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ORIGINAL ARTICLE

Increased skin autofluorescence of advanced glycation end products (AGEs) in subjects with cardiovascular risk factors

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Abstract

Background As a clinical and non-invasive tool, the AGE Reader measures skin autofluorescence (SAF) to estimate the accumulation of advanced glycation end products (AGEs) in the skin. Accumulation of AGEs has been implicated in several inflammation-associated diseases, including diabetes and cardio-metabolic diseases. This study aimed to assess SAF in subjects with and without cardiovascular risk (CVR) factors and examine the association between SAF and various bio-clinical parameters.

Methods In a cross-sectional study, we included 250 participants between 19 and 86 years of age divided into two groups: a healthy group ($n = 88$) and subjects with CVR factors ($n = 162$ in total, diabetes $n = 48$, hypertension $n = 62$, and both $n = 52$). We assessed skin AGE measures and biological and clinical data.

Results SAF was significantly higher in subjects with CVR factors than in healthy participants (2.42 ± 0.38 vs 1.90 ± 0.29 respectively; $p < 0.001$). SAF was associated with age, gender, BMI, duration of diabetes, HbA1c, triglyceride, and obesity. Multivariate analysis showed that age and duration of diabetes were the independent determinants of SAF. The ROC analysis indicated that a SAF > 2.25 AU was the optimal cut-off point to predict the presence of diabetes and/or hypertension and dyslipidemia ($p < 0.001$).

Conclusion This Tunisian population-based study shows an increased SAF level in subjects with diabetes and/or hypertension and dyslipidemia compared to healthy subjects. The AGE Reader device is a rapid and non-invasive tool in clinical practice to evaluate and screen CVR factors in Tunisia with a North African phototype.

Keywords Skin autofluorescence · Advanced glycation end products · Cardiovascular risk factors

Introduction

The prevalence of cardio-metabolic diseases, including diabetes mellitus, dyslipidemia, and hypertension is currently increasing and represents a significant health problem in Tunisia [1–4]. It is well known that diabetes mellitus combined with the myriad of cardiovascular factors is responsible for the development of long-term microvascular and macrovascular complications, which contribute to the increased risk of morbidity and mortality [4, 5].

Hyperglycemia induces glycation and oxidative pathways directly or indirectly on proteins, lipids, and nucleic acids [6, 7]. Serum glucose and glycated hemoglobin (HbA1c) concentrations are the standard biomarkers for detecting diabetes. Still, these parameters do not fully reflect the adverse effects in tissues for diabetic patients with or without vascular

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complications. Several studies have shown the role of accumulation of so-called advanced glycation end products (AGEs) in tissues as a biomarker for early detection, screening, and diagnosis of many diseases [8, 9]. The accumulation of AGEs contributes to tissue damage in several chronic and aging-related diseases, such as diabetes, atherosclerosis, chronic kidney disease, neurodegenerative disorders and even erectile dysfunction in diabetes mellitus [10–13]. AGEs are a complex and heterogeneous group of non-fluorescent and fluorescent compounds that becomes irreversibly cross-linked adducts that bind to amino acids (lysine/arginine residues) of proteins and accumulate on proteins a slow turnover [14]. AGEs are formed by non-enzymatic glycation and oxidation during aging and are further increased in conditions of hyperglycemia. Many different AGEs have been identified, such as pentosidine, crossline, methyl-glyoxal-lysine dimer (MOLD), and glyoxal-lysine dimer (GOLD) as fluorescent AGEs, and N-carboxymethyl-lysine (CML), methyl-imidazolone, argpyrimidine, glucosepane, and pyrriline as non-fluorescent AGEs [6, 7]. The degree of AGE accumulation in the body is associated with increased production, decreased degradation, and renal clearance [15].

We have shown previously that serum AGEs have been implicated in individuals with diabetes, with and without vascular complications in Tunisian patients. Serum pentosidine levels, a fluorescent AGE product, were markedly increased in individuals with diabetes and nephropathy, retinopathy, and coronary artery disease [16–18].

There is no study about skin AGE accumulation in Tunisian subjects with and without CVR factors. Previous studies have shown that non-invasive measurement of skin autofluorescence (SAF) with the AGE Reader can easily estimate AGE accumulation and identify those at risk for developing diabetes and those at risk for diabetes-related complications [19, 20]. In this cross-sectional study, we have measured SAF in healthy subjects and people with diabetes and/or hypertension and dyslipidemia. We have examined the relationship between SAF and various bio-clinical parameters.

Methods

Study population

We have included 250 participants from the Monastir region in Tunisia for the current study. Participants were either healthy control subjects (n = 88) or individuals with type 2 diabetes (n = 48) or hypertension (n = 62) or both (n = 52). The inclusion criteria were subjects with history of diabetes, hypertension, and dyslipidemia. The exclusion criteria were patients with history of coronary artery disease, chronic kidney disease, and stroke disease. The medical ethical review committee of the hospital Fattouma Bourguiba at Monastir approved the study protocol, and all participants provided written informed consent.

Clinical data collection

For each subject, we have collected the following data: age, sex, height (measured manually), weight (measured by calibrated weighing scale), diagnosis of diabetes (and duration of disease), hypertension, and dyslipidemia. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L and/or HbA1c ≥ 6.5% or the use of blood-glucose-lowering medication. Hypertension was measured by automated blood pressure and was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or use of anti-hypertensive medication. Dyslipidemia was defined as hypercholesterolemia (total serum cholesterol ≥ 6.2 mmol/L) or hypertriglyceridemia (serum triglycerides ≥ 1.7 mmol/L) or the use of lipid-lowering medication. BMI was calculated as weight/height^2, and obesity was defined as BMI ≥ 30 kg/m^2.

Skin autofluorescence measurement

For all participants, SAF was measured with the AGE Reader (Diagnoptics, Groningen, The Netherlands) as described previously [21, 22]. The device, a non-invasive tool, evaluates AGEs in the skin using the principle that several AGEs emit autofluorescence when excited by UV light. The excitation light source wavelength is between 300 and 420 nm, and the peak intensity is at ~ 370 nm. This light source is projected approximately onto 4 cm^2 on the volar side of the forearm skin surface, and the intensity of any light (420–600 nm) emitted is measured with an internal spectrometer. SAF was expressed in arbitrary units (AU) and was calculated from the mean value of the emitted light intensity divided by the excitation light intensity and multiplying by 100. Subjects with dark skin color (Fitzpatrick classes > 5) were not included due to their skin pigmentation, as they had ultraviolet reflectance of < 6% considered to be too unreliable for adequate SAF estimation [8]. In a pilot reproducibility study in 32 participants, we obtained a mean coefficient of variance of 5–7% between measurements, comparable to Western Europeans' data [21]. For every participant, mean SAF was calculated from the three consecutive measurements on normal skin without scars, tattoos, or other skin abnormalities. Age-adjusted SAF scores (z scores) were calculated separately for men and women as described previously [8].

Laboratory assessments

Biochemical parameters were routinely measured at the local biochemistry laboratory in hospital. Fasting blood glucose, total cholesterol, and triglyceride were measured using

standardized enzymatic methods (Randox-Antrim, UK). The measurement of HbA1c was done using reagents according to the manufacturer's instructions by cation-exchange high-pressure liquid chromatography (HPLC) (Bio-Rad Laboratories, Hercules, CA, USA).

Statistical analysis

Data are shown as mean ± standard deviation (SD) or median and interquartile range in case of non-normally distributed data. Between groups, comparisons were performed using the Student's *t* test or Mann-Whitney test, and the correlation coefficient was estimated using the Pearson or Spearman rank-order correlation analysis. Linear regression analysis was performed to determine predictors of SAF. The significant variables in the univariate analysis were selected for the multivariate regression analysis. Multiple logistic regression analysis was performed to assess the independent determinants that influence the metabolic disorders. The receiver operating characteristic curves were constructed to determine the optimal SAF cut-off levels for the prediction of metabolic disorders. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS-17.0 statistical software (IBM, USA) or R with the ggplot2 package.

Results

Characteristics of the study population

The demographic and clinical characteristics of the study population are presented in Table 1. As expected, participants with diabetes or hypertension had significantly higher age, BMI, blood glucose, and HbA1c and lipid levels than the healthy controls. Mean SAF was increased in subjects with CVR factors compared to healthy subjects. Mean SAF z score was 0.65 ± 0.85 in subjects with CVR factors and 0.18 ± 0.55 in those without ($p < 0.001$). For gender, we showed no significant difference in healthy subjects. However, women with CVR factors had higher SAF values compared to men (2.48 ± 0.37 vs. 2.32 ± 0.39 AU respectively; $p = 0.011$), while SAF z score in women was 0.88 ± 0.78 and in men was 0.28 ± 0.83; $p < 0.001$ as shown in Fig. 1. SAF levels in subgroups with CVR factors (diabetes, hypertension, and both) are presented in Table 2. SAF levels and SAF z score were markedly increased compared to those of healthy subjects for each subgroup.

Correlation of SAF levels with other variables

The relationship between SAF and other variables in the study population is shown in Table 3. Univariate linear regression analysis showed a significant relationship between SAF, age, BMI, and obesity for healthy subjects. Multivariate analysis showed that age was an independent determinant of SAF ($\beta = 0.552$, $p < 0.001$). For the patient's group, univariate analysis showed a significant relationship between SAF, age, gender, duration of diabetes, HbA1c, and triglyceride levels. Multivariate analysis showed that age and duration of diabetes were independent determinants of SAF ($\beta = 0.270$, $p = 0.008$; $\beta = 0.515$, $p < 0.001$, respectively). Using logistic regression in the unadjusted model indicated that SAF had a significant association with the presence of diabetes and/or hypertension ($p < 0.001$). After adjusting for age, sex, smoking, and BMI, the p value for the trend was 0.009 (Table 3). For all participants, a significant correlation was shown between SAF and HbA1c levels ($r = 0.361$, $p < 0.001$).

Receiver operating characteristic curve

To predict the presence of CVR factors based on SAF, a receiver operating characteristic curve was created as shown in Fig. 2. The maximum Youden index indicated that a SAF > 2.25 AU was the optimal cut-off point to predict the presence of CVR factors. Area under the curve (AUC) = 0.854 (95% CI: 0.809–0.899), $p < 0.001$, with sensitivity of 69% and specificity of 91%.

Discussion

This is the first study reporting skin autofluorescence measurements in a large cohort of individuals from an Arab population residing in Tunisia in northern Africa. We demonstrated increased SAF levels in individuals with diabetes and/or hypertension and dyslipidemia compared to healthy subjects.

Previously, it was shown that SAF values may vary in different ethnicities, as described by Mook-Kanamori et al. [23]. People of Arab and Filipino descent had a significantly higher SAF than the South Asian population. Nevertheless, SAF levels were considerably higher in the Arab population with diabetes than healthy individuals [23]. Another study reported in more detail on the effects of seven different ethnicities: Arab, Central-East African, Eastern Mediterranean, European, North African, South Asian, and Southeast Asian on SAF. The highest SAF values were observed in the North African population, followed by East Mediterranean, Arab, South Asian, and European populations [24]. Two major reasons may explain the difference between the above Arab studies: the Tunisian population's lifestyle and habitual diet adapted. For gender, our study showed no significant difference in healthy subjects. However, a significant difference was shown in subjects with metabolic disorders. Our results showed significantly increased SAF values in women compared to men. For other Arab studies, authors showed that

Table 1 Clinical and biochemical characteristics of the participants

Characteristics	Subjects without CVR (n = 88)	Subjects with CVR (n = 162)	p
Age, years	43 ± 13	56 ± 10	< 0.001
Male gender, n (%)	27 (30.7)	61 (37.7)	0.305
BMI, kg/m^2	27.9 (24.6–30.7)	30.2 (27.7–33.0)	< 0.001
SBP, mmHg	123 ± 15	139 ± 27	< 0.001
DBP, mmHg	76 ± 12	83 ± 13	< 0.001
Obesity, n (%)	25 (28)	83 (51)	< 0.001
Diabetes, n (%)		73 (58)	
Duration of diabetes, years		8 (3–14)	
Dyslipidemia, n (%)		41 (32.3)	
Hypertension, n (%)		95 (74.8)	
Blood glucose, mmol/L	5.6 (5.4–5.8)	8.6 (8.4–8.9)	< 0.001
Hemoglobin A1c, %	5.4 (5.2–5.6)	6.8 (5.8–8.0)	< 0.001
Total cholesterol, mmol/L	4.7 (4.5–4.9)	5.3 (4.9–5.6)	< 0.001
Triglycerides, mmol/L	1.20 (0.80–1.40)	1.90 (1.50–2.10)	< 0.001
SAF (AU)	1.90 ± 0.29	2.42 ± 0.38	< 0.001
SAF z score	0.18 ± 0.55	0.65 ± 0.85	< 0.001

Data are shown as the median (interquartile range) and mean ± SD or number (percentage)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CVR* cardiovascular risk

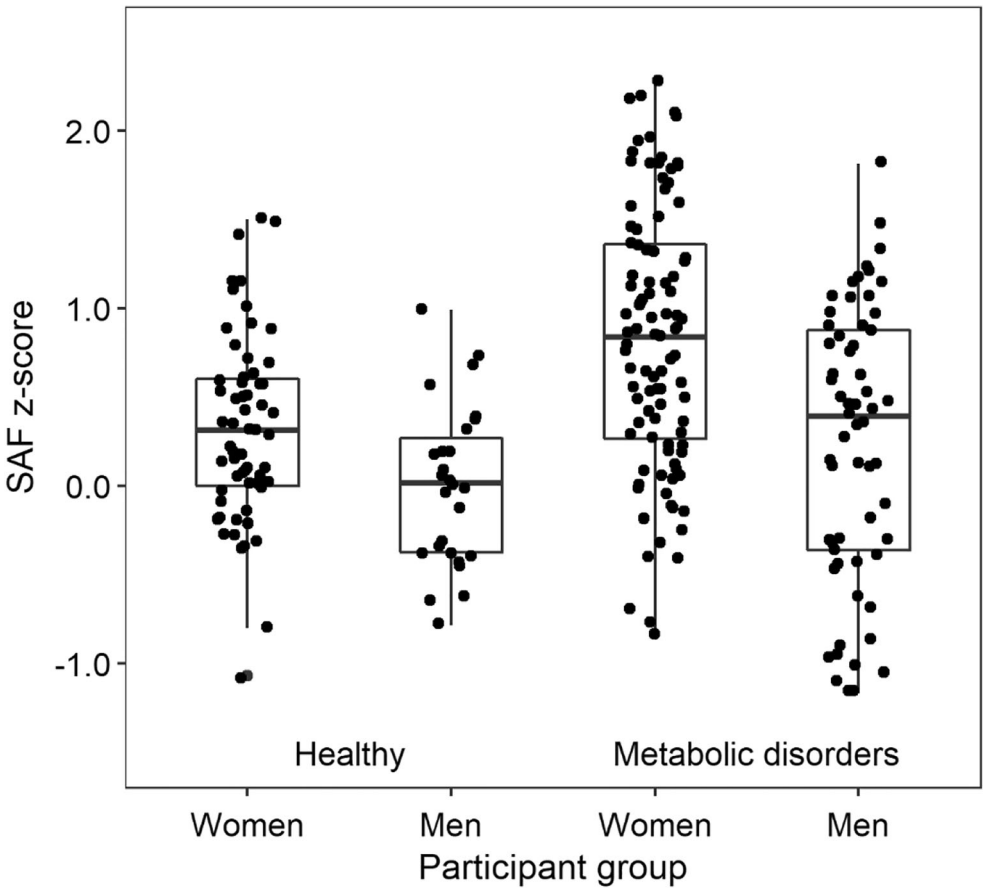

Fig. 1 SAF z score levels according to gender in healthy subjects and subjects with metabolic disorders (diabetes and/or hypertension)

Table 2 Clinical and biochemical characteristics in subject subgroups with CVR factors

Characteristic	Subjects (n = 162)		
	DM (n = 48)	HTA (n = 62)	DM and HTA (n = 52)
Age, years	56 ± 9	58 ± 8	61 ± 9[a]
BMI, kg/m^2	29.8 ± 5.1	31.2 ± 6.0	31.1 ± 3.7
SBP, mmHg	127 ± 12	147 ± 20	145 ± 24
DBP, mmHg	75 ± 14	89 ± 14	86 ± 13
Dyslipidemia, n (%)	12 (25)	25 (40)	16 (30)
Obesity, n (%)	25 (52)	28 (45)	29 (55)
SAF (AU)	2.37 ± 0.42	2.30 ± 0.33	2.47 ± 0.45
SAF z score	0.58 ± 0.76	0.40 ± 0.77	0.59 ± 0.92

Data are shown as the median (interquartile range) and mean ± SD or number (percentage)

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *HTA* hypertension

[a] p = 0.023 compared to patients with DM

gender affects SAF levels in both groups of healthy subjects and patients [23, 24]. Cigarette smoking can also affect the SAF levels, and previous studies showed that cigarette smokers had higher SAF than nonsmokers [22, 25]. Due to the limited number of smokers in our study population, we have not evaluated this further in our participants.

Table 3 Linear and multiple logistic regression analyses of SAF relationships with variables and CVR factors

	Healthy subjects				Subjects with metabolic disorders			
	Univariate		Multivariate		Univariate		Multivariate	
	r	p	β	p	r	p	β	p
Variables[a]								
Age	0.550	< 0.0-01	0.552	< 0.0-01	0.181	0.045	0.270	0.008
Gender	− 0.1-75	NS	–	–	− 0.220	0.013	–	NS
BMI	0.241	0.020	–	NS	0.116	NS	–	–
Obesity	0.284	0.006	–	NS	0.119	NS	–	–
Duration of diabetes	–	–	–	–	0.560	< 0.0-01	0.515	< 0.0-01
Glucose	0.145	NS	–	–	0.193	NS	–	–
HbA1c	0.197	NS	–	–	0.240	0.011	–	NS
Cholesterol	0.163	NS	–	–	0.188	NS	–	–
Triglycerides	0.193	NS	–	–	0.236	0.010	–	NS
Metabolic disorders[b]								
Analysis	OR				95% CI			p
Model 1	1.734				1.258–2.478			< 0.0-01
Model 2	1.043				1.012–1.075			0.009

NS not significant

[a] Linear regression analysis

[b] Multiple logistic regression analysis (model 1: not adjusted; model 2: age, sex, smoking, BMI)

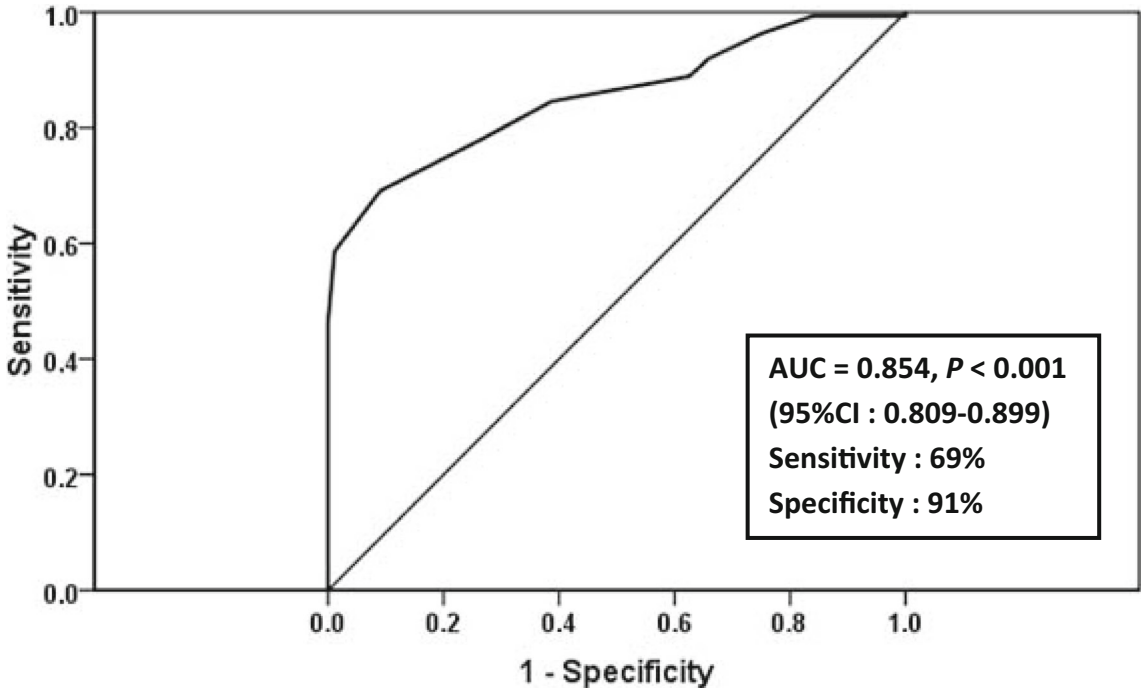

Fig. 2 The receiver operating characteristic curve analysis for the prediction of metabolic disorders (diabetes and/or HTA and dyslipidemia) based on SAF. Maximum Youden index indicated that a SAF > 2.25 AU was the optimal cut-off point to predict metabolic disorders. AUC: area under the curve

Our finding of elevated levels of SAF in people with diabetes and hypertension is in line with the results of several previous studies [9, 26]. In subjects with diabetes, the formation of AGEs is accelerated due to chronic hyperglycemia. Glucose plays an essential role in the formation of AGEs as protein amino groups and lipids are non-enzymatically glycated to form stable structures on long-lived tissues [27]. AGE formation is also produced by glucose autoxidation, by lipid peroxidation, and by the reactive carbonyl compounds [7]. Elevated blood pressure is one of the factors determining metabolic syndrome [28]. Our participants with hypertension had the highest BMI and prevalence of dyslipidemia, and previous studies have indeed shown higher SAF in individuals with metabolic syndrome [9]. Elevated blood pressure may also be a consequence of increased AGE accumulation. Several AGEs can form cross-links within collagen in the vascular wall, resulting in impaired vascular elasticity and increased arterial stiffness, and causing blood pressure to rise [29]. Also, several metabolites released from metabolic dysfunction were associated with elevated blood pressure, as described recently [28]. These observations may suggest that AGEs could influence directly or indirectly blood pressure via modulation of metabolic processes and increase the risk of cardiovascular disease.

The prevalence of diabetes and hypertension in Tunisia is snowballing; therefore, we consider it important to use new technologies in clinical practice to detect early disease and monitor patients' health over time. The AGE Reader is a non-invasive device that measures tissue accumulation of AGEs and predicts vascular risk [8]. Several studies have already shown the usefulness of SAF as a new marker in predicting diabetes and its complications [8, 19–21]. In the present study, we found significant associations between SAF and other additional factors such as age, gender, BMI, duration of diabetes, HbA1c, and obesity. Our finding is in line with several studies showing the same results [9, 30–34]. Moreover, we found that age and diabetes duration were independent risk factors associated with SAF. The value of SAF for screening metabolic disorders was assessed by ROC analysis and revealed that the optimal cut-off value was 2.25 AU which suggests that it could be used as a prognostic indicator.

Some limitations of this study should be noted. The number of healthy subjects and patients was small, and we had limited information on medication use and long-term glycemic control of diabetes.

In conclusion, this Tunisian population-based study shows an increased SAF level in subjects with diabetes and/or hypertension and dyslipidemia compared to healthy subjects. The value of SAF for screening metabolic disorders revealed that the optimal cut-off value is above 2.25 AU which suggests that it could be used as a prognostic indicator to detect early metabolic disorders in healthy subjects. The AGE Reader device is a rapid and non-invasive tool in clinical practice to evaluate and screen metabolic disorders in people from Tunisia and more generally those with a North Africa phototype. Further investigations in a larger number of

individuals are required to do the multicentric study in future to correlate the AGE levels with micro/macro vascular complications.

Abbreviations AGEs, advanced glycation end products; BMI, body mass index; CVR, cardiovascular risk; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HTA, hypertension; SAF, skin autofluorescence; SBP, systolic blood pressure

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Author contribution MK, BHRW, SA, and SN conceived the idea and edited and finalized the manuscript. RS and MK performed the study design, skin autofluorescence measurement, data analysis, data interpretation, and writing. IK, WB, and HB helped in the recruitment of patients and clinical fulfillment. All authors read and approved the final manuscript.

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations The study protocol follows the ethical guidelines of the declaration of Helsinki and has been approved by the ethics committees at the Hospital of Fattouma Bourguiba at Monastir-Tunisia. All participants signed the informed consent in writing before inclusion in the study.

Consent for publication Not applicable

Competing interests The authors declare no competing interests.

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