Oral L-Carnitine Supplementation Increases Trimethylamine-*N*-oxide but Reduces Markers of Vascular Injury in Hemodialysis Patients

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Objectives: Food or supplement-derived L-carnitine is changed to trimethylamine (TMA) by interstinal microbiota, which is further metabolized to trimethylamine-*N*-oxide (TMAO), being involved in the promotion of atherosclerosis in animal models. Meanwhile, carnitine deficiency has played a role in accelerated atherosclerosis in hemodialysis (HD) patients. However, effects of oral L-carnitine supplementation on circulating levels of TMAO and markers of vascular injury and oxidative stress in patients on HD remain unclear. In this study, we addressed the issue.

Methods: Thirty-one HD patients with carnitine deficiency were treated with oral L-carnitine (900 mg/d) for 6 months. At baseline and after treatment, clinical variables including circulating levels of carnitine fractions, TMA, TMAO, advanced glycation end products (AGE), soluble forms of intracellular adhesion molecule-1 (sICAM-1), vascular cell adhesion molecule-1 (sVCAM-1), and malondialdehyde (MDA) were measured.

Results: Oral L-carnitine supplementation significantly increased total, free, acyl carnitine, and plasma TMA and TMAO levels, whereas it decreased markers of vascular injury and oxidative stress such as sICAM-1, sVCAM-1, and MDA levels. TMA and TMAO levels at baseline were correlated with each other, and free carnitine was independently associated with TMAO levels. Furthermore, change in AGE values from baseline (ΔAGE) was positively correlated with ΔsICAM-1 ($P = 0.043$) and was a sole independent determinant of ΔsICAM-1 ($R^2 = 0.133$, $P = 0.043$).

Conclusions: This study demonstrated that although oral L-carnitine supplementation was associated with increased TMAO levels, it might be beneficial on vascular injury in patients on HD. Vasculoprotective properties of L-carnitine supplementation in HD patients might be ascribed partly to its inhibitory actions on AGE.

Key Words: L-carnitine, hemodialysis, TMA, TMAO, atherosclerosis

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INTRODUCTION

Trimethylamine-*N*-oxide (TMAO) is an organic compound in the class of amine oxides, which is produced from trimethylamine (TMA) in the liver by flavin-containing monooxygenase isoform 3 enzyme.[1] Because choline and L-carnitine produce TMA in an intestinal microbiota–dependent manner, dietary intake of animal products such as red meat or L-carnitine supplementation has been considered to be the major source of TMAO in humans.[1–3] Recently, diet supplemented with choline or TMAO has been shown to promote foam cell formation within the atherosclerotic plaques in mice.[3,4] Furthermore, fasting plasma levels of TMAO are positively associated with cardiovascular disease phenotypes including peripheral artery disease, coronary artery disease, and history of myocardial infarction, and an increased level of TMAO could predict future cardiovascular events in patients undergoing elective coronary angiography.[2] These observations suggest that over intake of choline and/or supplementation of L-carnitine might be harmful and could accelerate atherosclerosis in high-risk patients for cardiovascular disease through the elevation of TMAO.

Meanwhile, carnitine, a natural substance that is essential for transport of long-chain fatty acids from the cytoplasm to mitochondria, not only plays a central role in fatty acid β-oxidation and subsequent ATP production but also modulates the function of mitochondrial respiratory chain in a variety

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This trial was registered with the University Hospital Medical Information Network clinical trials database (UMIN000010953, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi).

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of cells.[5] Because serum carnitine levels are decreased in hemodialysis (HD) patients,[6] carnitine deficiency might be involved in muscle weakness, cardiac hypertrophy, and accelerated atherosclerosis in these subjects.[6–8] In addition, we have recently found that serum carnitine levels are inversely associated with skin accumulation values of advanced glycation end products (AGE), and oral L-carnitine supplementation significantly decreases the AGE levels in HD patients with carnitine deficiency.[6,9] Given the pathological role of AGE in accelerated atherosclerosis,[10] it is also conceivable that L-carnitine supplementation might play a protective role against vascular injury in patients on HD through the suppression of AGE accumulation. However, effects of oral L-carnitine supplementation on circulating levels of TMAO, AGE, and markers of vascular injury and oxidative stress in HD patients remain unclear. In this study, we addressed the issue.

METHODS

Patients

Forty-two Japanese patients receiving HD for more than a year, whose serum free carnitine levels were <40 μmole/L, were enrolled in this study. Control subjects were composed of ethnic-matched 47 healthy controls (mean age ± SD: 55.9 ± 5.2 years; male/female: 12/35 as compared with mean age ± SD: 64.6 ± 10.8; $P < 0.001$). We excluded any patients with acute coronary syndrome, symptomatic stroke within at least 6 months before the enrollment, heart failure, neoplastic disorders, or active inflammatory diseases. All HD patients were given oral L-carnitine supplementation (900 mg/d) and followed up for 6 months. Seven subjects dropped out of the study during the assessment or treatment due to poor drug adherence (n = 4), nausea (n = 1), acute abdomen (n = 1), and cerebral infarction (n = 1). Therefore, the compliance rate for patients taking L-carnitine supplementation was 83.3% (35/42), which was confirmed by the elevation of total, free, and acyl carnitine levels. We further excluded 4 patients who were given oral antibiotics during the study period because treatment with antibiotics could influence TMA and TMAO levels.[2] Finally, 31 HD patients (mean age: 64.6 ± 10.8 years; mean duration of HD: 80.1 ± 57.7 months) completed the study. At baseline and 6 months after the L-carnitine treatment, patients underwent a complete history, physical examination, and determination of blood chemistry just before the HD session. Patients were dialyzed for 4–5 hours with high-flux dialyzers 3 times a week. Ten patients had diabetes mellitus, 23 patients received inhibitors of renin–angiotensin system for the treatment of hypertension, and 6 received statins for dyslipidemia (Table 1). Informed consent was obtained from all subjects, and the study protocol was approved by the Institutional Ethics Committees of Kurume University School of Medicine. This work was conducted in accordance with the Declaration of Helsinki. This trial was registered with the University Hospital Medical Information Network clinical trials database (UMIN000010953).

Data Collection

The medical history was ascertained by a questionnaire. Blood pressure (BP) was measured in the sitting position using an upright standard sphygmomanometer just before starting HD. Vigorous physical activity and smoking were avoided for at least 30 minutes before BP measurement.

Blood was drawn from arteriovenous shunt just before starting HD session for determination of hemoglobin (Hb), total protein, albumin, lipids (total cholesterol and triglycerides), blood urea nitrogen, creatinine, uric acid, calcium, phosphate, C-reactive protein, intact parathyroid hormone (iPTH), total, free, and acyl carnitine, TMA, TMAO, AGE, soluble form of intracellular adhesion molecule-1 (sICAM-1), soluble form of vascular cell adhesion molecule-1 (sVCAM-1), and malondialdehyde (MDA), a marker of lipid peroxidation. iPTH was evaluated by an immunoradiometric assay (Allegro I-PTH; Nichols Institute, San Juan Capistrano, CA). Serum carnitine fractions were determined by enzyme cycling methods as described previously.[11] Plasma TMA level was determined by a headspace gas chromatography after

TABLE 1. Clinical Variables at Baseline and After Oral L-Carnitine Therapy in HD Patients

	Baseline	After Treatment	*P*
No. patients	31	31	—
Age, yr	64.6 ± 10.8	65.1 ± 10.8	—
HD duration, mo	80.1 ± 57.7	86.1 ± 57.7	—
Sex (no. male/female)	22/9	22/9	—
Body mass index, kg/m^2	21.2 ± 1.9	21.2 ± 2.0	0.780
Systolic BP, mm Hg	**151.0 ± 17.3**	**141.5 ± 16.1**	**0.006**
Diastolic BP, mm Hg	81.4 ± 12.1	79.3 ± 16.1	0.467
Hemoglobin, g/dL	11.4 ± 0.8	11.2 ± 0.8	0.344
Total protein, g/dL	**6.93 ± 0.46**	**6.77 ± 0.48**	**0.002**
Albumin, g/dL	**4.11 ± 0.28**	**4.00 ± 0.26**	**<0.001**
Total cholesterol, mg/dL	160.4 ± 25.1	161.5 ± 22.4	0.756
Triglycerides, mg/dL	113.4 ± 57.5	119.3 ± 73.0	0.611
Blood urea nitrogen, mg/dL	71.1 ± 17.1	68.2 ± 16.8	0.182
Creatinine, mg/dL	11.8 ± 1.8	11.6 ± 1.8	0.323
Uric acid, mg/dL	8.63 ± 1.53	8.22 ± 1.15	0.065
Corrected Ca, mg/dL	**9.29 ± 0.50**	**9.07 ± 0.50**	**0.024**
Phosphate, mg/dL	4.75 ± 0.82	5.06 ± 1.22	0.189
iPTH, pg/mL	103.2 ± 38.2	126.8 ± 89.0	0.151
C-reactive protein, mg/dL	0.17 ± 0.16	0.15 ± 0.18	0.656
AGE, U/mL	10.1 ± 3.0	9.5 ± 1.6	0.235
Total carnitine, μmole/L	**43.7 ± 8.7**	**257.0 ± 71.9**	**<0.001**
Free carnitine, μmole/L	**25.2 ± 4.7**	**164.1 ± 47.1**	**<0.001**
Acyl carnitine, μmole/L	**18.3 ± 5.4**	**92.8 ± 29.0**	**<0.001**
Acyl-to-free carnitine ratio	**0.73 ± 0.22**	**0.57 ± 0.12**	**<0.001**
TMA, μmole/L	**39.1 ± 15.3**	**85.1 ± 36.5**	**<0.001**
TMAO, μmole/L	**222.5 ± 111.7**	**548.4 ± 206.4**	**<0.001**
ESA dose, IU·kg^{-1}·wk^{-1}	58.8 ± 27.4	59.1 ± 34.1	0.945
Diabetes (−/+) (no.)	21/10	21/10	—
Medication			
Renin–angiotensin system inhibitors (−/+) (no.)	8/23	8/23	—
Statins (−/+) (no.)	25/6	25/6	—

Values are shown as mean ± SD. Bold indicates statistical significance.
ESA, erythropoiesis-stimulating agent.

basifying with 10 M NaOH and preheating at 95°C for 20 minutes. TMAO concentrations were calculated by subtraction of the free TMA concentrations from total TMA values after chemical reduction of TMAO to TMA using $TiCl_3$.[12] Intra- and inter-assay variations for free and total TMA were within 5% as previously described.[13] sICAM-1, sVCAM-1, and MDA levels were measured with commercially available kits (R&D Systems, Minneapolis, MN for sICAM-1 and sVCAM-1 and Cusabio Biotech Co, Ltd, Hubei, China for MDA). Serum AGE levels were measured by a competitive enzyme-linked immunosorbent assay system as described previously.[14] Other blood chemistry was measured by standard enzymatic methods as described previously (BML, Inc, Tokyo, Japan).

Statistical Analysis

Data are presented as mean ± SD or SE. Sex, use or nonuse of renin–angiotensin system inhibitors and statins, and presence or absence of diabetes mellitus were coded as dummy variables. Because serum MDA levels were not normally distributed, log-transformed values were used for analysis. To determine the difference of carnitine fraction, TMA, and TMAO between HD patients and healthy subjects, unpaired *t* test was performed. To examine the difference of variables between baseline and 6 months after the treatment, paired *t* test was performed. To evaluate the correlation between TMA and TMAO, between change in TMA values from baseline (ΔTMA) and ΔTMAO, and between ΔsICAM-1, ΔsVCAM-1, or ΔlogMDA and Δother clinical variables, univariate regression analysis was performed. To determine the independent correlates of baseline TMAO and ΔsICAM-1, multiple stepwise regression analysis was performed. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with SPSS system (version 20; Chicago, IL).

RESULTS

Demographic Data at Baseline

Demographic data at baseline and after treatment of L-carnitine are shown in Table 1. At baseline, total and free carnitine levels just before the HD session were significantly lower, whereas acyl carnitine levels and acyl-to-free carnitine ratio were higher in HD patients compared with those in 47 healthy controls (total carnitine: 43.7 ± 8.7 vs. 58.7 ± 7.2 μmole/L, free carnitine: 25.2 ± 4.7 vs. 46.0 ± 6.4 μmole/L, acyl carnitine: 18.3 ± 5.4 vs. 12.7 ± 3.2 μmole/L, acyl-to-free carnitine ratio: 0.73 ± 0.22 vs. 0.28 ± 0.09, $P < 0.001$, respectively). Plasma TMA levels in HD patients were significantly lower, and TMAO levels were higher compared with those in healthy subjects (TMA: 39.1 ± 15.3 vs. 55.1 ± 18.8 μmole/L, $P < 0.001$; TMAO: 222.5 ± 111.7 vs. 174.3 ± 99.7 μmole/L, $P = 0.05$, respectively).

Effects of Oral L-Carnitine Supplementation on Carnitine Fractions and Clinical Variables

After the oral administration of L-carnitine (900 mg/d) for 6 months, total, free, and acyl carnitine levels were increased to about 4-fold (total carnitine: 257.0 ± 71.9 μmole/L, free carnitine: 164.1 ± 47.1 μmole/L, acyl carnitine: 92.8 ± 29.0 μmole/L, $P < 0.001$, respectively), whereas systolic BP ($P = 0.006$), total protein ($P = 0.002$), serum albumin ($P < 0.001$), corrected calcium ($P = 0.024$), and acyl-to-free carnitine ratio (0.57 ± 0.12, $P < 0.001$) levels were decreased (Table 1).

Effects of Oral L-Carnitine Supplementation on Plasma Levels of TMA and TMAO and Circulating Levels of sICAM-1, sVCAM-1, MDA, and AGE

After 6-month treatment of L-carnitine supplementation, plasma TMA and TMAO levels were significantly increased (TMA: 85.1 ± 36.5 μmole/L, $P < 0.001$; TMAO: 548.4 ± 206.4 μmole/L, $P < 0.001$, respectively) (Table 1, Figs. 1A, B). Plasma TMA and TMAO levels at baseline were correlated with each other ($R^2 = 0.568$, $P < 0.001$, Fig. 2A). ΔTMAO was positively associated with ΔTMA ($R^2 = 0.302$, $P = 0.001$, Fig. 2B).

Serum levels of sICAM-1, sVCAM-1, and logMDA were significantly decreased by the L-carnitine treatment [sICAM-1 level at baseline vs. after treatment: 204.0 ± 70.6 vs. 191.8 ± 64.9 ng/mL ($P = 0.016$), sVCAM-1:

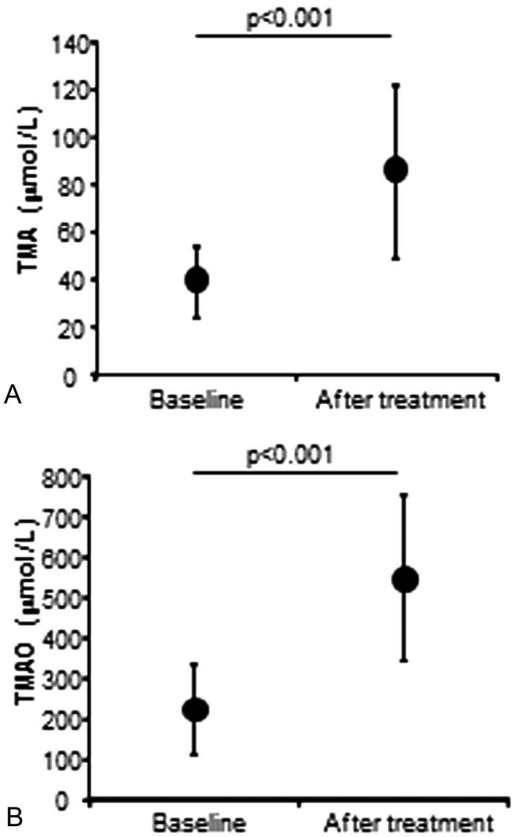

FIGURE 1. Effects of oral L-carnitine supplementation (900 mg/d) for 6 months on plasma TMA and TMAO levels in HD patients. A, TMA and (B) TMAO levels at baseline and after the L-carnitine treatment.

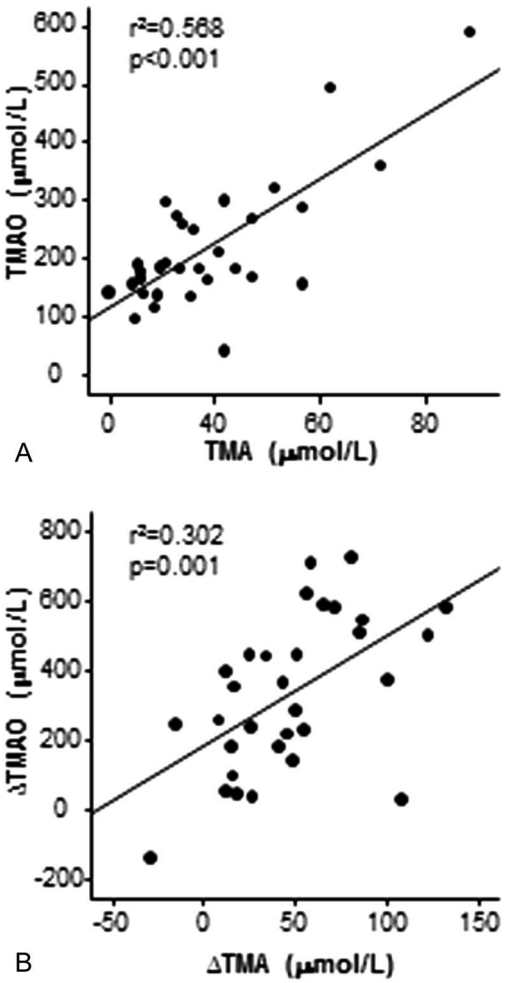

FIGURE 2. Effects of oral L-carnitine supplementation (900 mg/d) for 6 months on plasma TMA and TMAO levels in HD patients. A, Correlation between TMA and TMAO levels at baseline in HD patients (n = 31). B, Correlation between ΔTMA and ΔTMAO levels in HD patients (n = 31).

1952 ± 679 vs. 1777 ± 374 ng/mL ($P = 0.015$), logMDA: 7.23 ± 1.14 vs. 6.36 ± 0.81 ($P < 0.001$)] (Figs. 3A–C). Serum AGE level had a tendency to decrease by L-carnitine supplementation (10.1 ± 3.0 vs. 9.5 ± 1.6 U/mL, $P = 0.235$).

Correlates of Baseline TMAO

We next examined which clinical variables were correlated to TMAO at baseline in our subjects. In univariate analysis, systolic BP (inversely, $P = 0.04$), blood urea nitrogen ($P = 0.023$), phosphate ($P = 0.009$), iPTH ($P = 0.042$), and free carnitine ($P = 0.011$) were correlated with plasma TMAO level. Multiple stepwise regression analysis revealed that systolic BP, phosphate, and free carnitine were independent determinants of TMAO in our patients ($R^2 = 0.470$, $P = 0.001$, Table 2).

Correlates of ΔsICAM-1, ΔsVCAM-1, and ΔlogMDA

We further investigated which Δclinical variables were independently correlated with ΔsICAM-1, ΔsVCAM-1, and

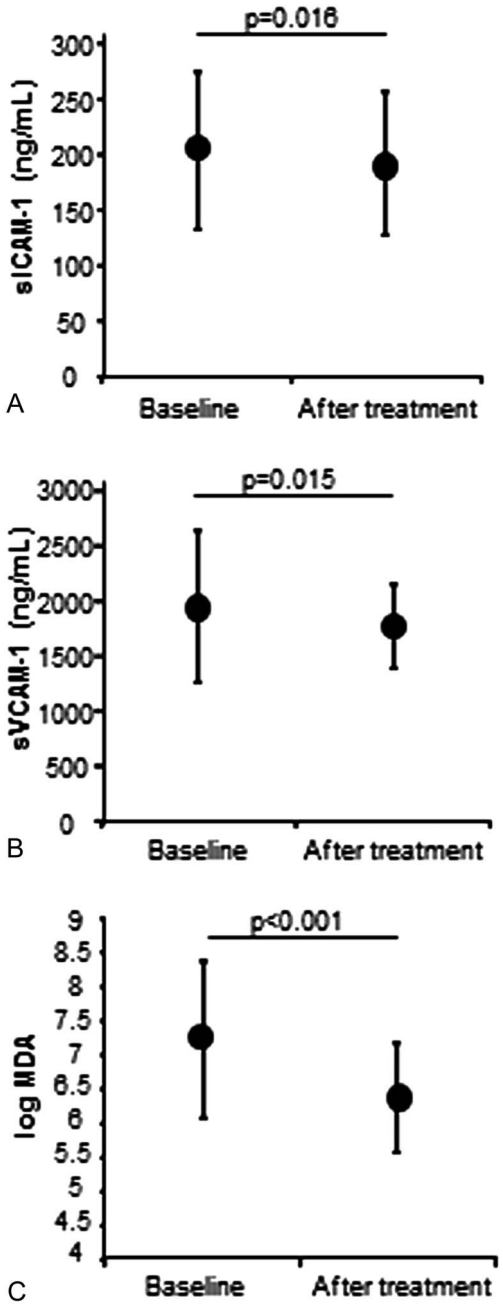

FIGURE 3. Effects of oral L-carnitine supplementation (900 mg/d) for 6 months on markers of vascular injury and oxidative stress in HD patients. A, sICAM-1, (B) sVCAM-1, and (C) logMDA levels at baseline and after the L-carnitine treatment.

ΔlogMDA. Univariate analysis showed that ΔAGE was a sole independent determinant of ΔsICAM-1 ($R^2 = 0.133$, $P = 0.043$) (Table 3). Furthermore, Δcorrected calcium (inversely, $P = 0.014$) and ΔiPTH (inversely, $P = 0.004$) values were independently associated with ΔsVCAM-1, whereas Δuric acid was a sole independent correlate of ΔlogMDA values in our patients ($R^2 = 0.131$, $P = 0.049$).

TABLE 2. Univariate and Multiple Stepwise Regression Analysis for the Correlates of TMAO Levels at Baseline

	Univariate			Multiple Stepwise Regression		
Variables	**β**	**SE**	***P***	**β**	**SE**	***P***
Age	−0.290	1.890	0.120			
Sex	−0.103	44.731	0.580			
HD duration	−0.088	0.358	0.636			
Body mass index	0.179	10.490	0.336			
Systolic BP	**−0.371**	**1.113**	**0.040**	**−0.378**	**0.967**	**0.018**
Diastolic BP	−0.068	1.756	0.719			
Hemoglobin	−0.179	23.911	0.335			
Total protein	−0.012	45.555	0.949			
Albumin	−0.192	73.960	0.302			
Total cholesterol	−0.115	0.822	0.539			
Triglycerides	−0.270	0.348	0.143			
Blood urea nitrogen	**0.406**	**1.111**	**0.023**			
Creatinine	0.315	10.930	0.085			
Uric acid	0.181	13.317	0.331			
Corrected Ca	0.184	40.539	0.322			
Phosphate	**0.461**	**22.395**	**0.009**	**0.262**	**20.543**	**0.095**
iPTH	**0.367**	**0.506**	**0.042**			
C-reactive protein	−0.046	128.609	0.809			
Free carnitine	**0.453**	**3.899**	**0.011**	**0.461**	**3.479**	**0.004**
AGE	−0.145	6.770	0.437			
sICAM-1	−0.343	0.276	0.059			
sVCAM-1	0.026	0.031	0.890			
logMDA	0.116	18.491	0.543			
Diabetes	−0.006	43.668	0.974			
Renin–angiotensin system inhibitors	0.051	46.591	0.784			
Statins	0.026	51.652	0.890			

Bold indicates statistical significance.
β, standardized regression coefficients.
$R^2 = 0.470$.

DISCUSSION

The salient findings of this study were (1) oral L-carnitine supplementation (900 mg/d) for 6 months was associated with a significant increase in all carnitine fractions and plasma TMA and TMAO levels in HD patients, (2) TMA and TMAO levels at baseline were correlated with each other, the levels of TMA in HD patients just before HD session were significantly lower, and TMAO levels were higher than those in healthy controls, (3) TMAO value at baseline was independently correlated with free carnitine and phosphate levels, (4) circulating sICAM-1, sVCAM-1, and MDA levels were significantly decreased by L-carnitine treatment, and (5) ΔAGE was a sole independent determinant of ΔsICAM-1 in HD subjects. These observations suggest that TMA and TMAO levels in HD patients could be regulated by exogenously derived L-carnitine and animal food products containing phosphate. In this study, although free carnitine levels in HD patients were significantly lower than those in healthy controls, plasma TMAO levels were higher in HD subjects. Therefore, TMAO values might also be regulated by renal function and not sufficiently removed by HD. Food or supplement-derived choline and L-carnitine are changed to TMA by intestinal microbiota, which is further metabolized to TMAO, playing a role in the promotion of atherosclerosis in animal models.[2,15] Indeed, Koeth et al[15] recently reported that consumption of an L-carnitine–enriched diet exacerbated the atherosclerotic lesions in the aorta of C57BL/6J apolipoprotein E (apoE)–deficient mice. However, this study suggests that oral L-carnitine supplementation might be beneficial in vascular injury of HD patients with carnitine deficiency, although it increased plasma TMAO levels in these subjects.

In this study, oral L-carnitine supplementation significantly reduced circulating levels of sICAM-1, sVCAM-1, and MDA, a marker of lipid peroxidation, and had a tendency to decrease AGE values in HD subjects. Furthermore, ΔAGE was independently correlated with ΔsICAM-1. We, along with others, have shown that AGE could stimulate ICAM-1 and VCAM-1 expression in both cell culture and animal models through the induction of oxidative stress generation.[14,16–18] One early phase of atherosclerosis involves the recruitment and firm adhesion of inflammatory cells to endothelial cells, whose process is mainly mediated by ICAM-1 and VCAM-1.[19,20] Indeed, many experimental and clinical studies have shown that ICAM-1 and VCAM-1 expression is increased at atherosclerotic lesions,[21–23] and selective targeting of ICAM-1 or VCAM-1 protects against atherosclerosis in apoE-deficient or high fat–fed mice.[24–26] Given that sICAM-1 and sVCAM-1

TABLE 3. Univariate and Multiple Stepwise Regression Analysis for the Correlates of ΔsICAM-1 Levels

	Univariate			Multiple Stepwise Regression		
Variables	**β**	**SE**	***P***	**β**	**SE**	***P***
ΔBody mass index	−0.053	8.191	0.777			
ΔSystolic BP	0.170	0.281	0.361			
ΔDiastolic BP	0.155	0.317	0.413			
ΔHemoglobin	−0.194	4.252	0.296			
ΔTotal protein	−0.143	18.167	0.444			
ΔAlbumin	−0.142	32.416	0.445			
ΔTotal cholesterol	0.107	0.268	0.567			
ΔTriglycerides	0.041	0.077	0.828			
ΔBlood urea nitrogen	−0.188	0.406	0.310			
ΔCreatinine	−0.295	5.038	0.108			
ΔUric acid	−0.196	4.095	0.289			
ΔCorrected Ca	−0.082	9.608	0.660			
ΔPhosphate	0.059	3.760	0.752	**0.262**	**20.543**	**0.095**
ΔiPTH	−0.322	0.052	0.077			
ΔC-reactive protein	−0.072	20.308	0.392			
ΔFree carnitine	−0.159	0.104	0.392			
ΔAGE	**0.365**	**1.833**	**0.043**	**0.365**	**1.833**	**0.043**
ΔTMA	−0.276	0.124	0.133			
ΔTMAO	−0.311	0.021	0.088			
ΔsVCAM-1	0.266	0.013	0.148			
ΔlogMDA	−0.181	4.115	0.339			

Bold indicates statistical significance.
β, standardized regression coefficients.
$R^2 = 0.133$.

could reflect endothelial ICAM-1 and VCAM-1 expression and be a marker that predicts future cardiovascular events,[27,28] this study suggests that vasculoprotective properties of L-carnitine supplementation in HD patients could be ascribed partly to its inhibitory actions on AGE formation. In vitro study has shown that L-carnitine significantly inhibits AGE modification of bovine serum albumin,[29] and its antiglycating capacity is more potent than that of aminoguanidine, a prototype inhibitor of AGE.[29,30] In addition, we have previously shown that L-carnitine supplementation significantly decreases skin accumulation levels of AGE in HD patients, thus supporting our speculation. A recent systematic review and meta-analysis has revealed that L-carnitine therapy reduces all-cause mortality and the risk for ventricular arrhythmia and angina symptoms in patients experiencing an acute myocardial infarction.[31] These observations further support the concept that oral L-carnitine supplementation might be beneficial rather than harmful in HD patients with carnitine deficiency. We found that markers of endothelial injury sICAM-1 and sVCAM-1 were shown to be significantly different when L-carnitine supplementation is given, yet these markers are not strongly correlated with TMAO. Therefore, any of these metabolites could independently impact upon endothelial injury in HD subjects. In our study, L-carnitine supplementation significantly decreased systolic BP. Furthermore, because L-carnitine administration could improve endothelial function through the suppression of oxidative stress generation in spontaneous hypertension rats,[32] L-carnitine supplementation might reduce systolic BP partly by improving endothelial function through reduction of AGE and MDA formation, which might also protect against the development of atherosclerosis in HD patients.

Limitations

First, the weakest point of this study is that we did not measure the responses to placebo. Therefore, patterns of TMAO and TMA observed could have occurred spontaneously irrespective of the use of L-carnitine because of the absence of an appropriate control group. Second, we did not know here the reason why L-carnitine supplementation decreased systolic BP, total protein, serum albumin, and corrected calcium levels in our patients. Modest decreases in total protein and systolic BP may be explained by the regression to the mean. Third, we compared here TMA and TMAO levels in HD patients with those of healthy controls. Therefore, some difference of age and sex between the 2 groups could affect the present findings. Fourth, in this study, Δcorrected calcium values were inversely associated with ΔsVCAM-1, but the underlying molecular mechanism remained unclear. Moreover, although subjects were instructed not to change their lifestyles and to continue taking the same dose of any concomitant oral drugs during the study period, we cannot totally exclude the possibility that medication could affect the present results. Finally, this study was of small sample size with high dropout rates. This is a possible reason why AGE levels were not altered by L-carnitine supplementation, yet this was a sole independent determinant of endothelial damage shown by ΔsICAM-1 levels in HD patients. Therefore, longitudinal, large sample–sized placebo-controlled study is needed to clarify whether oral L-carnitine treatment could block the harmful effects of AGE and subsequently reduce the risk of future cardiovascular events in HD patients with carnitine deficiency.

CONCLUSIONS

We demonstrated that although oral L-carnitine supplementation significantly increased TMA and TMAO levels in HD patients, L-carnitine supplementation might have beneficial effects on vascular injury in these subjects. Given the fact that carnitine deficiency could exacerbate the accumulation of AGE and exert harmful effects in HD patients,[6,33,34] L-carnitine supplementation might be a useful strategy for the treatment of HD patients with carnitine deficiency.

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