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Original Article

Tissue level of advanced glycation end products is an independent determinant of high-sensitivity C-reactive protein levels in haemodialysis patients

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SUMMARY AT A GLANCE

This study demonstrates the association between tissue advanced glycation end products (AGE) level and high-sensitivity C-reactive protein (hsCRP) in haemodialysis patients. In addition, tissue AGE and hsCRP levels could in concert contribute to the progression of atherosclerosis in these subjects.

ABSTRACT:

Aim: **C-reactive protein (CRP) level predicts future cardiovascular events in patients on haemodialysis (HD). Advanced glycation end products (AGE) play a role in cardiovascular disease (CVD) in HD patients. However, which variables including tissue AGE levels are independently associated with CRP remains unknown. Therefore, whether tissue AGE and CRP levels were correlated with atherosclerosis in HD patients was examined.**

Methods: **Fifty-four HD patients underwent determinations of blood chemistries and tissue AGE. Tissue AGE levels were evaluated by measuring skin autofluorescence. Pulsatility index (PI) in the carotid artery was measured using a Doppler ultrasonography.**

Results: **Univariate analyses showed that age, white blood cells, serum albumin (inversely), alkaline phosphatase (inversely), tartrate-resistant acid phosphatase 5b (TRAP5b) (inversely) and skin AGE levels were significantly correlated with high-sensitivity CRP (hsCRP). Multiple stepwise regression analysis revealed that serum albumin, TRAP5b and skin AGE levels were independent determinants of hsCRP. Further, PI was highest among HD patients with high skin AGE and high hsCRP levels.**

Conclusion: **The present study suggests that tissue AGE level is one of the independent determinants of hsCRP in HD patients. Tissue AGE and hsCRP levels may be correlated with each other, which could in concert contribute to the progression of atherosclerosis in these subjects.**

Cardiovascular disease (CVD) is a major cause of morbidity and high mortality rates in patients on haemodialysis (HD).[1,2] Recently, chronic inflammation is shown to be involved in accelerated atherosclerosis, which could lead to increased risks of CVD in these high-risk patients.[3] Indeed, several epidemiological studies have shown that an inflammatory biomarker, C-reactive protein (CRP) level, is elevated in patients with HD, which predicts future cardiovascular events and death.[4] Although various metabolic and haemodynamic derangements are supposed to cause chronic inflammation in HD patients,[5–7] which factors are independently associated with CRP level is not fully understood, because these variables are correlated with each other and associated with inflammation.[8,9]

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).[10–12] Recently, 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 chronic kidney disease, thus playing a role in the development and progression of a CVD in these subjects.[13–18] Because AGE are reported to elicit oxidative stress generation and vascular inflammation in both cell culture and animal models, it is conceivable that accumulation of AGE is one of the causative factors for the elevation of CRP levels in patients with HD.

Many AGE form molecular cross-links and fluorescence *in vivo*.[19,20] Therefore, tissue AGE levels could be evaluated non-invasively by measuring skin autofluorescence (AF). Indeed, skin AF value has been shown to be associated with vascular complications in diabetes and predict cardiovascular mortality in patients with HD.[19,20] In this study, we investigated which anthropometric and metabolic variables, including tissue AGE levels which were evaluated quantitatively by measuring skin AF with an AGE reader, were independently associated with CRP in HD patients. We further examined whether tissue AGE and CRP levels were correlated with atherosclerosis in these subjects.

METHODS

Patients

Fifty-four consecutive outpatients on HD (32 men and 22 women; mean age 54.2 ± 14.0 years) underwent a complete history and physical examination, determinations of blood chemistries, anthropometric and metabolic variables. Mean duration of HD was 7.9 ± 5.1 years. Patients were dialyzed for 5 h with high-flux dialyzers three times a week. Nine patients had diabetes mellitus (DM). Thirteen patients had angiographically proven CVD and/or a history of coronary heart disease. The remainders had no history of CVD. Forty-one patients received inhibitors of the renin–angiotensin system, and only two patients received statins for the treatment of dyslipidaemia. We excluded any patients with inflammatory, neoplastic disorders and those who had a recent (<3 months) acute coronary syndrome, stroke and any acute infection.

Data collection

The medical history was ascertained by a questionnaire. Height and weight were measured, and body mass index (BMI) (kg/m^2) was calculated as an index of presence or absence of obesity. Blood pressure (BP) was measured in the sitting position using an upright standard sphygmomanometer. 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 for determinations of lipids (total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides), haemoglobin, haemoglobin A1c (HbA1c), albumin, blood urea nitrogen (BUN), creatinine (Cr), uric acid, Ca, P and Fe. Intact parathyroid hormone (PTH) was evaluated by an immunoradiometric assay (IRMA, Allegro Intact PTH; Nichols Institute, San Juan Capistrano, CA, USA). Tartrate-resistant acid phosphatase 5b (TRAP5b) activity, a bone resorption marker unaffected by renal function, was measured by a novel fragment-absorbed immunocapture enzymatic assay (FAICEA) as described previously.[21] High-sensitivity CRP (hsCRP) was measured with nephelometry (N-Latex, CRPII; Dade Behring, Tokyo, Japan). The other 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).[22] Single-pool Kt/V was calculated by the following formula:

$$\mathrm{Kt/V} = -\ln(\mathrm{Ce/Cs} - 0.008 \times \mathrm{t}) + (4 - 3.5 \times \mathrm{Ce/Cs}) \times \Delta\mathrm{BW/BW} \quad (1)$$

where Ce/Ce is post-serum/pre-serum urea nitrogen ratio, t is dialysis time, ΔBW/BW is the ratio of the ultrafiltrate volume removed from the post-dialysis weight and ln is a natural logarithmic (ln) transformation.

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

Pulsatility index (PI) in the carotid artery, a surrogate marker of atherosclerosis, was evaluated by high-resolution ultrasonography with a 7.5 MHz linear probe (GE Yokogawa Medical Systems, Tokyo, Japan). Common carotid PI was measured as a reflection of impedance to flow distal to the point of sampling.[23] PI was automatically calculated and indicated as ((peak systolic velocity) − (end diastolic velocity)) / mean flow velocity.

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).[20]

Statistical analysis

Results are presented as mean ± standard deviation (SD). The medications for hypertension and dyslipidaemia (renin–angiotensin system (RAS) inhibitors and statins) and the presence or absence of DM were coded as dummy variables. Because of their skewed distributions, a natural logarithmic (ln) transformation was performed for hsCRP. Univariate analysis was performed for determinants of hsCRP. To determine independent determinants of hsCRP and tissue AGE, multiple stepwise regression analysis was performed. PI levels stratified by tissue AGE and hsCRP levels were compared using unpaired Student's *t*-test. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with SPSS software (SPSS, Chicago, IL, USA).

RESULTS

Demographic data are shown in Table 1. Univariate analyses showed that age ($\beta = 0.298$, $P = 0.03$), white blood cells (WBC) ($\beta = 0.294$, $P = 0.03$), serum albumin ($\beta = -0.506$, $P < 0.001$), alkaline phosphatase (ALP) ($\beta = -0.275$, $P = 0.04$), TRAP5b ($\beta = -0.412$, $P = 0.002$) and skin AGE levels ($\beta = 0.378$, $P = 0.005$) were significantly correlated with serum levels of hsCRP (Table 2). Because these significant parameters could be closely correlated with each other, multiple regression analysis was performed. Multiple stepwise regression analysis revealed that serum albumin ($\beta = -0.431$, $P < 0.001$), TRAP5b ($\beta = -0.390$, $P < 0.001$) and skin AGE levels ($\beta = 0.308$, $P = 0.004$) were independent determinants of hsCRP (Table 2). We also found that the presence of DM ($\beta = 0.385$, $P = 0.002$) and hsCRP ($\beta = 0.379$, $P = 0.002$) were independently associated with skin AGE levels in our subjects.

Further, we found that hsCRP was significantly correlated with PI ($\beta = 0.396$, $P = 0.003$) and that hsCRP was one of the independent determinants of PI in our patients ($R^2 = 0.311$, $P = 0.009$).

Table 1 Clinical characteristics of the patients

No. of patients	54
Age (years)	54.2 ± 14.0
Sex (*n*) (male/female)	32/22
Body mass index (kg/m^2)	20.8 ± 3.53
Systolic blood pressure (mmHg)	134.0 ± 21.1
Diastolic blood pressure (mmHg)	80.0 ± 12.2
Haemoglobin (g/dL)	11.4 ± 1.25
Albumin (g/dL)	3.60 ± 0.35
BUN (mg/dL)	59.9 ± 11.1
Serum Cr (mg/dL)	11.2 ± 2.36
Uric acid (mg/dL)	7.40 ± 1.08
Ca (mg/dL)	9.53 ± 0.86
P (mg/dL)	5.45 ± 1.11
Fe (mg/dL)	66.8 ± 22.7
Total cholesterol (mg/dL)	159.5 ± 34.9
LDL cholesterol (mg/dL)	82.1 ± 28.1
Triglycerides (mg/dL)	127.6 ± 94.9
ALP (U/L)	17.9 ± 9.32
Intact PTH (pg/mL)	71.8 ± 52.0
TRAP5b (U/L)	384.2 ± 175.3
Log hsCRP	2.89 ± 0.72
HbA1c (%)	5.09 ± 0.87
Diabetes (*n*) (–/+)	45/9
PI	2.04 ± 0.73
HD duration (years)	7.9 ± 5.1
Kt/V	1.77 ± 0.33
Skin AGE (a.u.)	2.84 ± 0.71
Medication	
RAS inhibitors (*n*) (–/+)	13/41
Statins (*n*) (–/+)	52/2

Values are shown as mean ± standard deviation. AGE, advanced glycation end products; ALP, alkaline phosphatase; a.u., arbitrary units; BUN, blood urea nitrogen; HbA1c, haemoglobin A1c; HD, haemodialysis; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PI, pulsatility index; PTH, parathyroid hormone; RAS, renin–angiotensin system; TRAP5b, tartrate-resistant acid phosphatase 5b.

Then, in order to examine the relationships among skin AGE, hsCRP and carotid PI, we divided the study participants into four groups according to their AGE (low AGE, ≤2.84; high AGE, >2.85) and hsCRP (low hsCRP, log ≤2.42; high hsCRP, log >2.43) levels. As shown in Figure 1, carotid PI was found to be highest among HD patients with high skin AGE and high hsCRP levels.

DISCUSSION

The salient findings of this study are: (i) tissue AGE levels evaluated by skin AF with a specific AGE reader is one of the independent determinants of hsCRP levels in HD patients; (ii) besides the presence of DM, hsCRP is a sole determinant of skin AGE levels; and (iii) carotid PI, a surrogate marker of atherosclerosis, is highest among HD patients with high tissue AGE and high hsCRP levels. Therefore, our present study suggests that: (i) tissue accumulation of AGE might be one of the causative factors for the elevation of hsCRP in HD patients; and (ii) tissue AGE and CRP are correlated with each other, both of which could in concert contribute to the progression of atherosclerosis in patients with HD.

In this study, we evaluated tissue AGE levels by measuring skin AF because: (i) measurement of skin AF with a commercially available AGE reader is a non-invasive, reliable and time-saving method to estimate tissue accumulation of AGE;[3] (ii) skin AF values are reported to significantly correlate with skin AGE levels evaluated by high-performance liquid chromatography (HPLC) in both diabetic and non-diabetic subjects;[20] and (iii) skin AF was positively associated with the severity of vascular complications in patients with both type 1 and type 2 diabetes mellitus and a predictor of future cardiovascular events and death in patients with HD.[19,20] Skin AF levels in our HD patients were 2.84 ± 0.71, whose value was 1.6-fold higher than that in age- and sex-matched Japanese controls.[24] The results were consistent with the previous findings of Arsov *et al*., who showed that skin AF values were increased by approximately 1.4-fold in HD patients compared with controls.[25] These observations further support the concept that measurement of skin AF with an AGE reader is a reliable diagnostic tool to evaluate tissue AGE accumulation in HD patients.

This study was cross-sectional one and thus could not assess the questions of whether elevation of tissue AGE level was a cause or consequence of chronic inflammation. However, we have previously shown that AGE could induce CRP production by hepatoma cells through oxidative stress and inflammatory reactions.[26] Further, inflammation is shown to cause oxidative stress generation, which could lead to promotion of the formation and accumulation of AGE.[16] These observations suggest that decreased renal clearance of AGE in HD patients could contribute to enhanced tissue accumulation of AGE and subsequently evoke inflammatory reactions, which may in turn further stimulate the formation and accumulation of AGE. In other words, AGE accumulation and inflammatory reactions may be correlated with each other in patients with HD, which could account for the positive correlations between skin AF and hsCRP levels in our subjects. Tan *et al*.[27] reported that serum AGE levels were independently associated with CRP in patients with type 2 diabetes as well.

In the present study, PI, a surrogate marker of atherosclerosis, which reflects the degree of vascular resistance,[25,28] is highest among HD patients with high skin AGE and high hsCRP levels. Nakatou *et al*. have demonstrated that the PI is significantly correlated with the atherosclerosis risk score and the existence of cerebral infarction in diabetic patients.[28] There is a growing body of evidence that AGE could elicit vascular inflammation and thrombogenesis, playing a central role in atherosclerosis. Further, recently, CRP has been shown to evoke endothelial cell damage, pro-inflammatory reactions and smooth muscle cell proliferation, thereby being involved in the pathogenesis of CVD as well. An enhanced positive feedback loop between tissue AGE accumulation and CRP induction as described above could in concert contribute to the development and progression of atherosclerosis-

Table 2 Univariate and multiple stepwise regression analysis for the correlates of log hsCRP

Variables	Univariate			Multiple stepwise regression		
	β	SE	*P*-value	β	SE	*P*-value
Age	**0.298**	**0.007**	**0.029**			
Sex	0.033	0.2	0.811			
Systolic BP	0.1	0.005	0.471			
WBC	**0.294**	**0**	**0.031**			
Haemoglobin	–0.183	0.078	0.185			
ALP	**–0.275**	**0.01**	**0.044**			
Albumin	**–0.506**	**0.244**	**<0.001**	**–0.431**	**0.208**	**<0.001**
BUN	0.041	0.009	0.771			
Uric acid	0.054	0.092	0.697			
Total cholesterol	0.105	0.003	0.456			
LDL cholesterol	0.124	0.004	0.377			
Intact PTH	–0.139	0.001	0.315			
TRAP5b	**–0.412**	**0.001**	**0.002**	**–0.39**	**0**	**<0.001**
Skin AGE	**0.378**	**0.13**	**0.005**	**0.308**	**0.103**	**0.004**
Kt/V	–0.146	0.296	0.293			
DM	–0.002	0.264	0.991			
CVD	0.188	0.226	0.174			

Bolded text indicates statistically significant values. β, standardized regression coefficients. $r^2 = 0.495$. ALP, alkaline phosphatase; BP, blood pressure; BUN, blood urea nitrogen; CVD, cardiovascular disease; DM, diabetes mellitus; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase 5b; SE, standard error; WBC, white blood cell.

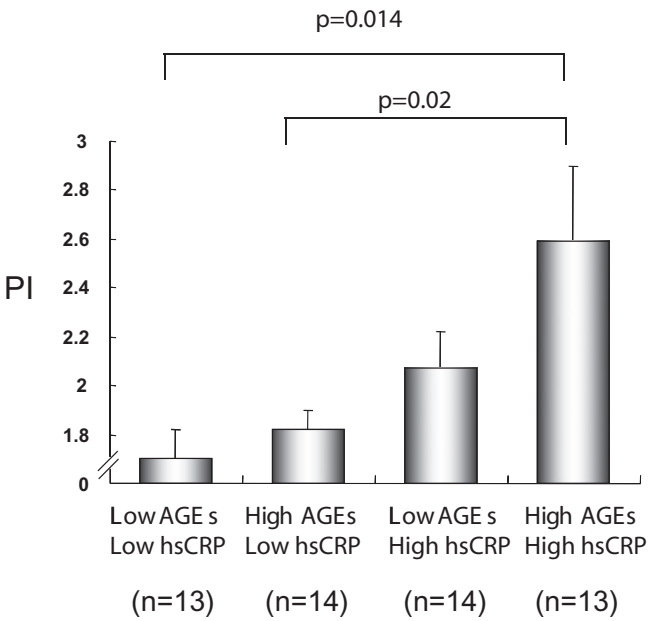

Fig. 1 Relationships among skin AGE, hsCRP and carotid PI in HD patients. AGE, advanced glycation end products; hsCRP, high-sensitivity C-reactive protein; PI, pulsatility index.

rosis in HD patients. However, it should be noted that Mulder *et al*. reported that skin AF values were elevated in patients with stable coronary artery disease, but not correlated with CRP levels.[29] We did not know the exact reasons for the discrepant results between ours and theirs. The difference of subject population and ethnicity could account for the discrepancy.

In this study, low serum albumin and TRAP5b levels were also independently correlated with hsCRP. There is accumulating evidence to show that malnutrition is involved in inflammation and atherosclerosis in chronic kidney disease patients.[30] Further, chronic inflammation is shown to impair bone turnover in HD patients.[31] The findings suggest that low serum albumin and low TRAP5b levels could reflect malnutrition and impaired bone turnover in our patients, respectively, which could explain the link between high hsCRP and low serum albumin or TRAP5b levels.

The study was a cross-sectional non-intervention one. Therefore, it did not elucidate the causative relationships between tissue AGE and hsCRP levels. However, as described above, AGE are reported to stimulate CRP production by the liver *in vitro*.[28] So, it is conceivable that tissue AGE accumulation could be one of the causative factors for the elevation of hsCRP in HD patients. Tissue AGE accumulation and hsCRP elevation may act in concert to promote atherosclerosis in these patients. Longitudinal and/or interventional studies are needed to clarify whether suppression of AGE formation could decrease tissue AGE and hsCRP levels and subsequently reduce the risk of future cardiovascular events in HD patients.

In this study, we measured tissue AGE levels by evaluating skin AF with an AGE reader. However, we have to say that there are some limitations of this method: (i) not only tissue AGE, but also other fluorescent contents of skin are measured with this method; (ii) some AGE are not fluorescent; and (iii) the measurement could be influenced by skin abnormalities.[32]

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