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Letter to the Editor

## Anaphylaxis to xylitol diagnosed by skin prick test and basophil activation test

Dear Editor,

Xylitol, a sugar alcohol, is present naturally in plants. Although it has a sweetness level similar to that of sucrose, it has 40% fewer calories and 75% fewer carbohydrates. Xylitol has also been reported to have some useful physiological functions *in vivo*, including protective efficacy against caries and otitis media.<sup>1</sup> In Japan, xylitol was approved as a food additive on April 17, 1997, and it is now often added in sugarless gums and tooth powders as a low-calorie artificial sweetener. Adverse reactions, mostly commonly diarrhea, to xylitol are mild, and very few cases of allergic reactions associated with xylitol have been reported. Here we report a case of a 2-year-old girl with a history of anaphylactic episodes that were suspected to be allergic reactions to xylitol based on her medical history and the results of a skin prick test and basophil activation test (BAT).

The patient had a history of allergy to cow's milk and raw hen's egg and had experienced anaphylaxis to cow's milk 6 months ago. Prednisolone, cetirizine hydrochloride, and an adrenaline auto-injector were prescribed after that reaction. On the day of the episode, she ate one soda pop-flavored tablet containing 400 mg of xylitol probably for the first time 6 h after her usual supper without egg or milk and then took a bath. Thirty minutes after ingesting the tablet, she developed flushing of her face, cough, and wheezing. After taking prednisolone and cetirizine hydrochloride and receiving adrenaline intramuscularly from an auto-injector, she was immediately taken to an emergency hospital. She was treated with oral methylprednisolone and beta-2 agonist and adrenaline inhalation. The symptoms gradually disappeared, and she was discharged from the hospital after 2 days.

Her supper did not contain an egg nor milk, and there were almost 6 h after taking supper until the symptoms developing. Therefore, anaphylaxis to xylitol was suspected from the patient's history, and examinations for the diagnosis were conducted. Regarding the oral xylitol challenge to confirm diagnosis, informed consent was not obtained from her parents due to the patient's history of anaphylaxis. Serum concentrations of IgE specific to milk and egg white were higher than 100 UA/mL and 6.68 UA/mL, respectively, but the measurement of IgE specific to xylitol are not currently available. We then performed a skin prick test for xylitol (10 mg/mL xylitol dissolved in normal saline); the result was positive, with a wheal diameter of 4 × 4 mm compared with a wheal diameter of 8 × 8 mm for the positive control (10 mg/mL histamine dihydrochloride) and that of 0 × 0 mm for the negative control (normal saline), while that was negative in 5 healthy adult controls.

Subsequently, we investigated the reactivity of basophils stimulated with xylitol. A commercial kit (Allergen Kit; Beckman Coulter, Fullerton, CA, USA) was slightly modified to simultaneously quantify CD203c and CD63 expressions on basophils. Briefly, peripheral whole blood samples were incubated with serially diluted concentrations of xylitol for 15 min, basophils were identified based on CRTH2<sup>pos</sup>CD203c<sup>pos</sup>CD3<sup>neg</sup>, and CD203c and CD63 expressions on basophils were analyzed using a fluorescence-activated cell sorter (FACS Caliber; Becton Dickinson, Mountain View, CA, USA).<sup>2</sup> Xylitol was found to enhance CD203c and CD63 expressions on basophils in a concentration-dependent manner (Fig. 1). Totally, 6.6% basophils were CD203c<sup>bright</sup> at a xylitol concentration of 0.16 mg/dl and 13.6% were CD203c<sup>bright</sup> at a xylitol concentration of 1.6 mg/dl (positive control, 74.1%). Further, 7.7% basophils were CD63<sup>pos</sup> at a xylitol concentration of 0.16 mg/dl and 15.8% were CD63<sup>pos</sup> at a xylitol concentration of 1.6 mg/dl (positive control, 71.0%), whereas no reactions were observed in the healthy controls. Additional BAT with erythritol to confirm cross-reactivity resulted in no reaction. Based on these results, we instructed the patient's parents to not allow her to ingest or use products that included xylitol, and ever since, she has never experienced an allergic reaction after ingesting any food without eggs or milk.

Based on a nationwide questionnaire survey on immediate-type allergy caused by sugar alcohols in Japan, Ebisawa *et al.*<sup>3</sup> reported 10 cases in which allergies were suspected to be caused by xylitol, and the most frequent causative allergen was erythritol. In fact, the number of cases on allergy caused by erythritol that are reported in the English literature is increasing.<sup>2,4,5</sup> Cases on allergy caused by xylitol are rarely reported. Hanakawa *et al.*<sup>6</sup> presented a case of a patient who developed oral erosions due to contact allergy to xylitol-containing chewing gum. This was a case of delayed-type allergy as severe allergic reactions were induced by patch testing to xylitol-containing gums. To the best of our knowledge, ours is the first case to be reported on immediate-type allergy caused by xylitol.

Xylitol has a linear chain structure, with a molecular weight of only 152.15. Most substances that can cause immediate allergic reactions have sufficiently high molecular weight to cause an immune reaction. A low-molecular weight compound is less likely to be an allergen. In addition, because xylitol does not have any reactive side chains, it cannot form conjugates with macromolecular carriers by itself. One hypothesis to explain the immunogenicity of xylitol were proposed by Sreenath *et al.*<sup>7</sup> using the reductive aminated product of D-xylose conjugated to bovine serum albumin (BSA) as the immunogen. They reported that rabbits immunized with xylitol–BSA conjugate exhibited a good antibody

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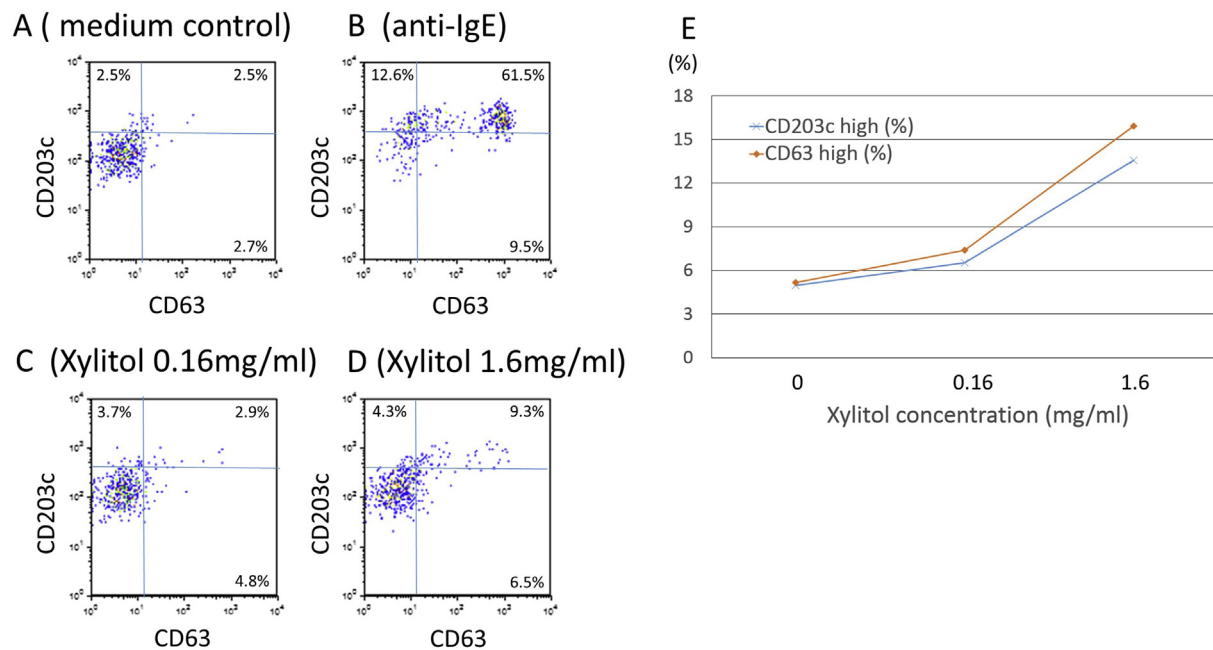


Fig. 1. Basophil Activation Test using the patients' blood sample.

response. Similar results were reported for erythritol<sup>8</sup> and mannitol.<sup>9</sup> We also performed BAT using patient's blood that had the plasma removed by washing, and no reaction was observed. This result may support the existence of molecules that combine with xylitol in plasma. However, we could not detect IgE against xylitol–human serum albumin conjugates in the patient's serum (data not shown).

Because sugar alcohols, including xylitol, are nontoxic and very useful as sweeteners, their use is expected to expand in the future. However, they can be an allergic causative agent, and the diagnosis of allergy to sugar alcohols is difficult because of the paucity of tests to detect specific IgE. BAT may be a useful tool to diagnose and investigate the mechanism of allergic reactions to sugar alcohols.<sup>10</sup>

We obtained written informed consent about use of her blood sample for research of food allergy from her parents. Ethical approval was obtained from the Fujita Health University Ethics Committee in May 2015 (reference number: 15–202).

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## Conflict of interest

The authors have no conflict of interest to declare.

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