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Research Article

Relations between Skin Autofluorescence and Hemorheology Assessed by a Microchannel Method in Patients with Traditional Cardiovascular Risk Factors

Abstract

Aim: In recent years, skin autofluorescence (AF), a marker of tissue accumulation of advanced glycation end products, and hemorheology assessed by a microchannel method have been noted for their significance in detecting cardiovascular risk factors. However, there have been no reports regarding the relation between these two biomarkers. The present study attempts to clarify the relation and background factors of these two biomarkers in patients with traditional cardiovascular risk factors.

Methods: A total of 807 outpatients with traditional cardiovascular risk factors (306 males and 501 females; mean age: 64 ± 11 years) and no history of cardiovascular events were enrolled in this study. Skin AF and whole blood passage time (WBPT) as a marker of hemorheology were measured using a commercial device, and the relations among various clinical parameters, including that between skin AF and WBPT, were examined.

Results: There was a significantly positive correlation between skin AF and WBPT ($r = 0.41$, $p < 0.001$). Furthermore, multiple regression analysis revealed that these two markers showed a significant correlation ($p < 0.01$). Furthermore, derivatives of the reactive oxygen metabolites test, an oxidative stress marker, the cardio-ankle vascular index, an arterial function marker, smoking habits, and a number of traditional cardiovascular risk factors in an individual were also selected as independent variables for both skin AF and WBPT.

Conclusion: The results of this study indicated the significant relation between skin AF and hemorheology assessed by a microchannel method in patients with traditional cardiovascular risk factors. In addition, oxidative stress, arterial dysfunction, smoking habits, and a clustering of traditional cardiovascular risk factors were associated with these two biomarkers.

Abreviations

AGEs: Advanced glycation end products, AF: Autofluorescence, MC-FAN: Micro Channel Array Flow Analyzer, WBPT: Whole blood passage time, eGFR: Estimated glomerular filtration rate, hs-CRP: high-sensitivity C-reactive protein, d-ROMs: Derivatives of reactive oxygen metabolites, CAVI: Cardio-ankle vascular index, PWV: Pulse wave velocity.

Introduction

Cardiovascular risk management in outpatients is mainly based on the treatment of traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity and smoking habits. In fact, these risk factors are most commonly used to assess cardiovascular risk in clinical practice. Although these risk factors are very important predictors of cardiovascular events, they do not always explain all these events [1]. Therefore, exploring novel biomarker of cardiovascular diseases, in addition to traditional risk factors, is needed for further prevention of cardiovascular events.

Advanced glycation end products (AGEs) play an important role in various diseases, such as diabetic complications, renal dysfunction, or cardiovascular diseases [2,3]. In recent years, simpler methods of detecting AGE accumulation at the volar side of the arm, such as skin autofluorescence (AF), have been explored and used in clinical settings [4]. Skin AF is known

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to be a more reliable marker of tissue AGE levels in vivo than serum AGEs. In fact, some clinical studies have indicated that an increase in skin AF is significantly associated with the development of a range of kidney dysfunctions or vascular complications [5,6].

Impairment of blood rheology has also been reported as an important factor for the incidence of cardiovascular diseases as well as atherosclerosis [7]. Recently, a commercial device that evaluates hemorheology [Micro Channel Array Flow Analyzer (MC-FAN)] using microscopic images has been explored and is being used in clinical settings [8]. MC-FAN is easier to use and is superior to other methods in terms of accuracy of channel dimensions and reproducibility. Furthermore, clinical studies have established the usefulness of whole blood passage time (WBPT), which is measured by MC-FAN, in evaluating cardiovascular disease risk factors [9-12].

Thus, skin AF and WBPT are considered novel risk factors of cardiovascular diseases. However, to the best of our knowledge, there have been no reports regarding the relation between skin AF and WBPT. Therefore, this study aims to clarify this relation in patients with traditional cardiovascular risk factors from the perspective of primary cardiovascular events. This study also examines the background factors of these two markers.

Materials and Methods

Subjects

This cross-sectional study was conducted at the Hitsumoto Medical Clinic in Shimonoseki City from June 2014 to May 2016. The study population comprised outpatients with risk factors of cardiovascular diseases such as hypertension, type 2 diabetes mellitus, dyslipidemia, obesity and smoking habits. None of the patients had a history of cardiovascular events, such as ischemic heart disease, stroke, and perivascular disease. The group of patients with cardiovascular risk factors comprised 306 men and 501 women with a mean age of 64 ± 11 years. All participants provided informed consent, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki as reflected by the a priori approval of the Local Ethics Committee.

Measurement of skin AF

Skin AF was measured using a commercial instrument (AGE Reader™; DiagnOptics, Groningen, Netherlands), as described previously [13,14]. Briefly, AF was defined as the average light intensity per nanometer between 300 and 420 nm. Levels of skin AF were expressed in arbitrary units (AU). With patients seated, all measurements were taken at the volar side of the lower arm, approximately 10–15 cm below the elbow. The validity and reliability of skin AF levels measured using this method in a Japanese population have been previously established [6,14].

Evaluation of hemorheology using MC-FAN

The evaluation of hemorheology was performed by measuring WBPT using an MC-FAN HR300 rheometer (MC Healthcare Inc., Tokyo) as previously reported [8]. Briefly, the microchannel passage time for 100 µL of physiologic saline was first measured as control. Then, the same measurement was determined for blood obtained from subjects with 100 µL of the heparinization sample. WBPT of the subjects was expressed after correcting for the passage time of physiologic saline. The microchannel formation had a width, length, and depth of 7, 30, and 4.5 µm, respectively. Examination was performed within 60 min of blood sampling. Inter- and intra-assay coefficients of variation for BPT were 8% and 5%, respectively.

Evaluation of cardiovascular risk factors

The degree of obesity was estimated from the body mass index, which was calculated as the weight in kilograms divided by the square of the height in meters; obesity was defined as a Japanese criteria (body mass index ≥25 kg/m2). Current smoking was defined as smoking at least one cigarette per day during the previous 28 days. Hypertension was defined as a systolic blood pressure greater than or equal to 140 mmHg, a diastolic blood pressure greater than or equal to 90 mmHg, or the use of anti-hypertensive medication. Diabetes mellitus was defined as a fasting blood glucose level greater than or equal to 126 mg/dL or the use of anti-diabetic medication. Dyslipidemia was defined as a low-density lipoprotein cholesterol level greater than or equal to 140 mg/dL, a high-density lipoprotein cholesterol level less than or equal to 40 mg/dL, a triglyceride level greater than or equal to 150 mg/dL, or the use of anti-dyslipidemic medication. The following blood parameters were measured: blood cell counts, plasma glucose, plasma insulin, serum lipid concentrations, estimated glomerular filtration rate (eGFR), serum high-sensitivity C-reactive protein (hs-CRP) concentrations, and derivatives of reactive oxygen metabolites (d-ROMs). Blood samples were collected from the antecubital vein in the morning after 12 h of fasting. Glucose and insulin concentrations were measured using the glucose oxidase method and an enzyme immunoassay, respectively. To measure insulin resistance, HOMA-IR was calculated as follows [15]: HOMA-IR = fasting glucose concentration (mg/dL) × fasting insulin concentration (µg/mL)/405. Total cholesterol and triglyceride concentrations were measured using standard enzymatic methods. High- and low-density lipoprotein cholesterol concentrations were measured using selective inhibition and Friedewald's formula, respectively [16]. Subjects with a serum triglyceride concentration ≥400 mg/dL were excluded considering the accuracy of this method. eGFR was calculated using the adjusted Modification of Diet in Renal Disease Study equation, proposed by the working group of the Japanese Chronic Kidney Disease Initiative [17]. The hs-CRP concentration was measured using high-sensitivity latex-enhanced immunonephelometrics, and inter- and intra-assay coefficients of variability has been shown to be less than 2%. The d-ROMs test, which reflects hydroperoxide levels, was measured as an oxidative stress marker in vivo using a commercial device (Diacron, Grosseto, Italy) [18].

Evaluation of arterial function

The cardio-ankle vascular index (CAVI) was measured as an arterial function marker using a VaSera CAVI instrument (Fukuda Denshi Inc., Tokyo, Japan) according to the previously

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described methods [19]. Briefly, the brachial and ankle pulse waves were determined using inflatable cuffs with the pressure maintained between 30 and 50 mmHg to ensure that the cuff pressure had a minimal effect on the systemic hemodynamics. Blood and pulse pressures were simultaneously determined, and the measurements were obtained with the subject in a supine position. CAVI was measured after the subject rested for 10 min in a quiet room. The average coefficient of variation in CAVI has been shown to be less than 5%, which is small enough for clinical use and indicates that CAVI measurement has good reproducibility.

Statistical analysis

A commercially available statistical software program (StatView-J 5.0; Hulinks Inc., Tokyo, Japan) was used for all statistical analyses. Continuous variables were expressed as mean ± standard deviation. Between-group comparisons were performed using the Student's t test or Mann–Whitney's U test. Simple regression analysis was estimated using Spearman's rank correlation analysis, while multivariate analysis was performed using multiple regression analysis. A p value of <0.05 was considered significant.

Results

Baseline clinical characteristics are shown in table 1, while the histograms of skin AF and WBPT are shown in figure 1. The mean value of skin AF was 2.5 ± 0.5 AU, ranging from 1.2 to 4.1 AU, with a median value of 2.5 AU. On the other hand, the mean value of WBPT was 60.7 ± 16.8 s, ranging from 31.1 to 113.5 s, with a median value of 58.3 s. These two parameters indicated nearly normal distribution. Correlations among skin AF, WBPT, and various clinical parameters are shown in table 2. Age, smoking habits, presence of diabetes mellitus, fasting blood glucose levels, insulin levels, HOMA-IR, a number of traditional cardiovascular risk factors, eGFR, hs-CRP, d-ROMs test, CAVI, and WBPT were significantly correlated with skin AF. On the other hand, sex differences, body mass index, smoking habits, white and red blood cell counts, hematocrit, serum triglyceride concentration, fasting blood glucose levels, insulin levels, HOMA-IR, a number of traditional cardiovascular risk factors, eGFR, hs-CRP, d-ROMs test, CAVI, and skin AF were significantly correlated with WBPT.

Multiple regression analysis for skin AF or WBPT as a subordinate factor was performed with explanatory variables that were significant during univariate analysis. WBPT, d-ROMs test, a number of traditional cardiovascular risk factors, CAVI, smoking habits, and age were selected as independent variables for skin AF. On the other hand, skin AF, a number of traditional cardiovascular risk factors, CAVI, d-ROMs test, smoking habits, and hematocrit were selected as independent variables for WBPT (Table 3).

Discussion

This study aimed to clarify the relation between skin AF, which reflects tissue accumulation of AGEs, and WBPT, a marker of hemorheology assessed by microchannel methods, in patients with traditional cardiovascular risk factors from the viewpoint of primary cardiovascular events. Results of the multivariate analysis showed a significant relation between skin AF and WBPT. In addition, oxidative stress, arterial function, smoking habits, and a number of traditional cardiovascular risk factors in an individual were significantly related with these two biomarkers.

Hemorheology estimated using MC-FAN is an in vitro study that uses artificial blood vessels, with the vessel lumen having a width and depth of 7 and 4.5 μm, respectively. Therefore, the lumen and capillary have similar sizes. On the other hand, levels of pentosidine, which is a major component of AGEs,

Table 1: Baseline clinical characteristics.

n	807
Sex (male/female)	306/501
Age (yrs)	64±11
Obesity (%)	213 (26)
Body mass index	23.2±3.8
Smoking (%)	167 (21)
Hypertension (%)	617 (77)
Systolic blood pressure (mmHg)	147±16
Diastolic blood pressure (mmHg)	86±12
White blood cell (/μl)	6580±1400
Red blood cell (104/μl)	426±43
Hematocrit (%)	38.4±4.1
Platelet (104/μl)	22.0±6.2
Diabetes mellitus (%)	299 (37)
Fasting blood glucose (mg/dl)	114±25
IRI (μg/ml)	7.3±4.4
HOMA-IR	2.1±1.4
Dyslipidemia (%)	566 (70)
Total cholesterol (mg/dl)	213±39
LDL-cholesterol (mg/dl)	134±37
Triglyceride (mg/dl)	119±65
HDL-cholesterol (mg/dl)	55±16
Number of risk factors	2.3±1.0
eGFR (ml/min/1.73m2)	65±12
log-hs-CRP (mg/L)	-1.2±06
d-ROMs test (U.Carr)	338±93
CAVI	9.2±1.3
Skin AF (AU)	2.5±0.5
WBPT (sec)	60.7±16.8
Medication	
RAS inhibitor, n (%)	322 (40)
DPP-4 inhibitor, n (%)	102 (13)
Statin, n (%)	366 (45)

Continuous values are mean±SD. IRI=immunoreactive insulin, HOMA-IR=homeostasis assessment insulin resistance, LDL=low-density lipoprotein, HDL=high-density lipoprotein, Risk factors=Obesity, Smoking, Hyprtension, Diabetes mellitus, Dyslipidemia, eGFR=estimated glomerular filtration rate, hs-CRP=high sensitivity C reactive protein, d-ROMs=derivatives of reactive oxygen metabolites, CAVI= cardio-ankle vascular index, AF= autofluorescence, WBPT=whole blood passage time, RAS= renin-angiotensin system, DPP=dipeptidyl peptidase.

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were measured at the volar side of the lower arm by skin biopsy and appeared to correlate with skin AF [20]. Capillary

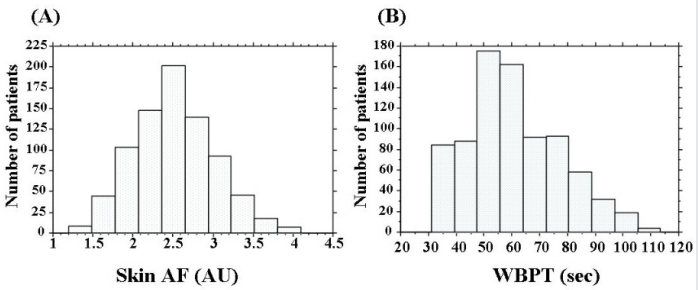

Figure 1: Histogram of skin AF and WBPT.
(A) The mean value of skin AF was 2.5 ± 0.5 AU, ranging from 1.2 to 4.1AU. The median value of skin AF was 2.5AU.
(B)The mean value of WBPT was 60.7 ± 16.8 sec, ranging from 31.1 to 113.5sec. The median value of WBPT was 58.3sec.
AF=autofluorescence, WBPT=whole blood passage time.

Table 2: Correlation between Skin AF, WBPT and various clinical parameters.

	Skin AF	WBPT
	r	r
Sex (Female=0, Male=1)	0.02	0.11**
	0.11**	0.06
Body mass index	0.07	0.09***
Obesity	0.06	0.10**
Smoking (No=0, Yes=1)	0.13*	0.17*
Hypertension (No=0, Yes=1)	0.06	0.01
Systolic BP	0.07	0.04
Diastolic BP	0.05	0.01
White blood cell	0.04	0.14*
Red blood cell	0.03	0.15*
Hematocrit	0.01	0.20*
Platelet	0.04	0.03
Diabetes mellitus (No=0, Yes=1)	0.11**	0.07
FBG	0.11**	0.10**
IRI	0.08***	0.08***
Log-HOMA-IR	0.10**	0.09***
Dyslipidemia (No=0, Yes=1)	-0.08	-0.02
Total cholesterol	0.07	0.06
LDL cholesterol	0.05	0.05
Triglyceride	0.05	0.13**
HDL cholesterol	-0.03	-0.04
Number of risk factors	0.43*	0.42*
eGFR	-0.13*	-0.12*
Log-hsCRP	0.11**	0.18*
d-ROMs test	0.35*	0.30*
CAVI	0.27*	0.34*
Skin AF	-	0.41*
WBPT	0.41*	-
RAS inhibitor (No=0, Yes=1)	-0.06	-0.05
DPP-4 inhibitor (No=0, Yes=1)	-0.06	-0.05
Statin (No=0, Yes=1)	-0.03	-0.04

r expressed correlation coefficient.
*p<0.001, **p<0.01, ***p<0.05,
Abbreviations as in Table 1.

Table 3: Multiple regression analysis.

Dependent variable		β	t value	p value
(A)	WBPT	0.29	8.4	<0.001
	Number of risk factors	0.26	7.7	<0.001
	d-ROMs test	0.24	7.3	<0.001
	CAVI	0.11	3.0	<0.01
	Smoking	0.07	2.1	<0.05
	Age	0.06	2.0	<0.05
	HOMA-IR	0.05	1.7	0.073
	Diabetes	0.04	1.2	0.212
	Log-hs-CRP	0.03	1.1	0.234
	Fasting blood glucose	0.03	1.0	0.701
	eGFR	-0.04	-1.2	0.220
	IRI	-0.07	-1.4	0.198
(B)	Skin AF	0.27	8.1	<0.001
	Number of risk factors	0.26	7.8	<0.001
	CAVI	0.23	7.1	<0.001
	d-ROMs test	0.13	4.0	<0.001
	Smoking	0.10	2.9	<0.01
	Hematocrit	0.08	2.3	<0.05
	Fasting blood glucose	0.07	1.9	0.052
	White blood cell	0.06	1.9	0.063
	Red blood cell	0.06	1.8	0.079
	Triglyceride	0.06	1.7	0.081
	Body mass index	0.05	1.6	0.096
	Obesity	0.05	1.6	0.099
	Log-hs-CRP	0.05	1.6	0.102
	Sex	0.04	1.6	0.113
	HOMA-IR	0.01	0.2	0.903
	IRI	-0.01	-0.2	0.910
	eGFR	-0.04	-1.5	0.201

(A) Subordinate factor is Skin AF. R2=0.27, F=27.9, p<0.001
(B) Subordinate factor is WBPT. R2=0.30, F=28.3, p<0.001
Abbreviations as in Table 1.

vessels are considered to be present in the area of skin biopsy. Therefore, a significant relation between skin AF and WBPT could possibly reflect the accumulation of AGEs in tissues through impairment of blood rheology within the capillaries. On the other hand, some basic studies have reported that AGEs influence hemorheology through mechanisms such as leukocyte–endothelial interaction or platelet aggregation [21,22]. Furthermore, skin AF has been reported to reflect various organ damages or accumulation of AGEs, including the coronary or carotid arteries, kidneys, retinas, neurons, and cardiomyocyte cells [5,6,23,24]. Thus, the results of this and previous studies indicate that AGEs are associated with the impairment of hemorheology not only at the volar side of the lower arm but also in various organs, consequently causing systemic organ damage. In addition, we can predict systemic organ damage by measuring skin AF and WBPT.

Several studies have indicated that oxidative stress contributes to the incidence of cardiovascular diseases. In this

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study, the d-ROMs test, a marker of oxidative stress in vivo, was significantly correlated with WBPT and skin AF by multivariate analysis. Several mechanisms, via oxidative stress, cause impairment of blood rheology, such as platelet aggregation and elevation of plasma viscosity [25,26]. In addition, several studies have reported significant relations among oxidative stress, AGEs, and receptors of AGEs [27]. In contrast, anti-diabetic, anti-hypertensive, or anti-hyperlipidemic drugs have been reported to decrease oxidative stress in vivo [28-30]. Furthermore, some researchers have reported the clinical usefulness of these drugs in improving AGE levels, receptors of AGEs, or hemorheology [31-33]. The results of this cross-sectional study indicated no significant relation between medications, such as renin–angiotensin system inhibitors, dipeptidyl peptidase-4 inhibitors, or statins, and WBPT or skin AF. However, interventional studies are warranted to examine their effectiveness on novel cardiovascular risk factors, such as d-ROMs test, skin AF, and WBPT. Consequently, we expect to discover new applications for these drugs.

CAVI is known to be a novel marker of arterial stiffness, which is independently associated with blood pressure levels [19]. On the other hand, some clinical studies have indicated the relation between skin AF or impairment of blood rheology and arterial stiffness using pulse wave velocity (PWV). Mac-Way et al. reported that skin AF is significantly related with carotid-femoral PWV [34]. Satoh et al. reported the relation between WBPT and stiffness of the aortic artery using PWV in patients with obesity [9]. Other clinical studies have reported that CAVI is indicative of endothelial dysfunction [35]. In addition, some clinical studies have indicated the significant relation between skin AF or increased WBPT and endothelial dysfunction [12,36]. Thus, both skin AF and WBPT reflect arterial function, such as arterial stiffness or endothelial function, which may consequently predict the incidence of cardiovascular events.

It is well known that smoking habits affect AGE levels or blood rheology. Some clinical studies have indicated the relation between smoking habits and skin AF or WBPT [11,37,38]. The results of the present study also indicated that smoking is an independent factor for determining skin AF or WBPT. Smoking has also been known to affect oxidative stress or CAVI [39]. Thus, smoking cessation is strongly recommended to prevent primary cardiovascular events considering various parameters including skin AF and WBPT.

Patients with just one cardiovascular risk factor will not always have a cardiovascular event. Patients with multiple risk factors are most likely to have a problem [40]. In the present study, clustering of traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity was significantly correlated with both skin AF and WBPT, even though each parameter was weakly correlated with these two markers. Thus, the results of this study suggest that control of each traditional cardiovascular risk factor in daily practice is important for novel cardiovascular risk factors such as skin AF and WBPT. Furthermore, estimation of WBPT and skin AF are expected to increase the reliability of prediction of cardiovascular disease in patients with traditional cardiovascular risk factors.

This study has several limitations. First, the medical treatments for hypertension, diabetes mellitus, and/or dyslipidemia may have influenced the study results. Second, this was a single-center cross-sectional study with a relatively small population. A prospective study involving a larger number of patients is necessary to confirm the effectiveness of the therapies such as anti-oxidant administration or smoking cessation in improving skin AF levels or blood rheology, as estimated using AGE Reader or MC-FAN. Third, hemorheology estimated using MC-FAN is an in vitro study that uses artificial blood vessels; therefore, the obtained hemorheological data were different from those obtained in vivo because of the influence of vascular factors such as endothelial cells or smooth muscle cells. Furthermore, evaluation of MC-FAN is simple method compared to Coulter-Harkness viscometer. However, the results of this and previous studies indicate that MC-FAN data for WBPT are useful markers for evaluating cardiovascular risk in clinical settings. Finally, an extensive examination of clinical studies will be required in the future to investigate the significance of skin AF and WBPT as novel cardiovascular risk factors.

Conclusions

In conclusion, the present study, which used commercial devices such as AGE Reader and MC-FAN in patients with traditional cardiovascular risk factors, indicated a significant relation between skin AF and WBPT. In addition, oxidative stress, arterial dysfunction, smoking habits, and a clustering of traditional cardiovascular risk factors were associated with these two biomarkers.

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