Pediatric Diabetes

ISPAD International Society for Pediatric and Adolescent Diabetes

Pediatric Diabetes 2016: 17: 426–432
doi: 10.1111/pedi.12311

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Original Article

Advanced glycation end products, measured in skin, vs. HbA1c in children with type 1 diabetes mellitus‡

Banser A, Naafs JC, Hoorweg-Nijman JJG, van de Garde EMW, van der Vorst MMJ. Advanced glycation end products, measured in skin, vs. HbA1c in children with type 1 diabetes mellitus.
Pediatric Diabetes 2016: 17: 426–432.

Background and objective: Advanced glycation end products (AGEs) are considered major contributors to microvascular and macrovascular complications in adult patients with diabetes mellitus. AGEs can be measured non-invasively with skin autofluorescence (sAF). The primary aim was to determine sAF values in children with type 1 diabetes mellitus and to study correlations between sAF values and HbA1c and mean HbA1c over the year prior to measurement

Research design and methods: In children with type 1 diabetes mellitus, sAF values were measured using the AGE Reader®. Laboratory and anthropometric values were extracted from medical charts. Correlations were studied using Pearson's correlation coefficient. Multivariable linear regression analysis was conducted to evaluate the effect of multiple study parameters on sAF values.

Results: The mean sAF value was 1.33 ± 0.36 arbitrary units (AU) in children with type 1 diabetes mellitus ($n = 144$). sAF values correlated positively with HbA1c measured at the same time ($r = 0.485$; $p < 0.001$), mean HbA1c over the year prior to measurement ($r = 0.578$; $p < 0.001$), age ($r = 0.337$; $p < 0.001$), duration of type 1 diabetes mellitus ($r = 0.277$; $p = 0.001$), serum triglycerides ($r = 0.399$; $p < 0.001$), and total cholesterol ($r = 0.352$; $p = 0.001$). sAF values were significantly higher in patients with non-white skin (1.56 vs. 1.27 AU, respectively, $p = 0.001$).

Conclusions: In children with type 1 diabetes, sAF values correlate strongly with single HbA1c and mean HbA1c, making the non-invasive sAF measurement an interesting alternative to provide information about cumulative hyperglycemic states. To determine the value of sAF measurement in predicting long-term microvascular and macrovascular complications, further prospective follow-up studies are needed.

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‡Preliminary results of the GLYCOD study have been presented at the International Student Congress of (bio)Medical Sciences (ISCOMS) 2014.

Key words: AGEs – children – HbA1c – sAF – type 1 diabetes mellitus

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Submitted 13 April 2015. Accepted for publication 3 August 2015

In patients with type 1 diabetes, HbA1c measurements are used to monitor short-term glycemic control. HbA1c is formed through irreversible glycation of hemoglobin during the life span of the erythrocyte (approximately 100–130 d) (1). HbA1c levels represent the glycemic control of the past 1–3 months (1, 2). This relatively short-term monitoring has driven the search for other markers encompassing long-term glycemic

control. Advanced glycation end products (AGEs) might provide an interesting new measure for long-term glycemic control.

AGEs are formed through irreversible glycation of proteins, lipids, and nucleic acids (3). AGEs accumulate in skin, where they link to collagen, a long-lived protein with a half-life of 15 yr (4).

Prolonged hyperglycemic states will cause elevated AGEs in skin, what is indeed measured in adult patients with diabetes (5, 6). The amount of AGEs in skin biopsies has already proved to be predictive for the progression of microvascular complications in adult patients with type 1 diabetes (7).

Because of their fluorescent characteristics, AGEs in skin can be measured non-invasively. Different devices are available for this measurement, either using a single peak excitation wavelength (370 nm) or a series of different peak excitation wavelengths (375, 405, and 420 nm) (8, 9). The AGE Reader® (DiagnOptics Technologies, Groningen, The Netherlands) is a device to measure the level of AGEs in skin, which is expressed as skin autofluorescence (sAF). In adult patients with type 1 diabetes, sAF values correlate with HbA1c, age, and, diabetes duration (10). Therefore, sAF values are already considered a reliable indicator for long-term glycemic control in adults with type 1 diabetes (11, 12).

Several studies have reported elevated AGEs in skin in children with type 1 diabetes. Children with type 1 diabetes were compared to their healthy siblings (13) and a correlation between skin intrinsic fluorescence (SIF) and HbA1c was described (8, 14, 15).

The aim of this study is to determine sAF values in a multi-ethnic group of children with type 1 diabetes, using the AGE Reader, and to examine the relationship between sAF values and single HbA1c, mean HbA1c over the year prior to sAF measurement, age, duration of diabetes, and type of skin.

Research design and methods

Study design

AGEs were studied in two populations: children with type 1 diabetes and children with obesity. Here, we report on children with type 1 diabetes. The study protocol (NL 45664.100.13) was approved by the Medical Ethical Committee of the St. Antonius Hospital (Nieuwegein/Utrecht, The Netherlands) on 17 September 2013.

Study population

The study population consisted of children with type 1 diabetes up to the age of 18 ye. Children visiting the pediatric diabetes outpatient clinic of the St. Antonius Hospital between September 2013 and October 2014 were asked to participate. Informed consent was obtained from the child (if applicable) and both parents (or guardians).

sAF measurement

The sAF measurements were performed using the AGE Reader (Model 'mu'; DiagnOptics Technologies). To perform a measurement, the patient had to put the forearm on the device, which emitted ultraviolet A (UV-A) light and illuminated a skin area of 4 cm^2. The device uses light reflecting from the skin to calculate the sAF value, which is expressed in arbitrary units (AU) (16). A more extensive technical description of the AGE Reader is available elsewhere (17, 18).

Three measurements were performed on different sites of the skin on the volar side of the dominant forearm. The mean sAF value of the three measurements was reported.

If the skin UV-reflectance is below 10%, the AGE Reader automatically aborts the measurement, as a dark skin might impede a reliable measurement (16). Children with a reported UV-reflectance below 10%, who initially agreed to participate, were thus excluded from further assessment.

Demographic and clinical data

At the day of sAF measurement, weight and height were measured using a standardized scale (Seca, Hamburg, Germany) and measuring rod (DGI 250D; De Grood, Nijmegen, The Netherlands). To calculate body mass index (BMI) and its age- and sex-specific standard deviation scores (SDS), the most recent Dutch growth calculator was used (available at http://groeiweb.pgdata.nl/calculator.asp).

Underweight was defined as a BMI-SDS below −1.1, healthy weight was defined as a BMI-SDS between −1.1 and 1.1, overweight was defined as a BMI-SDS between 1.1 and 2.3, and obesity was defined as a BMI-SDS $\geq$ 2.3. Skin type was determined using Fitzpatrick scale for skin type (19). Skin types I and II were considered white skin, whereas types III–VI were considered non-white skin. The date of diagnosis of type 1 diabetes was extracted from the electronic patient file and used to calculate disease duration. Finally, information was obtained on smoking habits and alcohol consumption.

HbA1c was assessed on the day of sAF measurement using a point-of-care device (DCA Vantage® Analyzer; Siemens Healthcare, Boston, Massachusetts, USA). Other laboratory results were extracted from the electronic patient file at the nearest possible date, with a maximum of 180 d (on each side) from the sAF measurement. Mean HbA1c was calculated using all HbA1c measurements from 1 yr prior to the sAF measurement. This included HbA1c values measured

by the hospital laboratory (Cobas® 6000 analyzer; Roche) as well.

Statistical analysis

All data were stored using Microsoft Excel version 2007. Statistical analyses were performed using spss version 22.0 (IBM SPSS Statistics, Chicago, IL, USA). Dichotomous and categorical data were described as N (%) and continuous variables as mean (±SD). To test for a correlation between sAF values and the study parameters, Pearson's correlation coefficients were calculated. A Student's t-test was applied to compare the sAF values from our study population with sAF values measured in healthy children (16).

Taking into consideration the size of the pediatric population with type 1 diabetes in the St. Antonius Hospital (a population of 150–180 children), we calculated that a number of 143 patients would be sufficient to detect correlations >0.32 (power 80% and $\alpha = 0.001$). The more strict significance level was chosen to prevent false positive findings due to multiple testing, as multiple study parameters were tested for correlations. Correlation analyses were performed for sAF values and HbA1c, age, disease duration, BMI-SDS, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and serum triglycerides. Besides single correlations, a multivariable linear regression analysis was conducted to identify which variables were independently associated with sAF. In this model, all variables with a p-value <0.05 were retained.

Results

During the study period, 160 children were asked to participate, of which 148 children agreed to participate. Four children were excluded due to a skin reflectance below 10%. A total of 144 children completed the measurement. The mean age of the study population was 12.3 yr, with a mean HbA1c of 8.2% (66 mmol/mol) and a mean disease duration of 4.1 yr. An overview of the baseline characteristics of the study population is presented in Table 1.

The mean sAF value in children with type 1 diabetes was 1.33 ± 0.36 AU. In children <10 yr old (n = 36), the mean sAF value was 1.19 ± 0.28 AU and for children ≥10 yr old (n = 108) the mean sAF value was 1.38 ± 0.37 AU, whereas sAF reference values in healthy children have shown to be significantly lower [0.99 ± 0.06 AU in children aged 1–10 yr (n = 52) and 1.13 ± 0.06 AU for children and adolescents aged 10–18 yr (n = 48), p-values < 0.001] (16).

No significant sex difference was found in mean sAF values in all children, nor in the prepubertal (<10 yr) and pubertal children (≥10 yr).

Table 1. Baseline characteristics of the study population (n = 144)

Characteristic	Mean ± SD or n (%)
Sex (male/female)	82/62
Age (yr)*	12.2 ± 3.8
Disease duration (yr)*	4.1 ± 3.7
BMI-SDS*	0.69 ± 1.07
Fitzpatrick skin type (%)	
White (I, II)	112 (78)
Non-white (III–VI)	32 (22)
Smoking habits: ever tried smoking (%)*	5 (3)
Alcohol consumption: sometimes (%)*	4 (3)
Single HbA1c (%)*	8.2 ± 2
Single HbA1c (mmol/mol)*	66 ± 22
Mean HbA1c (%)†	8.1 ± 1.5
Mean HbA1c (mmol/mol)†	65 ± 16
Triglycerides (mmol/L)‡	1.0 ± 0.7
Total cholesterol (mmol/L)‡	4.3 ± 0.9
HDL cholesterol (mmol/L)§	1.6 ± 0.3
LDL cholesterol (mmol/L)¶	2.3 ± 0.7

BMI-SDS, body mass index-standard deviation score; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*n = 144 †n = 115 ‡n = 84 §n = 82 ¶n = 81

The mean sAF values were significantly higher in children with non-white skin (1.56 vs. 1.27 AU, p = 0.001). Moreover, a significantly higher HbA1c level was seen in the non-white patients (9.2% or 76.7 mmol/mol vs. 7.9% or 62.7 mmol/mol; p = 0.009).

A significant correlation was found between sAF values and single HbA1c measurement as well as mean HbA1c over the year prior to measurement (Fig. 1). Moreover, sAF values correlated with age and disease duration (Fig. 2), serum triglycerides, and total cholesterol. An overview of all individual correlations examined is provided in Table 2.

In univariable analysis, seven variables showed a statistically significant correlation with sAF values (Table 2). When examining these variables in a multivariable linear regression model, it appeared that mean HbA1c measurement, age, and skin type were independently associated with sAF values (Table 3).

Discussion

This study confirmed that in children with type 1 diabetes, sAF values are significantly elevated compared to individuals without diabetes. Besides this, age, mean HbA1c, and skin type were identified as independent predictors for sAF.

A positive correlation between sAF values and both single and mean HbA1c levels was found in children with type 1 diabetes (r = 0.485; p < 0.001 and r = 0.578; p < 0.001, respectively). This study is thus the first to show that sAF values have the potential to serve as alternative biomarker to monitor long-term glycemic control in children with type 1 diabetes. As AGEs in skin link to collagen, which

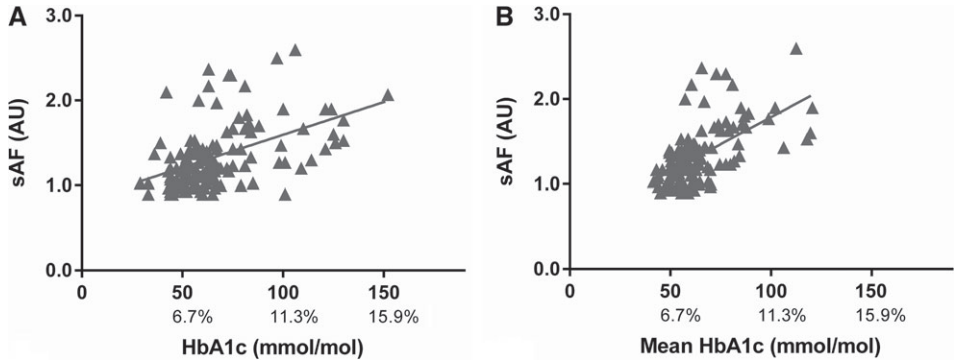

Fig. 1. Correlations between skin autofluorescence and single HbA1c (**A**) and mean HbA1c over the year prior to measurement (**B**) in children with type 1 diabetes (n = 144).

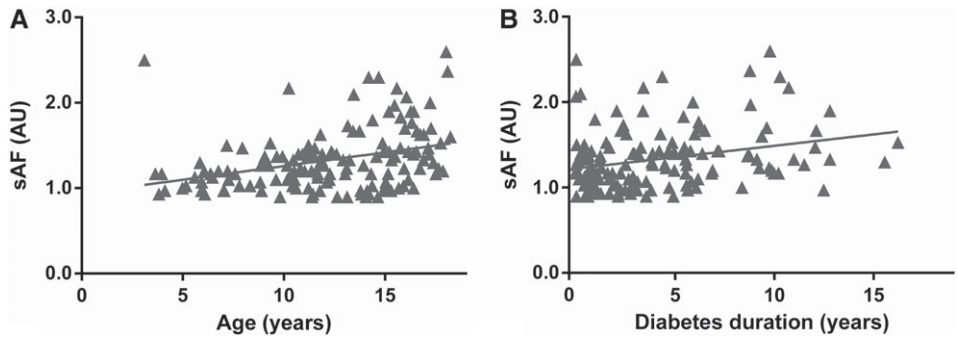

Fig. 2. Correlations between skin autofluorescence and age (**A**) and duration of diabetes (**B**) in children with type 1 diabetes (n = 144).

has a half-life of approximately 15 yr, sAF values can cover a much longer period compared to HbA1c (4, 20). The latter is supported by our finding of a large correlation coefficient (r = 0.578) with mean HbA1c values collected from the year prior to sAF measurement.

Moreover, significant correlations between sAF values and age and duration of diabetes were observed. Because AGEs accumulate in skin during the physiological aging process in all individuals, a positive correlation between sAF values and age had been expected (21, 22). The correlation with duration of diabetes is more specific and in accordance with previous study findings of Felipe et al., who reported an association between SIF values and duration of disease in children with type 1 diabetes (8). Both SIF and sAF values are based on the concept of protein glycation and thus provide information about cumulative hyperglycemic states.

Another significant correlation was observed between sAF values and serum triglycerides and total cholesterol, while no significant correlation between sAF values and LDL or HDL was found. The latter compares to previous study findings in children and adolescents with type 1 diabetes that reported a positive correlation between fluorescent AGEs in serum and serum triglycerides (23). It has been suggested that glycation of lipoproteins impairs their clearance (3, 23, 24). Alternatively, oxidized lipids might serve as precursors in the AGE formation (23).

In the multivariable linear regression model, mean HbA1c, skin type, and age were independently associated with sAF (Table 3). This confirms that skin type should be considered when interpreting sAF values. Development of a uniform tool to correct for skin type is needed to interpret sAF values in populations of patients with different skin types.

As sAF reference values have been determined in people of European descent with a white skin, the influence of skin type on sAF values is still being debated (9, 16). A low reflectance in patients with dark-colored skin (Fitzpatrick skin types V and VI) is associated with a lower sAF value (9, 17, 19). Unfortunately, we were not able to further examine differences between Fitzpatrick scale III–IV and V–VI because none of the participants in our study had skin type V or VI.

Study limitations

Before reaching a final conclusion, certain limitations of this study need to be discussed.

First, sAF measurements were performed without taking into account time and content of the patient's last meal. AGE-rich meals are known to affect sAF values; an increase in sAF values up to 10.4% 2 h

Table 2. Correlations between sAF and various parameters

	sAF	Single HbA1c	Mean HbA1c*	Age	Disease duration	BMI-SDS	Triglycerides†	Total cholesterol†	HDL‡	LDL§
sAF		0.485¶	0.578¶	0.337¶	0.277**	0.000	0.399¶	0.352**	0.031	0.230**
Single HbA1c	0.485¶		0.904¶	0.285**	0.187**	0.019	0.413¶	0.375¶	0.003	0.197
Mean HbA1c*	0.578¶	0.904¶		0.497¶	0.363¶	0.080	0.500¶	0.366**	0.080	0.210
Age	0.337¶	0.285**	0.497¶		0.494¶	0.157	0.285**	0.164	0.053	0.102
Disease duration	0.277**	0.187**	0.363¶	0.494¶		0.193**	0.229**	0.169	0.069	0.073
BMI-SDS	0.000	0.019	0.080	0.157	0.193**		0.166	0.137	0.201	0.169
Triglycerides†	0.399¶	0.413¶	0.500¶	0.285**	0.229**	0.166		0.531¶	0.244**	0.368**
Total cholesterol†	0.352**	0.375¶	0.366**	0.164	0.169	0.137	0.531¶		0.235**	0.899¶
HDL‡	0.031	0.003	0.080	0.053	0.069	0.201	0.244**	0.235**		0.073
LDL§	0.230**	0.197	0.210	0.102	0.073	0.169	0.368**	0.899¶	0.073	

BMI-SDS, body mass index-standard deviation score; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sAF, skin autofluorescence.
*n = 115 †n = 84 ‡n = 82 §n = 81 ¶<0.001 **<0.05

Table 3. Final multivariable linear regression model

	B (SE)	Beta	p-Value
Model			
Constant	0.429 (0.117)		<0.001
Mean HbA1c	0.010 (0.002)	0.434	<0.001
Skin type	0.212 (0.064)	0.246	0.001
Age	0.019 (0.008)	0.188	0.027

Dependent variable: skin autofluorescence.

after an AGE-rich meal has been reported (25, 26). In the Netherlands, the main course is consumed during dinner time in the evening. The AGE measurement was either performed during an afternoon or an evening visit to the pediatric diabetes outpatient clinic. We assumed the study population to follow a normal distribution; thus, the influence of dietary intake of AGEs was considered minimal. Moreover, this study design mimics daily life of a child with type 1 diabetes. However, the time of measurement might have influenced the AGE level. Therefore, in future studies, time and content of the patient's last meal should be taken into account.

Secondly, our comparison with non-diabetic individuals was based on data from an external reference cohort, instead of using an internal reference population. However, the sAF values in the reference population were measured using a similar AGE Reader. Results of the previously used AGE Reader (type SU) correspond with results from the AGE Reader (type mu), as adjustments have been made during the development of the AGE Reader (type mu). We consider the similarity in methods to have minimized the impact on our results.

Future perspectives

The results from our study suggest that sAF values might be a promising future tool to monitor long-term glycemic control in children with type 1 diabetes. To date, single and mean HbA1c values are still considered the most reliable predictors for diabetic complications in children with type 1 diabetes (27, 28). In adults with type 1 diabetes, however, there is growing evidence that sAF values may be used as a predictor for future microvascular complications as well (29–31). Moreover, there are already studies available showing strong associations between sAF values and the severity of nephropathy and neuropathy, but not retinopathy, in adults with type 1 diabetes (12, 32). It is speculated that in adults high sAF values can be regarded an indication to initiate a more intensive glucose control (24) as intensive glucose control has been shown to decrease the risk of microvascular complications in type 1 diabetes patients (6, 7, 33). For children, there is need for additional studies first, before similar recommendations can be made. We think the next step should be a prospective study on long-term complications in the adolescent population. The present study population could act as study cohort for these suggested studies, as baseline measurements now have been performed.

Conclusion

In summary, sAF values appear to correlate strongly with single HbA1c and mean HbA1c, making the sAF measurement a promising new tool to monitor long-term glycemic control in children with type 1 diabetes. The value of sAF measurement as a predictor for microvascular complications in children with type 1 diabetes should be studied using prospective studies, starting at the time of diagnosis.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Author contributions

AB and JCN recruited participating children, collected original data, analyzed the data, and wrote and revised the manuscript. JJGH-N recruited participating children and revised the manuscript. EMWvdG supervised statistical analysis and revised the manuscript. MMJvdV supervised data collection and revised the manuscript.

MMJvdV is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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