Bariatric surgery: relevant cofactor for systemic food-borne allergic reactions

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Clinical Implications

- Bariatric surgery may alter the digestion and hence allergenicity of food proteins, thereby leading to systemic allergic reactions in patients who before bariatric surgery experienced no or only mild oral allergy symptoms to these proteins.

TO THE EDITOR:

An estimated 70% of birch pollen allergic patients develop mild local allergic reactions to certain nutriments known as pollen food allergy syndrome (PFAS). PFAS is mainly caused by food allergens containing *Betula verrucosa* (Bet v1) homologues of birch pollen, such as tree nuts and Rosaceae fruit. Albeit at a lower incidence, PFAS may also develop in grass or mugwort pollinosis and in mite allergy.

PFAS is usually mild; however, up to 8.7% may spontaneously progress to more severe reactions, including anaphylactic shock. Several cofactors may modulate the severity of these systemic reactions, including underlying uncontrolled asthma, physiological triggers as exercise, and use of substances including alcohol, nonsteroidal anti-inflammatory drug, and proton pump inhibitors (PPI). Amongst others, these cofactors may act by increasing food protein allergenicity due to impaired digestion of the proteins.

Bet v1 homologues belong to the pathogenesis-related 10 (PR10) family of proteins that are usually digested in the acidic gastric environment. The low stomach pH facilitates the disintegration of proteins and activates proenzyme pepsinogen into pepsin, which further digests the peptides in the stomach. Moreover, the low pH of the chime bolus arriving at the duodenum stimulates secretin production, which releases pancreatic enzymes for further digestion.

Indeed, it was shown in both mice and men that the use of antiulcer drugs worsened symptoms of food allergy. In mice models of fish and hazelnut allergy, allergic reactions to food allergens were more severe when these were administered in conjunction with antacids or acid blockers. Similar effects were noticed in humans, as gastroenterologists patients more often became sensitized to hazelnut if they used PPI. In *vivo* models of codfish allergen digestion demonstrated that a slight pH increase completely abrogated protein digestion and enhanced the risk of anaphylaxis. As antiulcer drugs are able to change the allergenicity of food proteins, it may be expected that bariatric surgery can have substantial effects on allergen degradation and development of allergies. In most surgical procedures, stomach size is substantially minimized and an additional bypass of the duodenal tract affects food digestion and henceforth allergen degradation. With the global epidemic of obesity, almost half a million bariatric procedures were performed worldwide in 2013. A small prospective study on gastric bypass patients suggested an increased sensitization to both food and air-borne allergens, although its clinical relevance was not yet explored. One patient developed wheat-dependent exercise-induced anaphylaxis 2 years after bariatric surgery, while having *Helicobacter pylori* gastritis.

Recently, Blockhuys et al described a systemic reaction to peach in a birch pollen allergic patient who previously underwent bariatric surgery. Before her gastric bypass, she experienced only mild PFAS when eating a peach.

In line with this case report, we here describe 8 patients who developed systemic reactions to food after gastric bypass (Table I). All patients (median age 45 years, range 29-61 years) were females of Northern European descent and had bariatric surgery in the last decade. Seven of them had atopic features including allergic rhinoconjunctivitis, atopic dermatitis, and asthma. Potential aggravating cofactors were PPI use and exercise. The time of onset of the reaction ranged from minutes to several hours after ingestion, whereas the severity varied from grade I (generalized urticaria) to IV (hypotension requiring multiple epinephrine administrations) on the Müller classification. Culprits were Rosaceae fruit, tree nuts, and peanut. Importantly, those foods were either tolerated completely or caused only mild PFAS before bariatric surgery.

Sensitization was shown in all patients with specific IgE to the suspected culprits for patients 1 to 7, or a positive skin prick test to peanut (patient 8).

In severe food-borne allergic reactions, sensitization to allergens other than PR10 should be considered, because storage proteins or members of the nonspecific lipid transfer proteins (nsLTP) family generally have a higher stability and allergenicity. Additional laboratory diagnostics using component-resolved diagnostics showed sensitization to solely PR10 but not to nsLTP nor major storage protein allergens, which is consistent with a milder and usually localized reaction. In patients with grade II to IV reactions, systemic mastocytosis was ruled out by normal serum tryptase levels.

These cases support the hypothesis that bariatric surgery is a relevant cofactor for systemic allergic reactions to food. Because we identified multiple food culprits, we presume that all Bet v1 homologues and possibly even other PR10 homologues are potentially able to cause food-borne systemic allergic reactions. Whether these findings can be extended to other pollen cross-reactive proteins such as profilins and cross-reactive carbohydrate determinants remains to be determined.

There are some limitations to mention. The underlying pathogenesis remains unclear; whether the reactions are completely due to impaired digestion or that other indirect factors such as alteration of the gut microbiome or an adapted diet after surgery play a role needs clarification. Delayed gastric emptying could make patients more vulnerable to accidentally ingest larger amounts of allergen because they notice the symptoms too late.
<table>
<thead>
<tr>
<th>Patient no. Age; type of bariatric surgery</th>
<th>Atopic history before BS</th>
<th>Time interval between bariatric surgery and reaction; culprit</th>
<th>Reaction</th>
<th>Other cofactors</th>
<th>Specific IgE (in kU/L reference value &lt; 0.35)</th>
<th>Additional diagnostics</th>
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</thead>
<tbody>
<tr>
<td>1. 39 y; mRYGB at age 30 y</td>
<td>PFAS: apple, pear, cherry, sometimes peach, and nectarine Tolerant to tree nut and peanut AR, AC</td>
<td>After 9 y; 4-5 tree nuts of a mixture of hazelnuts, pecan, walnut, cashew, and Brazil nut</td>
<td>Within 15 min angioedema tongue, oropharyngeal edema, generalized pruritus, sense of impending doom</td>
<td>None</td>
<td>Tree pollen 32 Hazelnut 20 Hazelnut rCor a1* 31 Hazelnut rCor a9* &lt; 0.010 Peanut rAra h2</td>
<td>Tryptase 4.71</td>
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<td>Peanut rAra h8* 8.2 Brazil nut &lt; 0.010 Cashew &lt; 0.010 Pecan &lt; 0.010 Walnut &lt; 0.010</td>
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<td>2. 52 y; RYGB at age 50</td>
<td>PFAS: none AC</td>
<td>A few weeks after surgery; handful of mixed tree nuts</td>
<td>After 30 min facial and oropharyngeal angioedema, urticaria, pruritus</td>
<td>None</td>
<td>Tree pollen 1.4 Grass pollen &lt; 0.010 Hazelnut 1.3 Hazelnut rCor a1* 1.7 Hazelnut rCor a8* &lt; 0.010 Hazelnut rCor a9* &lt; 0.010 Peanut 0.020 Peanut rAra h2</td>
<td>OFC hazelnut: positive</td>
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<td>Peanut rAra h8* 0.36 Almond 0.18 Walnut &lt; 0.010 Cashew &lt; 0.010</td>
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<td>3. 49 y; mRYGB at age 46</td>
<td>PFAS: on pear, peach, nectarine, apricot, cherry, kiwifruit, tomato Tolerant to apple, melon, citrus fruits, tree nuts, peanut AR, AC</td>
<td>After 3 y; 1 pear, raw and unpeeled</td>
<td>Instant burning sensation in mouth. Within 15 min facial and oropharyngeal angioedema, sneezing, rhinitis, dyspnea, nausea, diarrhea</td>
<td>Exercise, PPI</td>
<td>Tree pollen 21 Hazelnut rCor a1* 40 Hazelnut rCor a9* 0.020 Cherry 0.35 Pear 0.14 kU/L Peach rPru p3</td>
<td>SPT: Oak 1.0, Fagales trees 0.9 HDM 0.7, hazelnut 0.6 Serum tryptase 2.57</td>
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<td>Peach rPru p3* 0.010</td>
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<th>Patient no.</th>
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<tr>
<td>4. 53 y; RYGB at age 51 y</td>
<td>PFAS: walnut, Tolerant to apple AR, AC</td>
<td>Apple, raw and peeled</td>
<td>Within minutes burning sensation of the eyes, oropharyngeal angioedema, dyspnea, wheezing</td>
<td>None</td>
<td>Birch rBet v1 13 Apple rMal d1 3.20&lt;sup&gt;*&lt;/sup&gt;</td>
<td>SPT: hazelnut 0.7, Fagales 1.2 Tryptase 5.9 OFC apple (Jonagold): prematurely ended due to full stomach</td>
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<tr>
<td>5. 42 y; mRYGB at age 37</td>
<td>PFAS: apple, Tolerant to pear AR</td>
<td>Hazelnut (quantity and processing unknown)</td>
<td>Facial and oropharyngeal angioedema, time course unknown</td>
<td>PPI</td>
<td>Tree pollen 4.6 IgE hazelnut 1.9 Hazelnut rCor a1&lt;sup&gt;†&lt;/sup&gt; 2.6 Hazelnut rCor a8&lt;sup&gt;x&lt;/sup&gt; &lt;0.010 Hazelnut rCor a9&lt;sup&gt;z&lt;/sup&gt; &lt;0.10 IgE pear 0.31</td>
<td>SPT: hazelnut 0.4, oak 0.8, Fagales trees 1.4 Tryptase 4.75</td>
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<td>6. 61 y; RYGB at age 60</td>
<td>PFAS: none Tolerant to walnut AR, AC, asthma, AD</td>
<td>After 5 y; 1 pear, raw and peeled</td>
<td>Within 15 min facial angioedema, generalized pruritus and urticaria, palpitations, sense of doom</td>
<td>PPI</td>
<td>Hazelnut 13.7 Hazelnut rCor a1&lt;sup&gt;†&lt;/sup&gt; 19.8 Hazelnut rCor a8&lt;sup&gt;x&lt;/sup&gt; &lt;0.010 Hazelnut rCor a14&lt;sup&gt;‡&lt;/sup&gt; &lt;0.35 Almond 0.47 Walnut &lt;0.35 Cashew &lt;0.35 Pistachio &lt;0.35</td>
<td>SPT: positive for Fagales trees, hazelnut, almond, borderline positive for pistachio Tryptase 7.5</td>
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<tr>
<td>7. 29 y; RYGB at age 24 y</td>
<td>PFAS: raw hazelnut, apple, kiwifruit, peach Tolerant to walnut, almond, cashew, peanut AR, AC</td>
<td>After 5 y; handful of mixed tree nuts containing hazelnut, cashew, almond, walnut, possibly traces of peanut</td>
<td>Facial and oropharyngeal angioedema within minutes; later dyspnea, generalized erythema, hypotension</td>
<td>Exercise, PPI</td>
<td>Tree pollen 3.0 Grass pollen 5.6 Hazelnut 2.5 Hazelnut rCor a1&lt;sup&gt;†&lt;/sup&gt; 3.5 Hazelnut rCor a8&lt;sup&gt;x&lt;/sup&gt; &lt;0.010 Hazelnut rCor a9&lt;sup&gt;‡&lt;/sup&gt; &lt;0.010 Peanut 0.50 peanut rAra h2 &lt; 0.010 peanut rAra h8&lt;sup&gt;‡&lt;/sup&gt; 0.72 Almond 0.18 Walnut 0.020 Cashew &lt; 0.010</td>
<td>Tryptase 3.50 OFC hazelnut: negative</td>
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<tr>
<td>8. 36 y; RYGB at age 34 y</td>
<td>PFAS: peanut AR, AC</td>
<td>After 1.5 y; some pieces of peanut brittle</td>
<td>After a few hours generalized urticaria and pruritus</td>
<td>None</td>
<td>Peanut &lt;0.35 Soy &lt;0.35 Almond &lt;0.35 Hazelnut &lt;0.35 Walnut &lt;0.35</td>
<td>SPT: positive for peanut, negative for hazelnut, walnut, cashew, pecan, pistachio</td>
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AC, Allergic conjunctivitis; AD, atopic dermatitis; AR, allergic rhinitis; BS, bariatric surgery; HDM, house dust mite; HEP, histamine equivalent prick test; mRYGB, modified Roux-en-Y bypass (Billroth II stomach—bowel connection); OFC, oral food challenge; PFAS, pollen food allergy syndrome; PPI, proton pump inhibitor; RYGB, Roux-en-Y gastric bypass; SPT, skin prick test.

Note: Culprit or suspected culprit food allergens are indicated in bold text.

*Pathogenesis-related 10 (PR10) protein, Bet v1 family member.

11S globulin, storage protein.

†Conglubin (2S albumin), seed storage protein.

‡Nonspecific lipid transfer protein (nsLTP).
Lastly, the allergic reactions could not always be reproduced. Of the 3 oral food challenges (OFC) that were performed, the symptoms could be reproduced only once. Possibly, the other OFC did not adequately represent the real-life situation; in patient 4, the ingested cultivar of apple was unclear and she could not finish the OFC, whereas patient 2 performed strenuous exercise (moving a fridge over several flights of stair) postprandial that was not imitated in her OFC. Nevertheless, these findings support the notion that certain circumstantial factors such as quantity of allergen, method of processing, and seasonal influences could have been involved, as well as other cofactors including exercise and PPI. Further investigations are required to determine the influence of several factors in changing the threshold for allergic reactions.

In conclusion, these cases demonstrate that bariatric surgery is a relevant new cofactor for systemic allergic reactions to food that usually causes only PFAS. Allergists should be aware of this phenomenon and ask for bariatric surgery in the patient’s history. Bariatric surgeons ought to include questions on pollen and food allergy in their preoperative screening and inform patients that allergic symptoms can deteriorate; referral to an allergist should be considered.

REFERENCE