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Evaluation of some predictive parameters for baked-milk tolerance in children with cow's milk allergy

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Abstract
Background: Inclusion of baked-milk products to the diet appears to markedly accelerate tolerance to unheated milk compared to a strict avoidance diet.
Objective: The present study aims to investigate the predictors of baked-milk tolerance in children with Immunoglobulin E (IgE)-mediated cow's milk (CM) allergy.
Methods: The study included 80 patients diagnosed with IgE-mediated CM allergy upon oral food challenge (OFC) testing at our clinic. Patients who developed and did not develop reactions during OFC with baked milk were compared considering clinical and laboratory parameters.
Results: Eighty patients with CM allergy comprised 48 male and 32 female infants with an average age of 7.25±2.45 (3-13) months. We found that 62.5% of them showed tolerance to baked milk in the OFC test performed with cakes containing 2.6-g milk protein. When the patients who tolerated and could not tolerate baked-milk products were compared for test results, we detected a statistically significant intergroup difference regarding diameter of wheal in skin prick test (SPT) performed with muffin slurry, levels of specific Immunoglobulin E (sIgE) in CM, sheep's milk (SM), goat's milk (GM), casein, and the amount of unheated milk consumed until a reaction developed in the OFC test performed with unheated milk ($P<0.05$).
Conclusion: We defined novel decision points based on CM, SM, GM, casein sIgE levels, wheal diameter in SPT with muffin slurry, and the amount of milk ingested during OFC performed with unheated milk that may be useful in predicting outcomes of baked-milk ingestion.

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Introduction

Food allergies have become an increasingly important public health issues in developed countries.[1,2] Today, the main treatment for individuals with cow's milk (CM) allergy is to eliminate milk and dairy products from their diet. However, since many foods contain milk proteins, it is difficult to prevent exposure to milk proteins by eliminating dairy products from individual's diet.[3] In addition, strict elimination of CM from diet also affects parents' quality of life.[4] Complete dietary elimination of CM may also cause nutritional deficiencies.[5] As such, many other treatment approaches are being investigated to treat food allergies. Recently, baked dairy products have been introduced in CM allergy treatment. Studies have shown that instead of unheated CM, baked CM may be a better desensitization option because of its convenience and fewer side effects.[6-10] Regular intakes of baked-milk products may accelerate overall CM tolerance.[6]

We aimed to determine baked-milk tolerance in children with an Immunoglobulin E (IgE)-mediated CM allergy, and investigated possible markers that could predict tolerance of baked-milk products in these children, as confirmed by an oral food challenge (OFC) test.

Materials and Methods

Study population

Children referred with a suspicion of CM allergies to a hospital-based outpatient center were enrolled in the study. Eighty infants diagnosed with IgE-mediated allergy to CM proteins were enrolled in this prospective follow-up study. Patients were subjected to an allergological work-up consisting of a detailed history, focusing on clinical signs of food allergy, combined with skin prick test (SPT), prick-to-prick test, food-specific Immunoglobulin E (sIgE), allergen patch test, and OFC test. Children with chronic systemic diseases were excluded.

Oral food challenge test with CM was performed in 58 patients with milk sIgE levels or SPT <95% predictive for clinical reactivity. In addition, these 58 patients received OFC test with sheep's milk (SM) and goat's milk (GM). Positive OFC test results were obtained with SM in all of 58 patients, and with GM in 46 of the 58 (79.3%) patients. Forty-one of the 58 patients were tolerant, but 17 were reactive to baked milk. The oral provocation test was not performed in 22 patients with CM sIgE levels or SPT >95% predictive for clinical reactivity (if patient was ≤2 years old, a level of ≥5 kUA/L; if >2 years old, a level of ≥15 kUA/L; and if patient was ≤2 years old, SPT wheal diameter of ≥6 mm; if >2 years old, SPT wheal diameter of ≥8 mm) and a history of an allergic reaction to milk within prior six months.[11,12] These 22 patients were neither tested for OFC nor accepted to have CM allergy and were included in the study. In addition, oral provocation tests were not performed with SM and GM in these 22 patients. Thirteen of these 22 patients were reactive, and nine were tolerant to baked milk (Figure 1).

Skin prick test and atopy patch test

Skin prick test was performed in all subjects. Commercial or freshly prepared extracts were used. Commercial

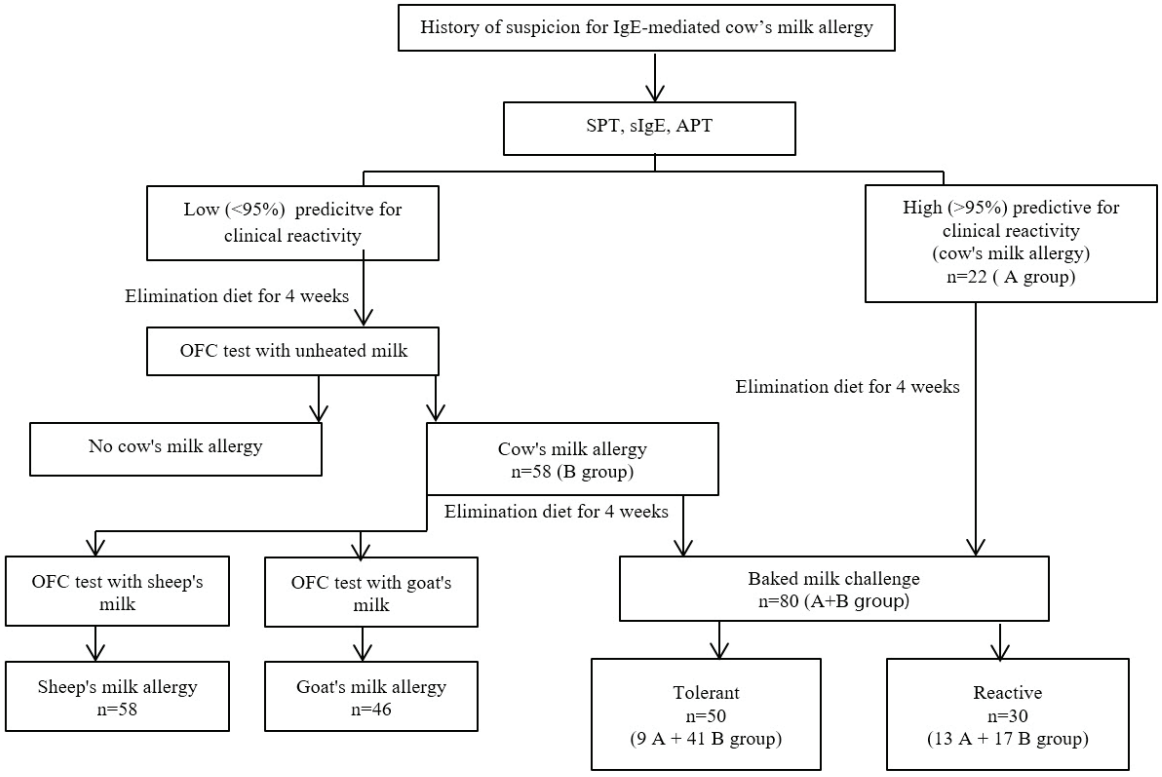

Figure 1 Study design.

extracts (from CM) were obtained from Allerbio (Varennes en Argonne, France). Raw foods used were CM, GM, and SM. Later, SPT was performed with fresh food extracts prepared from a baked-milk product. Approximately 1 g of muffin was thoroughly mixed with 10 mL of water.[13] Atopy patch tests with native food allergens were performed in all children.[14]

Oral food challenge

The initial dose for OFC was 3 mg, as recommended by the European Academy of Allergy and Clinical Immunology (EAACI) food allergy and anaphylaxis guidelines, and a total dose was given to patients that showed no reactions to the logarithmic dose increment.[15] The maximum dose included was 3 g of protein (3, 10, 30, 100, 300, 1000, 3000 mg). In total, about 4.5 g of CM protein was applied to patients in oral challenge test. The CM challenges were conducted using unheated CM (or formula milk for infants aged less than 12 months). Milk and dairy products were eliminated from the diets of patients diagnosed with CM allergy. Also, CM and dairy products were eliminated from mothers' diets if mothers were breastfeeding their child.

Baked Milk Challenge Test

Parents were instructed to prepare muffins or cupcakes at home according to a specific protocol provided by our clinic. Each muffin contained 1.3-g CM protein (baked products containing one cup of milk per one cup of flour). The muffin was baked at 180°C for 30 min in an oven.[8] The OFC with baked milk was applied as recommended by the EAACI food allergy and anaphylaxis guidelines.[15] Muffins were administered incrementally for 75 min in six steps with 15-min interval in-between. Dosing, expressed as a fraction of one muffin, was 1/8, 1/8, 1/4, 1/4, ½, and finally 3/4, totaling 2.6 g of milk protein. Oral challenge test with baked CM was applied when child was at least one year old (two-year old in most cases). Approval for the study was obtained from our Institutional Ethics Committee, and written informed consent was obtained from the parents of each enrolled child.

Statistical Analysis

IBM SPSS version 22.0 was used for all statistical analyses. The Kolmogorov–Smirnov test was used to test the normality of variables. Comparisons of continuous variables were made with independent-samples *t*-test and Mann–Whitney U test as appropriate. Pearson's Chi-square and linear-by-linear association tests were used with an exact test for the comparison of categorical data. Sensitivity and specificity between the classifications were determined using cut-off values calculated from group variables and analyzed using a receiver operating characteristic (ROC) curve.

Results

A total of 80 patients with CM allergy were enrolled. These comprised 48 males and 32 females with an average age of 7.25 ± 2.45 (3–13) months. The patients with CM allergy were further categorized in two groups based on the outcome of the baked-milk challenge: those who could tolerate and those who could not tolerate baked milk. The control group comprised 42 male and 30 female infants with a mean age of 7.55 ± 3.55 (3–24) months. There was no significant difference between the treatment group and control group regarding age, gender, weight, and height ($P > 0.05$). The mean vitamin D levels in the treatment and control groups were 28.32 ± 13.30 ng/mL and 26.09 ± 7.46 ng/mL, respectively, with no statistically significant difference between them ($P > 0.05$; Table 1). No statistically significant differences between the groups were detected when the patients who could tolerate and could not tolerate baked milk were compared for concomitant atopic diseases and other food allergies ($P > 0.05$). The other most frequently encountered food allergies were with eggs, peanuts, sesame seeds, walnuts, and wheat flour. When the patients tolerant and reactive to baked milk were compared for symptoms developed during the oral provocation test with unheated milk, a statistically significant difference

Table 1 The demographic and clinical characteristics of baked milk tolerant and baked milk reactive groups.

	Baked milk		
Parameters	Non-reactive (n = 50)	Reactive (n = 30)	p value
Gender n (%)			
Boy	32 (64)	16 (53.3)	0.3
Girl	18 (36)	14 (46.7)	
Living place n (%)			
Rural	12 (24)	0 (0)	0.003
Urban	38 (76)	30 (100)	
Breast milk intake only for the first six months n (%)	40 (80)	28 (93.3)	0.1
Age of starting complementary feeding (month)	5.80 ± 0.40	5.93 ± 0.25	0.1
Reaction with ingestion of breast milk, n (%)	19 (38)	13 (43.3)	0.6
Age at first reaction with unheated milk (month)	4.96 ± 1.67	4.36 ± 1.49	0.09
Age of diagnosis (month)	7.44 ± 2.40	6.93 ± 2.55	0.3
Family history of atopy n (%)	24 (48)	24 (80)	0.005
Other atopic conditions n (%)			
Asthma	11 (22)	9 (30)	0.4
Allergic rhinoconjunctivitis	16 (32)	12 (40)	0.4
Atopic dermatitis	34 (68)	21 (70)	0.5
Acute urticaria	31 (62)	21 (70)	0.6
Other food allergy	26 (52)	22 (73.3)	0.06
Symptoms with unheated milk provocation test n (%)			
Cutaneous	40 (80)	25 (83.3)	0.7
Upper Respiratory	14 (28)	10 (33.3)	0.6
Lower Respiratory	10 (20)	7 (23.3)	0.7
Gastrointestinal	11 (22)	11 (36.7)	0.1
Anaphylaxis	0 (0)	6 (20)	0.002

was detected only for anaphylaxis development. Similarly, a significant difference was found between patients who could tolerate and could not tolerate baked milk in terms of living place and familial atopy history ($P<0.05$; Table 1).

We detected a statistically significant intergroup difference between the patients who tolerated and could not tolerate baked-milk products in terms of wheal diameter in the SPT performed with a muffin slurry; CM, SM, GM, and casein sIgE levels; and the amount of unheated milk consumed until a reaction developed in the OFC test ($P<0.05$). Other parametres did not differ significantly with respect to statistics between the groups ($P>0.05$; Table 2).

When the patients who could tolerate and could not tolerate baked milk were compared, we found that amount of unheated milk ingested until the development of reaction during the OFC test performed with unheated milk was less in patients reactive to baked milk ($P<0001$). In addition, according to ROC curve analysis performed to analyze tolerance to baked milk, we observed that the cut-off value for the amount of unheated milk consumed until the development of reaction during the OFC test with unheated milk was ≤458 mg with 88.2% sensitivity and 51.2% specificity. (Figure 2, Table 3). Specifically, for diameter of wheal in the SPT performed with muffin slurry, patients who could not tolerate baked milk had significantly larger wheal diameters in terms of statistics ($P<0.05$). We found a cut-off value of >3 mm with 86.6% sensitivity and 56.0% specificity for wheal diameter in SPT (Figure 3, Table 3). Additionally, when compared with patients tolerant to baked milk, we found higher casein sIgE levels in patients reactive to baked milk ($P<0.05$). We determined a cut-off value of >3.01 kUA/L for casein sIgE level with 80.0% sensitivity and 84.0% specificity. In addition, we assessed cut-off values of CM, SM, and GM sIgE levels to predict clinical reactivity toward baked milk (Table 3).

Table 2 The laboratory findings of baked milk tolerant and baked milk reactive groups.

Parameters	Baked milk		p value
	Non-reactive (n=50)	Reactive (n=30)	
SPT wheal sizes (mm)			
Cow's milk (mm)	4.80±4.06	4.40±2.11	0.3
Prick-to-prick SPT wheal sizes			
Cow's milk (mm)	6.32±5.27	7.93±4.83	0.06
Sheep's milk (mm)	6.48±5.07	6.36±3.72	0.9
Goat's milk (mm)	7.36±6.40	5.90±3.27	0.6
Muffin SPT wheal sizes (mm)	3.84±3.48	6.06±3.30	0.002
Specific IgE levels			
Cow's milk (kU/L)	15.17±22.93	23.06±29.77	0.047
Sheep's milk (kU/L)	6.28±8.91	15.46±24.92	0.01
Goat's milk (kU/L)	5.89±8.11	15.10±24.23	0.006
α-laktalbumin (kU/L)	4.14±8.12	7.40±12.99	0.8
β-lactoglobulin (kU/L)	5.64±10.74	14.07±28.66	0.1
Casein (kU/L)	3.74±6.68	15.41±24.45	0.0001
Patch test with milk n (%)			
Cow's milk	22 (44)	14 (46.7)	0.8
Sheep's milk	18 (36)	16 (53.3)	0.1
Goat's milk	20 (40)	16 (53.3)	0.2
Goat milk OFC n (%)			
Negative	6 (12)	2 (6.7)	0.7
Positive	44 (88)	28 (93.3)	
The amount of unheated milk ingested during OFC test (mg)*	1458 (58-5958)	158 (3-1458)	0.001
Vitamin D levels	28 (6.8-60.6)	29 (1.5-47.8)	0.6
Classification of vitamin D status n (%)			
0-10	20 (40)	14 (46.7)	0.3
11-20	14 (28)	6 (20)	
21-29	14 (28)	6 (20)	
≥30	2 (4)	4 (13.3)	
Total IgE levels (kU/L)	145.18±304.22	147.37±195.32	0.1
Peripheral eosinophil count (mm^3)	849.20±906.07	750.00±365.30	0.2

*=The amount of unheated milk ingested during oral food challenge test until the development of reaction.
OFC: Oral food challenge, SPT: Skin prick test.

Discussion

Research has shown that 65–83% of children with milk allergies can safely consume baked-milk products.[8-10,16-23] Notably, Cherkaoui et al.[21] detected a positive rate of 23% in patients with CM allergy in oral provocation tests performed with baked milk. Nowak-Wegrzyn et al.,[8] who used muffins and waffles containing baked milk, reported an identical positive rate of 23%. In three different studies involving children with CM allergy, an OFC test was performed with cakes containing a total of 2.6-g milk protein. In these studies, Bartnikas et al.[17] with 83%, Kwan et al.[24] with 60%, and Mehr et al.[22] with 73% reported that the indicated percentages of their participants could tolerate baked milk. Contrary to these studies, Barbosa et al.[25] performed an OFC test on children with CM allergy with cakes containing a total of 2.8-g milk protein, and reported that 46.7% of patients tolerated baked milk. Karaman et al.[18] found that 34.3% of their patients tolerated baked milk in an OFC test performed with four cakes containing 4.5-g milk. In our study, we found that 62.5% of patients showed tolerance to baked milk in an OFC test performed with muffins containing 2.6-g milk protein.

In other extant studies, there was no significant difference between patients tolerant and reactive to baked-milk products in terms of age at onset of symptoms or diagnosis.[6,8,13,18,22] However, Bartnikas et al.[17] reported that patients reactive to baked milk were younger in age than those non-reactive to baked milk. Our study showed no significant difference between patients who tolerated and did not tolerate baked milk in terms of age at onset of symptoms or

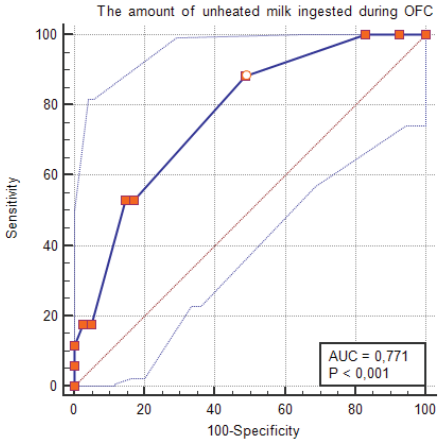

Figure 2 ROC curve analysis showed that ≤458 mg was the optimal cut-off value for the amount of unheated milk ingested during OFC to predict tolerance to baked milk, with a sensitivity of 88.2% and a specificity of 51.2%.

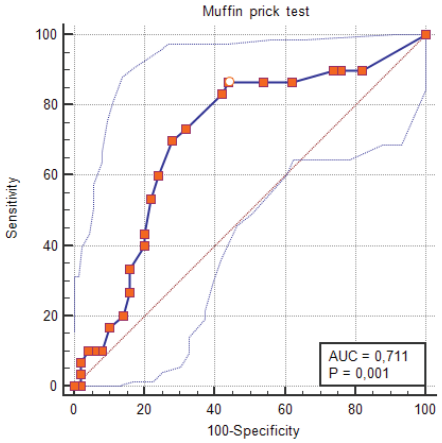

Figure 3 ROC curve analysis showed that >3 mm was the optimal cut-off value for wheal diameter in SPT made with muffin slurry to predict tolerance to baked milk, with a sensitivity of 63.3% and a specificity of 76.0%.

Table 3 ROC curve analysis showed the parameters found statistically significant for baked milk allergy.

Variable	Cut off value	Sensitivity %	Specificity %	PPV %	NPV %	AUC	p value
Muffin SPT wheal diameter	3.00	86.6	56.0	54.2	87.5	0.711	0.001
Casein sIgE levels	3,01	80.0	84.0	75.00	87.5	0,755	0.001
Amount of unheated milk ingested during OFC	458	88.2	51.2	42.9	91.3	0,771	0.001
Cow milk sIgE levels	5,77	73.3	60.0	52.4	78.9	0,633	0.046
Sheep milk sIgE levels	2,60	86.6	60.0	56.5	88.2	0,671	0.008
Goat milk sIgE levels	1,79	86.6	56.0	54.2	87.5	0,684	0.003

AUC: Area under the ROC curve, SPT: Skin Prick Test, OFC: Oral Food Challenge, sIgE: specific IgE, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

age of diagnosis. Nowak-Wegrzyn et al.,[8] Cherkaoui et al.,[21] Kwan et al.,[24] and Barbosa et al.[25] also evaluated tolerance to baked-milk products in children having CM allergy and reported no significant difference between groups with and without baked-milk tolerance in terms of gender, comorbid atopic diseases, or familial atopy history. Similarly, our study featured no difference between the groups with and without tolerance to baked milk in terms of gender and accompanying atopic diseases. However, there was a statistical difference between patients who tolerated and did not tolerate baked CM in terms of the patient's place of living and the family history of atopy. All the patients reactive to baked milk lived in cities. We speculate that more severe CM allergies could be observed in children living in cities, based on the hygiene hypothesis.

Barbosa et al.[25] showed that total IgE level, peripheral eosinophil count, CM sIgE level, and wheal diameter in an SPT performed with CM were not predictive of baked-milk tolerance. Similarly, Karaman et al.[18] reported that CM sIgE level, wheal diameter in an SPT performed with CM, eosinophil count in peripheral blood, and total IgE level couldn't predict baked-milk tolerance. In contrast, Nowak-Wegrzyn et al.[8] reported that the study group that tolerated baked milk had lower CM sIgE levels and a smaller SPT wheal diameter. They also found that no subject with a milk SPT wheal diameter of <5 mm reacted to baked milk. Similarly, Bartnikas et al.[17] did not detect any reaction to baked milk in patients with a wheal diameter of <7 mm in SPTs performed with CM. In our study, there was no statistically significant difference between patients who tolerated and did not tolerate CM in terms of total IgE level, peripheral eosinophil count, or wheal diameter in an SPT with CM. In addition, contrary to other studies, we measured vitamin D, SM, and GM sIgE levels by performing prick-to-prick SPT and patch testing with CM, SM, and GM. CM, SM, and GM sIgE levels were higher in patients reactive to baked milk, but we did not find statistically significant differences in other parameters between patients who tolerated and did not tolerate baked milk.

Some studies in literature reported that patients reactive to baked CM had higher casein, a-lactalbumin, and β-lactoglobulin sIgE levels compared to nonreactive patients to baked CM.[8,17-19,21] Cherkaoui et al.[21] showed that casein, a-lactalbumin, and β-lactoglobulin sIgE levels were higher in children reactive to baked milk. Similarly, Nowak-Wegrzyn et al.[8] found that patients reactive to baked milk had higher levels of casein and β-lactoglobulin sIgE. Caubet et al.[19] also established that CM, casein, and β-lactoglobulin sIgE levels were significantly higher in patients reactive to baked milk compared to tolerant patients, writing of a cut-off value of 4.95 kUA/L with 74% sensitivity and 77% specificity for casein sIgE. In our results, we established

that patients reactive to baked milk had higher CM and casein sIgE levels compared to tolerant patients; for casein sIgE, we found that a cut-off value of 3.01 kUA/L had 80% sensitivity and 84% specificity. Many related studies have reported that a-lactoalbumin and β-lactoglobulin sIgE levels are weak markers in predicting baked-milk tolerance.[17,18,25] Barbosa et al.[25] reported that low casein sIgE levels can predict tolerance of baked milk, but a-lactoalbumin and β-lactoglobulin sIgE levels cannot have tolerance for baked milk. Similar to literature, we also found that the a-lactoalbumin and β-lactoglobulin sIgE levels in our study were not significant predictors of baked-milk tolerance.

Kwan et al.[24] reported that all participants with negative SPT results performed with baked milk could tolerate OFC tests with baked milk. In this study, 91% sensitivity and 61% specificity were determined using a 4-mm cut-off value for wheal diameter produced in the SPT test performed using baked milk. In addition, Karaman et al.[18] found that eight of the 14 participants (57%) whose SPT results were negative tolerated baked milk. However, they reported that wheal diameter in an SPT with baked milk was a weak marker to predict baked milk reactivity, as did Mehr et al.[22] In our study, we found that wheal diameter in an SPT with muffin slurry was greater in patients reactive to baked milk with an estimated 86.6% sensitivity and 56% specificity with a cut-off value of 3 mm.

Finally, we investigated the amount of milk protein consumed until a reaction developed in an OFC test performed with unheated milk to predict the development of tolerance toward baked milk. We showed that a cut-off value of 485 mg for consumed milk featured an 88.2% sensitivity and 51.2% specificity in predicting baked-milk tolerance. A recent study likewise has reported that tolerance to more than 620 mg of milk protein during an OFC with unheated milk could predict baked-milk tolerance at 83.3% sensitivity and 82.6% specificity.[18]

In conclusion, our study defines novel decision points based on CM, SM, GM, and casein sIgE levels; wheal diameter in an SPT with muffin slurry; and the amount of milk ingested during an OFC performed with unheated milk. These results may prove useful in predicting the outcomes of baked-milk ingestion. We also found that casein, CM, SM, and GM sIgE levels can better predict the results of an OFC test with baked milk compared to wheal diameter in an SPT performed with CM alone. From here, the future studies can validate our findings in a larger patient population.

Statement of Ethics

The authors have no ethical and financial conflicts to disclose.

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

MK is conceived of the research, involved in data collection, performed statistical analysis, and wrote the manuscript.

LC and ET supervised the study.

MK and LC were responsible for experimental and laboratory assay.

MK and ET assisted with conception of the research question and study design as advisor.

All authors read and approved the final manuscript.

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