0, 143.0)</td>
<td>22.0 (14.0, 45.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Week 2</td>
<td>20.5 (10.0, 143.0)</td>
<td>25.0 (0.0, 44.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Week 4</td>
<td>23.0 (10.0, 143.0)</td>
<td>23.5 (0.0, 47.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Baseline – week 2</td>
<td>1.0 (–20.0, 12.0)</td>
<td>–1.0 (–23.0, 17.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline – week 4</td>
<td>0.0 (–8.0, 13.0)</td>
<td>0.0 (–13.0, 16.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>(Baseline – week 2)/baseline (\times 100%)</td>
<td>6.1 (–37.0, 33.3)</td>
<td>–3.9 (–109.5, 100.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>0.0 (–38.1, 27.3)</td>
<td>0.0 (–42.9, 100.0)</td>
<td>0.62</td>
</tr>
<tr>
<td>HsCRP, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.1 (0.0, 0.5)</td>
<td>0.0 (0.0, 0.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Week 2</td>
<td>0.1 (0.0, 0.6)</td>
<td>0.1 (0.0, 1.2)</td>
<td>0.78</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.0 (–0.3, 0.2)</td>
<td>0.0 (–1.1, 0.7)</td>
<td>0.69</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>0.0 (–157.0, 85.8)</td>
<td>0.0 (–412.0, 75.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>185.5 (98.0, 267.0)</td>
<td>182.5 (111.0, 238.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Week 4</td>
<td>198.5 (108.0, 267.0)</td>
<td>181.0 (121.0, 234.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Baseline – week 4</td>
<td>0.0 (–64.0, 38.0)</td>
<td>2.5 (–32.0, 43.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>0.0 (–65.3, 26.0)</td>
<td>1.3 (–17.6, 24.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>52.5 (26.0, 75.0)</td>
<td>51.0 (35.0, 112.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Week 4</td>
<td>55.5 (30.0, 73.0)</td>
<td>47.5 (26.0, 109.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Baseline – week 4</td>
<td>–0.5 (–13.0, 18.0)</td>
<td>1.5 (–8.0, 18.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>–0.8 (–50.0, 32.1)</td>
<td>2.4 (–17.5, 29.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>102.5 (42.0, 161.0)</td>
<td>89.5 (46.0, 143.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Week 4</td>
<td>104.5 (39.0, 217.0)</td>
<td>88.5 (38.0, 168.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Baseline – week 4</td>
<td>–0.5 (–124.0, 68.0)</td>
<td>1.0 (–32.0, 31.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>(Baseline – week 4)/baseline (\times 100%)</td>
<td>–0.5 (–133.3, 56.2)</td>
<td>0.8 (–38.9, 36.7)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

\(p\)-values are Wilcoxon rank sum values.

AdoMet, \(S\)-adenosyl-l-methionine; ALT, alanine aminotransferase; Hcy, homocysteine; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

Table 4. Comparison of Studies on the Effect of \(S\)-Adenosyl-l-Methionine (AdoMet) on Homocysteine (Hcy) Levels in Humans

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>AdoMet dose</th>
<th>Duration</th>
<th>Baseline</th>
<th>24 h</th>
<th>2 wk</th>
<th>4 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehrer et al, 1997(^8)</td>
<td>14</td>
<td>400 mg</td>
<td>1 dose</td>
<td>8.2</td>
<td>6.6(^a)</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Goren et al, 2004(^15)</td>
<td>15</td>
<td>1,600 mg/d</td>
<td>4 wk</td>
<td>6.93</td>
<td>ND</td>
<td>7.58</td>
<td>7.29</td>
</tr>
<tr>
<td>Present study</td>
<td>52</td>
<td>800 mg/d</td>
<td>4 wk</td>
<td>7.5</td>
<td>ND</td>
<td>7.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td>8.5</td>
<td>ND</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>AdoMet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Maximally decreased level seen over 24 hours.

ND, not determined.
integrity of Hcy metabolism. It is possible that higher AdoMet doses beyond those routinely used in humans could perturb the Hcy system and result in changes in Hcy level.

Several factors may limit the generalizability of our results. We did not measure in vivo AdoMet levels. Gören et al. found small but statistically significant increases in AdoMet levels with exogenous AdoMet administration. Since our study subjects had normal Hcy levels at baseline, we do not know the effect of exogenous AdoMet on subjects with above-normal Hcy levels. It is possible that there would be no effect on Hcy levels (as in this study); a decrease in Hcy levels by increasing the active form of folate (S-MTHF); or an increase in Hcy by a mass action effect of the substrate (AdoMet). Although our trial was larger than prior studies, the individual Hcy variations in a larger cohort were not accounted for and genetic factors that may change Hcy levels were not tested. Measuring plasma Hcy level may not determine tissue levels of Hcy. Also, changes in Hcy may take place over a longer period than that studied or be associated with conditions such as impaired kidney function. As the cosubstrate for methylation reactions, AdoMet may be of interest in epigenetic studies of DNA methylation and in studies of hypomethylating agents in cancer. Unfortunately, we did not measure the effect of AdoMet on the DNA methylation of specific genes or on global DNA methylation patterns.

Our study is strengthened by the study design (randomized, placebo-controlled, double-blind), a priori power calculations, a larger study group than prior studies, and measurement of other factors of interest (hsCRP, lipids, ALT). However, other studies have shown that an elevated blood Hcy level is a risk factor for atherothrombotic vascular disease. Elevated Hcy has been associated with increased risk of death from cardiovascular causes, coronary heart disease, carotid atherosclerosis, stroke, and deep vein thrombosis. Also, Hcy-lowering therapy has been found to improve outcomes after percutaneous coronary intervention. However, since our trial was conducted, the results of recent studies of Hcy-lowering therapy to prevent cardiovascular events have been negative. Some epidemiologic studies have associated Hcy as a risk factor for dementia, while a recent study did not find a benefit to Hcy-lowering therapy on cognitive decline. In vitro studies have demonstrated that exogenous AdoMet can restore normal gene expression and decrease β-amyloid production through gene methylation in neuroblastoma cells grown in folate- and vitamin B12-deprived media. Therefore, the lack of increase in Hcy and a potential benefit of AdoMet in dementia suggest additional clinical trials could be contemplated in humans. The role of AdoMet in epigenetic changes in other diseases, such as cancer, is an area for future research.

In conclusion, AdoMet seems well tolerated, and in a dose of 800 mg per day for 4 weeks does not appear to significantly affect plasma Hcy levels. Future clinical trials of AdoMet should monitor Hcy levels with extended use of AdoMet to confirm its safety with long-term use.

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Disclosure Statement

No competing financial interests exist.

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