Advanced Glycation End Product (AGE) Accumulation in the Skin is Associated with Depression

Research Article

ADVANCED GLYCATION END PRODUCT (AGE) ACCUMULATION IN THE SKIN IS ASSOCIATED WITH DEPRESSION: THE MAASTRICHT STUDY

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Background: *Depression is a highly prevalent disease with a high morbidity and mortality risk. Its pathophysiology is not entirely clear. However, type 2 diabetes is an important risk factor for depression. One mechanism that may explain this association may include the formation of advanced glycation end products (AGEs). We therefore investigated the association of AGEs with depressive symptoms and depressive disorder. In addition, we examined whether the potential association was present for somatic and/or cognitive symptoms of depression.* **Methods:** *Cross-sectional data were used from the Maastricht Study (N = 862, mean age 59.8 ± 8.5 years, 55% men). AGE accumulation was measured with skin autofluorescence (SAF) by use of the AGE Reader. Plasma levels of protein-bound pentosidine were measured with high-performance liquid chromatography and fluorescence detection. Nε-(carboxymethyl)lysine (CML) and Nε-(carboxyethyl)lysine (CEL) were measured with ultraperformance liquid chromatography and tandem mass spectrometry. Depressive symptoms and depressive disorder were assessed by the nine-item Patient Health Questionnaire and the Mini-International Neuropsychiatric Interview.* **Results:** *Higher SAF was associated with depressive symptoms (β = 0.42, 95% CI 0.12–0.73, P = .007) and depressive disorder (OR = 1.42, 95% CI 1.04–1.95, P = .028) after adjustment for age, sex, type 2 diabetes, smoking, BMI, and kidney function. Plasma pentosidine, CML, and CEL were not independently associated with depressive symptoms and depressive disorder.* **Conclusions:** *This study shows that AGE accumulation in the skin is independently associated with higher levels of*

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depressive symptoms and depressive disorder. This association is present for both somatic and cognitive symptoms of depression. This might suggest that AGEs are involved in the development of depression. Depression and Anxiety 34:59–67, 2017.

Key words: *depression; diabetes; advanced glycation end products; cohort*

INTRODUCTION

Depression is an important global public health problem due to its relatively high lifetime prevalence and the significant disability that it causes. According to the World Health Organization (WHO), depression is the third leading cause of burden of disease as measured by Disability-Adjusted Lived Years, and is expected to be the leading cause in 2030.[1] Therefore, the identification of its causes is a research priority. Although more and more research has been focusing on understanding the cause of depression, and several underlying mechanisms have been proposed, advanced glycation end products (AGEs) could present a novel mechanism in the etiology of diabetes and depression.

Type 2 diabetes mellitus (T2DM) is an important risk factor for depression, while it is associated with a 24% increased incidence of depression.[2] This may suggest that prolonged hyperglycemia, a key feature of T2DM, is involved in the development of depression. Prolonged hyperglycemia accelerates the formation of AGEs, which are the irreversible products of a nonenzymatic reaction between glucose and proteins.[3] AGEs can be measured in plasma (circulating AGEs, e.g., protein-bound Nε-(carboxymethyl)lysine [CML], Nε-(carboxyethyl)lysine [CEL], and pentosidine) or estimated in tissue using a relatively simple noninvasive measurement of skin autofluorescence (SAF), a method based on the fluorescent properties of AGEs.[4] SAF has been suggested to be a simple alternative to invasive measurement of AGE accumulation and has been shown to be correlated with fluorescent pentosidine and even nonfluorescent plasma AGEs CML and CEL in biopsy-derived skin tissue.[4]

A close link between depression and diabetes has been acknowledged for many years, but the exact nature of this relationship remains unclear.[5] There is convincing evidence that the relationship between T2DM and depression is bidirectional. Depression has been identified as a risk factor for the development of T2DM[6] and the presence of T2DM can contribute to the onset of depression.[2] AGEs form at a constant but slow rate in the normal body; however, their formation is markedly accelerated in diabetes due to prolonged hyperglycemia.[7] Therefore, AGEs could present a novel mechanism in the etiology of depression and diabetes.

AGE accumulation has detrimental effects through at least three mechanisms: (1) activation of the receptor for AGEs (RAGE) results in increased inflammation and endothelial dysfunction;[8] (2) intracellular accumulation of results in increased oxidative stress and endothelial dysfunction;[9,10] and (3) the formation of cross-links with, for instance, collagen in the arterial wall leads to increased arterial stiffness.[11] These three mechanisms are reflected by plasma levels of CML, CEL, and pentosidine, respectively, whereas SAF is a measure of tissue AGE accumulation.

Increased low-grade inflammation, endothelial dysfunction, and arterial stiffening are also implicated in the development of depressive symptoms.[12,13] Thus, depression may contribute, via the inflammatory pathway, to the development of long-term complications of diabetes via acceleration of the formation of AGEs, and AGEs in turn may contribute to the development of depression. The latter is supported by studies that observed an association between glycated hemoglobin (HbA1c) levels, which is a measure of average plasma glucose concentrations and sustained hyperglycemia, and the incidence of depressive symptoms.[14,15] Higher HbA1c levels can lead to more AGEs,[16] and may thus lead to the incidence of depressive symptoms. Nevertheless, these associations between AGEs and depressive symptoms are unexplored.

In view of the above, we aim to evaluate whether there is an independent association of SAF and plasma AGEs with depressive symptoms and depressive disorder. As previous research suggests that mainly the somatic symptoms of depression and not the cognitive symptoms of depression are associated with adverse health phenomena,[17] we additionally examined whether the potential association between AGEs and depressive symptoms is different for somatic symptoms compared with cognitive symptoms of depression. A final, subsidiary aim was exploring the association between AGEs and depression by diabetes diagnosis.

MATERIALS AND METHODS

STUDY POPULATION

In this study, we used data from the Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously.[18] In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of T2DM and is characterized by an extensive phenotyping approach. An extensive module on depressive symptoms and depressive disorder was part of the protocol. Eligible for participation were all individuals aged between 40 and 75 and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the

regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status for reasons of efficiency. The present report includes cross-sectional data from the first 866 participants, who completed the baseline survey between November 2010 and March 2012. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands, on the basis of the Health Council's opinion (Permit 131088-105234-PG). All participants gave written informed consent.

SKIN AUTOFLUORESCENCE

SAF was measured with the AGE Reader (DiagnOptics Technologies BV), which is a desktop device that uses the characteristic fluorescent properties of certain AGEs to estimate the level of AGE accumulation in the skin. More details of this noninvasive method have been described extensively elsewhere.[4,19] In short, the AGE Reader illuminates a skin surface of 4 cm^2 guarded against surrounding light, with an excitation wavelength range of 300–420 nm, with a peak excitation of 370 nm. SAF was calculated as the ratio between the emission light from the skin in the wavelength range of 420–600 nm (fluorescence) and excitation light that is reflected by the skin (300–420 nm), multiplied by 100 and expressed in arbitrary units (AU). Participants were asked not to use any sunscreen or self-browning creams on their lower arms within 2 days before the measurement. SAF was measured at room temperature in a semidark environment while participants were at rest in a seated position. The forearm of a participant was positioned on top of the device, as described by the manufacturer. The mean of three consecutive measurements was used in the analyses. Reproducibility was assessed in 14 individuals without diabetes (six males and eight females; mean age, 32.2 ± 7.1 years). The intraclass correlation coefficient (*ICC*) of three intraindividual consecutive SAF measurements was 0.83 (95% *CI* 0.65–0.94). SAF was calculated offline by automated analysis using AGE Reader software, version 2.3, and was observer independent.

ANALYSIS OF PROTEIN-BOUND AGES AND LYSINE IN PLASMA

Plasma AGEs were measured in EDTA samples obtained from fasting venous blood, which were stored at –80°C until analysis. Protein-bound pentosidine was quantified using high-performance liquid chromatography (HPLC) with fluorescence detection, as described in detail elsewhere.[20] Intra- and interassay coefficients of variation (*CV*s) were 6.5 and 7.8% for pentosidine, respectively. Protein-bound CML, CEL, and lysine were quantified using ultraperformance liquid chromatography tandem mass spectrometry (UPLC MS/MS).[21] Intra- and interassay *CV*s were 4.5 and 6.7% for CML, 6.2 and 10.3% for CEL, and 5.0 and 5.3% for lysine. Concentrations of protein-bound pentosidine, CML, and CEL were adjusted for levels of lysine and expressed as nanomoles per millimole lysine.

ASSESSMENT OF DEPRESSION

Depressive disorder was assessed by the Mini-International Neuropsychiatric Interview (MINI).[22] The MINI is a short diagnostic structured interview used to assess the presence of minor or major depressive disorder in the preceding 2 weeks according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition). Due to the low number of cases, we merged major and minor depression into a single variable. The MINI was conducted by trained staff members at the research center. Depressive symptoms in the preceding 2 weeks were assessed by a validated Dutch version of the nine-item Patient Health Questionnaire (PHQ-9).[23] The PHQ-9 is a self-administered questionnaire based on the DMS-IV[24] criteria for a major depressive disorder. It comprises nine items rated on a 4-point scale, ranging from 0 (*not at all*) to 3 (*nearly every day*). Response options can generate a continuous score ranging from 0 (*no symptoms*) to 27 (*all symptoms present nearly every day*). Both cognitive symptoms of depression, comprising thoughts about oneself and problems of the mind, and somatic symptoms of depression, comprising various bodily sensations that a depressed individual perceives as unpleasant or worrisome, are measured with the PHQ-9.[25]

GENERAL CHARACTERISTICS AND COVARIATES

Age, sex, partner status, diabetes duration in years, smoking behavior, alcohol consumption, and history of cardiovascular disease were assessed by means of a self-report questionnaire.[18] Fasting venous blood samples were used to assess glucose levels, HbA_{1c}, and lipid profile. Medication use was assessed by interview. Blood pressure was measured three times on the right arm after 10 min of seated rest, and the mean of these three measurements was used for analyses.

To determine T2DM status, all participants (except those who used insulin) underwent a standardized 7-point oral glucose tolerance test (OGTT) after an overnight fast. Blood samples are taken at baseline, and 15, 30, 45, 60, 90, and 120 min after ingestion of a 75 g glucose drink. For safety reasons, participants with a fasting glucose level above 11.0 mmol/l, as determined by a finger prick, do not undergo the OGTT. More details about this assessment method have been previously described.[18] Individuals without type 1 diabetes and on diabetes medication were considered to have T2DM as well.[18] Smoking behavior was based on self-report of smoking cigarettes, cigars, and/or pipe tobacco, and divided into three categories, that is, nonsmoker, former smoker, and current smoker. Additionally, lifetime smoking was expressed as pack-years; one pack-year was defined as one packet (20 cigarettes) per day, smoked over a course of 1 year. Alcohol consumption was categorized into nonconsumers, low consumers (less than or equal to seven glasses per week for women and ≤14 glasses per week for men), and high consumers (more than seven glasses per week for women and >14 glasses per week for men). Weight, height, waist, and hip circumference were measured by a trained staff member, and body mass index (BMI) and waist-to-hip ratio were calculated. Glomerular filtration rate (eGFR) was estimated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, based on serum creatinine.[26]

STATISTICAL ANALYSIS

All analyses were performed by use of SPSS software, version 20 for Windows. Baseline characteristics were compared between individuals with and without depressive disorder by use of independent samples *t*-test for normally distributed continuous variables, Mann–Whitney *U* test for continuous variables with a skewed distribution, and chi-square tests for categorical variables. Linear regression analyses were used to assess the associations of the four measures of AGEs (SAF, pentosidine, CML, and CEL) with depressive symptoms (PHQ-9). Logistic regression analyses were used to estimate the association of the four measures of AGEs (SAF, pentosidine, CML and CEL) with depressive disorder (MINI). Due to the low number of depression cases, we could only add a limited number of covariates in the analyses. Associations were adjusted for covariates; model 1 was the crude model; model 2 included the covariates age, sex, and T2DM. The latter might be an overadjustment given that AGEs accumulate more quickly with prolonged hyperglycemia and are thus presumably greater in people with type 2 diabetes. Model 3 additionally included smoking, BMI,

and eGFR (fully adjusted model). The latter variables were included because the kidneys are the major way the body has for excreting AGEs to maintain the body load of AGEs at nontoxic levels.[27] It has been shown that during aging and in diabetes, the glomerular basement membrane of the kidneys are thickened, leading to less efficient kidney filtration.[28] A *P*-value <0.05 was considered statistically significant in two-sided tests.

In a secondary analysis, interaction analysis was performed to examine whether the associations between AGEs and depression differed between individuals with and without T2DM. For interaction terms, a *P*-value of <0.05 was considered statistically significant. In addition, factor analysis with principal axis factor extraction was used to explore the underlying factor structure of the PHQ-9. The decision about the number of factors to retain was guided by the eigenvalues from the unreduced correlation matrix, using the Kaiser–Guttman rule (eigenvalues >1, both the Kaiser–Meyer–Olkin measure of sampling adequacy and the Bartlett's test of sphericity were checked) and scree plot criterion. As the factors of the PHQ-9 were expected to be moderately correlated, oblique rotation (of the initial factor solution) was applied to simplify interpretation of the factor structure. Items loading >|0.40| on one factor and <|0.30| on any other factor after rotation were considered to meet the criteria for simple structure.[29]

RESULTS

GENERAL CHARACTERISTICS

The total sample consisted of 852 participants. Table 1 demonstrates general characteristics of the study population (55% men, mean age 60 years), according to diagnosis of depressive disorder. Data on depression for the MINI interview were available in 852 individuals, PHQ-9 scores in 757. Missing data on depression scores were mainly due to not completing the questionnaires or refusal of the interview. Data on *SAF* were available in 831 individuals, plasma AGEs in 843. Missing data on SAF were mainly due to device nonavailability or technical problems. Missing data on plasma AGEs were caused by difficulties in blood withdrawal. In total, 6.5% ($n = 55$) of the participants scored positive for major or minor depressive disorder. These individuals had higher HbA1c levels, were more likely to smoke, and had higher levels of SAF. Levels of plasma AGEs pentosidine and CEL were not different in individuals with compared to individuals without depressive disorder, while plasma

TABLE 1. General characteristics of the Maastricht Study participants by diagnosis of depressive disorder

	Total population	Depressive disorder ($n = 852$; MINI)		
	($n = 852$)	No ($n = 797$)	Yes ($n = 55$)	*P*-value
Male sex (*n*)	55% (467)	55% (438)	53% (29)	.748[a]
Age (years)	59.8 ± 8.5	59.8 ± 8.5	59.0 ± 8.9	.463[b]
Having a partner (*n*)	85% (715)	86% (673)	76% (42)	.063[a]
T2DM (*n*)	29% (251)	29% (229)	40% (22)	.076[a]
Diabetes duration (years)	8.4 ± 6.9	8.1 ± 6.9	10.4 ± 6.7	.176[b]
HbA1c (%)	6.0 ± 0.8	6.0 ± 0.8	6.4 ± 1.2	**.042**[c]
Fasting glucose level (mmol/L)	6.1 ± 1.5	6.1 ± 1.4	6.6 ± 2.6	.140[c]
Smoking (pack-years)	14.6 ± 21.5	14.0 ± 20.4	23.9 ± 33.6	**.002**[b]
Never/former/current (%)	31/53/16	32/53/15	19/51/30	**.009**[a]
Alcohol consumption No/low/high (%)	17/53/30	17/53/30	24/49/27	.511[a]
BMI (kg/m^2)	27.4 ± 4.5	27.3 ± 4.5	28.2 ± 5.1	.184[b]
Waist circumference (cm)	97.2 ± 13.6	97.0 ± 13.4	99.6 ± 15.8	.175[b]
Waist-to-hip ratio	0.95 ± 0.09	0.95 ± 0.09	0.96 ± 0.10	.266[b]
Systolic blood pressure (mmHg)	137.4 ± 19.0	137.1 ± 18.9	141.0 ± 20.4	.141[b]
Diastolic blood pressure (mmHg)	76.7 ± 10.3	76.7 ± 10.2	77.5 ± 12.3	.544[b]
Antihypertensive medication (*n*)	40% (342)	40% (316)	47% (26)	.265[a]
Total cholesterol (mmol/L)	5.2 ± 1.2	5.2 ± 1.2	5.2 ± 1.2	.991[b]
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.6	.784[b]
LDL-cholesterol (mmol/L)	3.3 ± 1.1	3.3 ± 1.0	3.3 ± 1.2	.989[b]
Triglycerides (mmol/L)	1.5 ± 1.0	1.5 ± 1.0	1.7 ± 0.9	.113[b]
Total-to-HDL cholesterol ratio	4.5 ± 8.6	4.5 ± 8.8	4.5 ± 1.5	.970[b]
Lipid-modifying medication (*n*)	37% (315)	37% (292)	42% (23)	.441[a]
History of CVD (*n*)	18% (147)	18% (139)	15% (8)	.610[a]
eGFR (mL/min/1.73 m^2)	84.7 ± 14.6	84.7 ± 14.7	84.7 ± 13.6	.998[b]
SAF (AU)	2.71 ± 0.53	2.69 ± 0.52	2.87 ± 0.59	**.021**[b]
Pentosidine (nmol/mmol LYS)	0.52 ± 0.30	0.51 ± 0.30	0.55 ± 0.28	.405[b]
CML (nmol/mmol LYS)	74.22 ± 14.69	74.41 ± 14.71	71.57 ± 14.26	.166[b]
CEL (nmol/mmol LYS)	34.13 ± 10.25	34.18 ± 10.15	33.38 ± 11.57	.577[b]

Data are presented as mean ± standard deviation unless otherwise indicated.
[a]Chi-square.
[b]Independent samples *t*-test.
[c]*t*-Test, equal variances not assumed.

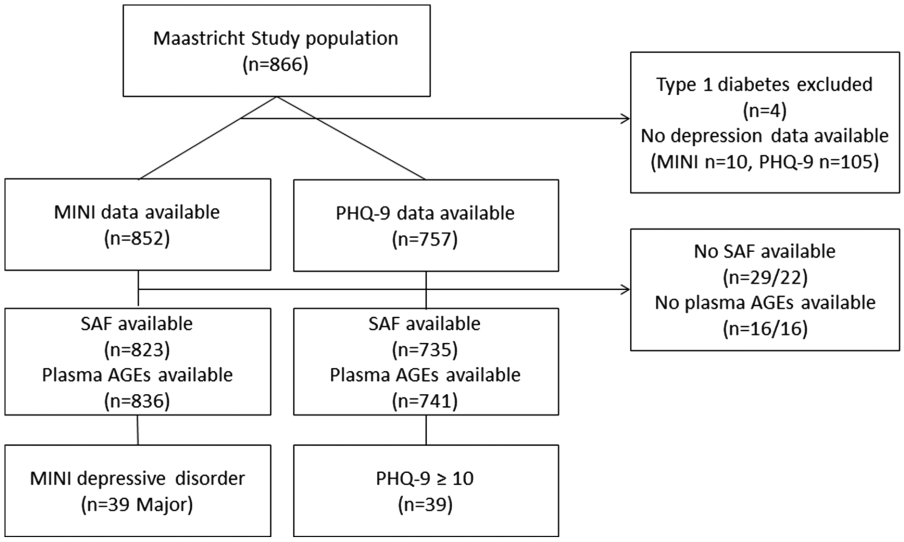

Figure 1. Flow diagram missing data.

levels of protein-bound CML were slightly higher in individuals without depressive disorder as compared to individuals with depressive disorder. Figure 1 depicts a flow diagram of the missing data.

ASSOCIATIONS AMONG AGE ACCUMULATION, DEPRESSIVE SYMPTOMS, AND DEPRESSIVE DISORDER

Table 2 shows a significant association of higher SAF with depressive symptoms (PHQ-9; $\beta = 0.42$, 95% *CI* 0.12–0.73, $P = .007$) after adjustment for age, sex, T2DM status, smoking, BMI, and eGFR. In addition, 1 *SD* higher SAF was associated with a 42% higher odds of depressive disorder (MINI; fully adjusted model, 95% *CI* 1.04–1.95, $P = .028$). Plasma pentosidine, plasma CML, and plasma CEL were not associated with depressive symptoms (respectively; $\beta = 0.23, -0.11, -0.16$) and depressive disorder (respectively; $OR = 1.05, 0.90, 0.83$) after full adjustment.

ADDITIONAL ANALYSES

To determine whether the associations between AGEs and measures of depression were different across diabetes status, an interaction term was added to the regression models. No significant interactions were observed, suggesting that the relationship between AGEs and measures of depression were not different for individuals with or without T2DM.

Explanatory factor analysis was performed to explore the underlying factor structure and depression

TABLE 2. Associations among measures of AGE accumulation, depressive symptoms, and depressive disorder

		Depressive symptoms (PHQ-9)			Depressive disorder (MINI)		
Independent variable	Model	*β*	95% *CI*	*P*-value	*OR*	95% CI	*P*-value
SAF (AU)	1	0.19	−0.09; 0.46	.181	**1.36**	**1.05–1.76**	**.021**
	2	**0.42**	**0.12**; **0.73**	**.007**	**1.52**	**1.14–2.04**	**.004**
	3	**0.42**	**0.12**; **0.73**	**.007**	**1.42**	**1.04–1.95**	**.028**
Plasma pentosidine	1	0.20	−0.06; 0.45	.138	1.10	0.88–1.36	.409
(nmol/mmol LYS)	2	**0.30**	**0.04**; **0.55**	**.023**	1.12	0.91–1.39	.291
	3	0.23	−0.02; 0.48	.067	1.05	0.81–1.36	.722
Plasma CML	1	**−0.43**	**−0.69**; **−0.16**	**.002**	0.82	0.61–1.09	.165
(nmol/mmol LYS)	2	**−0.32**	**−0.59**; **−0.06**	**.018**	0.87	0.65–1.16	.344
	3	−0.11	−0.39; 0.16	.421	0.90	0.65–1.23	.494
Plasma CEL	1	0.03	−0.23; 0.30	.815	0.92	0.70–1.22	.577
(nmol/mmol LYS)	2	−0.06	−0.32; 0.21	.672	0.88	0.66–1.17	.374
	3	−0.16	−0.42; 0.09	.212	0.83	0.61–1.12	.216

Model 1 = crude.
Model 2 = model 1 + age, sex, type 2 diabetes.
Model 3 = model 2 + smoking, BMI, eGFR.

TABLE 3. Associations between measures of AGE accumulation and cognitive and somatic symptoms of depression

		Cognitive symptoms of depression (PHQ-9)			Somatic symptoms of depression (PHQ-9)		
Independent variable	Model	*β*	95% *CI*	*P*-value	*β*	95% *CI*	*P*-value
SAF (AU)	1	0.09	−0.05; 0.23	.219	0.06	−0.07; 0.20	.333
	2	**0.20**	**0.04; 0.36**	**.016**	**0.15**	**0.00; 0.30**	**.049**
	3	**0.19**	**0.02; 0.35**	**.024**	**0.16**	**0.02; 0.31**	**.031**
Plasma pentosidine	1	0.08	−0.06; 0.21	.257	0.11	−0.01; 0.23	.078
(mmol/mmol LYS)	2	0.13	−0.01; 0.26	.065	**0.15**	**0.03; 0.27**	**.015**
	3	0.09	−0.05; 0.22	.204	**0.13**	**0.01; 0.25**	**.032**
Plasma CML	1	**−0.21**	**−0.35; −0.07**	**.003**	**−0.18**	**−0.31; −0.06**	**.003**
(nmol/mmol LYS)	2	**−0.15**	**−0.29; −0.01**	**.040**	**−0.15**	**−0.27; −0.03**	**.018**
	3	−0.06	−0.21; 0.08	.389	−0.06	−0.19; 0.08	.403
Plasma CEL	1	−0.00	−0.14; 0.14	.974	0.04	−0.09; 0.12	.549
(nmol/mmol LYS)	2	−0.05	−0.19; 0.09	.498	0.00	−0.12; 0.12	.996
	3	−0.09	−0.23; 0.04	.177	-0.06	−0.18; 0.07	.373

Model 1 = crude
Model 2 = model 1 + age, sex, type 2 diabetes.
Model 3 = model 2 + smoking, BMI, eGFR.

dimensions of the PHQ-9. Subsequent regression analyses was used to investigate whether differential associations between AGEs and various dimension of depression existed. The appropriateness of using this factor analysis was verified with both the Kaiser–Meyer–Olkin measure of sampling adequacy (0.912), and the Bartlett's test of sphericity ($P < .001$). Two factors were extracted with eigenvalues >1, accounting for 52 and 11% of the total item variance. As expected, two latent factors underlie the PHQ-9, the first factor corresponding with cognitive symptoms of depression (lack of interest, depressed mood, negative feelings about oneself, concentration problems, psychomotor agitation/retardation, and suicidal ideation), and the second factor representing somatic symptoms of depression (sleeping problems, fatigability, and appetite problems).[30] Both factors showed a high internal consistency, with Cronbach's alpha values of respectively .88 and .70.

Higher SAF was significantly associated with both cognitive and somatic symptoms of depression ($\beta = 0.19$, 95% *CI* 0.02–0.35, $P = .024$ and $\beta = 0.16$, 95% *CI* 0.02–0.31, $P = .031$, respectively; Table 3), which suggests that the association of *SAF* with depressive symptoms is not merely due to somatic symptoms, but due to depression as an illness itself. In addition, a positive association between pentosidine and both cognitive ($\beta = 0.09$, 95% *CI* = –0.05–0.22, $P = .204$) and somatic symptoms ($\beta = 0.13$, 95% *CI* 0.01–0.25, $P = .032$) of depression was shown; however, only statistically significant for somatic symptoms. Similar analyses showed negative associations between CML and both cognitive ($\beta = –0.06$, 95% *CI* = –0.21–0.08, $P = .389$) and somatic symptoms of depression ($\beta = –0.06$, 95% *CI* –0.19–0.08, $P = .403$), although not statistically significant. Analyses showed no association between CEL and both cognitive and somatic symptoms of depression (Table 3).

DISCUSSION

The present study is the first to our knowledge to investigate the association of AGEs with depressive symptoms and depressive disorder and has the following main findings. First, a higher level of SAF, a marker for tissue accumulation of AGEs, was significantly associated with depressive symptoms and depressive disorder. These results were independent of possible confounders, and did not differ between individuals with or without T2DM. Second, a high level of plasma pentosidine was borderline significantly associated with depressive symptoms. In addition, *SAF* was associated with both cognitive and somatic symptoms of depression, while pentosidine was associated with somatic symptoms only. Finally, CML and CEL were not significantly associated with depressive symptoms or depressive disorder.

One possible mechanism that may explain our results is the cross-linking of AGEs leading to arterial stiffening. Several studies postulate that the formation of AGE cross-links in the arterial wall leads to increased arterial stiffening.[11,31,32] Increased arterial stiffness leads to an increased pulsatile pressure load, which can damage the microcirculation, especially in the brain.[33,34] This microvascular damage in the brain can manifest itself as white matter hyper intensities (WMH), cerebral microbleeds, and lacunar infarcts, which may ultimately result in depression. In support of this hypothesis, several longitudinal cohort studies[13,35] show an independent association of arterial stiffness with depression in the general population.

Alternatively, activation of inflammatory pathways may play a role in the association between AGEs and depression. AGEs are known to activate the RAGE, which in turn activate genes that lead to the production of cytokines that can bind to many different pro-inflammatory molecules, thereby leading to an amplification of the inflammatory process, endothelial

dysfunction, and oxidative stress.[36] In addition, inflammation, oxidative stress, and endothelial dysfunction are known to be involved in the development of depression.[12,37]

In support of this hypothesis, levels of soluble RAGE (sRAGE), which can bind to AGEs and counteract their detrimental actions,[38] are demonstrated to be lower in individuals with depression.[39,40] This might suggest that high sRAGE levels could have a protective effect against the development of depression.

In contrast to SAF and pentosidine, we did not find any association among plasma CML, plasma CEL, and depression. As previously suggested,[21] plasma levels of CML and CEL may not adequately reflect AGE accumulation in tissues. For instance, trapping of CML via RAGE in adipose tissue can cause a decrease in AGE plasma levels,[8] while depression is frequently accompanied by obesity.[41] Furthermore, plasma AGE levels are determined to a large extent by the half-life of plasma proteins, which is significantly shorter than the half-life time of long-lived proteins in the skin or the vascular wall.[42]

We found a significant association between SAF and both cognitive and somatic depressive symptoms by use of factor analysis. Previous research suggests that mainly the somatic symptoms of depression (e.g., sleeping problems, fatigue, appetitive problems) and not the cognitive symptoms of depression (e.g., depressed mood, negative feelings about oneself, concentration problems) are associated with adverse health outcomes in individuals with physical illness such as diabetes.[17] The theory behind this is that somatic symptoms of depression are associated with metabolic risk factors for diabetes (obesity, dyslipidemia), or metabolic changes in diabetes and the associated inflammation may induce somatic symptoms of depression.[43] Our findings suggest that the association between SAF and depressive symptoms is not limited to only somatic manifestations, but extends to depression as an illness, as cognitive symptoms were also associated with SAF.

The results of the present study should be interpreted in the light of some limitations. First, due to the cross-sectional nature of the study, causal relationships are hard to determine, as AGE accumulation might be the cause or the result of having depressive symptoms. Depression can contribute to suboptimal glycemic control via less-adequate self-care behaviors, for example, lower levels of physical activity and unhealthy diet,[44] and in turn can lead to the formation of AGEs. Depression may influence levels of oxidative stress directly via activation of the physiological stress axes. An increase in catecholamines, in response to stimulation of, for example, the sympatho–adrenal–medullary axis, is common in persons with depression; this may contribute to prooxidants activity, which in turn causes oxidative stress and subsequently to the formation of AGEs.[45] The level of antioxidant concentrations was also found to be lower in case of more symptoms of depression,[46] which can also lead to increased oxidative stress. Second, the percentage of participants with depressive symptoms or depressive disorder in our sample was relatively small compared with the prevalence of depression in other diabetes samples (10–30%).[47] This is possibly due to the fact that our study population is health conscious. The Maastricht Study selected those individuals who are able and/or willing to participate in four half-day visits to the research center. Moreover, participants received information about their health (e.g., do I have diabetes? Is my blood pressure OK?). As a result, participants showed a selection bias toward being health conscious and having a high educational level, and participants with type 2 diabetes were relatively healthy with a median diabetes duration of 8.4 years and a low prevalence of diabetes complications. The relatively small number of participants with depressive symptoms or depressive disorder limits the power of the current analyses. However, despite the relatively small numbers we were able to demonstrate significant and independent associations between SAF and depression. Without the selection bias, the effect estimates could be even stronger. Third, the AGE reader we used to assess tissue AGE accumulation only measures fluorescent AGEs. However, previous studies found a good correlation of *SAF* with both fluorescent and nonfluorescent AGEs in skin biopsies.[48]

Several strengths of the present study should also be highlighted. This is the first study that tested whether multiple markers of AGEs, both SAF and plasma AGEs, are associated with depression. In addition, depression status was extensively assessed, both by the PHQ-9 questionnaire and the MINI diagnostic interview. The extensive characterization of participants enabled us to adjust for multiple potential confounders.

WIDER IMPLICATIONS AND GENERALIZABILITY OF THE FINDINGS

We believe that we have conducted the first study that distinguished cognitive symptoms of depression versus somatic symptoms of depression in relation to AGEs. In addition, we are the first study that explores the association of pentosidine with depression. It is possible that the results that we found are only valid for our study sample, however, more studies are needed to confirm or reject our results.

In addition, in vitro and animal experiments have shown that various interventions can inhibit formation and/or actions of AGEs, in particular the specific AGE inhibitor aminoguanidine and the AGEs crosslink breaker alagebrium, and the B vitamins pyridoxamine and thiamine, and the latter's synthetic derivative benfotiamine.[49] Although the potential clinical value of these interventions remains to be established, it could be a potential future intervention/treatment for AGE-induced depression.

CONCLUSION

In conclusion, this study shows that AGE accumulation in the skin is independently associated with higher levels of depressive symptoms and depressive disorder. This association is both present for somatic and cognitive symptoms of depression. Additionally, pentosidine was found to be independently associated with somatic symptoms of depression. Our results might suggest that AGEs in the skin are involved in the development of depressive symptoms, possibly through the pathway of vascular stiffening, inflammation, or oxidative stress. Further research is needed to examine the causation of our observations.

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Conflict of interest. The authors declare that they have no conflicts of interest.

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