Genetically modified foods and food allergy

Stefani Su, M.D., Idil Daloglu Ezhuthachan, M.D., and Punita Ponda, M.D.

ABSTRACT

Genetic modification of foods is one of the many ways of processing that can enhance foods to increase desirable qualities, such as herbicide tolerance, bacteria and insect resistance, improved nutritional value, and delayed ripening. However, a theoretical potential to increase the allergenicity of food proteins has been the subject of concern from critics. To prevent adverse effects from genetically modified (GM) crops, national and international organizations tightly regulate their production and recommend rigorous safety testing. Some safety tests were developed to assess potential allergenicity by studying the product's similarity to known allergenic proteins, its resistance to pepsin digestion, and its binding to immunoglobulin E (IgE) from sera of patients with known relevant allergies. To date, these safety assessments have only identified rare GM foods with the potential to lead to immunologic reactions. These foods were stopped from being marketed commercially, and the products on the market now have passed required safety assessments. The rise in the prevalence of food allergy preceded the commercialization of GM foods and has also occurred in countries with limited access to GM crops, which highlights a lack of causative association between the two. Several studies provided further reassurance with no evidence of higher potency in specific IgE binding to GM foods. There are no studies that demonstrate adverse reactions due to GM food consumption, and GM foods may have the beneficial potential to silence major allergenic proteins. Therefore, physicians and other health-care professionals should counsel patients that the scientific data do not support an increased risk of allergic responses to GM foods.

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DEFINITION OF GENETICALLY MODIFIED FOODS

Genetically modified (GM) foods are foods that are produced after a genetic change or a DNA modification has been introduced. New traits can be incorporated into the genome in this manner. This can be used as a part of processing of food. The idea that food processing might affect the allergenicity of foods was first suggested by German physicians Otto Carl Willy Prausnitz and Heinz Küstner in 1921 and was later shown to occur with shelling, skinning, or thermal treatment.[1] Genetic modification is one of the more recent forms of processing and is being progressively more used.[1] The majority of food allergies are caused by specific proteins encountered in consumed food. This food has oftentimes undergone multiple forms of processing.

Manipulating the genetics of crops is not a novel concept that arose in the past few decades. Farmers used selective breeding techniques to grow domestic crops with specific desired traits for thousands of years.[2] These breeding techniques typically involve mating and/or crossing parental lines with certain traits, then selecting those offspring that have inherited the desirable traits. Starting in the 1980s, the ability to isolate and use specific genes with desired traits became possible and the field of GM crop production began.[2] The most common modifications in GM crops are made for the purpose of producing proteins to increase herbicide tolerance, delay ripening, and provide resistance to bacteria and insects. The process entails inserting a gene for the desired trait into a plasmid. The plasmid is then injected into the *Agrobacterium tumefaciens* bacterium, which transfers the gene into the cells of the plant, which results in a transgenic plant.[2] With the increasing presence of GM crops in our food chain, there is interest in and concern about the contribution of GM crops to food allergies.[2,3]

POLICIES

GM crops are tightly regulated under the guidance of national and international organizations, such as the U.S. Food & Drug Administration (FDA), the U.S. Environmental Protection Agency, the U.S. Department of Agriculture, the European Food Safety Authority, Food and Agriculture Organization of the United Nations, and the World Health Organization.[4] In its 1992 policy statement on foods derived from new plant varieties, the FDA recommended that producers of GM crops consult with the FDA on relevant safety,

From the Division of Allergy and Immunology, Northwell Health System, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York
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Address correspondence to Punita Ponda, M.D., Division of Allergy and Immunology, Northwell Health System, 865 Northern Boulevard, Suite 101, Great Neck, NY 11021
E-mail address: pponda@northwell.edu

Table 1 **Current list of genetically modified crops reviewed by the U.S. Food and Drug Administration (as of 2019)***

Name of Crop	Year of Review
Alfalfa	2004
Apple	2015
Canola	1995
Cantaloupe	1999
Corn	1995
Cotton	1995
Flax	1998
Papaya	1997
Pineapple	2016
Plum	2009
Potato	1995
Radicchio	1997
Rice	2000
Soybean	1995
Squash	1995
Sugar beet	1998
Tomato	1995
Wheat	2004

**From Ref. 15.*

nutritional, or other regulatory issues, including allergenicity testing protocol requirements.[5] As of 2019, the FDA has reviewed 18 GM crops (Table 1). The FDA also recommends that foods that contain GM crops be labeled to show known or possible major allergen content.[5]

The Codex Alimentarious Commission of the World Health Organization is responsible for developing the standards, codes of practice, guidelines, and recommendations that constitute the international food code, and, in 2003, recommended a weight-of-evidence approach for allergenicity assessment of GM crops.[3] These assessments address factors such as whether the source of the gene inserted is one known to induce allergy, if the molecular structure or amino acid sequence is significantly similar to known allergenic proteins, how stable the new protein is to pepsin digestion, and how much exposure will occur with the new protein in the gastrointestinal tract due to the abundance of the protein in the food.[3] In addition to the Codex requirements for allergenic risk assessment, the European Food Safety Authority suggests screening with specific serum immunoglobulin E (IgE).[6] This is done to evaluate whether there are similar amounts of IgE binding to the food from the GM crop and the closest conventionally grown crop (isogenic crop).

SAFETY TESTING

Safety assessments for GM foods consider seven domains, which are composition, dietary intake, nutritional data, toxicology, and characteristics of the donor and host organisms as well as allergenicity.[4] Allergenicity assessments of GM plants are done by evaluating the entire plant as well as the newly expressed proteins. When considering that eight major food groups are responsible for 90% of food allergies, it is an industry-accepted best practice not to use genes from these sources.[2] To assess the risk of new proteins, comparison of the amino acid sequence of the newly expressed proteins with the known allergenic proteins is done by comparing the identity and location of each amino acid in the protein to the known allergens in a data base. If there is a ≥35% shared identity over ≥80 amino acids, or if there is a match of ≥8 amino acids in a continuous sequence, potential cross-reactivity of the novel protein with known allergic proteins must be evaluated. This is done by specific IgE-binding studies.[3] To investigate the potential cross-reactivity with a known allergen, sera from patients who are allergic to the specific allergen are used.[7] However, because the predictive value of this testing is not well established, its clinical value remains unclear.[3]

A correlation between resistance to pepsin digestion and allergic potential has been proposed, and, later, *in vitro* pepsin digestion assays were developed to investigate this correlation in the laboratory setting. Because there are examples of proteins that are not digestible but are not allergenic, results of these assays are also not enough to solely rely on.[3] Lastly, animal models and cell culture systems have been developed to assess the allergenicity of the new proteins used in GM crops. Although these models can provide mechanistic information, there is a lack of data on the reproducibility and predictive value or utility; as a result, their use to predict allergic reactions on exposure to new proteins has not been validated.[3,4]

CURRENT STATE OF KNOWLEDGE

Since their first introduction into the market in 1994, there have been two instances in which immune-mediated reactions to GM crops were suspected. The first involved transfer of a Brazil nut protein into soybean to enhance its nutritional value. During this process, an allergenic protein was transferred. A study done by using serum IgE from subjects with known Brazil nut allergy demonstrated IgE binding to the transgenic soybean and a positive skin test result in three subjects.[8,9] The second instance involved a bean engineered to enhance pest resistance, which resulted in antigen-specific $CD4^+$ T-helper type 2 inflammation in the mouse model. In light of the study findings, neither product reached the market, which suggests that the safety measures were useful.[4]

In the early 2000s, ~28 cases of anaphylaxis were reported after suspected exposure to Starlink corn

(Aventis Crop Science of Research Triangle Park, North Carolina), a GM crop that was intended for animal use only but made its way to human food supply. Subsequently, the Centers for Disease Control and Prevention led a study that disproved this suspicion *via in vitro* testing and oral food challenges.[10] Therefore, GM crops currently on the market have not been associated with any known adverse effects.[10] Data collected thus far on GM crops have shown that the levels of allergic proteins of the GM crop when compared with the conventionally grown crop are within the normal variation that is seen in the conventionally grown crops.[11] Similarly, the potency of IgE binding has not been found to be different between GM and conventional crops. Specifically, in a study that compared binding of human IgE in a GM soybean to that in six non-GM soybeans, the experimenters found that the GM soybean was not significantly more potent in IgE binding than the non-GM soybeans.[12]

Critics of GM crops have attributed the increase in incidence of food allergic reactions in the recent decades to GM foods. However, to our knowledge, there have been no studies to support this. In 2016, the National Academy of Sciences noted that the increased prevalence of food allergy in the United States began before the commercial introduction of GM foods.[2] Likewise, the rise in the number of individuals with soybean allergy in the United Kingdom was temporally linked to the development of GM soybean, but this may have been due more to an increase in the overall consumption of soybean in this population. In addition, U.K. population exposure to GM soybean during that time was limited because most of the GM crop was targeted for the U.S. market.[4]

Amid the controversy with regard to a possible increase in allergic reactions with GM crops, it is also important to note a potential benefit of GM crops in reducing the allergenicity of foods. Such an example was observed with use of apple trees that were transformed with a silenced major allergen, Mal d 1, by using RNA interference.[13] The clinical allergenicity of these apples were tested in patients with apple allergy, of whom, 43–63% remained symptom free after consumption of the low Mal d 1 containing apples.[13] However, the study was limited because the apple challenges did not occur during the birch pollen season when symptoms of pollen food allergy syndrome are often more severe or more likely.[14]

PRACTICE PARAMETERS

Food allergy: A practice parameter update—2014 does not support an increased risk in GM foods (strength of recommendation: weak; D evidence).[11] The parameters do not recommend any additional concerns about ingesting GM foods. Up to the date of publication of the practice parameters, there had been no evidence of allergic reactions to any GM novel proteins or, in general, any known adverse human reactions specifically or directly associated with eating GM crops. A review of the literature since that publication similarly has shown no evidence of increased allergenicity with GM foods.[11] This may largely be due to the allergenicity assessments required during product development before GM foods can be introduced to the public. However, because these safety assessments are based on comparisons with known allergenic structures and associated expected allergenicity, evidence of the assessment of neo-allergens is limited. Methods to predict the allergenicity of novel proteins is needed.

CONCLUSION

The introduction of GM crops in the food supply is tightly regulated by national and international organizations. GM foods have not been shown to have increased allergenicity compared with conventionally grown crops. Therefore, ingesting GM foods should not be an area of concern or fear.

CLINICAL PEARLS

- Various methods of food processing or enhancement exist, and genetic modification of food has occurred for many decades; GM foods are currently safely present in our food supply chain.
- GM crops undergo rigorous safety and allergenicity assessments before being released on the market.
- To our knowledge, to date there is no published evidence of increased allergenicity to GM novel proteins compared with those found in conventionally grown food.
- There is no evidence thus far to suggest that GM foods are contributing to the rise of the prevalence of food allergies.
- Physicians and other health-care professionals should counsel patients that the current available information does not suggest an increased risk of allergenicity of GM foods.

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