

Letter to the Editor

Bovine and porcine gelatin sensitivity in children sensitized to milk and meat

To the Editor:

Gelatin is a protein derived from collagen, and it is obtained principally from cow and pig bones, hides, and fish skin. It is a common ingredient in foods such as jellies, sweets, yogurt, and frozen desserts. It is also found in lunch meats, and it is used extensively as clarifying agents in wine, juices, and other beverages. Bovine and porcine gelatins, in particular, also have numerous applications throughout the pharmaceutical industry as integral components in drug capsules, plasma expanders, and stabilizers in vaccines, including measles, mumps and rubella (MMR), varicella, yellow fever, rabies, and some influenza vaccines. Severe allergic reactions, including anaphylaxis, have been reported after intravenous administration of modified fluid gelatins as plasma substitutes.¹ Postvaccination allergic reactions to MMR and varicella vaccines have been linked to the gelatin excipient.^{2,3} Systemic allergic reactions have also been observed with the ingestion of gelatin-containing foods and administration of gelatin-containing medical products (eg, suppositories). These gelatin exposures have been associated with sensitization as evidenced by the induction of gelatin-specific IgE antibodies.²⁻⁵

American⁶ and Finnish⁷ groups have reported that 27% and 14% to 28%, respectively, of children who experienced systemic reactions after measles, mumps, and rubella vaccination had gelatin-specific IgE antibodies. In contrast, a Japanese study reported that at least 86% of children who manifested an immediate-type hypersensitivity reaction after receipt of a gelatin-containing vaccine (measles, rubella, mumps, or varicella) had detectable gelatin-specific IgE in their blood.⁸ Type I hypersensitivity reactions to gelatin have even been reported with specific IgE levels as low as 0.8 kUa/L or kilo allergen-specific IgE units per liter.⁸

In the current study, we chose to not study fish gelatin sensitivity because the gelatins used in medical applications are almost exclusively bovine and porcine. We hypothesized that subjects who are sensitized to beef and pork meat and/or cow's milk are at greater risk for sensitization to bovine and porcine gelatin. Moreover, we hypothesized that there is cross-reactivity between bovine and porcine gelatin. These hypotheses were investigated by using serologic techniques to determine the prevalence and extent of cross-reactivity of bovine and porcine gelatin-specific IgE antibodies among children with confirmed sensitivity (IgE antibodies > 0.35 kUa/L) to pork or beef meat and cow's milk and a clinical history of cow's milk allergy.

Serum from children (n = 141; age, 3 months to 17 years; median age, 4 years; 74% boys; total IgE range, 19-49,457 kU/L; median, 909 kU/L) were selected for evaluation in the current study on the basis of a positive IgE antibody serology to cow's milk, beef, and/or pork meat. The exception was 1 subject who had a weak bovine and porcine gelatin-specific IgE <0.5 kUa/L in the absence of detectable milk, beef meat and/or pork meat specific IgE antibody. Each subject had a positive history sufficient to warrant evaluation for sensitization to cows' milk, beef, and/or pork meat. Bovine and porcine gelatin, beef and pork meat, and cow's milk-specific IgE levels were quantified by ImmunoCAP250 (analytical sensitivity, 0.1 kUa/L; Phadia, Kalamazoo, Mich). We chose the conservative

0.35 kUa/L threshold to identify positive IgE antibody responses. Cross-reactivity of bovine and porcine gelatin specific IgE antibody was studied by competitive cross-inhibition by using soluble homologous and heterologous gelatins at 2 mg/mL (Sigma-Aldrich, St Louis, Mo) or Phadia diluent as the sham negative control.

In this selected population of beef and/or pork meat-sensitized children, 93% of children had beef meat-specific (range, 0.35-99 kUa/L; median, 2.4 kUa/L), 84% pork meat-specific (range, 0.39-266 kUa/L; median, 2.3 kUa/L), and 79% both beef and pork meat-specific IgE antibodies. Ninety-seven percent of the subjects were also sensitized to cow's milk (milk-specific IgE, range, 0.39-464 kUa/L). There was a significant correlation ($r = 0.66$; $P < .001$) between the level of IgE antibovine and IgE antipork (meat) in the 111 subjects who had both antibody specificities. The IgE antimilk levels also correlated weakly but significantly with the levels of beef meat-specific IgE ($r = 0.41$; $P < .001$; n = 111) and pork meat-specific IgE ($r = 0.30$; $P = .002$; n = 100) in the same serum.

Bovine gelatin-specific IgE was detected in 21 (16%; range, 0.35-4.12 kUa/L; median, 0.48 kUa/L) of the 130 beef meat-specific IgE-positive children. Only 4 sera that contained low levels of bovine gelatin-specific IgE (0.42-1.06 kUa/L) had no detectable beef meat-specific IgE. No significant correlation was detected between the quantitative level of bovine gelatin-specific IgE and beef-specific IgE ($r = -0.11$). The majority of IgE antibovine gelatin-positive sera (88%) also contained detectable porcine gelatin-specific IgE. Within each serum that was positive for both, the quantitative levels of IgE antibovine and IgE antiporcine gelatin were significantly correlated ($r = 0.73$; $P < .001$; n = 21), suggesting antibody cross-reactivity among the gelatins. Competitive inhibition experiments (Table I) verified partial IgE antibody cross-reactivity among the gelatins. Although homologous bovine gelatin inhibited bovine gelatin-specific IgE binding to solid phase bovine gelatin by 72% to 85%, heterologous porcine gelatin only partially inhibited (13% to 47%) equivalent levels of bovine gelatin-specific IgE binding. Our data confirm partial cross-reactivity seen by others between bovine and mammalian gelatins.⁹ Our observations, however, are the first empirical demonstration of cross-reactivity between bovine and porcine gelatin.

Porcine gelatin-specific IgE was detected in 44 (38%; range, 0.35-17.98 kUa/L; median, 0.59 kUa/L) of the 116 pork meat-specific IgE-positive children. Only 4 sera negative for pork meat-specific IgE were positive for porcine gelatin-specific IgE (0.36-6.60 kUa/L). No significant correlation was detected between the quantitative levels of porcine gelatin-specific and pork meat-specific IgE ($r = -0.16$). Homologous solubilized porcine gelatin inhibited porcine gelatin-specific IgE antibody binding to the solid phase porcine gelatin by 35% to 85% (Table I). Bovine gelatin was a more effective cross-inhibitor of IgE anti-porcine binding to porcine gelatin allergosorbent (81% to 94% cross-inhibition). The less effective self-inhibition of porcine gelatin-specific IgE binding to the porcine ImmunoCAP by soluble porcine gelatin may have resulted from 1 of 2 factors. First, higher concentrations of porcine gelatin could not be used because it gelled at concentrations above 2 mg/mL. Second, the source of porcine gelatin used for insolubilization onto the ImmunoCAP

TABLE I. IgE antibody cross-reactivity between bovine and porcine gelatins, as measured by the ImmunoCAP-250 autoanalyzer.

Sample no.	IgE antibovine gelatin				IgE antiporcine gelatin	
	Uninhibited kUa/L	Inhibited with		Uninhibited kUa/L	Inhibited with	
		Bovine gelatin kUa/L (% inhibition)	Porcine gelatin kUa/L (% inhibition)		Bovine gelatin kUa/L (% inhibition)	Porcine gelatin kUa/L (% inhibition)
1	4.1	0.9 (79)	2.6 (37)	16.6	2.0 (88)	3.5 (79)
2	3.0	0.5 (85)	2.0 (33)	7.7	1.5 (81)	3.4 (56)
3	4.1	1.2 (72)	3.6 (13)	18.0	2.5 (86)	2.7 (85)
4	1.0	0.2 (80)	0.5 (47)	3.7	0.2 (94)	1.1 (69)
5	0.5	<LOD (*)	0.4 (17)	6.6	0.8 (88)	4.3 (35)

LOD, Limit of detection.

*The percentage of inhibition could not be accurately determined.

Note: Sera from only the 5 subjects noted in the table were in sufficient quantities to permit repetitive inhibition.

allergosorbent was different from that available for soluble antigen competitive inhibition.

In conclusion, 16% and 38% of beef and pork meat-sensitized children, respectively, have IgE antibodies to gelatins that are cross-reactive. The presence of IgE antigelin may place them at risk for potential allergic reactions after exposure to gelatin-containing foods, vaccines, or other medical products. However, the true clinical significance of these will require further, prospective study.

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