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The effect of baked milk on accelerating unheated cow's milk tolerance: A control randomized clinical trial

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Abstract

Background: Assessing the effect of adding baked milk products to the diet of patients with cow's milk allergy on accelerating the formation of tolerance.

Method: A randomized clinical trial was carried out with 84 patients (6 months–3 years old) diagnosed with allergy to cow's milk who tolerated baked milk in form of muffin in oral food challenge (OFC). The subjects were divided randomly into case and control groups matched for age and sex. Patients in the case group were asked to consume baked milk in the form of muffin for 6 months and then to consume baked cheese in the form of pizza for another 6 months. The control group were instructed to strictly avoid any milk products for 1 year. Skin prick test (SPT) and serum-specific immunoglobulin E (sIgE) levels (ImmunoCAP) of milk, casein, and beta-lactoglobulin were measured before and after the study. In addition, those in the case group who had satisfactorily tolerated baked products during the study as well as all the subjects in the control group underwent an OFC to evaluate unheated milk tolerance at the end of the study.

Results: It was shown that by the end of the 1-year study period, 88.1% (37/42) of the patients in the case group and 66.7% (28/42) of those in control group had developed tolerance to unheated milk (*P*-value: 0.018). The results of milk-specific SPT and sIgE levels showed a significant decrease in the case group. Initial sIgE levels could not predict unheated milk tolerance in case and control groups.

Conclusion: Introducing baked milk products into the diet of patients with milk allergy can accelerate the tolerance of unheated milk in these patients. sIgE levels of milk, casein, and beta-lactoglobulin did not predict the tolerance of unheated milk.

KEYWORDS

allergy, baked milk, cow's milk, cow's milk allergy, immune tolerance

1 | INTRODUCTION

Milk allergy is one of the most common food allergies among children. Some studies have estimated the prevalence of immunoglobulin E (IgE)-mediated milk allergy in the pediatric population to be 1.6%–3%.^{1,2} This type of allergy manifests with more severe

symptoms and a lower rate of spontaneous tolerance as compared to the non-IgE-mediated type.³ Although the clinical history plays a crucial role in the diagnosis of milk allergy, diagnostic tests such as milk-specific serum IgE levels (sIgE), skin prick testing (SPT), oral food challenge (OFC), and the elimination diet are also employed for a more reliable diagnosis.⁴

The majority of the patients with milk allergy have reportedly developed spontaneous tolerance of milk by age 3.¹ It has been claimed, however, that the definite management for food allergies is food avoidance. Nevertheless, for some popular foods, including milk, this approach is difficult for many patients to adopt.⁵ As a result, current studies are making every attempt to find alternative treatments for this type of food allergy. Some studies have recommended oral immunotherapy (OIT)^{5,6}; however, the adverse effects of this kind of desensitization, especially gastroenteric complications, as well as the low induction tolerance to milk, render the long-term efficacy of OIT desensitization dubious.⁷

On the other hand, about 70% of the patients with allergy to cow's milk have been shown to tolerate baked milk.⁸ Moreover, there is evidence that tolerating baked milk products could be an indicator of a transient phenotype of cow's milk allergy.⁹ At the same time, it has been hypothesized that adding baked milk to the diet of patients with milk allergy can accelerate the formation of tolerance of unheated milk.^{4,9,10} A shortcoming of the studies carried out so far to look into the accuracy of this hypothesis, however, is that they have mostly been carried out in the form of cohort studies or retrospective ones.⁹ Few clinical trials have been carried out to question this hypothesis using a control group which could help verify whether the tolerance produced in patients who were given baked milk products was due to the phenotype of the patients or to the exposure to the intervention.^{9,11} This study was conducted in view of such a methodological gap. It was designed as a randomized controlled clinical trial which aimed at finding out whether or not baked milk products could accelerate the formation of tolerance of milk.

2 | MATERIALS AND METHODS

2.1 | Trial design

A randomized controlled clinical trial with an allocation ratio of 1:1 was performed on 100 patients aged between 6 months and 3 years of age (mean age: 1.7). Twelve patients that did not tolerate baked milk OFC were excluded, and four of the patients dropped out of the study for personal reasons.

2.2 | Participants

2.2.1 | Inclusion criteria

In order for the patients to be included in the study, they needed to have a positive history of IgE-mediated milk allergy that would present by gastrointestinal, cutaneous, respiratory, or systemic manifestations following milk exposure. The allergy of those who met this criterion had then to be confirmed by one of the diagnostic tests. These included milk extract skin prick test (SPT) more than 8 millimeters or milk sIgE levels (ImmunoCAP, Fisher-Phadia, Uppsala, Sweden) more than 5 kUA/L in patients with ages <2 years and more than 15 kUA/L in ones with ages more than 2 years old. Baked milk

OFC was performed for all the patients. Those who passed the test were then randomly distributed to the case and control groups.

2.2.2 | Exclusion criteria

The patients with any of the following were excluded from the study: non-specific history, negative SPT and undetectable sIgE levels, unstable asthma, severe atopic dermatitis, severe allergic rhinitis, eosinophil gastroenteropathy following milk ingestion, recent reaction to baked milk products in past 6 months, and finally positive baked milk OFC.

2.3 | Case group

The case group consisted of 42 patients who had proved tolerant of muffin baked milk in the OFC. These patients consumed, on a daily basis, baked milk products in the form of muffin for 6 months and then pizza for another 6 months. Patients who had allergic reactions during the daily use of the muffin were instructed to avoid all milk products for 6 months. This was followed by an initiation of a new round of challenge.

2.4 | Control group

Forty-two patients with milk allergy matched for sex and age with the case group and having proved tolerant in the baked milk OFC were recruited. They were instructed to avoid all milk products for 12 months. At the end of this period, unheated milk OFC was performed on them to observe whether tolerance of milk had been induced spontaneously.

2.5 | Place of study

The patients were recruited from patients who had referred to Allergy Tertiary Center of Shiraz University of Medical Sciences, Shiraz, Iran, from 2016 to 2017.

2.6 | Intervention

2.6.1 | Baked milk product

Baked milk was prepared in the form of muffin containing 1.3 gram (g) of milk protein baked at 350 F for 30 minutes. In a controlled tertiary setting, the patients were exposed to a cumulative dose of 100 g of muffin divided into 9 increasing doses given in 15-minute intervals: 0, 0.5, 1, 4, 10, 20, 20, 20, 25 g, respectively. The patients were observed for possible emerging allergic reactions while performing the challenges as well as over the following 3 hours.

Patients with tolerance of baked milk were instructed to ingest a muffin a day for 6 months, followed by a weekly consumption for 1 month and then a monthly use for another 5 months. The dose was adjusted for children under 1 year of age, the minimum dose being 50 g of muffin (0.65 g of milk protein).

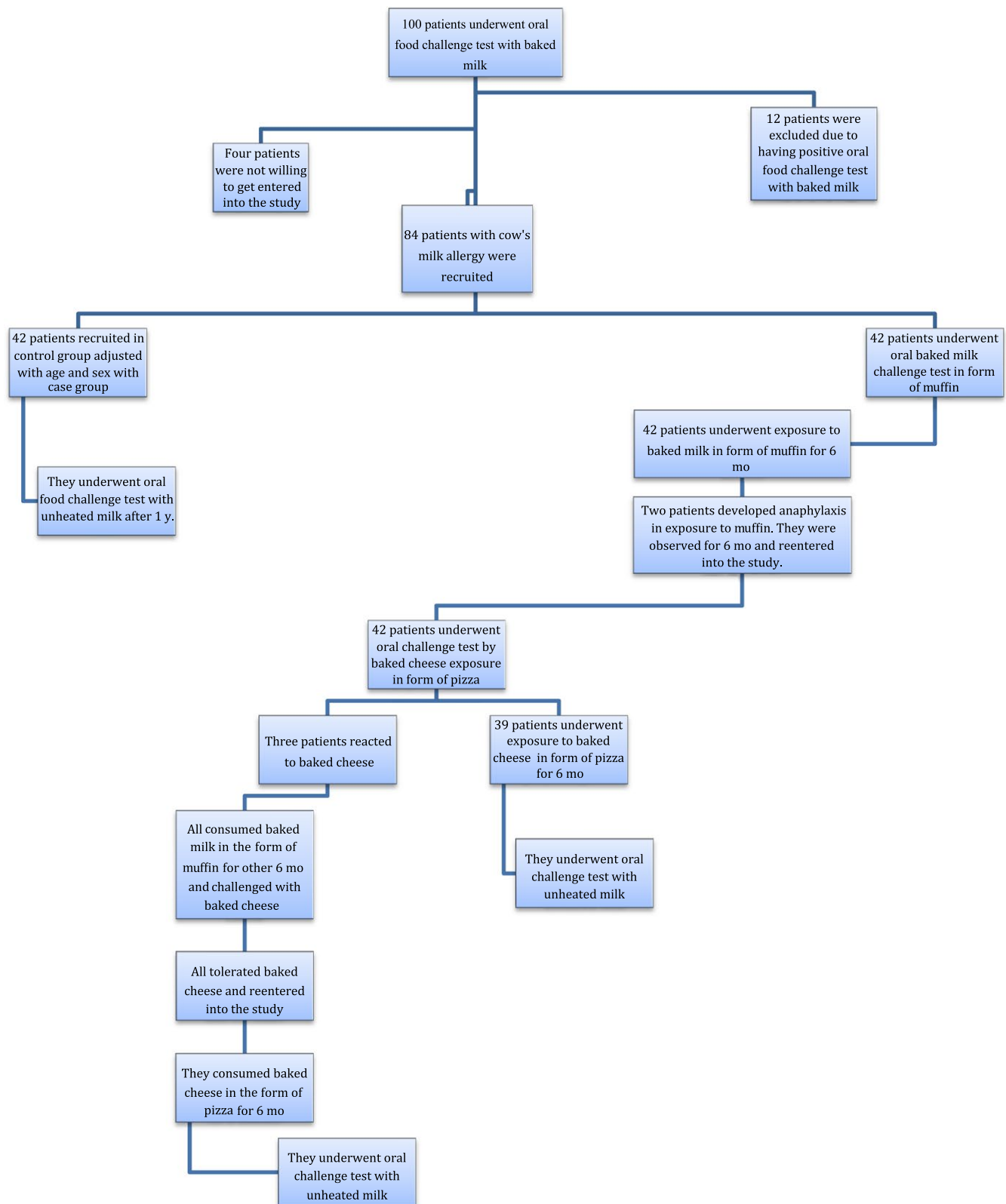


FIGURE 1 Diagram of the participants entered into the study and remained up to the end of the study [Colour figure can be viewed at wileyonlinelibrary.com]

2.6.2 | Baked cheese product

After 6 months of consuming muffins, the patients stopped having

this product and were given baked cheese in the form of pizza, containing 4.6 g of milk proteins and baked at 425°F for 13 minutes. Patients who proved tolerant of this product were instructed to

TABLE 1 Demographic and clinical characteristics of the patients in case and control groups

Demographic information	Case group	Control group	P-value
Age (mean $\pm$ SD)	2.2 $\pm$ 0.7	1.2 $\pm$ 0.7	0.63
Sex (female/male)	18/24	15/27	0.32
Past history of allergy (% (NO./Total NO.))			
1. Atopic dermatitis	54.7 (23/42)	50 (21/42)	0.41
2. Allergic rhinitis	33.3 (14/42)	30.9 (13/42)	0.5
3. Asthma	11.9 (5/42)	7.14 (3/42)	0.35
4. Urticaria	14.2 (6/42)	4.76 (2/42)	0.13
5. Latex allergy	4.76 (2/42)	0	0.24

include this form of baked cheese in their diet for 4-7 days per week over 6 months. Patients who had failed to pass the baked pizza OFC remained on the daily muffin (Figure 1). The patients visited their physician once a month.

2.6.3 | Unheated milk

All the subjects in the control group and those patients in the case group who had consumed muffin and pizza for at least 1 year, as well as the whole control group, went through OFC with 240 mL of skim milk or other products like yogurt containing at least 8-10 g of skim milk at the end of the study.

2.7 | Outcome

2.7.1 | Confirming tolerance

SPT and serum sIgE levels of milk, casein, and beta-lactoglobulin were measured at the beginning, after 6 months, and at the end of the 12-month study. Patients who tolerate baked products satisfactorily went through unheated milk OFC at month 12.

2.8 | Sample size

The sample size was determined following similar previous studies using power of 80% and *P*-value of 0.05.^{9,11}

2.9 | Randomization

The patients were divided randomly into 2 groups (case and control) using computer-randomized division in block size 2.

2.10 | Blinding

This study was performed in a non-blind manner due to the need for involving the caregivers in preparing the baked milk products.

2.11 | Statistical analysis

Data were entered into Statistical Package for the Social Sciences (SPSS) 19. Descriptive analysis was performed to report the mean and percentage of the variables. The chi-square test was used to compare the qualitative variables. To compare nonparametric quantitative variables between the two groups, the Mann-Whitney *U* test was performed. In addition, logistic regression was employed to determine the role of immunologic markers in predicting milk tolerance. The significant *P*-value in all studies was taken to be <0.05.

3 | RESULTS

Eighty-four patients with confirmed milk allergy were recruited to this study. They had been divided randomly into the case and control groups. Demographic and clinical characteristics of patients are summarized in Table 1, while Figure 1 presents the statistics for the participants.

In the control group, 11.9% (5/42) of the patients had a past history of anaphylaxis to milk products; all of these patients remained reactive in unheated milk OFC at the end of the study. Within the case group, 40.5% (17/42) had a past history of anaphylaxis; among these, 41.1% (7/17) had developed milk tolerance by the end of the study.

The results of SPT and sIgE levels of milk, beta-lactoglobulin, and casein in both groups at the beginning of the study are summarized in Table 2.

As many as 88.1% (37/42) of the patients in case groups and 66.7% (28/42) of those in the control group had developed milk tolerance by the end of the study (*P*-value = 0.018). Comparison of the results of milk extract SPT in case group demonstrated a decrease in median skin test wheal size pre- and post-baked product in diet. [64.3% (27/42) pre- and 26.2% (11/42) post-*P*-value 0.033].

The results of a comparison of sIgE before and after baked milk exposure are also summarized in Figure 2 for the case group.

Baseline sIgE levels of cow's milk, beta-lactoglobulin, and casein did not predict unheated milk tolerance at the end of the study in the case and control group (Table 3).

The association between sIgE level of milk, casein, and beta-lactoglobulin at the beginning of the study and the achievement of tolerance of unheated milk is shown in Table 4 for both the case and the control groups.

4 | DISCUSSION

Milk allergy is one of the most common food allergies in young children, with a great impact on both children's and their caregivers' lives.¹² Research had always focused on therapies other than food avoidance for milk allergy such as oral desensitization.^{5,6} Because a standard protocol in pediatric guidelines is non-existent, and due to the scarcity of randomized clinical trials with long-term follow-ups,

TABLE 2 The results of skin prick test and specific immunoglobulin E (sIgE) studies at the beginning of the studies in both groups (cutoff point in sIgE level is considered <0.1 kU/L)

Immunologic variables	Case group	Control group	P-value
Positive prick of milk extract % (no/total no.)	64.3% (27/ 42)	61.9% (26/42)	0.5
Positive milk sIgE % (no/total no.)	73.8% (31/ 42)	50% (21/42)	0.021
Mean of milk sIgE (mean $\pm$ SD)	14.85 $\pm$ 30.4	5.4 $\pm$ 17.24	0.013
Positive sIgE beta-lactoglobulin % (no/total no.)	76.2% (32/42)	40.5% (17/42)	0.001
Mean of beta-lactoglobulin sIgE (mean $\pm$ SD)	4.6 $\pm$ 9.3	3.8 $\pm$ 15.6	0.007
Positive casein sIgE % (no/total no.)	64.3% (27/42)	52.4% (22/42)	0.18
Mean of casein sIgE (mean $\pm$ SD)	9.5 $\pm$ 23.3	4.4 $\pm$ 16.42	0.087

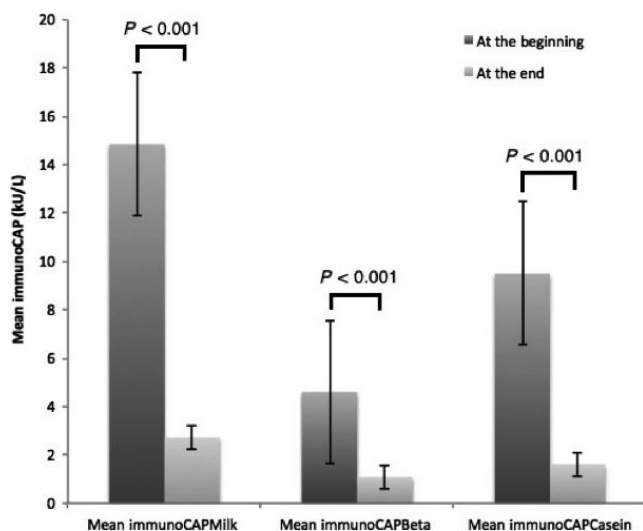


FIGURE 2 Comparing Mean of specific immunoglobulin E (sIgE) levels for milk, casein, and beta-lactoglobulin before and after the study in case group

an avoidance therapeutic approach is not widely used.⁶ Moreover, the ability of OIT to induce long-term food tolerance and the adverse effects, especially gastroenteric complications, are yet to be established.^{7,13}

It has been reported that many children with milk allergy can better tolerate the modified allergens in baked milk products.¹⁴ Some studies have sought to assess the efficacy of baked milk

products in accelerating tolerance to unheated milk.^{4,10} As stated earlier, most of these studies have been based on cohort or retrospective studies, with few randomized clinical trials having been performed. Kim et al⁹ in a clinical trial on patients with milk allergy attempted to investigate the effect of baked milk products in the form of muffin and pizza on unheated milk tolerance; however, they encountered obstacles in recruiting the patients for the control group and had all the patients go through exposure to baked milk. The fact that the majority of the patients with cow's milk allergy can spontaneously develop tolerance until the age of 3 requires the existence of a control group in clinical trials.¹ It was in view of this requirement that the decision to perform a control randomized clinical trial was made; one whose objective was to assess the effect of interventional baked milk products with spontaneous tolerance induction in the control group.

The results of the present study showed that the number of the patients who had developed tolerance to unheated milk by the end of the study was significantly higher in the case group as compared to the control group (88.1% in case group and 66.7% in control group, P -value 0.018). It had previously been reported that the patients who remained intolerant of milk often had more severe reactions as compared to patients who developed spontaneous tolerance.¹⁵ However, our results indicate that 41.1% of the patients in the case group who had a past history of anaphylaxis to milk products developed tolerance of unheated milk. These results were in agreement with those of the previous studies on the effect of baked milk products on accelerating unheated milk tolerance.^{9,11,12,16}

TABLE 3 Comparing the specific immunoglobulin E (sIgE) levels at the beginning of the study between patients who developed tolerance at the end of the study and ones who remained intolerant at the end of the study in case and control groups (cutoff point in sIgE level is considered <0.1 kU/L)

Immunologic markers	Unheated milk tolerated (kUA/L)	Unheated milk intolerant (kUA/L)	P-value
Control group			
Milk sIgE	0.5 $\pm$ 0.94	15.1 $\pm$ 27.9	<0.001
Beta-lactoglobulin sIgE	0.21 $\pm$ 0.29	11.08 $\pm$ 26.2	<0.001
Casein sIgE	0.43 $\pm$ 0.83	12.4 $\pm$ 27.2	0.001
Case group			
Milk sIgE	11.31 $\pm$ 24.9	41.06 $\pm$ 53.8	0.26
Beta-lactoglobulin sIgE	4.69 $\pm$ 9.8	4.60 $\pm$ 5.05	0.25
Casein sIgE	5.38 $\pm$ 11.8	40.46 $\pm$ 54.3	0.12

Group	Variables	OR	OR adjusted	CI	P-value
Control	Milk sIgE titer	1.9	7.87	0.12-517	0.33
Control	Beta-lactoglobulin sIgE titer	4.8	5.47	0.11-271	0.39
Control	Casein sIgE titer	1.6	0.07	0.001-9.45	0.29
Case	Milk sIgE titer	1.02	0.97	0.56-1.69	0.93
Case	Beta-lactoglobulin sIgE titer	0.99	0.87	0.25-2.99	0.82
Case	Casein sIgE titer	1.04	1.1	0.69-1.75	0.68

OR, odds ratio; OR adjusted, odds ratio adjusted for age and sex; CI, confidence interval.

The results of milk extract SPT before and after giving baked milk to the patients in the case group showed that the number of patients with positive SPT at the end of the study was significantly lower than it was the beginning of the study (64.3% at the beginning and 26.2% at the end of the study, *P*-value 0.033). This is in line with the report by Nowak-Węgrzyn et al,¹⁷ who showed that the size of wheal in milk skin prick test significantly dropped after giving baked milk products to the patients.

Furthermore, the result of the comparison of sIgE for milk, casein, and beta-lactoglobulin showed that all the three sIgE levels decreased significantly after giving baked milk products to the patients in the case group. The study by Kim et al⁹ showed that casein Ig G4 levels, a marker of milk tolerance, would increase significantly after giving baked milk products to children with cow's milk allergy; however, milk sIgE levels showed no significant difference.

In addition, the effect of milk, casein, and beta-lactoglobulin sIgE levels at the beginning of the study was also assessed to predict unheated milk tolerance. The results of the present study showed that, in the control group, the sIgE levels of milk, beta-lactoglobulin, and casein were significantly higher in patients who remained intolerant of unheated milk as compared to those who developed spontaneous tolerance. No significant association was found between these immunologic markers and unheated milk tolerance. In other words, sIgE levels at the beginning of the study could not predict whether or not unheated milk tolerance would be obtained. This is contrary to the findings of other studies, which had shown that higher levels of milk sIgE were associated with lower probability of successful oral immunotherapy outcomes.¹⁸⁻²⁰ These controversies between the results of the previous studies and those obtained here are most probably due to differences in methods employed and in the duration of study, which calls for further investigations focused on this specific aspect.

Furthermore, previous studies have suggested that patients with cow's milk allergy who had primarily higher levels of beta-lactoglobulin as compared to casein were more likely to develop milk tolerance.²¹ However, the results of the present study did not show any significant difference between the patients who developed milk tolerance and those with higher levels of beta-lactoglobulin or casein.

TABLE 4 The association between specific immunoglobulin E (sIgE) levels at the beginning of the study and unheated milk tolerance at the end of the study

4.1 | Generalizability

This study is the first randomized clinical trial to assess the effect of baked milk products on unheated milk tolerance. Considering the considerable number of patients with anaphylaxis to cow's milk who developed milk tolerance in the case group and the small number of patients who reacted to baked milk products during the study, baked milk exposure for patients with cow's milk allergy can be introduced as a safe therapeutic alternative method to the previously used OIT.

4.2 | Limitation

One of the limitations of the present study is that patients with poor income who did not have an oven at home were not able to participate in the study. Moreover, due to financial restrictions, sIgE study could not be performed for patients in the control group at the end of the study.

5 | CONCLUSION

The results of present study show that introducing baked milk products in the form of muffin and pizza in the diet of patients with milk allergy can accelerate unheated milk tolerance in these patients. No association was detected between the initial measures of sIgE levels of milk, casein, and beta-lactoglobulin or milk SPT on the one hand and developing unheated milk tolerance on the other.

6 | REPOSITORY

6.1 | Registration

The study was registered in ClinicalTrials.gov with the registration number NCT02738060. Shiraz University Ethical Committee approved the study as per the provision of Helsinki guideline.²²

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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