

Original Article

Decreased serum carnitine is independently correlated with increased tissue accumulation levels of advanced glycation end products in haemodialysis patients

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SUMMARY AT A GLANCE

This study demonstrated decreased serum carnitine levels and elevated skin advanced glycation end products in haemodialysis patients, and provides a possible novel marker of cardiovascular outcomes in this group of patients.

ABSTRACT:

Aim: There is accumulating evidence that advanced glycation end products (AGE) play a role in cardiovascular disease (CVD) in patients with haemodialysis (HD). Carnitine deficiency is frequently observed in HD patients, which may also contribute to CVD. In this study, we examined whether carnitine deficiency was independently associated with increased tissue accumulation levels of AGE in HD patients.

Methods: One hundred and twenty-nine HD patients underwent determinations of blood chemistries including serum level of carnitine. Tissue AGE levels were evaluated by measuring skin autofluorescence with an AGE-reader.

Results: Serum carnitine levels were significantly lower, while skin AGE levels were significantly higher in HD patients compared with healthy controls ($P < 0.001$). In univariate analysis, β_2 -microglobulin (β_2 -MG) and carnitine (inversely) were correlated with skin AGE levels. Multiple stepwise regression analysis revealed that carnitine levels were one of the independent determinants of skin AGE levels ($P = 0.024$). When β_2 -MG-adjusted skin AGE levels were stratified by serum carnitine levels, a statistical significance and dose-response relationship were observed ($P = 0.043$). Furthermore, skin AGE levels were one of the independent determinants of serum carnitine levels as well ($P = 0.012$).

Conclusion: The present study demonstrated that decreased carnitine levels were independently associated with increased skin AGE levels in HD patients. Since carnitine is reported to inhibit the formation of AGE *in vitro*, our study suggests that supplementation of carnitine may be a therapeutic target for preventing the accumulation of tissue AGE and subsequently reducing the risk of CVD in HD patients.

Reducing sugars can react non-enzymatically with the amino groups of proteins to initiate a complex series of rearrangements and dehydrations, and then to produce a class of irreversibly cross-linked, fluorescent moieties termed advanced glycation end products (AGE).^{1–3} The formation and/or accumulation of AGE have been known to progress in a normal aging process, and at an accelerated rate under diabetes or end-stage renal failure, thereby playing a role in the development and progression of cardiovascular disease (CVD) in these subjects.^{4–10} Recently, accumulation of tissue

AGE levels has been able to be evaluated non-invasively by measuring skin autofluorescence (AF) with an AGE-reader.^{11–13} Indeed, it has been reported that skin AF was strongly correlated with collagen-linked fluorescence and with skin pentosidine levels in haemodialysis (HD) patients.¹¹ Moreover, we have previously found that skin AF was positively associated with high-sensitive C-reactive protein (CRP), a well-known prognostic marker of future cardiovascular events in patients with HD.¹² In addition, skin AF values evaluated by an AGE-reader have been associated

with the severity of vascular complications in diabetes and predict cardiovascular mortality in HD patients.^{11,13}

Carnitine is a natural substance, which is supplied through protein-rich foods and synthesized by the liver, kidney, skeletal and cardiac muscles in humans, while it is excreted from the kidney.¹⁴ Carnitine is involved in fatty acid β -oxidation and energy production by transporting long-chain fatty acids from the cytoplasm to mitochondria.¹⁴ Recently, although the underlying molecular mechanism is unclear, carnitine levels were significantly decreased in patients undergoing chronic HD.¹⁵ Furthermore, carnitine deficiency has been associated with erythropoietin-resistant anaemia, muscle weakness and cardiac hypertrophy in patients with HD, all of which were ameliorated by administration of L-carnitine.^{16,17} Since carnitine was reported to inhibit the formation of AGE *in vitro*,¹⁸ it is conceivable that carnitine deficiency may contribute to tissue AGE accumulation. However, which clinical, metabolic and inflammatory variables including carnitine levels were independently associated with AGE accumulation were not fully understood. Therefore, in this study, we examined whether carnitine deficiency and tissue accumulation levels of AGE were correlated with each other in HD patients.

METHODS

Patients

One hundred and twenty-nine maintenance HD patients (75 male and 54 female; mean age, 68.2 ± 13.6 years; mean duration of HD, 98.7 ± 84.9 months) and 75 healthy subjects (44 male and 31 female; mean age, 65.4 ± 10.3 years, estimated glomerular filtration rate (eGFR); 78.5 ± 17.6 mL/min per 1.73 m^2) without diabetes and/or kidney diseases underwent a complete history, physical examination, and determinations of blood chemistries. Patients were dialyzed for 4–5 h with high-flux dialyzers three times a week. Forty-six patients had diabetes mellitus (DM). Seventy-seven patients received inhibitors of renin-angiotensin system (RAS), and only 26 patients received statins for the treatment of dyslipidemia.

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 min before BP measurement.

Blood was drawn from arteriovenous shunt just before starting HD sessions for determinations of haemoglobin, albumin, lipids (low-density lipoprotein (LDL)-cholesterol and triglycerides), blood urea nitrogen (BUN), creatinine (Cr), uric acid, calcium (Ca), and phosphate (P). Whole parathyroid hormone (Whole-PTH) was evaluated by an immunoradiometric assay (IRMA, Allegro I-PTH; Nichols Institute, San Juan Capistrano, CA, USA). β_2 -microglobulin (β_2 -MG) was measured by Latex immunoagglutination assay (Eiken Chemical Co., Ltd. Tokyo, Japan). Serum carnitine levels were determined by the enzyme cycling methods as described previously.¹⁹

Other blood chemistries were measured at a commercially available laboratory as described previously (Wako Pure Chemical Industries, Osaka, Japan). HD adequacy was evaluated by a single-pool fractional clearance of body water for urea (Kt/V).²⁰ Single-pool Kt/V was calculated as a following formula; $\text{Kt/V} = -\ln(\text{Ce/Cs} - 0.008 \times t) + (4 - 3.5 \times \text{Ce/Cs}) \times \Delta\text{BW/BW}$ (Ce/Cs; postserum/preserum urea nitrogen ratio, t; dialysis time, $\Delta\text{BW/BW}$; the ratio of the ultrafiltrate volume removed to the postdialysis weight). Tissue AGE levels were evaluated quantitatively by measuring skin AF with an AGE-reader according to the supplier's recommendations (DiagOptics BV, Groningen, The Netherlands).¹¹

Informed consent was obtained from all patients, and the study protocol was approved by the Institutional Ethics Committees of Kurume University School of Medicine and Sugi Cardiovascular Hospital.

Statistical analysis

Results are presented as mean \pm standard deviation (SD). The medications for hypertension and dyslipidemia (RAS inhibitors and statins) and the presence or absence of DM were coded as dummy variables. Clinical data that were not normally distributed such as TG, whole-PTH, CRP and Kt/V were log-transformed. To compare differences between healthy subjects and HD patients, the unpaired *t*-test was performed. To determine independent correlates of tissue AGE or carnitine, multiple stepwise regression analysis was performed. More important clinical markers related to renal function, metabolic, haemodynamic and inflammatory variables were included in the linear regression analysis. In multiple stepwise regression analysis, statistically significant factors ($P < 0.05$) were included in our model, that is, non-significant factors were excluded in this model. Mean skin AF levels stratified by the values of carnitine levels were compared using analysis of covariance adjusted for β_2 -MG. Further, mean carnitine levels stratified by the levels of skin AF were compared using analysis of covariance adjusted for LDL-cholesterol, serum Cr and uric acid. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with SPSS 19 system.

RESULTS

Demographic data

Demographic data are shown in Table 1. Serum carnitine levels were significantly lower than those in healthy controls ($n = 75$) (37.5 ± 10.6 vs 58.9 ± 7.2 $\mu\text{mol/L}$, $P < 0.001$). Skin AF levels were significantly higher in HD patients compared with normal subjects (3.21 ± 0.81 vs 2.25 ± 0.44 a.u., $P < 0.001$).

Correlates of skin AGE

Univariate analyses showed that serum carnitine ($\beta = -0.263$, $P = 0.003$), β_2 -MG ($\beta = 0.296$, $P < 0.001$) and HD duration ($\beta = 0.239$, $P = 0.007$) were significantly correlated with skin AGE levels (Table 2). Because these significant parameters could be closely correlated with each other,

Table 1 Clinical characteristics of patients receiving haemodialysis

No. patients	129
Age (years)	68.2 ± 13.6
Sex (No.) (male/female)	75/54
Body mass index (kg/m ²)	21.8 ± 4.1
Systolic BP (mmHg)	151.9 ± 26.0
Diastolic BP (mmHg)	79.7 ± 15.8
Haemoglobin (g/dL)	10.6 ± 1.2
Albumin (g/dL)	3.62 ± 0.34
ALP (U/L)	273.2 ± 97.0
LDL-cholesterol (mg/dL)	70.5 ± 23.2
Triglycerides† (mg/dL) (range)	84.4 (31–537)
BUN (mg/dL)	59.8 ± 13.9
Serum Cr (mg/dL)	9.48 ± 2.2
Uric acid (mg/dL)	7.23 ± 1.08
Corrected Ca (mg/dL)	8.94 ± 0.55
P (mg/dL)	4.50 ± 0.98
Whole-PTH† (pg/mL) (range)	49.7 (12–473)
CRP† (mg/dL) (range)	0.23 (0.1–7.7)
β ₂ -MG (mg/l)	31.2 ± 0.7
Serum carnitine (μmol/l)	37.5 ± 10.6
HD duration (months)	98.7 ± 84.9
Kt/V† (range)	1.56 (0.93–2.30)
Skin AF (a.u.)	3.21 ± 0.81
Diabetes (No.) (–/+)	83/46
Medication	
RAS inhibitors (No.) (–/+)	52/77
Statins (No.) (–/+)	103/26

†These variables are shown in the original scale after using log-transformed values. Values are shown as mean ± SD or range. No., number. a.u., arbitrary units. β₂-MG, β₂-microglobulin; AF, autofluorescence; ALP, alkaline phosphatase; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; CRP, C-reactive protein; HD, haemodialysis; LDL, low-density lipoprotein; P, phosphate; PTH, parathyroid hormone; RAS, renin angiotensin system.

multiple regression analysis was performed. Multiple stepwise regression analysis revealed that serum carnitine ($\beta = -0.192$, $P = 0.024$), β₂-MG ($\beta = 0.248$, $P = 0.004$), HD duration ($\beta = 0.187$, $P = 0.027$) were independent determinants of skin AGE levels (Table 2). When mean AF levels stratified by serum carnitine levels were compared using analysis of covariance adjusted for β₂-MG, a linear and significant trend ($P = 0.043$) was observed (Fig. 1).

Correlates of serum carnitine

We next examined which clinical variables are independent determinants of serum carnitine in our subjects. Univariate analyses revealed that age ($\beta = -0.234$, $P = 0.008$), serum albumin ($\beta = 0.214$, $P = 0.015$), LDL-cholesterol ($\beta = 0.243$, $P = 0.006$), serum Cr ($\beta = 0.357$, $P < 0.001$), uric acid ($\beta = 0.342$, $P < 0.001$), skin AF ($\beta = -0.263$, $P = 0.003$), Kt/V ($\beta = -0.237$, $P = 0.007$) and the presence of DM ($\beta = -0.195$, $P = 0.027$) were significantly correlated with serum carnitine levels (Table 3). Multiple stepwise regression analysis showed that LDL-cholesterol ($\beta = 0.211$, $P = 0.006$), serum

Cr ($\beta = 0.257$, $P = 0.001$), uric acid ($\beta = 0.257$, $P = 0.001$), skin AF ($\beta = -0.194$, $P = 0.012$) and Kt/V ($\beta = -0.183$, $P = 0.016$) were independent determinants of serum carnitine levels in our patients (Table 3). When mean serum carnitine levels stratified by skin AF levels were compared using analysis of covariance adjusted for LDL-cholesterol, serum Cr and uric acid, a linear and significant trend ($P = 0.017$) was also observed (Fig. 2).

DISCUSSION

The salient findings of this study are (i) serum carnitine levels are significantly lower, whereas skin AGE levels are significantly higher in HD patients compared with healthy subjects; (ii) carnitine deficiency is significantly correlated with increased skin AGE levels, and serum carnitine levels are one of the independent determinants of tissue AGE levels in HD patients; (iii) tissue AGE levels evaluated by an AGE-reader are also one of the independent correlates of serum carnitine levels.

The present study was a cross-sectional and non-interventional one. So it did not elucidate the causal relationship between carnitine deficiency and accumulation of tissue AGE levels in HD patients. However, recent *in vitro* study has shown that L-carnitine significantly inhibits the AGE-modification of bovine serum albumin, and its anti-glycating capacity is more potent than that of aminoguanidine, a prototype inhibitor of AGE.^{18,21} Furthermore, administration of L-carnitine significantly reduced skin levels of glycated collagen and improved insulin resistance in fructose-fed rats.¹⁸ These observations suggest that decreased carnitine levels may promote the accumulation of tissue AGE in HD patients via oxidative stress generation and/or decreased insulin sensitivity. Carnitine deficiency, in concert with accumulation of AGE, may play a role in the progression of atherosclerosis in patients with HD.

In this study, we found that HD duration and serum β₂-MG levels were positively associated with skin AGE levels, which were independent of serum carnitine levels. There is accumulating evidence that AGE-modification of β₂-MG is involved in HD-related amyloidosis.^{22,23} Since skin AGE levels were an independent determinant of serum β₂-MG levels in our subjects as well (data not shown), the present observations suggest that skin AGE fluorescence and decreased carnitine levels may be a marker of β₂-MG-related amyloidosis in HD subjects.

In the present study, besides skin AF, LDL-cholesterol, serum Cr, uric acid and Kt/V were independently correlated with serum carnitine levels. Skeletal muscle is a major source of serum Cr, uric acid and carnitine levels in humans.¹⁴ Skeletal muscles mass are decreased in long-term HD patients.²⁴ Indeed, in the analysis, when mean serum carnitine levels were stratified by dry weight in analysis of covariance adjusted for age and sex, a linear and significant trend ($P = 0.008$) was observed. These findings suggest that

Table 2 Univariate and multiple stepwise regression analysis for the correlates of skin advanced glycation end products (AGE) levels

Variables	Univariate			Multiple stepwise regression		
	β	SE	P-value	β	SE	P-value
Age	0.143	0.005	0.107			
Sex	-0.082	0.145	0.357			
Systolic BP	0.075	0.003	0.400			
Haemoglobin	-0.112	0.061	0.208			
Albumin	-0.127	0.212	0.154			
LDL-cholesterol	0.148	0.003	0.094			
Serum Cr	-0.008	0.003	0.928			
Uric acid	0.162	0.001	0.067			
Corrected Ca	-0.009	0.131	0.916			
P	-0.095	0.074	0.287			
Whole-PTH†	-0.096	0.102	0.282			
CRP†	-0.082	0.068	0.355			
β_2-MG	0.296	0.009	<0.001	0.248	0.009	0.004
Serum carnitine	-0.263	0.007	0.003	-0.192	0.006	0.024
HD duration	0.239	0.001	0.007	0.187	0.001	0.027
Kt/V†	0.064	0.443	0.470			
DM	0.171	0.149	0.055			
RAS inhibitors	-0.012	0.146	0.893			
Statins	-0.001	0.179	0.991			

†These variables are shown in the original scale after using log-transformed values. $r^2 = 0.168$. β , standardized regression coefficients. SE, standard error. β_2 -MG, β_2 -microglobulin; BP, blood pressure; Ca, calcium; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HD, haemodialysis; LDL, low-density lipoprotein; P, phosphate; PTH, parathyroid hormone.

Table 3 Univariate and multiple stepwise regression analysis for the correlates of serum carnitine levels

Variables	Univariate			Multiple stepwise regression		
	β	SE	P-value	β	SE	P-value
Age	-0.234	0.067	0.008			
Sex	-0.115	1.884	0.195			
Systolic BP	0.005	0.036	0.055			
Haemoglobin	0.096	0.800	0.281			
Albumin	0.214	2.718	0.015			
LDL-cholesterol	0.243	0.039	0.006	0.211	0.097	0.006
Serum Cr	0.357	0.398	<0.001	0.257	0.374	0.001
Uric acid	0.342	0.819	<0.001	0.257	0.768	0.001
Corrected Ca	-0.083	1.704	0.352			
P	0.035	0.962	0.693			
Whole PTH†	0.053	1.330	0.552			
CRP†	-0.008	0.884	0.928			
β_2 -MG	-0.168	0.122	0.057			
HD duration	-0.158	0.011	0.074			
Kt/V†	-0.237	5.622	0.007	-0.183	4.900	0.016
Skin AF	-0.263	1.125	0.003	-0.194	0.999	0.012
DM	-0.195	1.937	0.027			
RAS inhibitors	-0.034	1.901	0.706			
Statins	0.070	2.326	0.429			

†These variables are shown in the original scale after using log-transformed values. $r^2 = 0.326$. β , standardized regression coefficients. SE, standard error. β_2 -MG, β_2 -microglobulin; AF, autofluorescence; BP, blood pressure; Ca, calcium; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HD, haemodialysis; LDL, low-density lipoprotein; P, phosphate; PTH, parathyroid hormone.

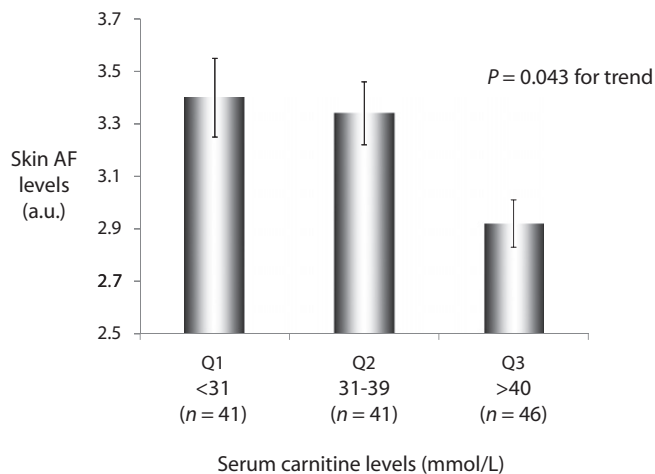


Fig. 1 β_2 -microglobulin (β_2 -MG)-adjusted mean autofluorescence (AF) levels stratified by tertiles of serum carnitine levels. A linear and significant trend ($P = 0.043$) was observed.

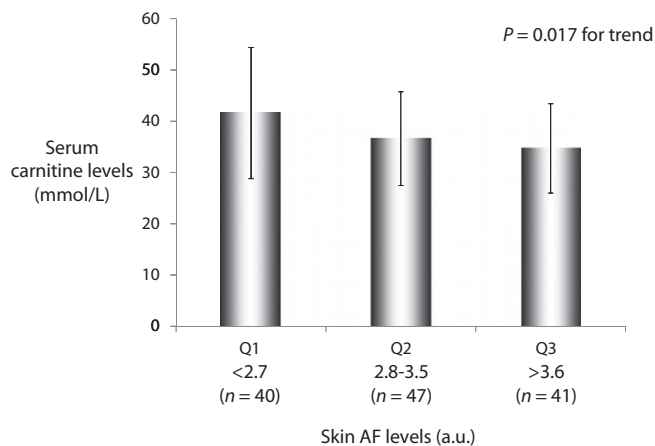


Fig. 2 Low-density lipoprotein (LDL)-cholesterol-, serum Cr- and uric acid-adjusted mean carnitine levels stratified by tertiles of skin autofluorescence (AF) levels. A linear and significant trend ($P = 0.017$) was observed.

the link between carnitine deficiency and decreased serum Cr and uric acid may be explained, at least in part, by skeletal muscle loss in our subjects. Increasing skeletal muscle mass by exercise may ameliorate carnitine deficiency and decrease tissue accumulate levels of AGE. Decreased appetite and/or restricted consumption of protein-rich foods have been reported to lead to carnitine deficiency, hypocholesterolemia and hypoalbuminemia in malnourished HD patients.²⁵

In this study, serum carnitine levels were positively associated with serum albumin and LDL-cholesterol levels. Therefore, although mean serum albumin levels of our cohort were reasonably good (3.6 g/dL), loss of appetite and/or some type of malnutrition may be involved in decreased carnitine levels in our subjects.

Unmeasured factors such as food intake of carnitine and/or glycotoxins could result in lower carnitine and higher

AGE fluorescence levels. Therefore, further longitudinal and/or interventional studies are needed to clarify whether carnitine supplementation could decrease tissue AGE levels and subsequently reduce the risk of future CVD in patients with HD.

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