Original article

Dietary baked milk accelerates the resolution of cow's milk allergy in children

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Background: The majority (approximately 75%) of children with cow's milk allergy tolerate extensively heated (baked) milk products. Long-term effects of inclusion of dietary baked milk have not been reported.
Objective: We report on the outcomes of children who incorporated baked milk products into their diets.
Methods: Children evaluated for tolerance to baked milk (muffin) underwent sequential food challenges to baked cheese (pizza) followed by unheated milk. Immunologic parameters were measured at challenge visits. The comparison group was matched to active subjects (by using age, sex, and baseline milk-specific IgE levels) to evaluate the natural history of development of tolerance.
Results: Over a median of 37 months (range, 8-75 months), 88 children underwent challenges at varying intervals (range, 6-54 months). Among 65 subjects initially tolerant to baked milk, 39 (60%) now tolerate unheated milk, 18 (28%) tolerate baked milk/baked cheese, and 8 (12%) chose to avoid milk strictly. Among the baked milk–reactive subgroup (n = 23), 2 (9%) tolerate unheated milk, and 3 (13%) tolerate baked milk/baked cheese, whereas the majority (78%) avoid milk strictly. Subjects who were initially tolerant to baked milk were 28 times more likely to become unheated milk tolerant compared with baked milk–reactive subjects ($P < .001$). Subjects who incorporated dietary baked milk were 16 times more likely than the comparison group to become unheated milk tolerant ($P < .001$). Median casein IgG_4 levels in the baked milk–tolerant group increased significantly ($P < .001$); median milk IgE values did not change significantly.
Conclusions: Tolerance of baked milk is a marker of transient IgE-mediated cow's milk allergy, whereas reactivity to baked milk portends a more persistent phenotype. The addition of baked milk to the diet of children tolerating such foods appears to accelerate the development of unheated milk tolerance compared with strict avoidance. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: *Cow's milk allergy, milk allergy, tolerance, extensively heated, baked, immunotherapy, immunomodulation*

Cow's milk is the most common childhood food allergen, affecting approximately 1% to 3% of young children,[1,2] and is responsible for up to 13% of fatal food-induced anaphylaxis.[3] Studies have differed in methodology, but tolerance appears to be slower to develop.[4-10] Bishop et al[7] prospectively followed 100 children with challenge-proved milk allergy. Findings were published in 1990; tolerance was achieved in 78% by age 6 years. By 2007, resolution was considerably delayed; tolerance was achieved in 79% of children in a specialty practice by age 16 years.[10] The mechanism of tolerance induction remains unclear.

Subjects with transient milk allergy produce IgE antibodies primarily directed at conformational epitopes (dependent on the protein's tertiary structure), whereas those with persistent allergy also produce IgE antibodies against sequential epitopes, which are heat stable.[11-15] Greater IgE epitope diversity and higher IgE affinity are associated with more severe milk allergy.[16] Because high temperatures (baking) reduce allergenicity by destroying conformational epitopes of milk proteins, we hypothesized that children with transient milk allergy would tolerate baked milk products. We found that the majority (75%) of children with milk allergy tolerate baked milk products (eg, muffins and waffles).[17] None of the baked milk–tolerant children received epinephrine for reactions during unheated milk challenges. In contrast, 35% of baked milk–reactive children received epinephrine for anaphylaxis during baked milk (muffin) challenges. Based on these observations, we proposed 2 phenotypes of IgE-mediated milk allergy. Those with the mild phenotype were tolerant of baked milk products but not unheated milk, whereas those with the more severe phenotype were baked milk reactive.

We subsequently hypothesized that children with the milder phenotype of milk allergy (baked milk–tolerant children) would

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Abbreviations used
EoE: Eosinophilic esophagitis
OIT: Oral immunotherapy
SPT: Skin prick test

be able to ingest baked milk products daily, thus benefiting from improved nutrition and dietary variety without negative effects on development of tolerance to unheated milk.

METHODS

Participants

Subjects were recruited from the Mount Sinai pediatric allergy clinics from June 2004 to October 2007. The study was approved by the Mount Sinai Institutional Review Board, and informed consent was obtained. Eligible subjects were aged 0.5 to 21 years, had positive skin prick test (SPT) responses or detectable serum milk-specific IgE, and had a history of an allergic reaction to milk within 6 months before study entry or milk-specific IgE levels or SPT responses greater than 95% of predicted value for clinical reactivity (if ≤2 years old, a level >5 kU_A/L; if >2 years old, a level >15 kU_A/L[18,19]; SPT mean wheal diameter, ≥8 mm[20,21]). Exclusion criteria included a negative SPT response and an undetectable milk-specific IgE level; unstable asthma, allergic rhinitis, or atopic dermatitis; previously diagnosed milk-induced eosinophilic gastroenteropathy; a recent reaction (within 6 months) to a baked milk product; or pregnancy.

Design

Active group. Based on the initial baked milk oral challenge, subjects were categorized as baked milk reactive or baked milk tolerant (Fig 1).[17] Baked milk–reactive subjects were instructed to completely avoid all forms of milk but were offered a repeat challenge 6 or more months from the initial challenge. Baked milk–tolerant subjects were instructed to incorporate baked milk products daily into their diets and after 6 or more months were offered challenges to baked cheese products. Similarly, after 6 or more months, baked cheese–tolerant children were offered challenges to unheated milk.

Baked milk. Each muffin contained 1.3 g of milk protein (nonfat dry milk powder; Nestle Carnation, Glendale, Calif). The muffin was baked at 350°F for 30 minutes. Baked milk–tolerant subjects were instructed to ingest 1 to 3 servings per day of store-bought baked milk products with milk listed as a minor ingredient or home-baked products with an equivalent amount of milk protein.

Baked cheese. Amy's cheese pizza (Amy's Kitchen, Inc, Petaluma, Calif), containing 4.6 g of milk protein, was baked at 425°F for 13 minutes or longer. Baked cheese–tolerant subjects were instructed to eat any brand of well-cooked cheese pizza 4 to 7 times weekly and limited to 1 daily serving.

Unheated milk. Challenges were performed with skim milk totaling 240 mL (or other product containing 8-10 g of unheated milk protein, such as yogurt).

Comparison group. The original protocol was designed to have a prospective control group, such that all baked milk–tolerant subjects would be randomly assigned to introduce dietary baked milk or practice strict avoidance, but recruitment was unsuccessful, failing to enroll a single subject over 1 year. Therefore a comparison group was retrospectively gathered consisting of subjects who fulfilled the inclusion criteria but were not initially challenged to baked milk products. This group reflects current "standard of care," representing how children with cow's milk allergy are traditionally managed in the clinical setting.

Follow-up allergy evaluations

Serum samples were collected for the measurement of IgE and IgG_4 antibodies to milk, casein, and β-lactoglobulin by using UniCAP (Phadia, Uppsala, Sweden). Unblinded food challenges were performed under a physician's supervision in the clinical research unit. Muffin and pizza were administered in 4 equal portions over 1 hour. Unheated milk was administered in gradually increasing doses. Subjects were monitored throughout and for 2 to 4 hours after completion of the challenge. Challenges were discontinued at the first objective sign of a reaction or due to convincing persistent subjective symptoms, and treatment was initiated immediately. Anthropometric measurements (weight and height percentiles and *z* scores) and intestinal permeability (measured as a ratio of urinary excretion of lactulose and mannitol) were monitored for 12 months in the active group, as previously described.[17]

Statistics

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Inc, Cary, NC). The Wilcoxon rank-sum test was used to compare medians of continuous measures, whereas the 2-sample χ^2 test (and the Fisher exact test when the expected cell count was <5) was used to compare distributions of categorical measures between various patient groups. Regression models with discrete outcomes using a generalized logit link function were used to estimate odds ratios, corresponding 95% CIs, and *P* values. Probabilities of unheated milk tolerance were estimated by using the Kaplan-Meier product limit method with comparison between groups evaluated by using the log-rank statistic. The Cox proportional hazards model was used to estimate hazard ratios, corresponding 95% CIs, and *P* values. Immunologic responses over time were compared between various patient groups by using mixed models with random intercepts and unstructured variance/covariance parameters. These mixed models were used to account for the correlation among immunologic response measures taken over time within a subject. Analysis of covariance was performed to compare the change from baseline to the last visit between patient groups while adjusting for baseline measures. For the mixed modeling, immunologic responses were naturally log transformed to render them normally distributed. For the analysis of covariance modeling, the analysis was performed on the ranked data.

Intent-to-treat versus per-protocol analysis

The intent-to-treat analysis includes 88 subjects who underwent the initial baked milk challenge, were available for follow-up, and either reacted to baked milk, unheated milk, or tolerated baked milk but had immunologic indications of greater than 95% risk of reaction to unheated milk.[18-21] The per-protocol analysis includes those subjects (n = 70) who underwent treatment (ie, added dietary baked milk; Fig 1).

RESULTS

Unheated milk tolerance within the active group

Eighty-nine children (median age, 6.6 years; range, 2.1-17.3 years) were enrolled[17]; 1 subject was not followed beyond baseline. Over a median of 37 months (range, 8-75 months), 88 children were challenged to progressively less heated forms of milk at varying intervals (range, 6-54 months). Among 88 "active" children, 41 (47%) now tolerate unheated milk, 21 (24%) tolerate some form of baked milk/baked cheese in their diet, and 26 (30%) avoid all forms of milk (Table I, intent-to-treat).

Unheated milk tolerance within the active group stratified by initial baked milk challenge outcome

Among 88 children, 65 (74%) tolerated their initial muffin challenge (Table I). Among this initially baked milk–tolerant subgroup, the majority (60%) had tolerance to unheated milk over the 5-year follow-up period. Despite tolerating their initial baked milk challenge, 8 (12%) subjects later chose to avoid all forms of milk for a variety of reasons. One subject's family reported it became "easier to avoid" all milk products. Because of anxiety about possible reactions, another subject refused to incorporate

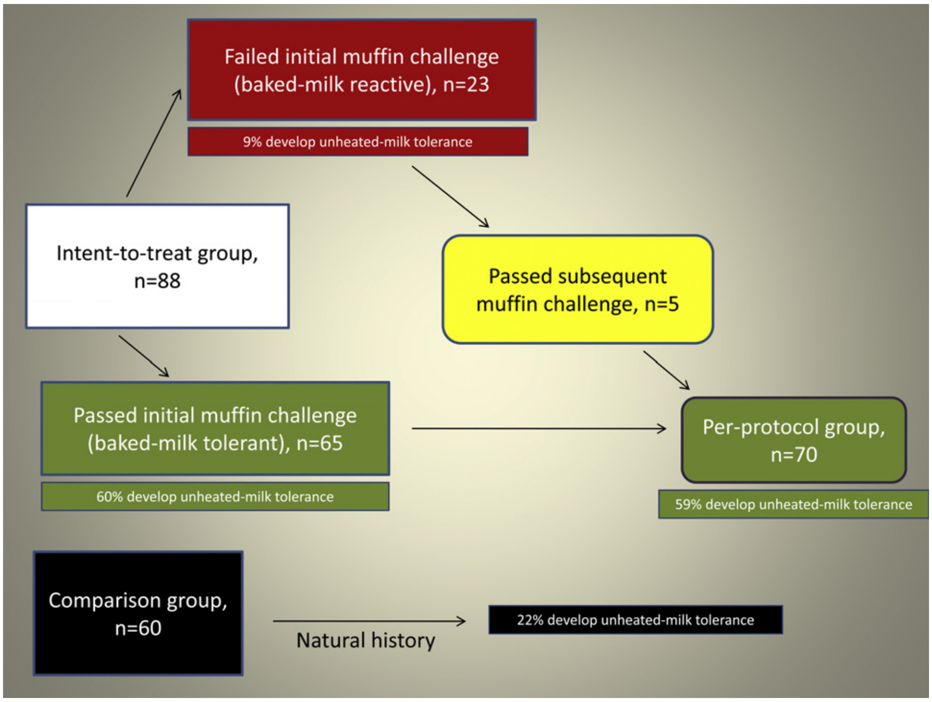

FIG 1. Flow diagram of study participants.

TABLE I. Follow-up status of milk allergy

Final follow-up status	Initially baked milk tolerant (n = 65)	Initially baked milk reactive (n = 23)	Active intent-to-treat (n = 88)	Active per-protocol (n = 70)	Comparison (n = 60)
Unheated milk tolerant	39 (60%)	2 (9%)	41 (47%)	41 (59%)	13 (22%)
Baked milk/cheese tolerant	18 (28%)	3 (13%)	21 (24%)	21 (30%)	13 (22%)
Avoiding strictly	8 (12%)	18 (78%)	26 (29%)	8 (11%)	34 (56%)

baked milk products into his diet. The remainder (n = 5) reported symptoms to lesser heated forms of milk products. Two failed unheated milk challenges, and one required epinephrine during a pizza challenge. Another (without egg allergy) reacted to an accidental ingestion of mozzarella hidden in an omelet (throat "numb" and vomiting within 5 minutes). Two others had mild oral symptoms to unintentionally undercooked waffle and pizza, respectively. It is important to note that no subjects reacted to properly cooked foods previously tolerated during challenges. Repeat baked milk challenges to re-establish nonreactivity were subsequently declined by these families.

Among the initially baked milk–reactive subgroup (n = 23), only 2 (9%) developed tolerance to unheated milk, whereas 78% (n = 18) continued strict milk avoidance (Table I). Of these 18 subjects, 6 had failed subsequent baked milk challenges performed 23 to 54 months after baseline. One subject had a total of 4 failed muffin challenges over 5 years. Three subjects did not repeat baked milk challenges because of anxiety; 3 others retained persistently high milk-specific IgE levels or large SPT wheal sizes and were not rechallenged. The remainder reported interim reactions to accidental ingestions.

Overall, baked milk–tolerant subjects were 28 times more likely to become tolerant to unheated milk (compared with subjects strictly avoiding milk) than baked milk–reactive subjects (odds ratio, 27.8; 95% CI, 4.8-162.7; $P < .001$; Table II).

Unheated milk tolerance within the comparison group

Sixty children were identified as age-, sex-, and baseline milk-specific IgE–matched control subjects. The median age of the comparison group was 5.4 years (range, 2.2-17.0 years), which was not statistically different from the active group (data not shown). If unheated milk challenges were offered, they were performed as part of routine care. At follow-up (median, 40 months; range, 2-71 months), 13 (22%) tolerated unheated milk, of whom 8 demonstrated nonreactivity to unheated milk in an unblinded oral challenge at the Mount Sinai Pediatric Allergy clinic; the remainder reported at least weekly ingestion of cow's milk, yogurt, or ice cream. Another 13 (22%) subjects tolerated baked milk/baked cheese, and 34 (56%) continued to avoid all milk (Table I). Those reporting tolerance to baked milk/baked cheese introduced these foods after asymptomatic inadvertent ingestions.

Development of unheated milk tolerance in the per-protocol versus comparison groups

Forty-one (59%) active subjects had unheated milk tolerance in contrast to 13 (22%) subjects in the comparison group (Table I). Subjects who underwent active treatment (the per-protocol group, which excludes those with persistent baked milk reactivity) were 16 times more likely than the comparison group to become

TABLE II. ORs for tolerance comparing the baked milk–tolerant versus baked milk–reactive groups

Final follow-up status	OR (95% CI)	*P* value
Unheated milk tolerant vs strict avoidance	27.8 (4.8-162.7)	<.001
Baked milk/cheese tolerant versus strict avoidance	8.7 (1.8-43.5)	.008

OR, Odds ratio.

unheated milk tolerant ($P < .001$, Table III) by using those subjects practicing strict milk avoidance as a reference group. The significance is maintained even after inclusion of those who were unable to undergo treatment (intent-to-treat vs comparison groups; Table III).

Time to tolerance of unheated milk

In the per-protocol group (n = 70) the probability of having unheated milk tolerance within 60 months was 76%. In the comparison group (n = 60) this probability was 33% (Fig 2). More striking, however, was the difference between the initially baked milk–tolerant and initially baked milk–reactive subjects. Among subjects initially tolerant to baked milk (n = 65), the probability of having unheated milk tolerance within 60 months was 80% (Fig 3). In contrast, this probability was only 24% among subjects who were initially baked milk reactive.

Severity of symptoms during failed oral food challenges

During the follow-up period, 172 challenges were performed, only 10% of which were completed in subjects who were initially baked milk reactive. Of 172 subsequent challenges, epinephrine was administered during challenges at a higher rate among the baked milk–reactive group than among the baked milk–tolerant group (17% vs 3%, $P = .04$, Table IV). Overall, 6 subjects had mild-to-moderate anaphylaxis during 8 challenges, 2 subjects twice to the same food, one to muffin (54 months apart) and the other to pizza (9 months apart). Three different subjects had anaphylaxis (wheeze, cough, or both) after ingestion of 100% of the serving, which was pizza in all 3 cases.

Immunologic responses over time

After adjusting for baseline milk IgE levels, median milk-specific IgE levels from the baseline to final visits (see Table E1 in this article's Online Repository at www.jacionline.org) were not significantly different between the per-protocol (2.6-1.5 kU_A/L) and comparison (5.40-5.41 kU_A/L) groups ($P = .09$). However, both casein IgE and β-lactoglobulin IgE values in the baked milk–tolerant group decreased significantly over time ($P < .001$ and $P = .02$, respectively).

Median casein IgG_4 values from the baseline to final visits in the initially baked milk–tolerant group increased significantly over time (0.6-1.3 mg_A/L, $P < .001$, see Table E2 in this article's Online Repository at www.jacionline.org). In contrast, β-lactoglobulin IgG_4 values in the baked milk–tolerant group did not change significantly over time ($P = .07$).

Casein IgE/IgG_4 and β-lactoglobulin IgE/IgG_4 ratios in the baked milk–tolerant group decreased significantly over time ($P = .001$ and $P < .001$, respectively).

TABLE III. ORs for tolerance comparing the active versus comparison groups

Final follow-up status	Per-protocol vs comparison, OR (95% CI)	*P* value	Intent-to-treat vs comparison, OR (95% CI)	*P* value
Unheated milk tolerant vs strict avoidance	16.2 (5.2-50.5)	<.001	5.8 (2.3-14.9)	<.001
Baked milk/cheese tolerant vs strict avoidance	7.9 (2.5-24.7)	<.001	2.8 (1.1-7.2)	.03

The per-protocol group consists of children in the active group who were or eventually had nonreactivity to baked milk over the length of the study. The intent-to-treat group consists of all subjects enrolled in the active arm of the study, including baked milk–reactive subjects.
OR, Odds ratio.

Safety of dietary baked milk

There was no increase in the severity of chronic asthma, atopic dermatitis, or allergic rhinitis among baked milk–tolerant children ingesting baked milk products. The anthropometric parameters and intestinal permeability[17] did not differ from baseline to 12 months (data not shown). Two (3.1%) male subjects in the active group had eosinophilic esophagitis (EoE). One was baked milk reactive and already strictly avoiding milk at the time of diagnosis. Another had EoE after "passing" his unheated milk challenge. Milk in all forms was removed for a period of time without improvement of EoE; thereafter, he safely resumed ingesting unheated cow's milk products. Five (8.3%) subjects in the comparison group reported EoE, which developed while strictly avoiding milk.

DISCUSSION

Cow's milk is the most common food allergen among children. Currently, there is no cure for food allergy. The standard of care focuses on strict dietary avoidance,[1] which is extremely difficult but has been the cornerstone of food allergy therapy for decades. The advice is practical because the amount of allergen necessary to induce an allergic reaction varies[22] and the severity of reactions is unpredictable.[23,24] Additionally, there has been a theory that lack of exposure will result in deletion of immunologic memory.[25] Thus children given a diagnosis of milk allergy were often advised by physicians to stop ingestion of baked milk products, despite previous nonreactivity to repeated ingestions of such foods.

Our study demonstrates that (1) tolerance to baked milk products is a marker of mild, transient, IgE-mediated cow's milk allergy whereas baked milk reactivity portends a more severe persistent phenotype and (2) 60% of baked milk–tolerant children ingesting baked milk products will have unheated milk tolerance at a significantly accelerated rate compared with subjects prescribed strict milk avoidance. This is further supported by immunologic measures; casein IgG_4 values in the baked milk–tolerant group increased significantly, which is consistent with children spontaneously outgrowing milk allergy[26-28] and children treated with milk oral immunotherapy (OIT).[29-32] Moreover, diets inclusive of baked milk products were easily implemented and had no adverse effects on growth or intestinal permeability.

There is a subset of patients with milk allergy in whom strict avoidance is clearly necessary because approximately 25% of

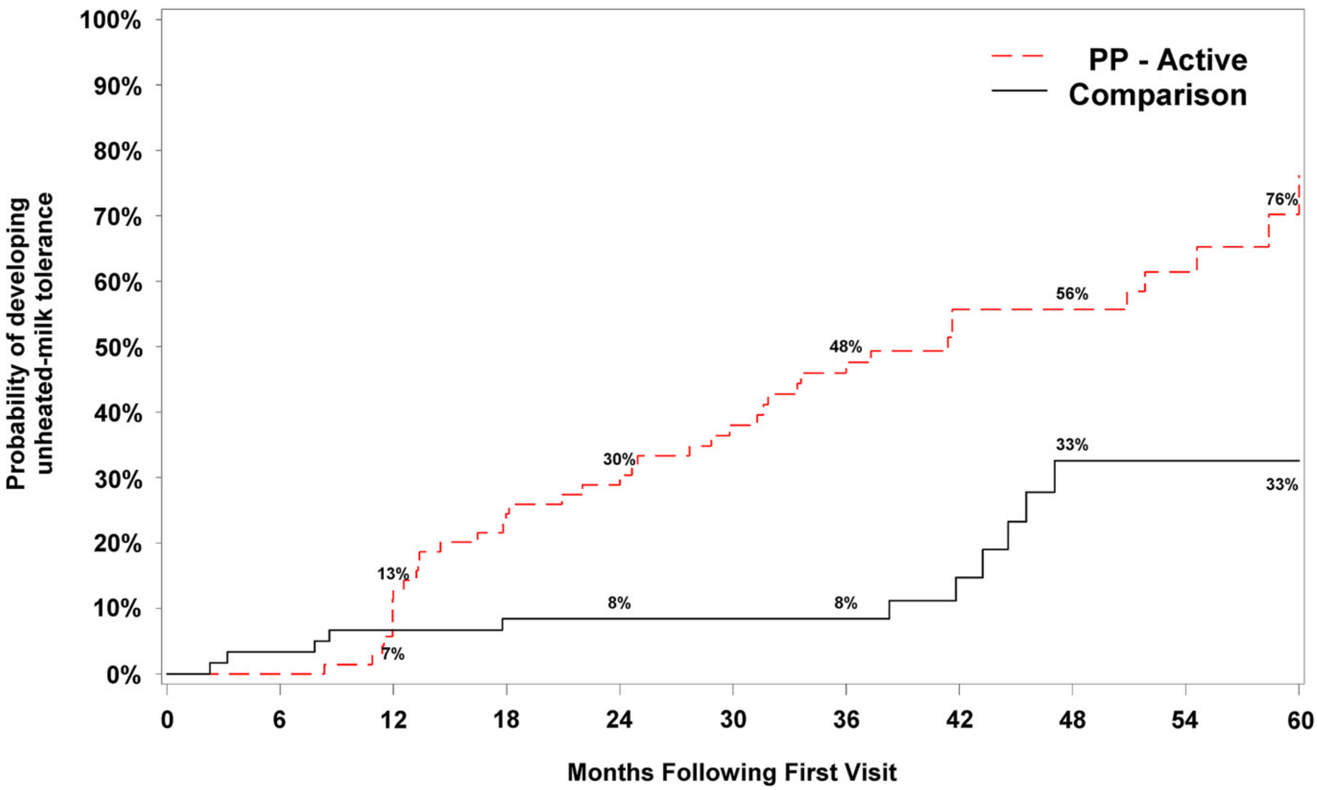

FIG 2. Development of tolerance: per-protocol *(PP)* versus comparison groups. The log-rank *P* value comparing survival between the per-protocol versus comparison groups is less than .001. Subjects in the per-protocol group were 3.6 times more likely to have unheated milk tolerance than subjects in the comparison group over the follow-up period (hazard ratio, 3.57; 95% CI, 1.78-7.16; $P < .001$) adjusted for sex, age at initial visit, and baseline milk-specific IgE levels. We present data up to 60 months because beyond 60 months, the CIs were very wide as a result of the large number of censored data.

children were initially baked milk reactive. In addition, approximately 10% of our cohort who passed their initial muffin challenge later stopped treatment because of reactions to less-cooked forms of milk, highlighting the challenges of strict adherence to proper food preparation and selection. Still, the vast majority of baked milk–tolerant subjects successfully introduced baked milk products into their diets.

Nonreactivity to foods (ie, desensitization) has been demonstrated in milk OIT,[29-32] a treatment approach that includes gradually increasing monitored administration of allergen over months to years. However, OIT's potential to induce permanent oral tolerance has not been established.[33] Moreover, adverse reactions are common. In a double-blind, placebo-controlled study of milk OIT, all active subjects experienced at least 1 adverse event, and 45% of active doses resulted in reactions.[31] Thus we propose that for 75% of children with milk allergy, ingestion of baked milk products is a safer, more convenient, less costly, and less labor-intensive form of immunotherapy.

Over the past 2 decades, there has been an apparent increase in the prevalence of food allergy and anaphylaxis,[2] as well as progressive delays in the development of tolerance in children with milk allergy. As suggested by this study, withdrawing small amounts of baked milk from diets might play a role in delaying development of tolerance. Moreover, strict milk avoidance can have negative effects on nutrition[34,35] and quality of life[36-39] by vastly limiting the variety of food products in the diet. We have demonstrated that the addition of baked milk products into the diet of baked milk–tolerant subjects has a therapeutic role in accelerating development of tolerance. Our findings also potentially affect children with egg allergy because similar effects of heating on egg allergenicity were described.[11,40] The effect of heat on allergenicity, however, is variable and food dependent; for peanut (dry roasting)[41] and shrimp (boiling),[42] high temperatures appear to increase allergenicity.

In conclusion, tolerance of baked milk products by children with IgE-mediated cow's milk allergy is a favorable prognostic indicator for development of tolerance to unheated milk. More importantly, the addition of baked milk products to the diet appears to markedly accelerate the development of tolerance to unheated milk compared with a strict avoidance diet, which currently is the standard of care. Moreover, addition of dietary baked milk is safe, convenient, and well accepted by patients. Prescribing baked milk products to children with milk allergy represents an important shift in the treatment paradigm for milk allergy. Given the risk of anaphylaxis in children who react to baked milk products, addition of such foods should be performed under the supervision of a physician with expertise in food allergy.

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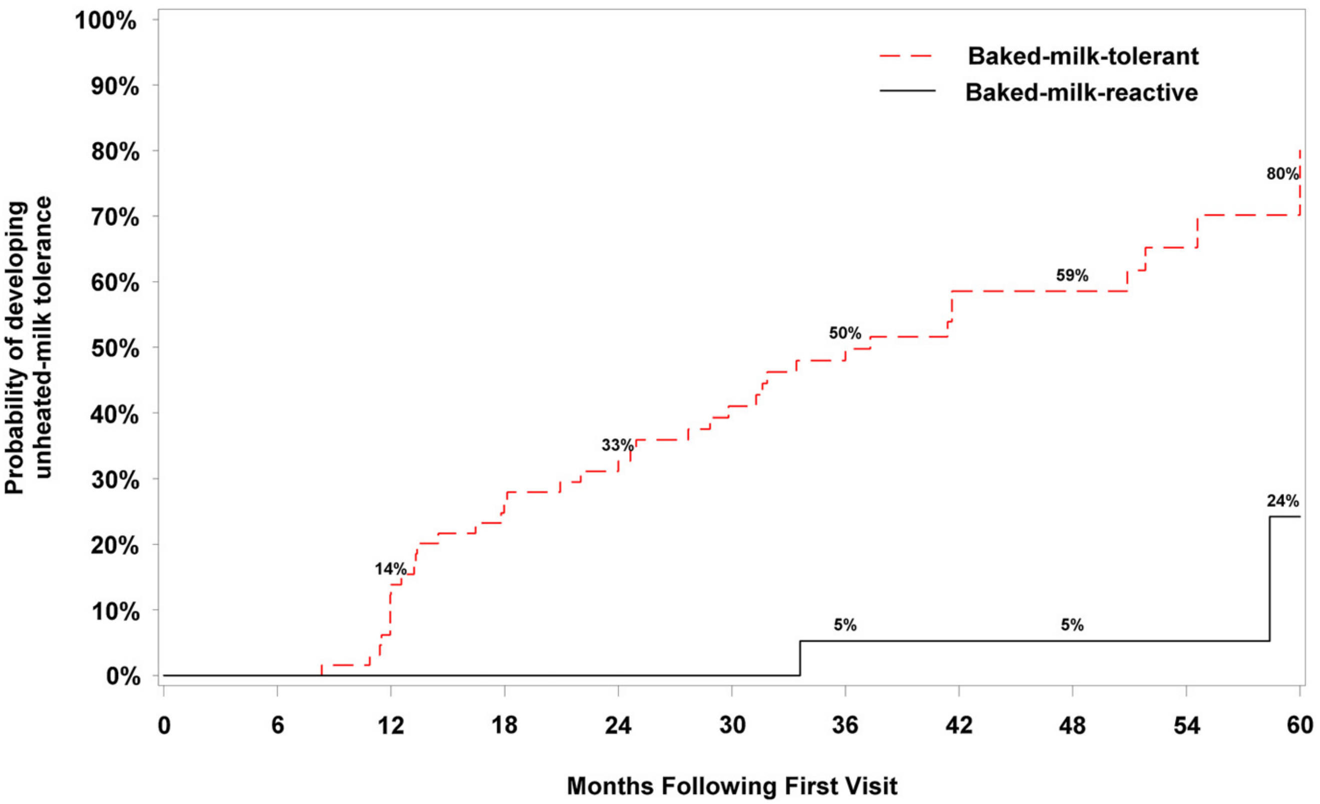

FIG 3. Development of tolerance in the active group stratified by initial baked milk challenge: tolerant versus reactive. The log-rank *P* value comparing time to development of tolerance between the initially baked milk–tolerant versus initially baked milk–reactive groups is less than .001. Subjects who were initially baked milk tolerant are 7.6 times more likely to have unheated milk tolerance than subjects who were initially baked milk reactive over the follow-up period (hazard ratio, 7.62; 95% CI, 1.75-33.14; $P = .007$) adjusted for sex, age at initial visit, and baseline milk-specific IgE levels. We present data up to 60 months because beyond 60 months, the CIs were very wide as a result of the large number of censored data.

TABLE IV. Follow-up oral challenge outcomes and treatment

	Total (n = 88)	Initially baked milk tolerant (n = 65)	Initially baked milk reactive (n = 23)	*P* value
No. of challenges performed	172	154 (90%)	18 (10%)	<.001
No. failed	58 (34%)	47 (31%)	11 (61%)	.009
No. treated with epinephrine	8 (4.7%)	5 (3.2%)	3 (17%)	.04

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Clinical implications: Addition of dietary baked milk is safe, convenient, and well accepted by patients. Prescribing baked milk products to children with milk allergy represents an important shift in the treatment paradigm for milk allergy.

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TABLE E1. Change in milk-specific IgE levels between the initial and final visits: per-protocol versus comparison groups

	No.	Mean	SD	Median	Minimum	Maximum
Per-protocol group						
Δ Specific IgE level (final − initial)	69	−0.54	6.89	−0.50	−21.16	24.90
Final IgE level	69	5.21	10.51	1.48	0.35	77.30
Initial IgE level	69	5.75	11.09	2.57	0.35	79.10
Comparison						
Δ Specific IgE level (final − initial)	45	0.04	11.87	−0.42	−33.56	54.50
Final IgE level	45	10.58	13.64	5.41	0.35	59.20
Initial IgE level	45	10.54	10.87	5.40	0.37	42.60

Results of rank analysis of covariance to compare baseline adjusted mean change in specific IgE levels (final − initial), $P = .09$.

TABLE E2. Changes in milk-specific IgG_4 levels between the initial and final visits: baked milk–tolerant versus baked milk–reactive groups

	No.	Mean	SD	Median	Minimum	Maximum
Baked milk tolerant						
Δ Casein IgG_4 level (final − initial)	61	2.34	5.04	0.44	−12.83	16.73
Final IgG_4 level	61	4.21	6.19	1.31	0.07	31.00
Initial IgG_4 level	61	1.87	3.87	0.61	0.06	23.80
Baked milk reactive						
Δ Casein IgG_4 level (final − initial)	4	0.94	1.55	1.16	−0.89	2.32
Final IgG_4 level	4	1.91	1.33	2.18	0.10	3.16
Initial IgG_4 level	4	0.97	0.46	0.92	0.47	1.58

Results of rank analysis of covariance to compare baseline adjusted mean change in casein IgG_4 level (final − initial), $P < .001$.