

OBSERVATIONS

Advanced Glycation End Products in Children With Type 1 Diabetes: Family Matters?

Advanced glycation end product (AGE) burden can be indirectly quantified in vivo by measuring skin autofluorescence (SAF) (1). It has been recently published by Felipe et al. (2) that SAF is correlated with glycated hemoglobin (GHb) but not with mean blood glucose (MBG) in type 1 diabetic children. This suggests that factors besides MBG exposure may be influential in skin AGE generation. In the current study, we have compared SAF in type 1 diabetic children and their nondiabetic sibling.

We included 52 type 1 diabetic children, 55% boys, aged 12 (6) years [median (interquartile range: 75th percentile – 25th percentile)], and 28 nondiabetic siblings, 46% boys, aged 11 (6) years. Among diabetic children, the duration of diabetes was 71 (45) months (min 13 to max 135) and median GHb levels since diabetes discovery were 8.0 (1.1) %. Diabetic children and sibling control groups were balanced in terms of BMI, waist circumference (WC), and blood pressure (BP). Informed consent was obtained from the children and their parents. At the time of the clinic visit between 2 and 6 P.M., SAF measurements were performed using the AGE Reader (DiagnOptics, Groningen, the Netherlands). Three consecutive SAF measurements per subject were carried out in the forearm of participants. SAF was expressed in arbitrary units (AUs) as the mean of the three separate measures. Comparisons were made using the Mann-Whitney test. Factors potentially associated with SAF levels were studied using a multivariate regression model with SAF level as the dependent variable

and age and sex as confounding factors (2,3).

Diabetic children had significantly elevated SAF levels compared with the sibling control group (1.36 [0.32] vs. 1.20 [0.24] AU, $P < 0.001$). In diabetic patients, SAF levels were associated with last GHb levels when adjusted for age and sex ($r = 0.33$, $P < 0.05$). No significant associations were observed between SAF levels and BMI, WC, BP, duration of diabetes, capillary blood glucose, and median GHb. However, a significant correlation of SAF levels was observed among siblings (binomial diabetic – nondiabetic siblings), even when adjusted for diabetic GHb and age ($n = 27$, $r = 0.43$, $P = 0.01$).

To our knowledge, our data are the first to report an increased SAF levels early in the medical history of diabetic children compared with sibling control subjects. The correlation between SAF and recent but not median GHb possibly reflects middle-term interactions with hyperglycemia. The association observed for SAF measurements, albeit regarding a small number of paired proband siblings, supports the hypothesis that important genetic/environmental factors besides hyperglycemia are involved in the elevated skin AGEs in diabetic children. A possible genetic explanation may come from the gene encoding glyoxalase I that has been shown to influence AGE burden and predisposition to vascular complications, the glyoxalase system being a detoxifying factor of AGE precursors (4). Skin pigmentation, under genetic influence, could also play a role in this association although theoretically controlled by the AGE Reader. Alternatively, familial nutritional habits could explain the sibling's correlation of SAF. Indeed, AGEs form in foods during heating, and orally absorbed AGEs have been shown to be one environmental risk factor for diabetes complications (5).

PASCAL BARAT, MD, PHD^{1,2}
BENOÎT CAMMAS, MD¹
AURÉLIE LACOSTE, MD¹
JÉRÔME HARAMBAT, MD¹
VANESSA VAUTIER, MD¹

FABIENNE NACKA, PHD³
JEAN-BENOÎT CORCUFF, MD, PHD²

From ¹Endocrinologie et Diabétologie de l'Enfant, Hôpital des Enfants, CHU de Bordeaux, Bordeaux, France; ²Nutrition et Neurobiologie Intégrée, UMR 1286, Université de Bordeaux, Bordeaux, France; and ³Hôpital Pellegrin Enfants, CIC 0005 INSERM Pédiatrie, CHU de Bordeaux, Bordeaux, France.

Corresponding author: Pascal Barat, pascal.barat@chu-bordeaux.fr.

DOI: 10.2337/dc11-1398

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

P.B. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. B.C., A.L., J.H., V.V., and F.N. researched data. J.-B.C. researched data, contributed to discussion, and reviewed and edited the manuscript.

References

1. Meerwaldt R, Graaff R, Oomen PH, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia* 2004;47:1324–1330
2. Felipe DL, Hempe JM, Liu S, et al. Skin intrinsic fluorescence is associated with hemoglobin A1c and hemoglobin glycation index but not mean blood glucose in children with type 1 diabetes. *Diabetes Care* 2011;34:1816–1820
3. Koetsier M, Lutgers HL, de Jonge C, Links TP, Smit AJ, Graaff R. Reference values of skin autofluorescence. *Diabetes Technol Ther* 2010;12:399–403
4. Kalousova M, Germanova A, Jachymova M, Mestek O, Tesar V, Zima T. A419C (E111A) polymorphism of the glyoxalase I gene and vascular complications in chronic hemodialysis patients. *Ann N Y Acad Sci* 2008;1126:268–271
5. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci U S A* 1997;94:6474–6479