Additional effects of dietary advanced glycation end products

To the Editor:

The excellent review by Smith et al[1] makes a convincing case for the contribution of dietary advanced glycation end products (AGEs) to the development of food allergy. There is also additional evidence that AGEs may be involved in asthma. Induced sputum levels of the AGE pentosidine are higher in patients with asthma than in those without asthma, and increase with age at a markedly faster rate in patients with asthma than in controls, such that they are higher in young patients with asthma than in old people without asthma.[2] In contrast to most tissues, where the receptor for advanced glycation endproducts (RAGE) is low or absent unless specifically upregulated, RAGE is present on eosinophils[3] and in upper and lower airways,[4] and at particularly high levels in the airways of patients with chronic obstructive pulmonary disease.[5]

In addition, there is at least 1 instance in which an allergy to a pharmaceutical results from the formation of immunogenic AGE epitopes on the drug.[6]

The negative effects of AGEs are not limited to allergy. There is strong evidence of a causal relationship between AGEs and aging, so much so that the beneficial effects of caloric restriction on decreasing oxidative stress and increasing longevity in mice are reversed when the restricted-calorie diet is modified to also be high in AGEs.[7]

AGEs do not appear on the list of ingredients printed on packaged foods. Anyone interested in eating a healthful diet that is not proinflammatory would do well to consider the high-temperature cooking that creates these immunoreactive compounds.

Jeffrey D. Miller, MD

From Mission: Allergy, Inc, Hawleyville, Conn, and the Department of Pediatrics, New York Medical College, Valhalla, NY. E-mail: JeffreyMillerMD@comcast.net.

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REFERENCES

1. Smith P, Masilamani M, Li X-M, Sampson H. The false alarm hypothesis: food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. J Allergy Clin Immunol 2017; 139:429-37.
2. Kanazawa H, Tochino Y, Kyoh S, Ichimaru Y, Asai K, Hirata K. Potential roles of pentosidine in age-related and disease-related impairment of pulmonary functions in patients with asthma. J Allergy Clin Immunol 2011;127:899-904.
3. Kvarnhammar AM, Cardell LO. Pattern-recognition receptors in human eosinophils. Immunology 2012;136:11-20.
4. Van Crombruggen K, Holtappels G, De Ruyck N, Derycke L, Tomassen P, Bachert C. RAGE processing in chronic airway conditions: involvement of *Staphylococcus aureus* and ECP. J Allergy Clin Immunol 2012;129:1515-21.e8.
5. Ferhani N, Letuve S, Kozhich A, Thibaudeau O, Grandsaigne M, Maret M, et al. Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;181:917-27.
6. Bozhinov A, Handzhiyski Y, Genov K, Daskalovska V, Niwa T, Ivanov I, et al. Advanced glycation end products contribute to the immunogenicity of IFN-β pharmaceuticals. J Allergy Clin Immunol 2012;129:855-8.
7. Cai W, He JC, Zhu L, Chen X, Zheng F, Striker GE, et al. Oral glycotoxins determine the effects of calorie restriction on oxidant stress, age-related diseases, and lifespan. Am J Pathol 2008;173:327-36.

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Reply

To the Editor:

We thank Dr Miller for his letter[1] in response to our recent Rostrum article in the *Journal*.[2] We agree that there is a strong body of literature linking advanced glycation end products (AGEs) in the diet and diseases such as atherosclerosis, renal failure, cataracts, and forms of dementia such as Parkinson disease and Alzheimer disease.[3-5] The focus of our article was to point out that increase in dietary AGEs and sugars (particularly fructose), which leads to the formation of AGEs, appears to have epidemiological associations with the rise of severe food allergy and there are laboratory correlates showing that the activation of the receptor for advanced glycation end products (RAGE) has pivotal roles in allergic inflammation.[2] From a health point of view, beyond possibly implications for allergy, we agree that food labeling indicating the AGE content would be desirable. For those who would like a guide now, Uribarri et al[6] have published a list of common foods and their AGE content. In addition, we take this opportunity to stress that RAGE—the ligand for AGEs—increases with lack of exercise, obesity, and hyperglycemia.[7,8] Exercise and vitamin D increase the production of a soluble form of RAGE,[9,10] which acts as a decoy and higher levels of soluble RAGE have been shown to be of benefit in asthma.[11] Awareness of AGEs and modifying diet and lifestyle would appear to have benefits well beyond those we hypothesize for risk of food allergy.

Peter K. Smith, MD[a]
Madhan Masilamani, PhD[b]
Xiu-Min Li, MD[b]
Hugh A. Sampson, MD[b]

From [a]Griffith University, Southport, Queensland, Australia; and [b]Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY. E-mail: pksm@mac.com.

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REFERENCES

1. Miller JD. Additional effects of dietary advanced glycation endproducts. J Allergy Clin Immunol 2017;140:319.
2. Smith PK, Masilamani M, Li XM, Sampson HA. The false alarm hypothesis: food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins. J Allergy Clin Immunol 2017; 139:429-37.
3. Uribarri J, Cai W, Sandu O, Peppa M, Goldberg T, Vlassara H. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. Ann N Y Acad Sci 2005; 1043:461-6.
4. Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology 2005;15: 16R-28R.
5. Luevano-Contreras C, Chapman-Novakofski K. Dietary advanced glycation end products and aging. Nutrients 2010;2:1247-65.
6. Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110:911-6.e12.
7. Torres-Graciano S, Villegas-Rodriguez E, Fajardo-Araujo ME, Malacara JM, Rivera-Cisneros AE, Garay-Sevilla ME. Advanced glycation end products, their receptors RAGE and AGER-1 and their association with insulin resistance and inflammation in obese and non-obese young subjects. Endocrine Abstr 2015; 37:EP633.
8. Yao D, Brownlee M. Hyperglycemia-induced reactive oxygen species increase expression of the receptor for advanced glycation end products (RAGE) and RAGE ligands. Diabetes 2010;59:249-55.
9. Talmor Y, Golan E, Benchetrit S, Bernheim J, Klein O, Green J, et al. Calcitriol blunts the deleterious impact of advanced glycation end