The false alarm hypothesis: Food allergy is associated with high dietary advanced glycation end-products and proglycating dietary sugars that mimic alarmins

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The incidence of food allergy has increased dramatically in the last few decades in westernized developed countries. We propose that the Western lifestyle and diet promote innate danger signals and immune responses through production of "alarmins." Alarmins are endogenous molecules secreted from cells undergoing nonprogrammed cell death that signal tissue and cell damage. High molecular group S (HMGB1) is a major alarmin that binds to the receptor for advanced glycation end-products (RAGE). Advanced glycation end-products (AGEs) are also present in foods. We propose the "false alarm" hypothesis, in which AGEs that are present in or formed from the food in our diet are predisposing to food allergy. The Western diet is high in AGEs, which are derived from cooked meat, oils, and cheese. AGEs are also formed in the presence of a high concentration of sugars. We propose that a diet high in AGEs and AGE-forming sugars results in misinterpretation of a threat from dietary allergens, promoting the development of food allergy. AGEs and other alarmins inadvertently prime innate signaling through multiple mechanisms, resulting in the development of allergic phenotypes. Current hypotheses and models of food allergy do not adequately explain the dramatic increase in food allergy in Western countries. Dietary AGEs and AGE-forming sugars might be the missing link, a hypothesis supported by a number of convincing epidemiologic and experimental observations, as discussed in this article. (J Allergy Clin Immunol 2017;139:429-37.)

Key words: *Food allergy, alarmins, glycation, advanced glycated end-products, receptor for advanced glycated end-products*

Food allergies have increased dramatically in the last 30 years, particularly in westernized developed countries. More recently, developing countries are observing a similar trend. Food allergy and its common comorbidity eczema represent "gateway" diseases, seemingly opening the door for the chronic inhalant diseases of allergic asthma, rhinitis, and conjunctivitis. Establishing the important factors in the development of food allergy has been a focus of research in many centers; however, there has not been a conclusive answer to firmly clarify the mechanisms by which food allergy occurs. The major explanations behind the increase in food allergy currently include a combination of the following:

1. Hygiene/microbiota type and microbial diversity. This theory developed from animal studies in which rearing in sterile environments resulted in allergic features including dermatitis, T_H2 responses, and anaphylaxis.[1,2] In 1989, Strachan[3] proposed the hygiene hypothesis, and studies demonstrating the influence of microbiota type, timing, diversity, farm exposure, and intervention studies with probiotics and prebiotics add credence to this line of thought.[4-6] Bach[7] convincingly correlated an increase in both allergic and autoimmune disease with a reduction in severe infections
2. The timing of complementary food introduction appears to be important in the development of tolerance. Recently, the concept of giving peanut in the first year of life has been shown to reduce peanut allergy in a high-risk cohort in the United Kingdom.[8,9]
3. Low vitamin D levels in infancy appear to be a risk factor for the development of peanut and egg allergy, and the distance one lives from the equator in the United States and Australia has been correlated with epinephrine autoinjector prescriptions used as a surrogate for food allergy.[10-12]
4. Other cofactors include antibiotics, diversity of feeding, use of antacids, and types of fatty acids (lower levels of omega 3 and linoleic acid) in the diet, and phylates in plastics appear to promote allergic responses.[13,14]

Food allergy involving IgE is a maladaptive and learned immunologic threat response to an innocent allergen (usually common foods) that should normally provide nutrition and health benefits. Something is likely to have changed dramatically in the Western lifestyle in the last half-century that is promoting this

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Abbreviations used
AGE: Advanced glycated end-products
CML: N(ε)-carboxymethyllysine
DC: Dendritic cell
HMGB1: High molecular group box 1
OVA: Ovalbumin
RAGE: Receptor for advanced glycated end-products
TLR: Toll-like receptor

immunologic misdirection. IgE-mediated milk allergy is reported to currently affect between 2% and 7.5% of children[15]; however, the first case of allergy to milk (fatal anaphylaxis) was reported in the German literature in 1905.[16]

Only recently, it has become apparent that allergic reactions are not solely based on IgE antibodies and T_H2 cells. Many other cell types, including innate lymphoid cells and epithelial barrier functions, for example, play a crucial role in the allergic response.[17-22] However, much of the research focus has attempted to link adaptive immune responses, such as IgE levels and cytokine patterns, to allergic phenotypes. Similarly, there have been risk associations made with a variety of genes involving barriers, IgE, cytokines, antiproteases, pattern recognition and response molecules, and food allergy. Human genetics could not have changed dramatically in the last 20 to 30 years in westernized countries; however, the way the genes function can be altered by environmental factors (eg, methylation, ubiquitination, and histone acetylation), and this is another direction of research. It appears that the extent and pattern of gene methylation can predict the likelihood of food allergy.[23] The parameters for the majority of epigenetic research remain focused at the level of allergic phenotypes and adaptive immune responses. Adaptive immune responses are largely guided by messages and signaling from the innate immune system; however, there has been minimal focus on innate immunity in terms of the mechanism of food allergy.

ALARMINS, ADVANCED GLYCATED END-PRODUCTS, AND RECEPTOR FOR ADVANCED GLYCATED END-PRODUCTS

High mobility group box 1 is a major alarmin that promotes T_H2 responses

Alarmins are normally released from all cells that undergo nonprogrammed cell death.[24] This is an innate mechanism by which dying cells signal danger and recruit elements of the adaptive immune response. The high mobility group box 1 (HMGB1) is a key alarmin released with tissue damage. Activated dendritic cells (DCs) secrete HMBG1, and this appears to be critical in the activation and proliferation of T lymphocytes.[25] HMGB1 can be released from cells during inflammation or through stimulation from pathogen-associated molecular patterns, such as Toll-like receptors (TLRs).[24]

HMGB1 binds to receptor for advanced glycated end-products

HMBG1 binds to its receptor, receptor for advanced glycation end-products (RAGE; an immunoglobulin family member only present in mammals), to induce maturation of DCs, neurite growth, and activation and migration of monocytes, macrophages, neutrophils, and DCs and to induce inflammation and oxidative pathways.[24,26-28] HMGB1 can signal through both RAGE and TLRs, such as TLR2 and TLR4.[29,30] Although TLR2/4 stimulation has been reported to be protective against food allergy,[31] an airway model of allergy has shown that TLR4 agonism in conjunction with HMBG1 amplifies the allergic response[32] and blocks the TLR4-attenuated allergic response to fungal proteinase.[33] RAGE also binds to and is activated by other alarmins, such as S100 proteins and amyloid β-peptide.[34]

HMGB1/RAGE alarmin signaling is critical for allergic responses

Activation of RAGE receptors is proinflammatory and promotes adaptive (and maladaptive in the cases of diabetes, atherosclerosis, and Alzheimer disease) immune responses.[35,36] RAGE knockout mice have attenuated responses to inhalant allergens.[37] Ullah et al[32] have recently demonstrated a role for the HMGB1-RAGE axis in airway sensitization and airway inflammation. The attenuated response to inhalant allergens in *Rage*$^{-/-}$ mice[37] might be due to significantly reduced numbers of DCs in the lung and draining lymph nodes. Recently, Oczypok et al[38] have shown that RAGE drives allergic airway inflammation by promoting IL-33 expression and accumulation of type 2 innate lymphoid cells in the airways. Thus far, there is no direct evidence suggesting advanced glycation end-products (AGEs) trigger food allergy through interaction with RAGE.

Western diet high in AGEs can induce alarmin signaling

The RAGE receptor also binds to and is activated by glycated proteins. High blood sugar levels (eg, in patients with diabetes) are associated with increased glycation of endogenous proteins and a proinflammatory state.[39] The Western diet can contribute significantly to the AGE pool, with up to 10% of dietary consumed AGEs being absorbed systemically and only an estimated one third being excreted.[35,40] Dietary AGEs are produced in high amounts, particularly with animal proteins and fats that are cooked at high temperatures (eg, fast foods and cooked meats are particularly high in AGEs), to expose amino acid chains to which sugars bind. There are several intermediate products in the formation of AGEs, such as Amadori, and Schiff base during the Maillard reaction. The Maillard reaction (also referred to as "glycation") describes a complex series of chemical reactions between carbonyl compounds, such as reducing sugar, and amino compounds, such as amino acids and protein. AGEs are a heterogeneous group of compounds that are produced at the late phase of the Maillard reaction.[41] We see glycation in many foods as the crispiness and browning of foods with cooking; however, AGEs are also readily formed with super-high heating, such as microwave cooking and frying.[40] Sugar moieties are bound to proteins or lipids, leading to formation of AGEs (also called glycotoxins). The most well-characterized glycotoxins are methylglyoxal[42] and N(ε)-carboxymethyllysine (CML).[43] Methylglyoxal is a carcinogen capable of cleaving DNA and inducing damage to nucleic acids.[42,44,45] Fructose is a key substrate in the formation of methylglyoxal.

As highlighted previously, RAGE activation by alarmins induces immunologic activation and multiple inflammatory

responses. RAGE is highly expressed on DCs, macrophages, T lymphocytes, and B cells, as well as mast cells and basophils.[32,46-49] AGEs binding to the RAGE receptor activate mast cells and induce exocytosis of histamine and generation of oxidative stress products in a dose-dependent mechanism (within 20 seconds).[49] T-cell activation and proliferation is dependent on RAGE activation,[25] and DCs require RAGE signaling for migration to lymph nodes in response to an antigen.[50] A RAGE knockout mouse model blocked immunologic responses to antigen, abrogating IL-5, IL-13, and exotoxin production, whereas an inhibitor of RAGE blocked responses to house dust mite.[37] Because DCs are at the forefront of immune responses, inadvertent sensitization to allergens by RAGE-activated DCs is likely important and a potential target for interventions. HMGB1 is recognized as an innate signal, along with S100, and both are released in conjunction with cell injury. HMGB1 expression is likely to recruit engagement of adaptive response elements, such as IL-33, thymic stromal lymphopoietin, and IL-25. Moreover, because of the antigen specificity of B and T cells, RAGE ligation in these cells is more likely to cause generalized immune activation during an AGE-induced (both dietary and endogenous) inflammatory reaction rather than a specific response to an allergen.

There is an indirect link between Western diet, AGEs, and allergic responses through production of another alarmin, uric acid. Fructose is metabolized by the liver, resulting in, among other waste products, large amounts of uric acid. Serum uric acid levels are a predictor of fructose toxicity. Uric acid has been shown to act as a sensor of inhaled allergens and a potent adjuvant to induce T_H2 responses during allergic inflammation.[51,52] Overproduction of uric acid has been shown to play a critical role in the induction of peanut-induced allergic sensitization through its action on DCs.[53]

HAS THE WESTERN DIET/LIFESTYLE CHANGED TO MIMIC TISSUE DAMAGE THROUGH AGE?

Dietary AGEs that glycate endogenous proteins can contribute to AGEs that are readily measured in serum.[39,40] Tobacco smoke generates measurable increases in AGE levels in serum and the skin.[54] The Western diet is high in AGEs, which are largely derived from cooked meat, oils, and cheese.[40,55] Recently, an environmental and ecologic analysis of national diets has linked Alzheimer disease to higher levels of dietary AGEs, and this correlates with findings of more rapid neurological decrease in patients with this disease with higher levels of serum methylglyoxal.[55,56]

Glycation of allergens

It is worthwhile pointing out that roasting of peanuts increases glycation and allergenicity,[57-60] whereas boiling reduces allergenicity.[58,61] In fact, prolonged heating might degrade Ara h 1, 2, and 6 antigens.[61,62] AGE-stimulated DCs have been shown to induce a stronger T_H2 and a weaker T_H1 cytokine response to ovalbumin (OVA).[63] Microwaving whole milk increases AGE production by 5-fold at 1 minute and 86-fold at 3 minutes.[40] Not all food glycation increases allergy. A high degree of glycation of β-lactoglobulin has a masking effect on the recognition of epitopes by IgE.[64] The Maillard reaction has been reported to reduce allergenicity of squid, scallop, cherries, apple, and buckwheat. This could be due to reduced heat stability of allergenic proteins in these foods unrelated to AGE formation or glycation masking allergenic epitopes.[65-68]

Fast food consumption and chronic lifestyle diseases

Bach[7] elegantly demonstrated an epidemiologic association with reducing severe infections in the Western world and an increase in autoimmune disease between 1950 and 2000. If these data are compared over time with increases in eczema, food allergy, and anaphylaxis discharge data,[69-71] a similar pattern of increase is apparent (Fig 1).[7] Using data from the US Department of Agriculture, the consumption of sugar, particularly fructose, has increased dramatically between 1950 and 2000.[72] Potato consumption has increased, and these are being consumed more in the form of French fries and crisps. French fries are the most consumed vegetable in American 2- to 4-year-olds, and almost 90% of 3- to 4-year-olds are consuming a fructose-sweetened drink, dessert, or candy every day.[73] Fig 1 also plots McDonald's outlets in the United States and common fast food outlets in Australia (data from company Web sites), and the period of actively promoting upsizing occurred from the 1980s to 2002.

Fast food outlets have been presented in the article not to attribute blame but to reflect the types of foods that are being more frequently consumed in these countries over time. In the 1950s, consumption of soda generally involved an infrequent social outing, whereas currently, the common and recurring consumption in Western countries is with large-volume multipacks.

Along with fast foods, the consumption of peanuts (and peanut products) has also increased in the westernized world, including the US, according to the American Peanut Shellers Association. This is in part due to US governmental subsidies and aggressive promotion and marketing. The majority of peanuts are consumed as peanut butter in the United States and other peanut products that are dry roasted because these are the most preferred snacks among all others types, resulting in enhanced exposure of the population to the more allergenic glycosylated peanut.[74-76]

Foods considered unhealthy by current standards are associated with lower socioeconomic levels and poverty.[77] The risk of food allergy in families of higher socioeconomic status has multiple contributing factors. Some recognized associations include increased hygiene, less microbial diversity, pollution, activities that result in lower vitamin D levels (indoor play, sunscreen, and urban environment), increased medical attention for illness, and prescription of antibiotics. Dietary factors (ie, high AGE load) such as consumption of sugars (sweets and beverages), autoclaved/processed foods, microwaved foods, more roasted/barbecued meat, and dessert after every meal might be more prevalent in families of higher socioeconomic status. Affluence is associated with increased protein consumption in the form of red meat; this does tail off with higher marked affluence. This requires further study in itself, but awareness of dietary AGEs and the possible metabolic consequences of glycation allow consideration of these when taking a dietary history.

Gestational diabetes mellitus is associated with increased fetal exposure to glycation products created from greater glycation of endogenous proteins through a nonenzymatic mechanism caused by higher levels of blood glucose. Gestational diabetes mellitus has been associated with an increased risk of atopic dermatitis and IgE sensitization (mainly from food) by 1.7- and 1.6-fold,

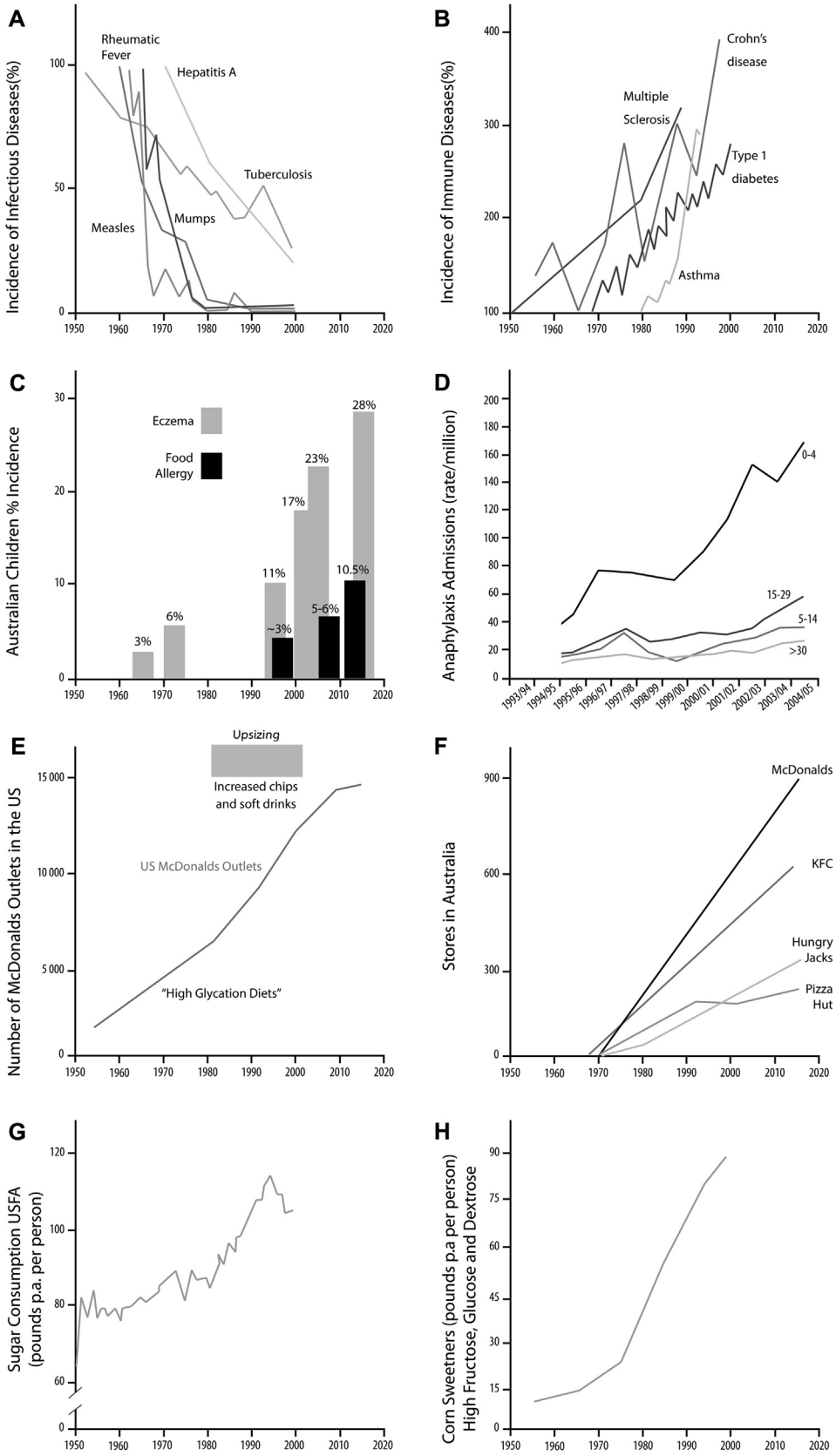

FIG 1. **A** and **B,** Time trends showing reduction in the incidence of infectious disease and increase in autoimmune disease.[7] **C,** Increases in eczema and food allergy in Melbourne, Australia. **D,** Hospital admissions in Australia with anaphylaxis. **E** and **F,** Number of McDonald's outlets in the United States and the 4 most common fast food companies in Australia. **G** and **H,** Increase in sugar and fructose consumption per capita in the United States.

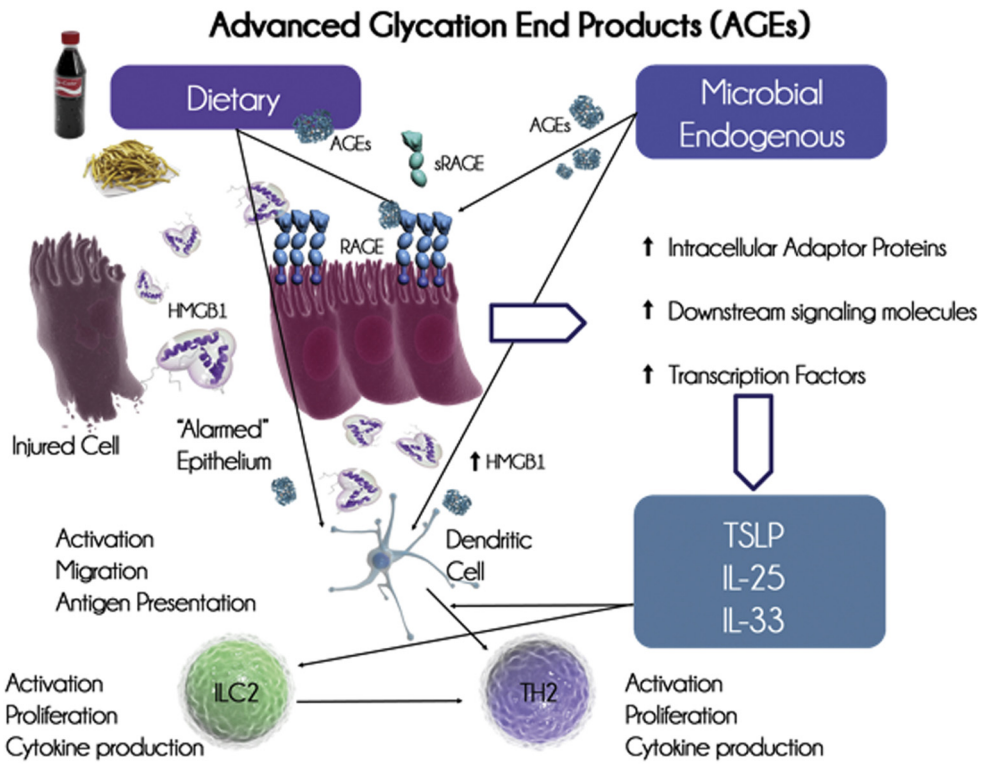

FIG 2. Total immunologic influence of AGEs should be considered as a sum of dietary AGEs that are absorbed. Dietary AGEs influence the pattern of microbiota, their production of AGEs, or glyoxalase enzyme activity. Low vitamin D levels are associated with epithelial injury and risk of infection and expression of RAGE. Dietary sugars bind to endogenous proteins and bacterial proteins to further add to the AGE pool. Soluble RAGE and the amount of endogenous glyoxalase enzymes will reduce the effect of the total AGE pool. RAGE activation influences multiple immune cells and multiple proallergic mediators. *ILC2,* Type 2 innate lymphoid cells; *TSLP,* thymic stromal lymphopoietin.

respectively, but only in those born after 37 weeks.[78] If endogenous or dietary AGEs are related to allergic risk, it would appear that the immunologic response is more vulnerable or capable of eliciting a response in later pregnancy. Children have the lowest levels of RAGE when measured.[79] Yet food allergy predominantly affects children. Poor eating habits start with the parents and are likely to commence in infancy/toddlerhood. Younger children have greater gastrointestinal/epithelial permeability and this has been suggested to contribute to the risk of atopic disease.[80] It is likely that dietary AGEs from the gastrointestinal tract would be absorbed more during the time of heightened permeability of the intestine. The immaturity of the immune system might also make infants more susceptible to environmental/epigenetic influences.[81] In addition, AGEs are also known to be passed through breast milk, contributing to the infant's AGE load.[82] Levels of CML, a potent AGE, were found to be 35- to 70-fold higher in infant formulas compared with breast milk.[83,84] However, to our knowledge, there are no studies that tested the direct effects of AGEs on the induction of food allergy in children.

Ways to mitigate deleterious effects of AGE/RAGE-induced inflammation

Living in a rural environment has been associated with a lower risk of food allergy, and this has helped to reinforce the hygiene hypothesis.[45] Microbial colonies appear to be influenced by diet.[85] Geographic remoteness has been attributed to a low incidence of childhood food allergy and anaphylaxis in Australia.[86] Children in rural areas consume less sugar (2 times less) in foods and fast food than urban children.[87-89] Within urban populations, food deserts (lack of access to supermarkets and increased consumption of fast foods) have been associated with an increased incidence of food allergy (odds ratio, 1.56).[90]

Bacteria signal HMGB1 through TLRs.[91] Probiotic bacteria, such as lactobacilli, produce the enzyme glyoxalase,[92] which is capable of degrading AGEs, and both prebiotics and probiotics have been demonstrated to reduce AGE levels in milk.[93] Milk normally has very low amounts of AGEs, but when heated to dry and create a milk powder, levels increase up to 670-fold.[83,94-96] *Escherichia coli* produces endogenous AGEs, and these have been shown to contribute to the inflammatory response.[97] Higher consumption of glycated dietary proteins has been shown to increase the amount of putatively harmful bacteria and reduce the proportion of putatively beneficial bacteria.[98] It is plausible that the "hygiene" effect is in part due to the AGE-RAGE axis influence on microbiota.

Dietary flavonoids, such as (-)-epigallocatechin 3-gallate (from green tea), phloridzin and phloretin (from apples), and quercetin and genistein (soy isoflavone), have been shown to trap methylglyoxal, a well-known precursor of AGEs.[99-102] Mouse models using antiglycation compounds, such as resveratrol and the soy isoflavones daidzein and genistein,[103,104] have been demonstrated to abrogate OVA and peanut allergy. The preventative effects of these compounds appear to reduce DC activation by means of

TABLE I. Evidence supporting the false alarm hypothesis

Evidence supporting the false alarm hypothesis	Reference
Alarmins, AGE, and RAGE	
1. *In vitro* data	
A. DCs	
I. Require HMGB1 for maturation and migration	24,26-28,50
II. Release HMGB1 when signaling antigen	24
B. T-cell activation	
I. Requires DC HMGB1 (or AGE) to activate, proliferate, and migrate	25
C. DNA	
I. HMGB1 and AGEs cause DNA damage and dysfunction	42,44,45
D. Mast cells	
I. RAGE ligation causes mast cell activation and release of histamine and oxidative mediators	49
E. Bacterial evidence	
I. *Lactobacillus* species make glyoxalase	92
II. *Escherichia coli* produces AGEs that contribute to inflammation	97
III. High-AGE diet does not favor probiotic flora	98
2. *In vivo* animal model studies	
A. Glycation reduction compounds blocking the development of food allergy	103,104
B. RAGE knockout reduced response to allergens	37,38
Western diet high in AGEs can induce alarmin signaling	
1. Epidemiologic studies: increased rate of food allergy and anaphylaxis	Current paper
A. Association with:	
I. Australian and US fast food outlets	
II. US sugar consumption*	
III. US fructose consumption*	
B. Increased food allergy in	
I. Urban vs rural areas (less consumption of AGEs/sugar in rural areas)	87,88
II. Urban food deserts	90
2. Observational studies	
Increased eczema and food sensitization in offspring of mothers with gestational diabetes	78
3. Allergic march data	
A. Association of asthma with sugar intake in early life	115
B. Association of asthma with excess free fructose from fruit juices and soft drinks in 2- to 9-year-olds	116
C. Association with asthma, rhinoconjunctivitis, and eczema with fast food and protection with healthy eating (fruit and vegetables)	69,111-113

In vitro studies and epidemiologic, statistical, and clinical data add to the understanding of the known mechanisms that have been associated with food allergy.
*Australia has similar patterns of consumption of sugar and fructose to the United States.

TABLE II. Key points

1. HMBG1 is a major alarmin that promotes T_H2 responses and appears critical for directing antigen responses.
2. HMBG1 binds to RAGE.
3. HMGB1/RAGE alarmin signaling is critical for allergic reactions.
4. Western diet high in AGEs can induce alarmin signaling.
5. Western diet has the potential to mimic tissue damage through glycation/AGEs.
6. Mitigation of AGE-induced reactions are beneficial.
7. We hypothesize that a diet high in AGEs can mimic innate alarms and skew toward allergic responses in genetic and environmentally predisposed subjects.

glycation; however, reduction of oxidative pathways is also likely to be a factor.[57,105] It is likely that the anti-AGE activity of these compounds could play a role in reducing food-induced allergic responses. When considering the glycation pool, consumed AGEs, sugars (particularly fructose), microbiota, and glycation-limiting and antioxidant foods should be considered, in addition to alarmin signaling (Fig 2).

Urribarri et al[106] have shown that culinary techniques practiced in Mediterranean and Asian cuisines limit dietary AGE generation compared with Western cooking practices (eg, frying and broiling). The association between the consumption of traditional soy food (particularly fermented soy food rich in isoflavones) in Asian countries and the low incidence of chronic health disorders are well known.[107,108] It is interesting to note that fermentation byproducts inhibit formation of CML, a major AGE.[109] The potential inverse correlation between the incidence of food allergy and exposure to sunlight and vitamin D levels might be explained by the *in vitro* observation that RAGE expression was downregulated by stimulation with calcitriol in human umbilical vein endothelial cells.[110] These findings, when considered

together, provide a compelling association between the incidence of allergic diseases, especially food allergy, and consumption of AGEs.

FOOD ALLERGY AND BEYOND

Food allergy is likely to be the first manifestation of excessive RAGE activation. If AGEs do influence the development of allergy, the greatest exposure to dietary AGEs and AGE-forming sugars will be in the gastrointestinal tract. The allergic march and development of rhinitis and asthma could also relate to ongoing unhealthy eating by current standards and reactivity of the immune system with inhaled allergens. The 3 published International Study of Asthma and Allergies in Childhood studies have repeatedly observed an association between fast food consumption being a risk factor and fresh foods and vegetables having protective effects for eczema, rhinoconjunctivitis, and asthma.[69,111-113] A low-AGE diet (reported as an antioxidant diet) has been reported to improve lung function and systemic inflammatory indices in adults with asthma.[114] Sugar consumption in early life is associated with severe asthma,[115] and specifically, excess free fructose consumption from fruit juices and soft drinks (popular soft drinks can contain 65% fructose/35% glucose) has been associated with increased risk of asthma.[116] It has been hypothesized that excess dietary fructose provides a substrate for the formation of AGEs with bacterial protein products, which then mimic alarmin signaling.[116] We hypothesize that food allergy is an early manifestation of a misdirected immune response to an innate signal. If a diet is high in AGEs and AGE-forming sugars, the child will be more likely to have allergic responses to inhalant allergens, manifesting as rhinitis and asthma.

There are implications in health policies and practices for westernized and developing countries for what we eat and how it is prepared, and already there are volumes of evidence regarding health benefits from a low-AGE diet. Emerging evidence suggests that a potential role of AGE modification of proteins is predisposing to food allergy.[63,117] AGE modifications have been found on a model food allergen, OVA, with concomitant binding of AGE OVA to RAGE, inducing a stronger allergic response than nonglycated OVA.[63] Similar glycation changes have been demonstrated on Ara h 1 and Ara h 3 (but not Ara h 2), with concomitant binding to RAGE. However, this modification did not seem to influence IgE binding.[118] It is interesting to note that more than 90% of patients with peanut allergy show IgE binding to Ara h 2,[119] despite the lack of AGE modifications in Ara h 2. This observation suggests that AGE adduct formation might not directly contribute to allergenicity of the proteins but might facilitate T_H2 skewing through other means (eg, DC activation[63]).

SUMMARY

Current hypotheses and models of food allergy do not adequately explain the dramatic increase in food allergy in westernized countries in the last 30 years. Dietary AGEs and AGE-forming sugars might be the missing link, and this hypothesis is supported by geographic and regional consumption and patterns of allergy appearing to match AGE consumption, fetal exposure to higher AGE levels in late pregnancy being associated with an increased incidence of atopic dermatitis and food sensitization, and allergy-protective microbiota interventional animal models and *in vitro* data on the effect of AGEs and activation of the RAGE receptor. The supporting materials discussed in this article are presented in Table I,* and key points are provided in Table II, which provides credence to but does not prove a false alarmin hypothesis caused by dietary changes in the Western world. This theory integrates knowledge of the effects of the hygiene hypothesis and nutritional aspects. Proof needs to be established of the biological relevance of dietary AGEs on immune responses with prospective epidemiologic and observational studies and specific laboratory research both *in vivo* and *in vitro*.

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