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Skin autofluorescence, renal insufficiency and retinopathy in patients with type 2 diabetes

Rabia Bentata [a,b,*], Audrey Cougnard-Grégoire [c,d], Marie Noëlle Delyfer [a,c,d], Cécile Delcourt [c,d], Laurence Blanco [b], Emilie Pupier [b], Marie Bénédicte Rougier [a,c,d], Kalina Rajaobelina [c,d], Marie Hugo [b], Jean François Korobelnik [a,c,d], Vincent Rigalleau [b,c,d]

[a] CHU de Bordeaux, Service d'Ophtalmologie, Bordeaux, F-33000, France
[b] CHU de Bordeaux, Department of Nutrition-Diabetology, Bordeaux, F-33000, France
[c] Univ. Bordeaux, ISPED, F-33000 Bordeaux, France
[d] Inserm, U1219 - Bordeaux Population Health Research Center, F-33000 Bordeaux, France

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ABSTRACT

Objectives: Advanced glycation end-products (AGEs) are involved in diabetic retinopathy (DR). Their accumulation in tissues can be analyzed by measuring the skin autofluorescence (sAF). We hypothesized that renal insufficiency, another cause of high sAF, may disturb the relation between sAF and DR.
Research Design and Methods: We measured sAF with an AGE-Reader in 444 patients with type 2 diabetes (T2D), and we analyzed their retinal status. The associations of sAF with DR, and interaction with renal insufficiency were estimated by multivariate logistic regression analysis.
Results: Mean age was 62 years (standard deviation (SD) 10 years), diabetes duration 13 (9) years and mean HbA1C 8.9% (1.8). The prevalence of DR was 21.4% and increased with age, diabetes duration, arterial hypertension, renal parameters (serum creatinine and albumin excretion rates), and sAF. The prevalence of macular edema (ME) was 8.6% and increased with the duration of diabetes, but not with sAF ($p = 0.11$). There was a significant interaction between renal insufficiency and sAF for the relation with DR or ME ($p = 0.02$). For the 83% patients without renal insufficiency (estimated GFR > 60 mL/min/1.73 m2), sAF was related to DR or ME after multivariate adjustment: OR 1.87 (1.09–3.19). The 17% patients with renal insufficiency had the highest rates of DR or ME (38.6%) and the highest sAF, unrelated to each other.
Conclusions: In T2D patients with renal insufficiency, the high sAF does not relate to retinopathy, which should be systematically searched due to its high frequency. For other patients, a high sAF argues for DR screening.

1. Introduction

Diabetic retinopathy (DR) is the first cause of visual impairment in the working age population (Klein, 2007). Diabetic eye complications, in particular ME, are the main cause of visual impairment in the developed countries (Saaddine et al., 2008). The main risk factors for DR are the duration and poor control of diabetes, arterial hypertension and dyslipidemia (Lee, Wong, & Sabanayagam, 2015). These abnormalities are especially frequent when diabetes is complicated by chronic kidney disease (CKD), which has recently been reported to double the risk for DR (Park, Shin, Han, Park, & Yim, 2015).

Advanced glycation end products (AGEs) play a critical role in the physiopathology of DR (Chen, Curtis, & Stitt, 2013). High levels of circulating AGEs have repeatedly been reported in patients with DR (Fosmark et al., 2006; Ghanem, Elewa, & Arafa, 2011; Mishra et al., 2016). The deposit of AGEs in diabetic retina has been reported first in diabetic rat retinas in the neuroglial and vascular part (Hammes et al., 1999) and in the human diabetic retina especially in the vascular wall and around the vessels (Murata et al., 1997). Another argument for its implication in the onset and progression of diabetic retinopathy is the co-localization with vascular endothelial growth factor which is known to play a critical role in the pathogenesis of DR (Murata et al., 1997). The accumulation of AGEs in skin biopsies is a good predictor of later progression of retinopathy in the DCCT (Genuth et al., 2005). However, due to the complexity of the assays for AGE and to the invasiveness of skin biopsies, these time-consuming methods cannot be used to improve the screening of DR.

Nowadays, the tissue accumulation of AGEs can be estimated by measuring the skin autofluorescence (sAF) (Meerwaldt et al., 2004). This non-invasive technique is based on the fluorescent property of some AGEs. sAF is well correlated with the concentrations of AGEs from skin biopsies in diabetic and hemodialysed patients (Meerwaldt et al., 2004). Cross-sectional studies have shown that sAF is high in patients with diabetes and microangiopathic complications (Geneviève, Vivot,

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* Corresponding author.
E-mail address: rabia.bentata@gmail.com (R. Bentata).

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Gonzalez, & Raffaitin, 2013; Lutgers et al., 2006; Noordzij et al., 2012; Rigalleau et al., 2015). Whether sAF relates to DR is however not established, because the relation did not reach significance in some studies (Chabroux et al., 2010; Noordzij et al., 2012). In the ZODIAC cohort, sAF was an independent predictor of the later incidence of neuropathy and microalbuminuria, but not DR in type 2 diabetes (T2D) (Gerrits et al., 2008). A significant correlation between sAF and micro- and macrovascular complications has been demonstrated in a type 2 diabetes primary (Lutgers et al., 2006) and secondary care populations (Noordzij et al., 2012). In type 2 diabetes, Rigalleau V et al. also demonstrated that sAF was associated with renal insufficiency and macroangiopathy (Rigalleau et al., 2015). In type 1 diabetes patients, Geneviève et al. showed that sAF was related to retinopathy (Geneviève et al., 2013) but not Chabroux's team after adjustment for several parameters (Chabroux et al., 2010). ME has been less investigated than DR because of its lower prevalence rate. Nevertheless, sAF was significantly associated with central macular thickness in T2D patients with early DR (Hashimoto et al., 2016). In another paper, sAF was not significantly elevated in patients with ME and there was no correlation between sAF and ME severity (Hirano et al., 2014). The value of sAF as a marker of DR is also challenged by the high sAF in patients with non-diabetic CKD (Tanaka et al., 2011), which is obviously not complicated by DR. This important point led us to hypothesize that the presence of CKD may disturb the relation between sAF and DR in patients with T2D.

In 444 patients with complicated or uncontrolled T2D, we studied the association between elevated sAF and DR and/or ME, and tested whether this association was modified by the renal function.

2. Methods

2.1. Patients

Four hundred and forty-four patients were consecutively included. All presented with uncontrolled or complicated T2D. They all had a clinical exam, blood sample and sAF measurement. Patients with high Fitzpatrick phototypes (V and VI) were excluded because of the impossibility of measuring sAF in this population (Koetsier et al., 2010). All the patients gave informed consent to participate the study.

2.2. Data

Several data were recorded during the clinical exam: age, gender, body mass index (BMI), smoking habits, arterial hypertension (blood pressure ≥ 140/90 mmHg and/or antihypertensive treatment), duration of diabetes (as reported by the patient), treatments by insulin and statins. Macroangiopathy was defined as a previous cardiovascular event (myocardial infarction, stroke or gangrene) or a previous revascularization procedure, from patient report at admission. Biological exams were performed on blood and urine samples: HbA1c, blood lipids (total, HDL, LDL-cholesterol and triglycerides), serum creatinine, albumin excretion rate (AER). The glomerular filtration rate (eGFR) was estimated by the EPI-CKD formula (Levey et al., 2009). Renal insufficiency was defined by eGFR <60 mL/min/1.73 m^2. DR was classified by an ophthalmologist as absent, non-proliferative (mild, moderate, severe) or proliferative together with the presence or absence of ME from fundus examination or retinophotography after dilation and, if required, by optical coherence tomography examination.

2.3. Skin Autofluorescence Measurement

The accumulation of AGEs in the skin was estimated by sAF measured during their hospitalization, using an AGEs reader (DiagnOptics BV, Groningen, the Netherlands). The measure of sAF was performed on the forearm at a normal skin site at room temperature with patients in a sitting position. sAF is expressed in arbitrary units (A.U.).

2.4. Statistical Analysis

The results are presented as mean +/− standard deviation (SD) for continuous variables and as percentages for categorical variables. The associations between the different stages of DR and ME (dependent variables) and potentially explanatory variables (age, gender, smoking, BMI, sAF, duration and control (HbA1C) of diabetes, blood lipids, insulin, statin, hypertension, macroangiopathy, AER and eGFR) were examined with Student t-test and chi-square test or Fisher exact test, as appropriate. The associations between "DR or ME" and characteristics of the patients were estimated using multivariate logistic regression analysis. We regrouped the four stages of diabetic retinopathy (mild, moderate or severe, proliferative stages) and the presence of macular edema in one class, "DR or ME" vs "no DR and ME". Variables significantly associated at $p < 0.05$ in univariate analyses were selected for entry in the multivariate model. Interaction between eGFR and sAF was tested. HbA1c was forced into the multivariate model. The associations are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Subjects without DR or ME were the reference in the multivariate model. p-values < 0.05 were considered as significant. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patients Characteristics (Table 1)

A total of 444 patients were included in the study. Their characteristics are summarized in Table 1: 261 patients were men (58.8%). Their mean

Table 1
Characteristics of the population.[1]

	N	(%)
Age (years)		
<60	182	(40.99)
[60;70[	162	(36.49)
≥70	100	(22.52)
Gender (males)	261	(58.78)
Smoker		
No	230	(51.80)
Former	156	(35.14)
Current	58	(13.06)
BMI (kg/m^2)		
25	32	(7.21)
[25;30[	125	(28.15)
≥30	287	(64.64)
Insulin therapy (n = 443)	282	(63.66)
Statin therapy (n = 439)	292	(66.51)
Hypertension (n = 440)	296	(67.27)
eGFR (n = 440)[1]		
<30 mL/min/1.73 m2	15	(3.41)
[30;60[	60	(13.64)
≥60	365	(82.95)
Macroangiopathy	168	(37.84)
Diabetic retinopathy		
No	349	(78.60)
Mild	35	(7.88)
Moderate to severe	25	(5.63)
Proliferative	35	(7.88)
Macular edema	38	(8.56)
Duration of diabetes (mean, SD)	13.38	(9.56)
LDL (g/l) (n = 422) (mean, SD)	1.11	(0.43)
HDL (g/l) (n = 410) (mean, SD)	0.46	(0.15)
Triglycerides (g/l) (n = 420) (mean, SD)	2.07	(3.76)
Hba1c (%) (mean, SD)	8.91	(1.80)
sAF (A.U.) (mean, SD)	2.52	(0.61)
AER (mg/24 h) (n = 365) (med, IIQ)	22.00	(7.60;71.61)

AER: Albumin excretion rate; eGFR: estimated glomerular filtration rate; LDL: low density lipoprotein; HDL: high density lipoprotein; sAF: skin autofluorescence.
[1] eGFR estimated with the CKD-EPI formula (Levey AS et al., 2009).

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