

Skin Autofluorescence as Marker of Tissue Advanced Glycation End-Products Accumulation in Formerly Preeclamptic Women

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Condensation. In women with a history of preeclampsia skin autofluorescence as marker of tissue AGEs accumulation is increased, supporting a common causal metabolic or vascular link between preeclampsia and cardiovascular diseases. **Objective.** To investigate whether skin autofluorescence (AF), as marker of tissue accumulation of advanced glycation end-products (AGEs), is elevated in women with a 4-year history of severe preeclampsia. **Methods.** About 17 formerly preeclamptic women and 16 controls were included. Skin AF and several traditional cardiovascular risk factors were recorded. **Results.** In comparison to controls, formerly preeclamptic women had higher skin AF of the legs, body mass index (BMI), blood pressure, and high-sensitivity C-reactive protein (hsCRP), HbA1C, and triglycerides in serum. **Conclusion.** Skin AF as well as cardiovascular risk factors is elevated in formerly preeclamptic women. These results suggest a common causal vascular link between preeclampsia and cardiovascular diseases.

Keywords Advanced glycation end-products, Preeclampsia, Cardiovascular diseases, Skin autofluorescence.

Preliminary data have been presented as a poster at the 16th World Congress of the International Society of Hypertension in Pregnancy (ISSHP), Washington, DC, USA, September 22, 2008.

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INTRODUCTION

Preeclampsia is a unique pregnancy-related syndrome characterized by the development of new onset hypertension and proteinuria in the second half of pregnancy (1). Formerly preeclamptic women appear to have an approximately twofold higher risk to develop cardiovascular diseases in later life (2–4). It is likely that preeclampsia and cardiovascular diseases share a common causal link, regarding the many identical risk factors and strong association with vascular (endothelial) dysfunction (2–4).

Pregnancy is accompanied by extensive physiological adaptations, which include metabolic, cardiovascular, and immunological responses (5). In preeclampsia, these metabolic changes are even much more exaggerated and are well known to be atherogenic. They may therefore accelerate the progression of atherosclerosis in this group of women (6). Persistence of metabolic abnormalities after preeclampsia could therefore contribute to the increased risk of cardiovascular diseases in these women.

Recently, the accumulation of advanced glycation end-products (AGEs) on tissue proteins has been implicated as a contributing factor to the progression of atherosclerosis (7). AGEs are irreversible products that result from glycation of proteins, lipids, and nucleic acids. Glycation is the effect of nonenzymatic reactions between proteins and sugars, leading to the formation of Schiff bases and Amadori products, and eventually to AGEs (8). AGE formation is increased in conditions of glycemic and/or oxidative stress and may therefore be considered as a measure of cumulative metabolic and oxidative stress (9,10).

AGEs affect the structure and function of the arteries by two different mechanisms. First, AGEs crosslink with proteins in the extracellular matrix of the vascular wall resulting in decreased vessel elasticity and increased vascular rigidity and thickness (11). Second, more frequently AGE–RAGE (receptor of AGE) interaction leads to endothelial cell activation and dysfunction and oxidative stress. Oxidative stress is a hallmark of both preeclampsia and cardiovascular diseases (12–15). Besides this, gestational diabetes can also play a part in the AGE formation as a result of glycemic stress (16).

The potential role of AGEs in the micro- and macrovascular abnormalities during and after preeclampsia has been sparsely investigated. Increased RAGE protein expression in myometrial and omental vascular beds and in serum has been presented in preeclamptic patients (17,18). In our previous study in 2004, accumulation of AGEs as measured by skin autofluorescence (AF) was significantly higher in women who have had preeclampsia as compared to women with a history of an uncomplicated pregnancy (19).

In the current study, 4 years after the preeclamptic pregnancy, we tested our hypothesis that the group of formerly preeclamptic women still has higher values of skin AF in concordance with a higher prevalence of cardiovascular and metabolic risk factors than the control group of women with normal pregnancies.

MATERIALS AND METHODS

Subjects

In 2007, we started our follow-up study; we included 16 Caucasian women with a history of severe early-onset preeclampsia (cases) and 17 women with

uncomplicated pregnancies (controls). Exclusion criterion was pregnancy or breastfeeding at time of study. Preeclampsia was defined according to the criteria of the International Society for the Study of Hypertension in Pregnancy (20). All measurements took place from October 2007 to February 2008 at the University Medical Center of Groningen (UMCG), the Netherlands. The study was approved by the Medical Ethical Committee of the UMCG. Cases and controls were fully informed and gave written informed consent before entering the study.

Measurements

We obtained information on personal history including diabetes mellitus, cardiovascular diseases, smoking habits, drug treatment, and family history of cardiovascular diseases by questionnaire. Weight, height, and blood pressure were measured during the examination. Blood samples were taken after an overnight fasting period of at least 12 h. Directly after collecting blood samples, we measured the levels of serum creatinine, high-sensitivity C-reactive protein (hsCRP), HbA1C, homocysteine, triglycerides, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and plasma glucose. Low-density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula: $\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - (0.45 \times \text{triglycerides})$. Homeostasis model assessment (HOMA) index was calculated to assess insulin resistance: $\text{fasting insulin} \times \text{fasting glucose} / 22.5$. Microalbuminuria was assessed in early-morning urine and was defined as an albumin-creatinine ratio of >3.4 g/mol in at least two of three samples of early-morning urine.

AGE Reader

The AGE Reader (DiagnOptics Technologies BV, Groningen, the Netherlands) is based on the noninvasive measurement of skin AF, which is strongly related to tissue AGEs (21). Measurements were performed at the volar site of the forearm and leg where the illuminating light enters the skin almost perpendicular over an area of ~ 4 cm². This excitation light is in the wavelength range of 350–420 nm (maximum intensity approximately at 370 nm). The AGE Reader uses a spectrometer (Avantes BV, Eerbeek, the Netherlands) to measure the light that is reflected by and emitted from the skin, from which skin AF is calculated. Dark and white reference measurements took place during each measurement to correct for detector properties and background light, and to calculate skin reflectance.

In contrast to the earlier used instrument in the study of 2004, the AFR which was a prototype of the current AGE Reader, the current device has a completely automatic measuring procedure of approximately 30 s, after which results are presented. The measurement principles and the optical path design are identical for both devices, and care has been taken to validate interchange ability of the measurement results obtained with both the devices. Both in apparently healthy persons and in patient groups (diabetes mellitus, renal failure) direct comparisons have been made over a wide age range, and results obtained with the different generations of the AGE Reader have been made directly translatable. Although using statistical measures such as mean, variability, and range, results are the same in all the different

subgroups, identical values at the individual level could not be guaranteed. The skin has to be normal and not too dark of color, because irregularities and dark pigmentation (Fitzpatrick class VI) could influence the measurement with the current software version. AF is expressed in arbitrary units (AU). AF was measured three times at both legs and arms and the median value of these three AF measurements at each location was used for analysis. Reproducibility was tested by Mulder et al. in 25 healthy persons and 25 diabetic patients, which showed a mean relative error in AF of 5% on a single day (21).

Statistical Analysis

For statistical analysis we used SPSS Data Editor 14.0. To determine whether or not data were normally distributed we used the Kolmogorov–Smirnov test. When data were normally distributed we used the unpaired Student's *t*-test to examine differences between cases and controls and the paired Student's *t*-test to examine differences in clinical and biochemical data of the same individual between the 2004 and 2008 study. The nonparametric Mann–Whitney *U*-test was applied when there was no normal distribution of the data. Nominal statistics on variables like smoking, family history of cardiovascular diseases, and numbers of pregnancies after index pregnancy were calculated with the chi-square test and shown as quantity and percentage. Correlations were performed using the Pearson test for normally distributed data and the Spearman rank test for non-normally distributed data. A two-tailed probability <0.05 was considered to be significant. Data are given as mean (SD) unless stated otherwise. Sample size was defined by a power calculation with $\alpha = 0.05$ and $\beta = 0.2$ with a minimum of 10 women in each group.

RESULTS

Subjects

From a total of 64 cases and controls from whom skin AF values and clinical and biochemical information had been assessed 4 years ago (19,22), 57 women responded to the invitation letter and 43 women were interested to participate. One case and six controls were lost for follow-up because of an unknown current address. We excluded five cases and four controls, because of current pregnancy or breastfeeding. Besides, one case was excluded because of a history of breast cancer with chemotherapy, which was considered to influence the vascular function (23). A total of 33 participants were finally tested: 17 cases and 16 controls.

After their first pregnancy in 2004, 13 cases and 9 controls had a new pregnancy. One case developed a mild preeclampsia at a gestational age of 38 weeks. None of the cases or controls used medication before their pregnancy in 2004. However, in 2008, three cases used blood-pressure-lowering medication. One case had developed insulin-dependent diabetes mellitus, three cases used thyroxin supplementation for hypothyroidism, one case used thrombocyte aggregation inhibitor Ascal[®] (calcium carbasalate), and two cases had increased homocysteine levels and used Cardox[®]. One control used Ascal[®] and one control had increased homocysteine levels and used Cardox[®].

Body mass index (BMI) and systolic and diastolic blood pressures were significantly higher in cases as compared to controls even with blood-pressure-lowering medication (Table 1). When cases and controls are combined, BMI correlated with systolic blood pressure ($r = 0.759$; $p < 0.001$) and diastolic blood pressure ($r = 0.447$; $p = 0.009$). In comparison to 2004, cases had higher BMI ($p = 0.025$) and systolic blood pressure ($p = 0.043$) in 2008. Controls in 2008 also had higher BMI ($p = 0.029$) and increased diastolic blood pressure ($p = 0.046$) in comparison to controls in 2004 (Table 1).

Skin Autofluorescence

Skin AF of the legs was significantly increased ($p = 0.038$) in cases (1.57 ± 0.34 AU) in comparison to controls (1.30 ± 0.36 AU, Figure 1). No difference was found in skin AF of the arms between the two groups (Figure 2). In both cases ($p < 0.001$) and controls ($p < 0.001$) the mean skin AF of the arms was higher than that of the legs. If data of cases and controls are combined, results of the measurements performed at the arms and those at the legs correlated with each other ($r = 0.695$; $p < 0.001$). No significant correlations were found in this study between skin AF and clinical or biochemical variables like blood pressure, age, insulin, glucose, HOMA index, or BMI.

Biochemical Characteristics

Biochemical characteristics are described in Table 2. Levels of hsCRP, HbA1C, and triglycerides were significantly higher in cases as compared to controls. None of the participants had microalbuminuria. When data of cases and controls were combined, insulin correlated positively with triglycerides ($r = 0.533$; $p = 0.001$) and hsCRP ($r = 0.434$; $p = 0.012$). Triglycerides correlated positively with systolic blood pressure ($r = 0.409$; $p = 0.018$), hsCRP ($r = 0.588$; $p < 0.001$), HOMA index ($r = 0.540$; $p = 0.001$), and total cholesterol ($r = 0.494$; $p = 0.003$).

In comparison to the biochemical data of both groups in 2004, glucose levels were higher in 2008 ($p = 0.005$) in both cases and controls. Over the same time span, the levels of triglycerides ($p = 0.025$) and total cholesterol ($p < 0.001$) were lower in cases.

COMMENT

This study shows that women with a 4-year history of preeclampsia have elevated skin AF of the legs as measure of skin accumulation of AGEs. Furthermore, they persistently show more markers and risk factors for cardiovascular diseases such as BMI, blood pressure, hsCRP, HbA1C, and triglycerides in comparison to controls. These results support the concept of a common causal metabolic and/or vascular link between preeclampsia and cardiovascular diseases.

The AGE Reader and the AFR have previously been established to be acceptable methods for measuring AGEs in the skin. Several studies have compared skin AF with the content of specific AGEs in extracts from skin biopsies in groups over a wide age range of diabetic and control subjects, and individuals with renal failure (24–26). Skin AF was also found to be elevated in diabetic patients (27,28), patients with stable coronary artery disease (25),

Table 1: Clinical characteristics of cases and controls in 2004 and 2008.

	A Cases 2004 (n = 17)		B Controls 2004 (n = 16)		p-Value (A vs. B)	C Cases 2008 (n = 17)		D Controls 2008 (n = 16)		p-Value (C vs. D)
Age (years)	29.7 ± 4.8		30.7 ± 3.6		0.505	33.4 ± 5.0		33.9 ± 3.8		0.740
Body mass index (kg/m ²)	28.2 ± 6.8*		23.3 ± 2.8 [†]		0.012	29.9 ± 6.5		24.4 ± 3.4		0.005
Systolic blood pressure (mmHg)	127.7 ± 10.4*		116.0 ± 6.4		<0.001	135.3 ± 13.4		114.7 ± 6.3		<0.001
Diastolic blood pressure (mmHg)	80.7 ± 10.0		69.0 ± 5.7 [†]		<0.001	79.7 ± 7.1		65.8 ± 6.0		<0.001
Current smoking	5 (29.4%)		7 (43.8%)		0.895	6 (35.3%)		3 (18.8%)		0.283
Family history of CVD	11 (64.1%)		9 (56.3%)		0.119	15 (88.2%)		10 (62.5%)		0.085
Women pregnant after 2004	–		–		–	13 (76.5%)		9 (56.3%)		0.218

CVD: cardiovascular diseases. Data were described as mean ± standard deviation or as number (percentage).

*Significant difference of <0.05 within cases in the time span 2004–2008 (A vs. C).

[†]Significant difference of <0.05 within controls in the time span 2004–2008 (B vs. D).

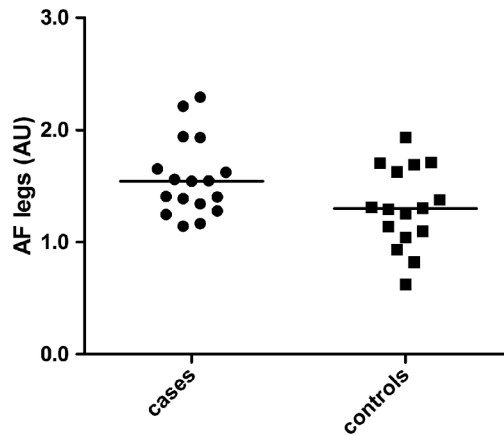


Figure 1: Boxplot of autofluorescence (AF) outcomes of legs in cases and controls in 2008. AF in the legs was significantly higher in cases as compared to controls ($p = 0.038$).

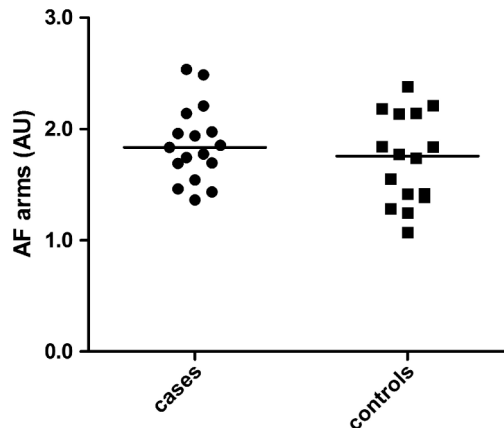


Figure 2: Boxplot of autofluorescence (AF) outcomes of arms in cases and controls in 2008. No difference ($p = 0.303$) was found between AF of the arms between both groups.

patients with renal failure, and systemic lupus erythematosus (29,30). Each of these disorders is associated with an acceleration of the atherosclerotic process and an increased risk for cardiovascular diseases.

Although the AGE Reader has a good reproducibility, this technique has its limitations (27). Other fluorescent substances than AGEs may also affect the skin AF and not all AGEs show fluorescent properties. Nevertheless, Meerwaldt et al. demonstrated that even nonfluorescent AGEs in skin biopsies for AGEs strongly correlated with skin AF (27). Thus, skin AF is not only a marker of fluorescent AGEs, but also a reflection of the total skin AGE pool.

Unfortunately, it was not possible to compare the absolute values of 2008 at an individual level with those of 2004, because of a change from the prototype AFR in 2004 to the AGE Reader in 2008. However, in another follow-up study with diabetic patients, the change in skin AF over periods of approximately 4 years was small measured with the same AFR (31). Other

Table 2: Biochemical data from cases and controls in 2003 and 2008.

	Cases 2004 (n = 17)	Controls 2004 (n = 16)	p-Value	Cases 2008 (n = 17)	Controls 2008 (n = 16)	p-Value
Creatinine ($\mu\text{mol/L}$)	76.8 \pm 7.9*	83.6 \pm 12.3 [†]	0.064	75.3 \pm 5.1	79.8 \pm 13.5	0.259
hsCRP (mg/L)	–	–	–	8.0 \pm 5.1	3.9 \pm 2.1	0.016
HbA1C (%)	–	–	–	5.2 (2.1–6.2)	5.2 (4.9–5.5)	0.045
Homocysteine ($\mu\text{mol/L}$)	8.7 \pm 1.7	11.1 \pm 7.5	0.653	8.7 \pm 1.7	11.0 \pm 6.0	0.127
Glucose (mmol/L)	4.5 \pm 0.3*	4.4 \pm 0.4 [†]	0.719	4.8 \pm 0.5	4.8 \pm 0.4	0.903
Triglycerides (mmol/L)	1.7 \pm 1.1*	1.0 \pm 0.4	0.028	1.2 \pm 0.6	0.8 \pm 0.3	0.035
Insulin (mU/L)	14.0 \pm 7.4	10.6 \pm 9.1	0.256	12.8 \pm 7.8	9.7 \pm 4.6	0.175
HOMA index	2.8 \pm 1.6	2.2 \pm 2.0	0.352	3.2 \pm 2.3	2.2 \pm 1.0	0.192
Cholesterol (mmol/L)	5.3 \pm 1.0*	4.8 \pm 0.9	0.122	4.6 \pm 0.8	4.4 \pm 0.7	0.705
HDL cholesterol (mmol/L)	1.5 \pm 0.3	1.5 \pm 0.3	0.557	1.6 \pm 0.3	1.5 \pm 0.2	0.421
LDL cholesterol (mmol/L)	3.0 \pm 0.9*	2.9 \pm 0.7 [†]	0.672	2.7 \pm 0.7	2.5 \pm 0.5	0.484
Albumin–creatinine ratio	3.6 \pm 6.1 [†]	0.7 \pm 0.4 [†]	0.068	0.7 \pm 0.9	0.3 \pm 0.2	0.095

hsCRP: high-sensitivity C-reactive protein; HOMA: homeostasis model assessment; HDL: high-density lipoprotein; LDL: low-density lipoprotein. Data are described as mean \pm SD, as number (range).

*Significant difference of <0.05 within cases in the time span 2004–2008.

[†]Significant difference of <0.05 within controls in the time span 2004–2008.

[‡]Three women had an albumin–creatinine ratio of >3.4 g/mol in 2004.

limitations of this study were the small sample size and the limited generalizability. In both groups, women got pregnant after the index pregnancy, which could have influenced our results. However, in both groups the number of pregnancies was comparable and therefore we assume that this influence will be marginal.

Remarkably, in our previous as well as in the current study, the difference in AGE accumulation between both groups could only be noticed in the legs and not in the arms. How to explain the increased skin AF of the legs that we found in the women who experienced a severe early-onset preeclampsia 4 years ago? The possibility that in 2004 the increase of skin AF was a temporary effect of the preeclamptic pregnancy appears to be very unlikely as we demonstrated by this study that this increase is constant over the time span. The finding of persistently increased skin AF of the legs as a marker of tissue AGE accumulations can be explained by the fact that removal of AGEs is mainly dependent on the removal of the proteins (e.g., skin collagen) they are attached to (8). This skin collagen has an estimated lifespan of at least 15–20 years (25). The specific pathophysiology of the preeclamptic pregnancy could also be an explanation. During normal as well as preeclamptic pregnancy there is an increased venous pressure in the legs because of relaxation of muscular walls of the blood vessels and the increasing weight of the enlarged uterus. Elevated venous pressure can lead directly to increased capillary pressure in the legs (32). The combination of increased oxidative stress during preeclampsia with locally increased venous pressure may explain why the accelerated AGE accumulation during preeclampsia becomes only manifest in the legs. We did not investigate skin AF before or during preeclampsia in this study group. Therefore, it could be possible that the case group already had higher skin AF before preeclampsia. Few other studies on the association between AGEs and preeclampsia have been performed, but none of these studies measured skin AF during normal or preeclamptic pregnancy.

Cooke et al. found elevated RAGE protein in vascular beds and Chekir et al. found higher levels of serum AGE and RAGE during preeclampsia in comparison to nonpregnant and normal pregnant women (17,18). Fasshauer et al. showed that endogenous soluble RAGE was elevated in preeclamptic women, but decreased after delivery (33). These studies indicate that there is already activation of the AGE–RAGE system during preeclampsia (34). In contrast, Harsem et al. did not find increased AGE levels in women during preeclampsia, but only in women with diabetes mellitus type 1 and gestational diabetes (16). This could indicate that increased AGE levels are not the result of preeclampsia, but are caused by diabetes mellitus. However, Harsem et al. used a different method to measure AGE values (16–18). In both other studies, AGE levels decreased after pregnancy (17,18). An explanation could be that AGEs are only irreversible when they are attached to vascular skin wall and this was not the case in both studies.

The difference in the results of the skin AF between cases and controls was relatively small (1.6 vs. 1.3 AU). Is this small difference of clinical importance? As we compare our findings with other studies that used the AGE Reader they had the same small, but statistically different, results (24–30).

Like in other studies, cases had significantly higher BMI, triglycerides, and systolic and diastolic blood pressures in comparison with controls (3,35,36). Interestingly, before their preeclamptic pregnancy none of the women had underlying cardiovascular-related diseases or used medication. However, in 2008 there were in total five cases with cardiovascular-related diseases and medication and three cases with hypothyroidism; this supports the theory of preeclampsia being an independent risk factor for cardiovascular diseases. It might be possible that these features influenced our skin AF results. However, skin AF has been shown to be a strong predictor of cardiovascular diseases, independent of these other cardiovascular risk factors, in several other conditions like diabetes mellitus, renal failure, and renal transplantation (37). In our study, renal function, glucose levels, and prevalence of smoking were not different from controls, even though the skin AF was higher in the cases. Also, none of these above-mentioned other cardiovascular risk factors were correlated with skin AF. This suggests that there is no direct influence of the cardiovascular risk factors measured in our study on the AF values.

In conclusion, skin AGE accumulation is 4 years later still elevated in women with a history of preeclampsia. Despite the small sample size, these results indicate the presence of vascular tissue damage and metabolic burden in formerly preeclamptic women. In combination with the traditional cardiovascular risk markers, these results may also offer a new pathway underlying an acceleration of atherosclerosis in this group of women. Why the differences in AGE accumulation could only be found in the legs and not in the arms, and whether these were already present before conception or are a direct cause of the preeclampsia *per se* has to be established.

ACKNOWLEDGMENTS

Graaff R MSc, PhD and AJ Smit MD, PhD are founders of DiagnOptics, the Netherlands, who manufacture the AGE readers (<http://www.diagnoptics.com>).

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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