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ORIGINAL ARTICLE

Should milk-specific IgE antibodies be measured in adults in primary care?

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Abstract

Objective. To study the association of milk-IgE antibodies in serum to milk-related gastrointestinal symptoms in adults in primary care. *Design.* Open clinical study. *Setting.* Five outpatient clinics in primary care in Southern Finland. *Subjects.* A total of 756 subjects who reported milk-related gastrointestinal symptoms in primary care and as controls 101 subjects with no such symptoms. *Methods.* IgE values for specific food antigens were measured (Pharmacia CAP System) in a total of 857 subjects. All food screen-positive samples (>0.35 IU/l) were analysed further for IgE for untreated skimmed milk (milk-IgE) and for boiled milk. Those found positive for milk-IgE were invited for an open milk challenge test. *Results.* Some 5.4% (46/857) of all subjects had a positive IgE antibody screen for food antigens. Of those with a positive food screen, 28% (13/46) had milk-IgE antibodies comprising 1.5% of the total group screened. The prevalence of milk-IgE was not statistically different between those with milk-related symptoms and those with no such symptoms. IgE antibodies for boiled milk were rare. All specific IgE antibody levels were low. Bloating was the only observed symptom in milk challenge tests. *Conclusion.* IgE antibodies to cow's milk were relatively rare in the adult population and were not indicative of milk protein allergy. The observed IgE levels were low and did not correlate with subjective milk-related symptoms. The measurement of milk-specific IgE in adults should be discouraged in outpatient clinics.

Key Words: *Abdominal symptoms, cow's milk, food hypersensitivity, primary care*

In clinical practice, concern regarding milk-related symptoms is common and often results in restriction in consumption of dairy products. Recently, we reported that more than 40% of adults in primary care suspect they have experienced gastrointestinal symptoms after milk ingestion [1]. Among the possible aetiological factors for milk-related symptoms, adult-type hypolactasia is frequent in populations with high dairy intake, the prevalence ranging from 4% to 60% in Caucasian populations [2]. In untreated coeliac sprue, another important trigger for milk-related gastrointestinal symptoms, villous destruction in the small intestine induces secondary hypolactasia [3]. Further, allergy to cow's milk may induce gastrointestinal symptoms in children [4–6]. Hypersensitivity to milk, however, may occur in adults also, as has recently been reported in, for example, Australia [7] and Finland [8,9], and hence may be one reason for milk-related gastrointestinal problems.

Food and especially milk-related gastrointestinal problems are common in general practice.

- Positive reactions in IgE food screening are relatively common in adults.
- Milk-specific IgE antibodies are rare.
- Measurement of milk-protein IgE is not likely to give any additional information on milk-related symptoms in adults and is of little value in general practice.

Recently, we investigated children and adolescents with abdominal complaints and unexpectedly found food-specific IgE antibodies in up to 31% of the children undergoing upper gastrointestinal

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endoscopy [10]. This and the recent reports of an increase in triggers of IgE class switching and allergy development [11] raised the possibility that IgE positivity for food antigens has increased and may in some cases be associated with abdominal symptoms. In this study we evaluate the prevalence of IgE-type food antibodies and focus on milk antibodies in adults and their attribution to gastrointestinal symptoms related to milk.

Material and methods

Milk consumption and milk-related abdominal symptoms were screened in a large population of 1900 adults in primary healthcare during spring 2004 [1]. All consecutive working-age patients in five primary care centres who had a referral for blood withdrawal in the laboratory were given the opportunity to join the study. The targeted sample size of 2000 participants was almost reached during a three-month period. However, the number of non-participants was not registered. At blood sampling, the participants were asked to fill in a structured questionnaire on milk consumption and abdominal symptoms. Data on previous diagnosis of atopy was also requested. The response rate was high as 99% of the participants returned the questionnaire [1]. All participants who reported milk-related symptoms (n = 756; 40% of those 1885 who filled in the questionnaire) were chosen for this study. A control group of 101 subjects was randomly selected from those who reported no milk-related symptoms (n = 638). Of the 1885 participants, 491 did not answer the question on milk-related symptoms and they were excluded from the selection. Thus, the study group in this study comprised 857 adults (aged 18–64 years) who were screened for food-specific IgE. In addition, the subjects had been genotyped for adult-type hypolactasia [1], and screened for coeliac disease [12].

The Pharmacia CAP System was used for screening of specific IgE against major food allergens (wheat, codfish, peanut, egg (ovalbumin), soybean, cow's milk). Values equal to or higher than 0.35 IU/l were considered positive. Those with a positive total screen were further screened for specific IgE to untreated skimmed milk (f2; milk-IgE) and boiled milk-IgE (f231; Pharmacia ImmunoCap System).

All individuals with a positive milk-IgE test were invited for an open milk challenge test, performed in a controlled hospital surrounding. A total amount of 570 ml of low-lactose and low-fat milk was given orally in 65 minutes and the participants were followed up at hospital for two hours. Skin reactions and gastrointestinal symptoms were registered. The follow-up continued for 24 hours afterwards by the subjects.

The study was approved by the Ethical Committee of Helsinki University Central Hospital. All the subjects gave their written informed consent.

Statistical analyses

Fisher's exact two-sided test and a Kruskall–Wallis test were used for group comparisons when appropriate. The level for statistical significance was $p < 0.05$.

Results

Food screen in adults

Specific IgE antibody screen against major food antigens was ≥ 0.35 IU/l, the cut-off level for a positive result, in 46 adults (5.4%; Table I). The

Table I. Background factors of the group screened for food allergens with Pharmacia CAP System.

	Group 1 Milk-related symptoms n = 756 (%)	Group 2 No milk-related symptoms n = 101 (%)	p-value* (<0.05 considered statistically significant)
Age 50–64 years (%)	n = 345 (46)	n = 34 (33.5)	<0.05
Male	n = 54	n = 17	
Female	n = 291	n = 17	
Age 34–49 years (%)	n = 281 (37)	n = 34 (33.5)	n.s.
Male	n = 62	n = 17	
Female	n = 219	n = 17	
Age 18–33 years (%)	n = 130 (17)	n = 33 (33)	<0.01
Male	n = 17	n = 17	
Female	n = 113	n = 16	
Drinks milk daily (%)	n = 255 (34)	n = 58 (57)	<0.01

Note: *Fisher's exact test.

prevalence of positive food screen was 8.5% (11/130) in the youngest age group (18–33 years); 3.5% (10/281) in those aged 34–49 years and 7.3% (25/345) in the oldest age group (p-values for differences between age groups >0.05). A positive specific IgE screen for food antibodies seemed more frequent in males (1:15) than in females (1:20) but the sex difference was not statistically significant.

Milk-IgE in adults

One-third (28%, 13/46) of the food screen positive individuals had specific IgE for cow's milk (Table II). Thus, milk-IgE was detectable in 1.5% of the adults screened (13/857). There was no correlation with milk drinking and IgE antibodies for milk.

In women the percentage of positive reactions for milk-IgE was 1.3% (9/673) and in men 2.2% (4/184; p = n.s.). Milk-IgE for boiled milk was positive in 3 subjects, one of them negative for standard milk-IgE antibodies (Table II). All subjects positive for milk-IgE antibodies were aged 35–49 years.

Milk-related symptoms and milk-IgE

All but one of the subjects positive for cow's milk-IgE antibodies reported milk- related symptoms (see Table II). The prevalence of milk-IgE, however, was not statistically different between those with milk-related symptoms and those with no such symptoms. Those reporting no milk-related problems used milk as a drink more often (58/101; $p<0.001$; see Table I).

Milk challenge

All 9/13 milk-IgE positive adults who could be traced agreed to a challenge test to cow's milk. In addition, the subject negative for milk-IgE but positive for boiled milk-IgE agreed to testing. Except for one person, these subjects had reported milk-related symptoms and to motivate them for participation they were informed of the reason for testing. During the open milk challenge at our hospital, all subjects experienced abdominal discomfort and bloating, one subject reported diarrhoea immediately after the ingestion of 570 ml of milk, but none of the subjects developed skin symptoms. The milk challenge was performed with low-lactose-containing milk to avoid symptoms related to lactose malabsorption. However, the subject who developed diarrhoea had the genotype C/C_{-13910} associated with low lactase level in the intestine (genotyped in our previous study on adult-type hypolactasia [1]).

History of atopy

Of those with a positive food screen, 36/46 reported that they had been screened for atopy either with skin-prick tests or with a blood screen and 26/36 (72%) had received a positive diagnosis for atopy. Among those with a positive test result for milk-IgE antibodies, a previous diagnosis of allergy to animals or pollen was reported by 6/13 (46%) of the subjects. In the total study population, a previous diagnosis of atopy based on skin-prick testing or RAST screening was reported by as many as 42% (349/857) of the adults (during childhood n = 129; at an adult age n = 162; as a child and at adult age n = 52; in six cases this information was not available).

Indications for blood withdrawal

The indication for blood sampling was health check-up at the primary care facility in the majority of the adults in this study (53%; 455/857; Table III). In 158 cases (18%) the indication was abdominal complaints, the main symptom being bloating. Of the subjects investigated for abdominal complaints,

Table II. Positive test results of IgE antibody screen (Pharmacia CAP System) for major food antigens in 857 adults screened in primary care.

	Food screen	Milk	Boiled milk	Egg	Wheat	Peanut	Soya	Fish
No. of positive (>0.35 IU/l) subjects (% of screened subjects)	n = 46 (5.4)	n = 13 (1.5)	n = 3 (0.4)	n = 14 (1.6)	n = 14 (1.6)	n = 17 (2.0)	n = 9 (1.0)	n = 3 (0.4)
Group 1: Milk-related symptoms (% of screened subjects)	n = 42 (6)	n = 12 (1.4)	n = 3 (0.4)	n = 14 (1.6)	n = 13 (1.5)	n = 15 (1.8)	n = 8 (0.9)	n = 3 (0.4)
Group 2: No milk-related symptoms (% of screened subjects)	n = 4 (4)	n = 1 (0.1)	n = 0 (0)	n = 0 (0)	n = 1 (0.1)	n = 2 (0.2)	n = 1 (0.1)	n = 0 (0)

Note: *Comparisons between Group 1 and 2 statistically non-significant (p-values >0.05, Fisher's exact test).

Table III. Abdominal complaints in a study group of 857 adults screened for specific IgE antibodies against major food allergens (Pharmacia CAP System).

	Group 1 Milk-related symptoms n = 756 (%)	Group2 No milk-related symptoms n = 101 (%)	p-value* (<0.05 considered statistically significant)
Indication for blood sampling			
Health check-up	n = 404 (53)	n = 51 (50)	n.s.
Abdominal complaints	n = 139 (18)	n = 19 (19)	n.s.
Other diagnostics	n = 213 (28)	n = 31 (31)	n.s.
Abdominal complaints during a 3-month period			
Heartburn	n = 270 (36)	n = 45 (45)	n.s.
Diarrhoea	n = 328 (43)	n = 34 (34)	n.s.
Flatulence	n = 651 (86)	n = 58 (57)	n.s.
Bloating	n = 517 (68)	n = 49 (49)	<0.01
Constipation	n = 182 (24)	n = 14 (14)	<0.05

Note: *Fisher's exact test.

11 (7%) had a positive IgE food screen and 2 subjects (1.3%) had IgE antibodies against cow's milk. Among those undergoing investigations for non-gastrointestinal indications, 11/699 (1.6%) were positive for milk-protein IgE. There was no statistical difference for positive milk- protein IgE between these two groups. The variety of abdominal symptoms is shown in Table III.

Discussion

Statement of principal findings

When actively screened, positive test results for IgE antibodies for major food allergens (antibody levels $\geq$0.35 IU/l, the cut-off level for a positive result) were found in as many as 5.4% of this group of Finnish adults investigated in primary care. Specific IgE antibodies to cow's milk were found in 1.5%. If we compare those reporting gastrointestinal symptoms from milk to those with no such symptoms, there were no statistically significant differences in the proportion of positive food screens (6%/4%) or in the prevalence of milk-protein IgE (1.6%/1%).

IgE antibodies to boiled milk were rare. All subjects with elevated milk-IgE antibodies were invited to a milk challenge test. In this test performed in an open manner we saw no skin reactions, which is in accordance with the low level of milk-protein IgE antibodies [13]. Against our expectations, all individuals tested experienced bloating and abdominal discomfort but the impact of these symptoms in an open test is unclear. Notably, only a minority of the subjects with a positive milk-IgE screen were currently undergoing investigations for abdominal complaints.

Strengths and weaknesses of the study

The number of participants in this study was large. Also, the exceptionally high response rate for the questionnaire further strengthens the findings. The weakness is that the data on gastrointestinal symptoms relied on subjective reports and could not objectively be evaluated in each subject. However, we have previously screened this study population for the most common causes of milk-related abdominal symptoms, namely adult-type hypolactasia and coeliac sprue.

To test the clinical relevance of milk-IgE positivity, food challenge with milk was performed. The open protocol that we used in the milk challenge test may have had a psychological impact in the prevalence of abdominal symptoms, which were more prominent in an open test than in a double-blind study. We also chose to challenge only subjects with elevated concentration of milk-protein IgE and did not include milk-protein IgE-negative subjects as it is well reported in the literature that immediate reactions are likely to occur only in those with IgE antibodies to the challenged food allergen [14–17]. Further, as the findings in the challenge tests were considered negative, a group with no IgE antibodies would not have changed the conclusions.

Our test milk had low lactose content to avoid symptoms related to adult-type hypolactasia and lactose malabsorption. Yet, the test milk contained a small amount of lactose (<1 g/100 g) that is sufficient to induce symptoms related to lactose malabsorption in predisposed individuals [18]. Indeed, the only case that developed diarrhoea during the test had previously been confirmed to have a genotype associated with low intestinal lactase level

and adult type hypolactasia [1] and thus was not manifesting an allergic gastrointestinal reaction.

The antigen used in the milk-IgE test is a mixture of milk proteins including casein and whey proteins [13]. The structure of the milk proteins changes by boiling, except for casein, and some subjects can be hypersensitive to fresh milk but tolerate boiled milk. We tested the milk-IgE antibodies for both untreated skimmed milk and boiled milk. The two subjects with positive test results for boiled milk attended a challenge test with low-lactose cow's milk with no major reactions (see above). However, we did not challenge them further with boiled milk.

Strength and weakness in relation to other studies

It is important to recognize that IgE antibody levels for various food allergens reflect dietary habits. In Finland dairy consumption is high [19–21]. The IgE levels for cow's milk protein, however, were low in comparison with earlier studies [14,19]. According to the well-described increase in inhalant IgE antibody levels in the younger age cohorts during recent years [22], it was unexpected that the number of positive results for IgE antibodies for food was similar among the youngest (18–33 years) and oldest participants (50–64 years). Further, the positive test result for IgE antibodies to cow's milk was not associated with the consumption of milk as a daily drink. So far, the aetiopathogenesis of the presence of low IgE levels for food antigens in adults is obscure.

To our surprise, a large number of those with a positive screen for major food allergens reported a previous, test-confirmed, positive diagnosis of atopy. Although we did not test the subjects for atopy, this suggests a link between atopy and the presence of IgE antibodies for food antigens. Indeed, it has been shown earlier that atopic individuals are more prone to food hypersensitivity [8,23,24]. In a recent report from Finland, it was noted that atopic individuals frequently report hypersensitivity to milk [10].

This study is strengthened with the previous assessment of the most common causes for milk related gastrointestinal symptoms. In our study population hypolactasia was present in 18%, according to the published data from Finland [2,25]. There was also no coeliac sprue in this study population that could explain the milk-related symptoms [2]. Food intolerance in gastrointestinal disorders (e.g. irritable bowel syndrome) and the clinical relevance of food-specific antibody levels are currently under active investigation [26–28] but we did not measure food antibodies except those of IgE class.

Meaning of the study

It is common for self-reported food allergy or food intolerance not always to be confirmed by food challenge [29]. People do suspect milk to be the reason for their gastrointestinal symptoms but in most cases a causative link cannot be verified [28]. Low levels of food-specific IgE, for example for milk, do occur in adults, but a positive antibody level is seldom related to objective symptoms of hypersensitivity. Screening for the food-specific IgE antibodies in outpatient clinics should therefore not be encouraged.

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Ethics committee

Ethical approval was received from the Ethics committee for outpatient clinics in Helsinki and surrounding areas (567/E1/03).

Competing interests

The authors have stated that there are none.

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