



## Skin autofluorescence, a marker of glucose memory in type 2 diabetes

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#### Abstract

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### 1. Introduction

Glycemic memory can be defined as the persistence of diabetic complications after glucose control has been achieved [1]. This concept has emerged from the results of the post-trial study of patients with type 1 diabetes (T1D) after the intervention period of the DCCT: lower rates of complications persisted for the formerly intensively treated patients, despite glucose control were then similar in both arms of the trial [2]. A legacy effect was later confirmed by the post-UKPDS study in type 2 diabetes (T2D), with less microangiopathic complications and also less myocardial infarctions and death for the formerly intensively treated patients [3]. The clinical implications are especially important in T2D, which can be ignored or neglected for many years due to its insidious clinical presentation: as endogenous insulin secretion persists, very long term hyperglycaemia due to insufficient treatment is possible, without any hyperglycemic crisis.

The underlying mechanisms of glycemic memory are not fully known. Inflammation, oxidative stress and epigenetic modulation during transient periods of hyperglycaemia are thought to lead to a “bad signature” [4] and a long term altered gene expression that persists after hyperglycaemia has resolved [5]. The long term deposit of Advanced Glycation End-products (AGEs) probably plays an important role, as reflected by the close relation between the skin concentrations of AGEs in cutaneous biopsies and later vascular complications in the DCCT/EDIC study [6]. But it seems difficult to

perform skin biopsies to predict complications outside research studies.

The fluorescent properties of some AGEs allow an indirect, non invasive evaluation by measuring the skin autofluorescence (sAF): sAF are correlated to the skin concentrations of AGEs in subjects with diabetes [7]. The ZODIAC study has shown that sAF predicts later vascular complications, except retinopathy, in T2D [8,9]. Several studies have reported that sAF relates to the previous glucose control in T1D [10,11], whereas the evidence is not clear in T2D, with a weak correlation [12]. Other factors, mainly age and renal function [13], also influence sAF, and they may probably play a role in its relation to diabetic complications, which are much more frequent in old, renal insufficient patients.

In order to evaluate the value of sAF as a marker of glycemic memory in T2D, we measured it in 905 patients hospitalized in our unit for uncontrolled or complicated T2D, and we searched whether it fulfilled the following criteria: Does it relate to ancient glucose control, as reflected by HbA1c of the previous years, when available? Does this relation persist after adjusting for well-known confounders, as age and renal function? Are sAF higher in patients with vascular complications? Do these associations persist after adjusting for the risk factors for these complications?

### 2. Subjects and methods

#### 2.1. Subjects

Nine hundred and five patients hospitalized in our unit for uncontrolled or complicated T2D were included. All were interviewed, had a clinical exam, and blood and urinary analyses. All the subjects

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gave their informed consent to participate in the study, which was approved by the local ethic committee.

## 2.2. Data

The following data were collected: age, sex, duration of diabetes, body mass index, arterial hypertension (defined by treatment with antihypertensive drug or blood pressure  $\geq 140/90$  mmHg), treatment by a statin, and the history of vascular complications in T2D patients: macrovascular as myocardial infarction, stroke, gangrene, revascularization; and microvascular as retinopathy, chronic diabetes-related kidney disease (DKD), history of diabetic foot ulcers. Diabetic retinopathy was diagnosed on 2 fundus photos per eye (one centered on the disc, one centered on the macula). The biological data recorded included HbA1c levels, blood lipids, the Albumin Excretion Rates (AER), and serum creatinine to estimate the Glomerular Filtration Rates (eGFR) calculated with the CKD-EPI formula. Diabetic Kidney Disease (DKD) was defined by eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> or/and albumin excretion rate  $> 30$  mg/24 h.

HbA1c was measured on the same day as the skin autofluorescence was measured. We also registered the available previous HbA1c from each of the three years before the admission, and the most ancient available HbA1c.

## 2.3. Skin autofluorescence measurement

The cutaneous accumulation of the Advanced Glycation End-products from the skin autofluorescence (sAF) using the AGE-READER (Diagnoptics, Groningen, the Netherlands). The device illuminated 1 cm<sup>2</sup> of the forearm skin. SAF values were calculated by dividing the mean emitted light intensity (excitation light source ranging from 300 to 420 nm) by the mean reflected excitation light intensity from the skin (over 300–420 nm). The patients with Fitzpatrick phototypes V and VI were not included due to their skin pigmentation, which had ultraviolet reflectance of  $< 10\%$ . The results were expressed in arbitrary units (AU). The reproducibility of sAF is indicated by a mean coefficient of variation  $\sim 5\%$  [7]. Reference values for healthy caucasians have been reported according to age: sAF = (0.024 X age) + 0.83 [14], we compared our results to these theoretical values.

## 2.4. Statistical analysis

The results of the continuous variables are expressed as mean  $\pm$  SD, and as median (IQR) for asymmetric distributions. The categorical variables are presented as numbers (percentages).

The association between previous HbA1c and sAF tertiles were tested using a mixed regression model with random effects after multiple adjustments. To test the glycaemic memory, the analyses were stratified by rising interval time of HbA1c measurements: recent ( $-3$  months [2, 4]), medium ( $-14$  months [12, 18]), and old ( $-36$  months [30, 60]). The associations between sAF tertiles and complications were tested by logistic regression analysis. By multivariate regression analysis, we searched whether the Log-transformed Albumin Excretion Rates were related to the sAF, adjusted for other explicative variables (age, gender, BMI, duration of diabetes, current HbA1c, lipid profiles and use of statins, arterial hypertension and estimated GFR). A value of  $p < 0.05$  was considered as significant.

## 3. Results

### 3.1. Study population characteristics (Table 1)

We included 905 patients: 57% men, age  $63 \pm 10$  years, diabetes

duration  $13 \pm 10$  years. The mean sAF was  $2.67 \pm 0.66$  AU, higher than the theoretical value calculated from age:  $2.33 \pm 0.24$  ( $p < 0.0001$ ). The Table 1 depicts the main clinical and biochemical characteristics of the patients according to the skin AF tertiles. Skin autofluorescence was significantly related to the age ( $\beta = +0.36$ ,  $p < 0.0001$ ), the duration of diabetes ( $\beta = +0.39$ ,  $p < 0.0001$ ), the plasma triglycerides ( $\beta = -0.08$ ,  $p = 0.03$ ), and the eGFR ( $\beta = -0.36$ ,  $p < 0.0001$ ). By multivariate analysis, the skin AF was related to the age ( $\beta = +0.23$ ,  $p < 0.0001$ ) and the eGFR ( $\beta = -0.22$ ,  $p < 0.0001$ ).

### 3.2. Relation between sAF and HbA1c

We registered 2485 values of HbA1c (mean  $\pm$  SD:  $8.9 \pm 1.9\%$ ). On the whole, the highest mean [95%CI] HbA1c were registered in the upper tertile of skin AF: T1 8.8% [8.6–9.0], T2 8.9% [8.7–9.1], T3 9.1% [8.9–9.3],  $p = 0.02$ , after adjustment for ID, sex, age, diabetes duration, plasma triglycerides, arterial hypertension, eGFR, AER, diabetic retinopathy, and macrovascular disease.

The timing of the HbA1c were:  $n = 905$  at the time of inclusion ( $8.8 \pm 1.9\%$ ), 653 during the year before inclusion ( $-4 \pm 4$  months,  $9.0 \pm 1.9\%$ ), 399 one more year before ( $-16 \pm 4$  months,  $8.7 \pm 1.8\%$ ), 259 two more years before ( $-30 \pm 4$  months,  $8.7 \pm 1.8\%$ ), and 266 most ancient values ( $-66 \pm 36$  months,  $9.0 \pm 2.2\%$ ). None of the HbA1c at any time interval were correlated to the skin AF, except the most ancient HbA1c:  $r = 0.16$ ,  $p = 0.009$ . After adjustment for the age and eGFR, the relation between this most ancient HbA1c and the skin AF persisted ( $\beta = +0.17$ ,  $p = 0.002$ ) and there was also a tendency for a relation between the 259 HbA1c registered  $30 \pm 4$  months before and the skin AF ( $\beta = 0.09$ ,  $p = 0.089$ ).

Because the numbers of registered previous HbA1c values were different according to the time of registration, we categorized them according as recent ( $N = 526$ ), medium ( $N = 527$ ) and old ( $N = 527$ ) HbA1c values. They are summarized in Table 2. The recent and medium HbA1c values did not differ according to the skin AF tertiles, but the old HbA1c were higher in the higher tertiles of skin AF:  $p = 0.004$  after adjustment for ID, sex, age, diabetes duration, triglycerides, hypertension, eGFR, AER, diabetic retinopathy, and macrovascular disease.

### 3.3. Relation between sAF and diabetic complications (Table 3)

Micro- and macrovascular diseases were observed in 576 and 315 patients, respectively. SAF was higher in participants with microvascular ( $2.79 \pm 0.67$  vs  $2.46 \pm 0.57$ ,  $p < 0.0001$ ) and macrovascular complications ( $2.78 \pm 0.66$  vs  $2.61 \pm 0.65$ ,  $p = 0.0004$ ) compared to others. As shown in Table 1, Diabetic retinopathies, Diabetic Kidney Diseases, Histories of foot ulcers, and macrovascular diseases, were more frequent in the highest tertiles of sAF (all  $p < 0.0001$ ). The Log-transformed Albumin Excretion Rates were related to the sAF:  $\beta = +0.166$  (95%CI: 0.128–0.300) after multi-adjustments. The sAF were  $2.58 \pm 0.61$  AU in subjects with normoalbuminuria ( $N = 560$ ),  $2.70 \pm 0.66$  in subjects with microalbuminuria ( $N = 240$ ,  $p < 0.05$  vs normoalbuminuria), and  $3.03 \pm 0.72$  in subjects with macroalbuminuria ( $N = 105$ ,  $p < 0.001$  vs normo and microalbuminuria).

Microvascular (T2 vs T1, OR [95% CI] 1.52 [1.06–2.17],  $p = 0.03$ ; T3 vs T1 2.47 [1.68–3.63],  $p < 0.0001$ ) and macrovascular complications (1.49 [1.01–2.21],  $p = 0.04$ ; 0.99 [0.66–1.50],  $p = 0.98$ ) were associated with the upper sAF tertiles in the adjusted model (Table 3).

Similar results were observed when we analyzed separately Diabetic Kidney Diseases (T2 vs T1, 1.40 [0.97–2.02],  $p = 0.07$ ; T3 vs T1, 1.68 [1.15–2.45],  $p$  for trend = 0.007) and diabetic retinopathy (T2 vs T1, 1.79 [1.14–2.79],  $p = 0.01$ ; T3 vs T1, 1.64 [1.03–2.61],  $p$  for

**Table 1**  
Characteristics of participants according to skin AF tertiles.

	Overall	Tertiles of skin autofluorescence			p
		T1	T2	T3	
N	905	302	302	301	
Skin AF (AU)	2.67 ± 0.66				
Age (years)	63 ± 10	59 ± 11	63 ± 9	66 ± 9	<0.0001
Female gender, n (%)	386 (43)	135 (45)	129 (43)	122 (41)	0.58
Duration of diabetes *, (years)	13 [6,20]	10 [4,16]]	13 [7,20]	15 [7,23]	<0.0001
BMI (Kg/m <sup>2</sup> )	32 ± 6	32 ± 6	32 ± 6	32 ± 6	0.57
Arterial Hypertension, yes	587 (65)	174 (59)	201 (67)	212 (70)	0.008
Triglycerides*, (mg/dl)	157 (111, 218)	171 (115, 241)	148 (109, 204)	150 (110, 209)	0.03
LDL-cholesterol (mg/dl)	107 ± 45	111 ± 43	107 ± 41	104 ± 50	0.16
HDL-cholesterol (mg/dl)	45 ± 14	45 ± 15	45 ± 13	45 ± 15	0.84
Treated by a statin	574 (64)	181 (61)	197 (65)	196 (65)	0.50
eGFR (mL/min/1.73m <sup>2</sup> )	84 ± 25	93 ± 21	84 ± 23	74 ± 27	<0.0001
Urinary albumin excretion *, (mg/24H)	16 (4, 64)	12 [4,40]	16 (5, 57)	21 (6, 169)	<0.0001
Diabetic Kidney Disease	405 (45)	105 [35]	138 (46)	162 (54)	<0.0001
Diabetic retinopathy	216 (24.5)	44 [15]	81 [28]	91 [31]	<0.0001
History of foot ulcer, yes	207 [23]	46 [15]	64 [21]	97 [32]	<0.0001
Microvascular disease	576 (65)	152 (52)	193 (65)	231 (77)	<0.0001
Macrovascular disease	315 [35]	80 [26]	121 [40]	114 [38]	0.0009

eGFR: estimated glomerular filtration rate (with the CKD-EPI formula); LDL: low density lipoprotein; HDL: high density lipoprotein. \* median (IQR).

**Table 2**  
Previous HbA1c levels according to skin autofluorescence tertiles— by timing of HbA1c measurements.

Timing	Number	Months	Tertiles of skin autofluorescence			p
			T1	T2	T3	
Recent	526	3 [2,4]	9.0 (8.6–9.4)	9.1 (8.7–9.6)	9.3 (8.9–9.8)	0.37
Medium	527	14 [12,18]	8.4 (8.0–8.8)	8.6 (8.1–9.0)	8.5 (8.1–8.9)	0.75
Old	527	36 (30, 60)	8.2 (7.7–8.7)	8.7 (8.2–9.2)	9.2 (8.7–9.6)	0.0004

Adjusted for ID, sex, age, diabetes duration, triglycerides, hypertension, eGFR, AER, diabetic retinopathy, and macrovascular disease.

**Table 3**  
Microvascular and macrovascular diseases according to skin AF tertiles.

Vascular disease	Skin AF tertiles	Vascular disease		Unadjusted model		Adjusted model	
		No	Yes	OR (95% CI)	p	OR (95% CI)	p
Microvascular	T1	142	152	Ref.	–	Ref.	–
	T2	104	193	1.73 (1.25–2.41)	0.001	1.52 (1.06–2.17)	0.03
	T3	70	231	3.08 (2.17–4.38)	<0.0001	2.47 (1.68–3.63)	<0.0001
Macrovascular	T1	222	80	Ref.	–	Ref.	–
	T2	181	121	1.86 (1.32–2.62)	0.0004	1.49 (1.01–2.21)	0.04
	T3	187	114	1.69 (1.20–2.39)	0.003	0.99 (0.66–1.50)	0.98

Adjusted for sex, age, diabetes duration, triglycerides, and hypertension, plus eGFR, AER and diabetic retinopathy (for macrovascular disease analyses), or macrovascular disease (for microvascular disease analyses).

trend = 0.04) after adjusting for sex, age, diabetes duration, triglycerides, hypertension, and macrovascular disease plus retinopathy (for DKD analyses) or eGFR and UAE (for retinopathy analyses). Similar results were observed also for histories of foot ulcers (T2 vs T1, 1.40 [0.90–2.17], p = 0.14; T3 vs T1, 2.27 [1.47–3.50], p for trend = 0.0002) after adjusting for sex, age, diabetes duration, triglycerides, hypertension, eGFR, AER, diabetic retinopathy, and macrovascular disease.

Finally, the relations between tertiles of sAF and vascular complications of diabetes as depicted in Table 3 were adjusted for sex, age, diabetes duration, triglycerides, arterial hypertension, and eGFR, AER and diabetic retinopathy (for macrovascular complications), or macrovascular disease (for microvascular complications), but they were not adjusted for long term glycemic exposure indexes as the HbA1c values. Searching for an independent predictive value of sAF for vascular complications, we further adjusted our binary logistic regression analysis for the last HbA1c and the mean of previous available HbA1c. After these adjustments, the relations between sAF

and vascular complications were significant for all complications (retinopathy + DKD + history of foot ulcer + macroangiopathy): OR: 1.079 [1.044–1.115], for microangiopathy (retinopathy + DKD): OR: 1.056 [1.030–1.084], for history of foot ulcers: OR: 1.050 [1.021–1.079], but not for macroangiopathy alone: OR: 1.011 [0.985–1.037].

#### 4. Discussion

We searched whether sAF could be considered as a marker of glucose memory in 905 subjects hospitalized for an uncontrolled or complicated T2D. sAF was related to their 2485 HbA1c values, this relation was significant only with their oldest HbA1c, adjusted for the other explicative variables for sAF. The highest tertiles of sAF were related to 2.47-fold more microangiopathic complications. The relation between sAF and macroangiopathy (X 1.49 for the 2<sup>nd</sup> tertile of sAF) was less closed. The relations between sAF and 1) ancient histories of poor glucose control and 2) vascular

complications, especially microangiopathy, argue for its value as a marker of glucose memory.

The relation between sAF and ancient glucose control has already been reported outside the context of T2D. In elderly subjects from the general population, we reported that sAF was related to the glycemia and HbA1c measured ten years before, and not to their current values [13]. In Type 1 Diabetes, sAF also is better related to previous than present HbA1c [10,11,15]. In T2D, associations with the duration of diabetes and HbA1c were reported in the pioneer work from Meerwaldt [7], but they were not detected in advanced and complicated diabetes [16]. The correlation between sAF and current or time-integrated HbA1c levels were weak in the ZODIAC study [12], that included well-controlled, stable T2D. The relation that we found in our uncontrolled patients was still significant after adjustment for age and DKD, which are both well-known to contribute to sAF: AGEs naturally accumulate in tissues during the aging process [14,17], and this accumulation accelerates when their precursors are less cleared due to impaired renal function [18]. Our work shows that the measurement of sAF integrates ancient periods of hyperglycaemia-driven overproduction of AGEs, as expected for a marker of glucose memory. This seems of great interest for T2D, that can be ignored for many years due to its insidious course.

Glucose memory, age and eGFR were the main explicative variables for sAF in our patients. They are also major contributors for vascular diabetic complications in T2D [19]. The relations between sAF and these complications, as already reported for T1D [20,21] were therefore expected. Numerous studies have reported high sAF in complicated T2D [16,22–24]. In accordance with our findings, the largest previous study (N = 563) from Noordzij et al. found that sAF was related both to macrovascular and microvascular complications, after multiple adjustments [16]. But none of these studies did report the relation between sAF and ancient glucose control. The relation between sAF and the history of diabetic foot ulcers seems of especial interest, as the diabetic foot syndrome both relies on micro (neuropathy) and macroangiopathy (peripheral arterial disease). The pioneer work from Meerwaldt already mentioned a relation between sAF and diabetic neuropathy [25], which was later confirmed in T1D [26]. sAF is high in subjects with peripheral arterial disease [27], and predicts rates of amputations [28] and mortality [29]. Two studies have already reported associations between sAF foot ulcers in T2D [30,31], on smaller groups of patients.

The relation between sAF and diabetic vascular complications was closer for microangiopathy (ascending OR with tertiles of sAF) than for macroangiopathy (higher OR only for the second tertile of sAF), which seems logical for a marker of glucose memory. The long term hyperglycaemic exposure may however not be the sole mechanism for the relation between sAF and microangiopathy, which kept significant after adjustment for diabetes duration and HbA1c. A specific toxic effect of accumulating AGEs on microvasculature may occur during transient bursts of hyperglycaemia [32], but this seems unlikely because sAF is not influenced by short-term glycemic variations [33]. In some of our patients, sAF may have increased during ignored and resolving episodes of acute kidney injuries [34]: we have shown that sAF quickly rises during an acute renal failure [35]. Acute kidney injuries predict cardiovascular events in T2D [36], and they may favor the progression of retinopathy [37]. Dietary sources of AGEs may have contributed to the accumulation of AGEs independent of hyperglycaemia [38], and high-AGE meals are known to impair vascular function in T2D [39]. Whatever the mechanism, the independent relation between the simple and non-invasive measure of sAF and microangiopathy in T2D is of interest.

The main limitation of our study is its retrospective design, which was mandatory to examine the relation between sAF and

ancient glucose control. As occurs in the real life, we could not systematically register HbA1c of previous years for all subjects, but the specific relation between sAF and the most ancient values argues for its value as a marker of glucose memory. We could not register ancient HbA1c values for all subjects, and the HbA1c data at onset time of diabetes were not available. The 266 HbA1c values registered  $66 \pm 36$  months before inclusion however seem an important information on the quality of ancient glucose control in subjects with a mean duration of diabetes ~13 years. Our study was cross-sectional. Longitudinal studies have already shown that sAF predicts diabetic vascular complications in T2D [8,9], but this was limited to macroangiopathy in the recent report from Yozgatli et al. [40]. We did not register the smoking habits of our participants, which may influence their sAF and risk of vascular complications.

In summary, we tested the interest of sAF, that reflects the accumulation of AGEs in tissues, as a marker of metabolic memory in 905 subjects hospitalized for uncontrolled or complicated T2D. sAF was independently related to their most ancient HbA1c, and it was higher in subjects with microangiopathic complications: retinopathy, DKD, histories of foot ulcers.

### CRediT authorship contribution statement

**Marine Rigo:** Investigation, Data curation, Writing - original draft, Writing - review & editing. **Maxime Lecocq:** Investigation, Resources. **Charlotte Brouzeng:** Investigation. **Marie Michelet:** Investigation. **Kamel Mohammedi:** Supervision, Formal analysis. **Laurence Blanco:** Investigation, Writing - review & editing. **Pauline Poupon:** Investigation. **Magalie Haissaguerre:** Resources. **Marie Monlun:** Investigation. **Ninon Foussard:** Resources. **Alice Larroumet:** Resources. **Anne-Claire Devouge:** Resources. **Claire Ducos:** Resources. **Quentin Bataglini:** Resources. **Vincent Rigal-leau:** Supervision, Writing - review & editing, Formal analysis, Project administration.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.metop.2020.100038>.

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