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Skin advanced glycation end-products evaluation in infants according to the type of feeding and mother's smoking habits

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Abstract

Objectives: This study was conducted to assess whether formula-fed infants had increased skin advanced glycation end-products compared with breastfed ones. We also evaluated the effect of maternal smoke during pregnancy and lactation on infant skin advanced glycation end-products accumulation.

Methods: Advanced glycation end-product–linked skin autofluorescence was measured in 101 infants.

Results: In infants born from non-smoking mothers, advanced glycation end-products were higher in formula-fed subjects than in breastfed subjects (0.80 (0.65–0.90) vs 1.00 (0.85–1.05), $p < 0.001$). Advanced glycation end-products in breastfed infants from smoking mothers were higher than in those from non-smoking mothers (0.80 (0.65–0.90) vs 1.00 (0.90–1.17), $p = 0.009$).

Conclusion: Formula-fed infants had increased amounts of advanced glycation end-products compared with the breastfed ones, confirming that breast milk represents the best food for infants. Breastfed infants from mothers smoking during pregnancy and lactation had increased skin advanced glycation end-products, suggesting that smoke-related advanced glycation end-products transfer throughout breast milk. Moreover, advanced glycation end-products may already increase during gestation, possibly affecting fetal development. Thus, we reinforced that smoking must be stopped during pregnancy and lactation.

Keywords

Advanced glycation end-products, skin autofluorescence, infants, breast-feeding, smoke

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Introduction

At present, a major problem in public health is the increasing incidence of age-related chronic diseases, such as obesity, diabetes, and cardiovascular and renal disorders. Even if clinical manifestations of these diseases are not apparent during pediatric age, pre-clinical alterations may be already present.[1,2] Recently, it has been reported that substances such as advanced glycation end-products (AGEs) are important contributors to oxidative stress and to inflammatory injury that promote and maintain vascular damage.[3–5] AGEs are produced through non-enzymatic glycation of proteins, lipids, or nucleic acids within the so-called Maillard reaction. This process, occurring also under physiological conditions, is exacerbated by hyperglycemia, hyperlipidemia, or increased oxidative stress.[6] AGEs may alter cellular functions via non-receptor-dependent and receptor-dependent mechanisms. For example, AGE-induced modification of the amino acids in the active center of an enzyme may alter its activity. In the receptor-dependent mechanism, AGEs bind to specific receptors inducing intracellular processes such as oxidative stress or inflammation.[6]

The Maillard reaction is important during food heating, giving them specific color and taste. It implies that in

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addition to diabetes mellitus, in which AGEs are formed by exposure of body proteins and lipids to high blood glucose,[7,8] a major source today is nutrition with the highest content found in heat-treated food,[9] especially lipid-rich and protein-rich food.[10] Approximately 10% of ingested AGEs are absorbed, and about two-thirds of them are deposited in tissues, where they remain biologically active and exert their pathological effects,[11] similar to their endogenous counterparts.[11–16] Thus, oxidative stress increases endogenous AGEs formation that, together with supply and tissue deposition of diet-derived AGEs, further increase oxidative stress and amounts of AGEs in tissues contributing, in a vicious loop, to the development of vascular complications in patients with and without diabetes.[6]

Until recently, determination of tissue AGEs was based on skin biopsy examination. In the last few years, a non-invasive optical method has given the opportunity to measure AGE-linked skin autofluorescence (sAF). This technique has been proven to be well related to skin AGEs accumulation and, being painless and easy-to-use, is particularly suitable for children.[17] In addition, the availability of age-specific reference data makes the assessment of sAF easier.[18,19] It should be underlined that plasma levels of AGEs do not reflect tissue accumulation and, in contrast to tissue AGEs, are not predictive for cardiovascular morbidity.[18,20] In patients with type 2 diabetes mellitus, sAF was higher in those with macrovascular complications than in those with microvascular complications only or in patients without complications.[21,22] In other studies, sAF demonstrated a predictive value, better than HbA1c and diabetes duration, to develop neuropathy and nephropathy.[23,24] sAF was also associated with retinopathy[25] and peripheral and autonomic neuropathy.[26,27]

As regards cardiovascular risk, several studies demonstrated that sAF correlated with early vascular changes, such as vascular stiffness and intima-media thickness.[28–32] In patients with peripheral artery disease, sAF was independently associated with all-cause mortality and fatal or non-fatal major adverse cardiovascular events within 5 years.[33] Chronic kidney disease (CKD) is associated with increased amounts of AGEs[11,34–36] so that patients with CKD stage 3,[37] or terminal CKD, or persons undergoing dialysis displayed higher sAF.[30,38] sAF was found to be a strong and independent predictor of CKD progression[39] and was proposed to be used for the identification and monitoring of patients at risk of renal transplant dysfunction.[40]

Since recently it was reported that formula milk contains higher amounts of AGEs in comparison with breast milk,[10,41–43] in this study we measured sAF in a group of infants to assess whether formula-fed infants had increased content of AGEs in the skin in comparison with breastfed ones. As another external source of AGEs is represented by smoking,[44] we also investigated the effect of smoking during pregnancy and breast-feeding on infant skin AGEs accumulation, in addition to birth weight and type of delivery.

Methods

Study population

We studied 131 healthy Caucasian infants (aged <4 months) who performed ultrasound screening of hip dysplasia at the Pediatric Unit of the University of Pisa during a 3-month period (April–June 2015). We chose this population to enroll healthy non-weaned subjects of similar age, to avoid confounding effects due to the intake of food other than milk. All infants were born at term (gestational age 37^0–41^6 weeks). Depending on feeding, we categorized them as breastfed or formula-fed infants. Mixed-fed infants were excluded (n = 8); none of the subjects were weaned. Other exclusion criteria were preterm delivery, Neonatal Intensive Care Unit hospitalization, and assumption of any drugs other than those administered for routine vitamin supplementation (n = 15).

A detailed oral interview was administered by one of us (F.V.) to infant's mothers to provide general information about smoking (i.e. "Have you smoked cigarettes during pregnancy and lactation?"; "If yes, how many cigarettes/daily did you smoke?; "Are you still smoking?"). We identified as smoking mothers those smoking at least one cigarette daily during pregnancy and feeding (median = 6, range = 2–10). Non-smoking mothers were those who had never smoked during pregnancy and feeding. Infants born from women with different habits about smoking were excluded (n = 7). Skin pre-prandial morning AGEs were evaluated in 101 infants by measuring sAF (median gestational age = 40 weeks, range = 37–42 weeks; 31 born by caesarean delivery). We used the Italian reference growth charts to calculate birth weight SDS (standard deviation score) and birth length SDS.[45]

Assessment of skin sAF

sAF was assessed using the AGE Reader device (Diagnoptics BV, Groningen, The Netherlands), as previously described.[1,46] Briefly, the ratio of average light intensity per nanometer in the range between 420 and 600 nm emitted by the source divided by the average of excited light intensity per nanometer in the range between 300 and 420 nm was used as the measure of autofluorescence. The intra- and inter-day coefficient was 2.6%. sAF was expressed as arbitrary units (AU) and was measured at three positions on the lateral side of the thigh, with the infant lying on the same side on a padded support, at the same level of the AGE Reader. In all infants, skin oils/ointments were not recently applied on the site of measurement before skin sAF assessment. The results of sAF were the mean of the three measurements.

Statistical methods

Continuous variables were checked for normal distribution by Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± standard deviation (SD),

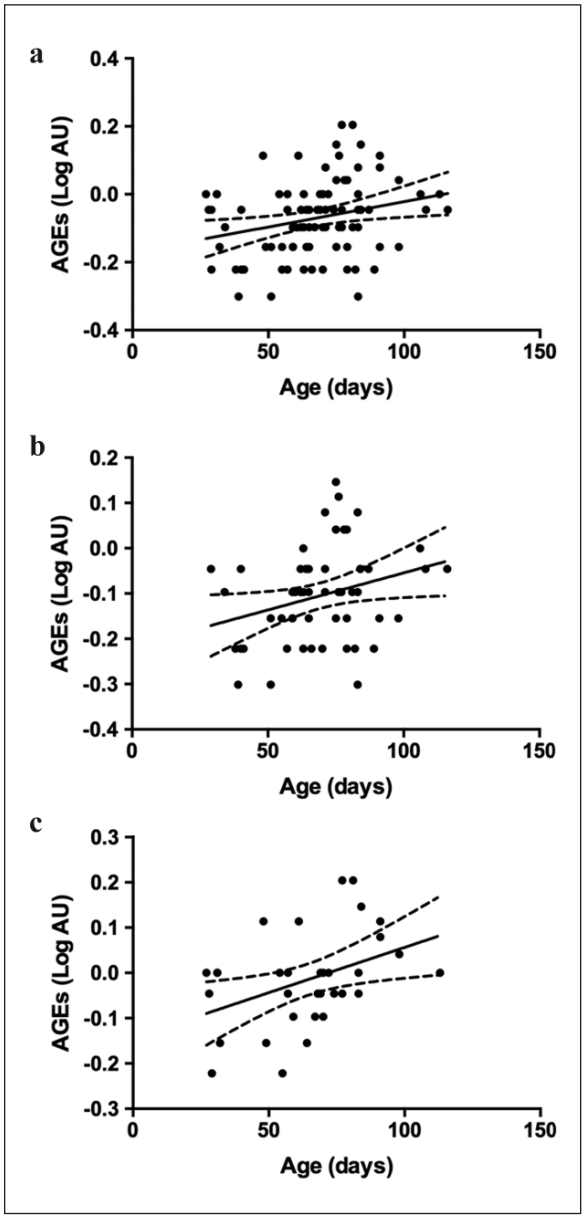

Figure 1. Linear regression analysis between logarithmically transformed skin AGEs and age, depending on the type of feeding: (a) entire sample ($R^2 = 0.068$, $p = 0.015$, $Y = 0.00149*X-0.171$), (b) breastfed infants ($R^2 = 0.083$, $p = 0.036$, $Y = 0.00164*X-0.218$), and (c) formula-fed infants ($R^2 = 0.167$, $p = 0.18$, $Y = 0.00200*X-0.144$).

while the non-normal distributed ones were reported as median and interquartile range (IQR).

As gestational age, birth weight SDS, and infant AGEs were not normally distributed, non parametric Mann–Whitney test was used to compare groups. Unpaired t-test was used to compare other continuous variables that were normally distributed. Fisher's exact test or chi-square test was used to compare categorical variables, as appropriate.

AGE levels of infants born from non-smoking mothers were also expressed as mean ± SD to give reference value, according to the type of feeding.

Table 1. Clinical details of the examined infants.

	N (%)
Gender	
Males	52/101 (51.5)
Females	49/101 (48.5)
Type of delivery	
Spontaneous	70/101 (69.3)
Caesarean section	31/101 (30.7)
Type of feeding	
Breast-feeding	61/101 (60.4)
Formula	40/101 (39.6)
Mothers	
Non-smoking	86/101 (85.1)
Smoking	15/101 (14.9)
	Mean (SD)
Birth length, SDS	0.22 (0.95)
Age at evaluation, days	67.9 (19.6)
Weight at evaluation, kg	5.27 (0.73)
Maternal age, years	32.0 (5.1)
	Median (IQR)
Gestational age, weeks	40 (39; 40)
Birth weight, SDS	−0.23 (−0.70; 0.62)

SD: standard deviation; SDS: standard deviation score; IQR: interquartile range.

Spearman's correlation coefficients were adopted to explore the relationship between infant AGE levels and continuous variables. Skin AGE results were logarithmically transformed to perform linear regression with age in both breastfed and formula-fed infants.

All statistical analyses were carried out using the SPSS (Statistical Package of Social Sciences, Chicago, IL, USA) software program version 20.0 for MAC OS. A p value < 0.05 was considered significant. Graphs in Figure 1 were performed using PRISM 6.00 for MAC OS (GraphPad Software, La Jolla, CA, USA).

Ethics statement and informed consent details

The study was approved by the Ethics Committee for Human Investigation at our Institution. Written informed consent to the study was obtained from all the parents of the enrolled children.

Results

Table 1 summarizes the clinical details of the examined population. The comparison between breastfed and formula-fed infants whose mothers were non-smoking (n = 86) is reported in Table 2. In particular, infants did not differ in post-natal age, weight, and gestational age. Interestingly, the amount of skin AGEs was statistically higher in formula-fed subjects than in breastfed subjects. However, infants did not differ in

Table 2. Comparison of auxological variables and skin AGE levels in breastfed and formula-fed infants born from non-smoking mothers.

	Breastfed infants (n = 53)	Formula-fed infants (n = 33)	p
	Mean (SD)	Mean (SD)	
Birth length, SDS	0.27 (0.85)	0.44 (0.89)	0.381
Age at evaluation, days	69.4 (18.6)	64.2 (21.6)	0.243
Weight at evaluation, kg	5.27 (0.73)	4.87 (0.89)	0.026
Maternal age, years	31.6 (4.8)	33.6 (5.0)	0.067
	Median (IQR)	Median (IQR)	p
Gestational age, weeks	40 (39; 40)	39 (39; 40)	0.268
Birth weight, SDS	0.01 (−0.61; 0.84)	−0.15 (−0.64; 0.55)	0.517
Skin AGEs, AU	0.80 (0.65; 0.90)	1.00 (0.85; 1.05)	<0.001

AGE: advanced glycation end-product; SD: standard deviation; SDS: standard deviation score; AU: arbitrary units; IQR: interquartile range.

Table 3. Comparison of auxological variables and skin AGE levels in breastfed infants and in formula-fed infants considering mother's smoking habits.

	Breastfed infants, non-smoking mothers (n = 53)	Breastfed infants, smoking mothers (n = 8)	p	Formula-fed infants, non-smoking mothers (n = 33)	Formula-fed infants, smoking mothers (n = 7)	P
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Birth length, SDS	0.27 (0.85)	−0.49 (1.48)	0.038	0.44 (0.89)	−0.34 (0.90)	0.043
Age at evaluation, days	69.4 (18.6)	69.3 (20.1)	0.986	64.2 (21.6)	73.3 (17.7)	0.307
Weight at evaluation, kg	5.27 (0.74)	4.48 (0.59)	0.005	4.87 (0.89)	4.92 (0.56)	0.875
Maternal age, years	31.6 (4.8)	29.5 (6.2)	0.278	33.6 (5.0)	30.7 (4.8)	0.173
	Median (IQR)	Median (IQR)	p	Median (IQR)	Median (IQR)	p
Gestational age, weeks	40 (39; 40)	40 (39; 41)	0.449	39 (39; 40)	40 (38; 40)	0.822
Birth weight, SDS	0.01 (−0.61; 0.84)	−0.57 (−1.13; −0.25)	0.033	−0.15 (−0.64; 0.55)	−1.02 (−1.87; −0.9)	0.004
AGEs, AU	0.80 (0.65; 0.90)	1.00 (0.90; 1.17)	0.009	1.00 (0.85; 1.05)	1.00 (0.90; 1.10)	0.784

AGE: advanced glycation end-product; AU: arbitrary units; IQR: interquartile range; SD: standard deviation; SDS: standard deviation score.

the skin content of AGEs when analyzed according to sex, birth weight, and type of delivery (data not shown).

AGE values (mean ± SD) for breastfed and formula-fed infants born from non-smoking mothers were 0.81 ± 0.20 and 0.99 ± 0.25, respectively.

We observed a direct, positive correlation between AGEs and days of life at evaluation either in the whole population ($r = 0.276$, $p = 0.010$) or after splitting in breastfed ($r = 0.286$, $p = 0.038$) and formula-fed ($r = 0.422$, $p = 0.014$) infants. Figure 1 shows the linear regression analysis between logarithmically transformed skin AGEs and age, depending on the type of feeding. The amount of AGEs did not relate to gestational age, birth weight SDS, birth length SDS, weight at evaluation, and maternal age (data not shown).

Table 3 summarizes the results according to both the type of feeding and the habit of mothers to smoke during pregnancy and feeding. Infants born from smoking mothers had a significantly reduced birth weight SDS and birth length SDS in comparison with that observed in those born from non-smoking mothers. Moreover, breastfed infants born from smoking mothers had reduced weight at evaluation in comparison to those born from non-smoking women.

Interestingly, among breastfed infants, the amount of AGEs found in ones from smoking mothers were significantly higher than in those from mothers who had never smoked. As regards formula-fed infants, skin AGEs amount was similar between infants from mothers who smoked during pregnancy and feeding and those from mothers who had never smoked.

Discussion

In our study, we assessed the accumulation of AGEs in the skin performed by using a completely non-invasive technique. Our data showed that formula-fed infants had higher amounts of skin AGEs than the breastfed counterparts. To our knowledge, we reported for the first time that infants

whose mothers smoked during pregnancy and breast-feeding had increased deposition of AGEs in their skin in comparison with breastfed infants whose mothers had never smoked.

Data on behavior of AGEs in infants are scarce in the literature.[19,43,47,48] Recently, proteomic characterization of AGEs in commercial milk samples[42] demonstrated that submitting milk to heat treatment, to preserve microbiological safety and to prolong shelf life, induced important physicochemical changes in milk proteins, depending on the duration/extent of the heating procedure. Among these changes there is the production of AGEs. Since several studies suggested that food-derived AGEs may play a role in a wide range of harmful health effects, for example, diabetogenic, pro-oxidative, and pro-inflammatory events,[3–5,15,49] one is wondering whether the intake of AGE-rich infant food, that is, formula milk, may precondition infants to metabolic and cardiovascular diseases. Our study was not designed to explore in depth this topic; consequently, our results cannot provide a clear answer. Nonetheless, we observed a significant, but limited, increase in skin AGE values (about 1 SD when sAF was expressed as mean ± SD) in formula-fed infants over breastfed counterparts (Table 2). A recent paper reported a similar increase in circulating AGEs in 3- to 6-month-old and 7- to 10-month-old formula-fed infants in comparison with breastfed ones, which did not contribute to insulin resistance associated with consumption of formula milk. The difference disappeared in the 11- to 14-month age group due to intake of solid food in addition to breast milk.[48] The same authors also studied skin AGEs during a wide age range, spanning from few days to 77 years old population.[47] They reported that in subjects ⩽6 months old, values of skin AGEs were lower than we found in both breastfed and formula-fed individuals (sAF: 0.52 ± 0.16 and 0.67 ± 0.20, respectively). We do not have a clear explanation for that, but data from that study showed, in general, slightly lower sAF than that reported by Koetsier et al.[19] in the Dutch population. Future studies reporting sAF normative data from different countries will contribute to clarify these observed differences among populations.

In our subjects, we observed a positive relationship between days of life and skin AGEs, irrespective of the type of feeding. This relationship, present during life,[19,47] possibly reflects a progressive accumulation of AGEs in skin.

In regard to infants of smoking mothers, their skin AGEs were higher than those observed in breastfed infants from mothers who had never smoked, but not significantly different from formula-fed infants. In addition, we did not observe any additional effect of smoking habit on formula feeding. There was not, in fact, any significant difference between skin AGEs in formula-fed infants and in formula-fed infants from smoking mothers. However, these infants were born lighter and thinner and were smaller than infants from non-smoking mothers at the assessment of AGEs. It is well known that smoking during pregnancy represents a major cause of small for gestational age newborns. Mericq et al.[50] showed a high significant correlation between maternal and infant circulating AGEs before the introduction of exogenous food to the infant. This correlation was observed in newborns and in breastfed infants, supporting a maternal transmission of AGEs throughout the placenta and breast milk. Thus, one could hypothesize that smoking-derived AGEs accumulate in both the mothers, contributing to affect placental development and function, and in the fetus, disturbing fetal development. In this case, in fact, excessive accumulation of AGEs starts very early in fetal life, exposing the fetus to an elevated oxidant stress state during a period of life so important for programming of fetal functions. Indeed, detrimental effects on health, although not evident in the immediate time frame, can become manifest later in life. To confirm our hypothesis, future studies should evaluate whether newborns of smoking mothers have higher post-partum sAF in comparison with ones born from non-smokers and whether human breast milk of smokers contains higher amounts of AGEs. In addition, the possible role of other lifestyle-related factors in changing the AGE content of human milk should be assessed.

Our cross-sectional study had some limitations. The enrolled sample is relative small, particularly regarding the number of smoking mothers. However, we expected this limitation considering that smoking in pregnancy and feeding is universally deprecated. Second, we did not evaluate maternal diet, with particular attention to consumption of AGE-rich foods. Finally, we did not consider a follow-up to determine whether the difference in skin AGEs between breastfed and formula-fed infants may persist with time.

Conclusion

Our data confirmed that formula-fed infants had increased amounts of skin AGEs in comparison with the breastfed counterparts. Even if this increase was limited and at present there is no clear evidence in the literature that it may be harmful to infant health, our results confirmed that breast milk represents undoubtedly the best food for infants. However, as formula milk becomes extremely important for newborns and infants from mothers who cannot breast-feed, industries producing formula milk should make any efforts to produce formulas with the possible lowest amount of AGEs.

Skin AGEs in breastfed infants from smoking mother were as high as those observed in formula-fed counterparts. However, as mothers were smoking during pregnancy, AGEs had already increased during fetal life, possibly affecting fetal development. After delivery, smoke-related AGEs transfer throughout breast milk may maintain amounts of AGEs higher than normal in the newborn/infant. Thus, the habit of smoking must be stopped during pregnancy and lactation, as worldwide recommended.[51]

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M.G., E.R., and F.V. performed infant skin advanced glycation endproducts evaluation. G.F. and F.V. performed statistical analysis. All authors contributed to interpretation of data, critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

This is an observational study performed using a quick, not invasive, quite painless, optical method (see Negrean et al.[16] and Conway et al.[26]) to assess skin AGEs in babies who had undergone an ultrasound examination of their hips (a not invasive, painless method, as well). According to the Ethics Committee for Human Investigation of our Institution, we collected a written informed consent from babies' parents.

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Informed consent

Written informed consent was obtained from babies' parents before the study.

Trial registration

An ethics approval number was not applicable to our study, according to the Ethics Committee for Human Investigation of our Institution.

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