

Position statement

Measurement of circulating IgG and IgE food-immune complexes

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Recently, several commercial laboratories have promoted assays measuring circulatory food-immune complexes (IgG or IgE antibodies to food antigens) as tests for sensitivity to specific foods. To evaluate the validity of this concept, a panel constituted by the Practice Standards Committee of the American Academy of Allergy and Immunology examined the published literature related to this theory.

Experiments in animals have clearly demonstrated that deposition of immune complexes can produce pathology.¹ By analogy, circulating soluble immune complexes have been suggested to play a significant role in the pathogenesis of a variety of human disease states, including glomerulonephritis, systemic lupus erythematosus, periarteritis nodosa, etc.² Certainly a sequence of well-characterized inflammatory events has been demonstrated to follow the deposition of immune complexes in tissue. Depending on the size of the complexes, the class of immunoglobulin in the complexes, etc., these events can include the activation of this complement pathway and chemotaxis of effector cells, such as polymorphonuclear leukocytes.² Nevertheless, despite the clear evidence that immune complexes can mediate immunopathologic mechanisms, the measurement of circulating immune complexes in these disease states has proven to be of limited value.^{3,4}

Several studies have demonstrated that macromol-

ecules from food can escape enzymatic digestion in the gastrointestinal tract and may be absorbed.⁵⁻⁷ This absorbed food protein is immunogenic,⁷⁻¹⁰ and normal humans form antibodies to these food proteins.¹⁰ The hypothesis has been advanced that a variety of reactions, especially late reactions, that is, reactions occurring several hours after ingesting the suspect food, are accounted for by the formation of immune complexes between absorbed food antigens and IgE or IgG antibodies.^{6,11-19} However, the generation of immune complexes would not be unexpected when food proteins are absorbed in the presence of circulating antibodies to the food²⁰ and may represent a normal mechanism for clearing the antigens from the circulation. Thus, the simple detection of food-immune complexes is not proof for disease association.

Several methods have been used to document the presence of circulating complexes, including ultracentrifugation or column chromatography that separate free and complexed immunoglobulin²¹ and precipitation of complexed immunoglobulin by polyethylene glycol.^{22,23} More recently, a simple method has been developed for identifying both the antigen and its bound immunoglobulin.^{19,20} This method involves a two-site recognition system in which antibody to the food is bound to a solid phase. This antibody, when it is incubated with the test serum, fixes the antigen-antibody complex, and subsequently, the bound complex is recognized by a labeled anti-immunoglobulin.^{19,20} The simplicity of this assay has allowed its modification for commercial application.

Leary and Halsey¹⁹ note two potential limitations that could lead to the assay failing to detect circulating immune complexes. Failure might occur when the

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complexes are in antigen or antibody excess such that binding between the detecting antibody and the complex is inhibited. Although the authors minimized these possibilities, the assay clearly needs to be subjected to a rigorous evaluation of efficacy, sensitivity, and specificity before being applied as a routine clinical assay.^{3, 24}

An even more important criticism of the commercial application of this assay is the lack of significant proof that circulating food-immune complexes are causal of human disease.^{19, 20, 21} Paganelli et al.¹⁸ and Brostoff et al.²¹ have suggested that the formation of food containing immune complexes in nonatopic individuals occur primarily through IgA antibodies, whereas IgE and IgG antibodies predominate in the atopic individual. However, it is not clear that this difference is causally related to disease.²⁵ Cunningham-Rundles et al.^{14, 15} have demonstrated the formation of high concentration of immune complexes to bovine albumin in IgA-deficient humans and have published a case report suggesting, but not proving, a pathophysiological role for these complexes in this one individual.²⁶ In contrast, Panush et al.²⁷ reported a case study of food-induced arthritis in which the aggravation of the arthritis by cow's milk was proven in a blind-controlled fashion. However, quantification of circulating immune complexes demonstrated no consistent relationship to the changes in clinical symptoms occurring after food challenge.²⁷ These data, although they support the need for further research, do not provide the definitive evidence that measurement of food containing immune complexes in serum are indicative of a food "sensitivity" or a disease state caused by these complexes. Moreover, none of the studies has established whether significant differences in sensitivity and specificity exist between IgG and IgE complexes. No body of literature exists that support the application of the assays for food-immune complexes to routine clinical practice.

It is the consensus of the panel evaluating this question that the literature currently available (1) does not support the validity of the measurement of food-immune complexes in clinical practice (i.e., lack of studies of sensitivity and specificity), (2) does not support the conclusion that either IgG or IgE food-immune complexes are causal of human disease (i.e., there is a lack of substantive proof that such complexes do not occur normally or that such complexes are quantitatively or qualitatively different in disease),

The Practice Standards Committee concludes that the value of the measurement of food-immune complexes toward the diagnosis of food allergy remains unproven and does not have a place in current clinical practice.

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