

# Calcium preparations do not inhibit allergic reactions: a randomized controlled trial

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## KEY WORDS

allergic rhinitis, allergy, asthma, calcium, skin prick test

## ABSTRACT

**INTRODUCTION** Massive consumption of dietary supplements, including vitamins and minerals, has recently become a serious health issue in Europe. Their use may negatively affect the pharmacological activity of various medications, including antiallergic drugs. Calcium preparations are commonly used in some European countries as a popular remedy for allergy-related skin reactions, such as itching, erythema, and wheals, as well as insect bites. However, so far there have been no reliable studies to prove their action.

**OBJECTIVES** The aim of this randomized, double-blind, placebo-controlled study was to investigate the efficacy of calcium salts in allergic reactions, using an allergen-induced skin prick test (SPT).

**PATIENTS AND METHODS** Forty adult volunteers with allergic rhinoconjunctivitis or asthma (or both) were recruited to receive oral calcium carbonate (1000 mg) or placebo 3 times a day for 3 days. SPTs were performed with 11 aeroallergen extracts at baseline and at 4 and 72 hours after drug administration. The wheal diameter was measured. We also used the visual analog scale to evaluate the intensity of pruritus.

**RESULTS** There was no difference in the wheal size or pruritus between patients receiving calcium or placebo at any of the time points ( $P > 0.05$ ). Calcium preparations were well tolerated.

**CONCLUSION** We found no evidence to support the efficacy of calcium preparations in allergy-related skin reactions associated with itching and wheals. Calcium preparations do not suppress SPT responses; moreover, their use in allergic patients should be discouraged due to their possible interference with the absorption of antiallergic drugs.

**INTRODUCTION** Consumption of dietary supplements in Europe has recently become a serious health issue.<sup>1</sup> Vitamins, minerals, and dietary supplements, commonly considered to be harmless, may negatively affect the pharmacological activity of various prescription medications.

Dietary supplements and a combination of minerals have a documented undesirable pharmacological activity. They may either augment or antagonize the activity of several drugs, causing dangerous interactions that many patients are unaware of.<sup>2-4</sup> Calcium preparations can impair intestinal absorption of some compounds, including corticosteroids, which are used in the treatment of allergy.<sup>5,6</sup>

Calcium is essential for maintaining electrolyte balance in the body. Calcium preparations are frequently used to prevent or treat calcium

deficiencies caused by insufficient supply of this macronutrient in the diet or by its malabsorption.<sup>7,8</sup> Calcium is also a component of antacids, currently less commonly used for gastric hyperacidity and peptic ulcer.<sup>8</sup>

Before the era of antihistamines, calcium preparations were commonly recommended in Germany for patients with skin allergy, allergic rhinitis, and after insect bites.<sup>9</sup> This treatment modality gained popularity in most of Central and Eastern Europe. It has been extensively used as an over-the-counter drug for many hypersensitivity-related skin reactions associated with severe itching, erythema, and wheals, as well as allergic rhinoconjunctivitis and insect bites.

Despite the widespread use of calcium in allergy-related skin reactions, its application remains controversial. Its possible mechanism of

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action has not been explained so far, and there have been no well-designed, controlled studies.<sup>10</sup> Despite the lack of evidence, the Summary of Product Characteristics for calcium preparations marketed in Poland recommends these preparations as an additional treatment in allergic diseases. However, this treatment is not recommended by any Polish or international guidelines or recommendations regarding allergic diseases.<sup>11-13</sup> Therefore, the aim of this study was to assess the efficacy of oral calcium in type I allergic reaction in the cutaneous wheal response (skin prick test [SPT]) model.

**PATIENTS AND METHODS** This was a randomized, double-blind, parallel-group, placebo-controlled study performed according to the CONSORT statement guidelines.<sup>14</sup> It was conducted at the Department of Pediatric Pneumology and Allergy at the Medical University of Warsaw, Warsaw, Poland, between October 2015 and March 2016.

The study group included adults suspected of pollen-induced allergic rhinitis or allergic rhinoconjunctivitis (or both) with or without asthma. Patients who tested positive to at least 1 aeroallergen in the SPT (wheal diameter  $\geq 3$  mm) were included in the study.

The exclusion criteria were as follows: an intake of medication that interfered with skin reactivity (oral antihistamines, anxiolytics, and antidepressants) and other conditions that might reduce the safety of SPT or calcium supplementation or interfere with SPT results (according to the European Academy of Allergy and Clinical Immunology [EAACI]), including hypercalcemia, hypercalciuria, the use of cardiac glycosides or calcium channel blockers, lactose intolerance, kidney failure, pregnancy, and breastfeeding.<sup>15</sup> Topical application of corticosteroids or calcineurin inhibitors on the volar forearms had to be discontinued for at least 2 weeks before testing. None of these agents were permitted during the study. Individuals with active skin disease, urticaria, dermatographism, or those receiving ultraviolet light treatment were also excluded.

Three study visits were scheduled: V0 (screening visit), V1 (4 hours after the administration of the first dose), and V2 (3 days after the study initiation). Visits V0 and V2 were scheduled in the morning (8–11 AM), and visit V1, 4 hours after visit V0. After the screening visit (V0), participants who met the inclusion criteria were randomly assigned to groups in a 1:1 ratio, using a computer-generated randomization schedule. A random block size between 4 and 8 was generated. Patients were randomly allocated to one of the treatment groups by assigning personal numbers in a consecutive and ascending order. Blinding of the patients and investigators was ensured by the identical size, shape, weight, color, taste, and smell of the study medication and packaging.

After visit V0, participants received oral calcium capsules or placebo to be taken 3 times a day for 3 days (FIGURE 1). Calcium carbonate (Calperos

1000, TEVA Pharmaceuticals Polska Sp. z o.o., Warsaw, Poland) containing 1000 mg of calcium carbonate, including 400 mg of elemental calcium) or placebo (lactose) were given to the participants, with the first dose administered shortly after completion of the first series of SPTs followed by 3 capsules a day for 3 days, according to the manufacturer's recommendation on the maximum dosage. We decided to use calcium carbonate because it contains the highest proportion of calcium and is generally well tolerated, although with lower bioavailability.<sup>16,17</sup>

At visits V0, V1, and V2, all participants were subjected to SPTs, performed according to the EAACI guidelines, using 11 standard aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat allergens, dog allergens, alder, birch, hazel, grass and cereals, *Artemisia*, *Alternaria alternata*, and *Cladosporium herbarum*).<sup>15</sup> Fifteen minutes after the inoculation of an allergen solution, wheal formation was recorded by outlining the contours with a black-ink pen on a transparent tape, and measuring the longest wheal diameter. The test was considered positive when the wheal diameter was equal to or greater than 3 mm. SPTs were conducted by 2 trained investigators blinded to the study groups. Histamine (1.7 mg/ml of histamine hydrochloride, equal to 1 mg/ml of histamine) was a positive control, and a diluent was a negative control (both Allergopharma J. Ganzer KG, Reinbeck, Germany).

Visits V0 and V2 were scheduled in the morning (8–11 AM), and visit V1, 4 hours after visit V0. To avoid a possible overlap between wheals, the forearms were alternated for the successive SPTs and the injection sites corresponded to baseline in each sequence.

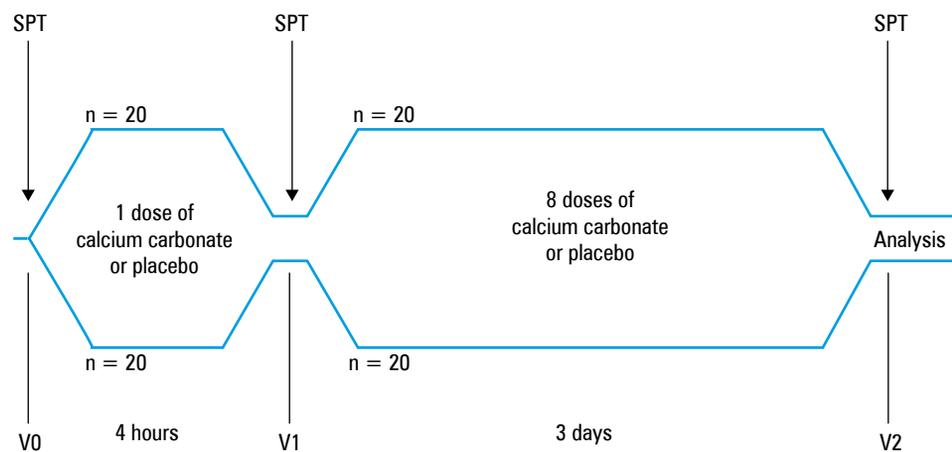
Skin reactivity was also evaluated subjectively using the visual analog scale (VAS) to assess pruritus intensity. The VAS consisted of a 10-cm line marked by the label “no itch” at one end, and by the label “very strong itch, as bad as could possibly be” at the other. Pruritus was scored from 0 (no pruritus) to 10 (maximum pruritus). Participants were asked to assess pruritus intensity 15 minutes after each SPT.

The size of the wheal in the SPTs and itching sensation afterwards in relation to placebo were the primary endpoints of this study. Adverse effects of the medications used were also recorded.

A sample size of 40 participants was computed with an assumption to obtain a 95% power to detect a between-drug difference of 20% in the inhibition of the wheal size (caused both by histamine and allergens) with an  $\alpha$  error of 5% (the sample size was calculated using an online calculator: [clincalc.com](http://clincalc.com)).

The values obtained for each measurement at 4 and 72 hours were compared with the baseline values. Responses with a mean wheal diameter of less than 3 mm were not included in the statistical analysis. The percentage change in wheal diameter was calculated (% change = [(baseline

**FIGURE 1** Study flowchart: calcium carbonate (1000 mg) or placebo were given to volunteers 3 times a day for 3 days. Skin prick tests were performed at baseline (V0), 4 hours after the intake of the first dose (V1), and 3 days later (V2), when all doses of the drugs were administered.



wheel diameter – wheel diameter time t) / wheel diameter baseline] × 100) for each test group for all time periods and compared with one another. The same method was used to calculate the percentage change of itching.

Statistical comparisons between the groups were performed using 1-way analysis of variance. A *P* value of less than 0.05 was considered statistically significant. The data were presented as the means and standard error (all computed with Statistica Version 13.2, Statistica, Tulsa, Oklahoma, United States).

The study was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and the requirements of national laws. All study documents were approved by an independent ethical committee (the primary responsible ethics committee: Medical University of Warsaw; number, 205/2014). All patients gave their written informed consent to participate in the study.

**RESULTS** In total, 78 volunteers were screened for this study. Of these, 40 individuals (12 men and 28 women; mean age, 25 years; range, 19–32 years) who met all the inclusion criteria were enrolled and randomized, and all of them completed the study. No dropouts were recorded. At baseline, there was no significant difference between the groups in mean wheal responses and itching sensations in SPTs.

Neither the mean wheal diameter nor itching sensation changed in any of the groups throughout the study compared with the baseline values (FIGURE 2A and 2B, FIGURE 3, TABLES 1 and 2). There was no difference between the calcium and placebo groups in the percentage change in wheal response at any time point (V1, V2), compared with the baseline values (TABLE 1). Moreover, there were no significant differences in itching sensation assessed using the VAS between the calcium preparation and placebo groups (TABLE 2).

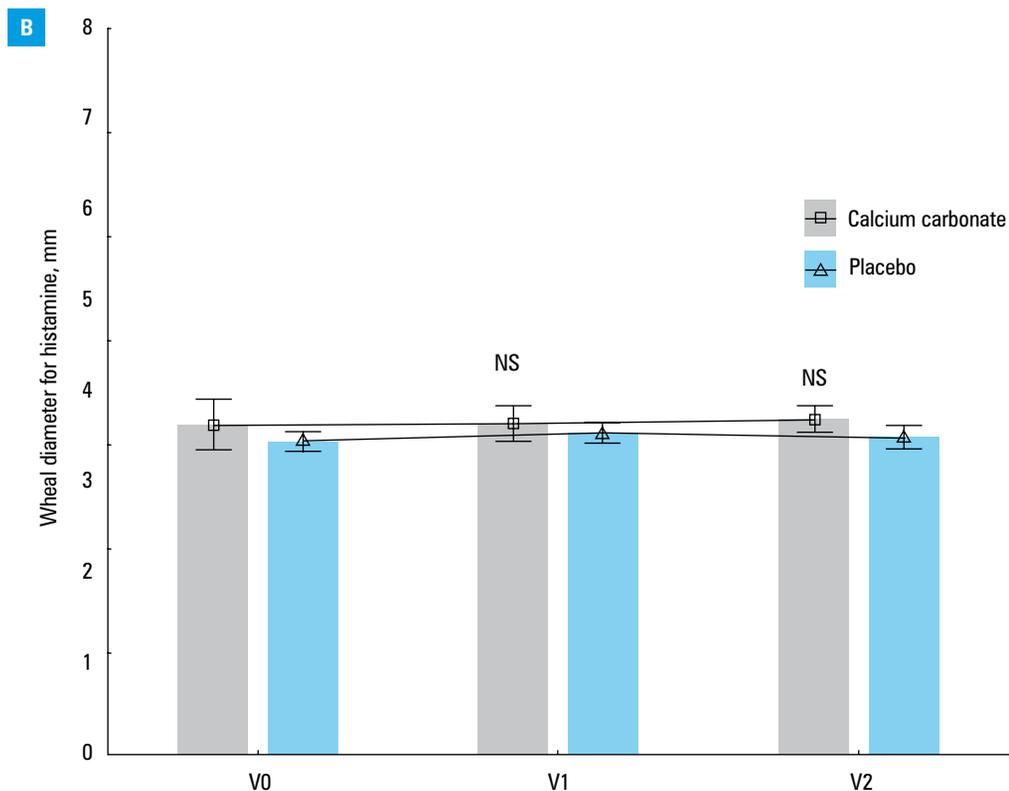
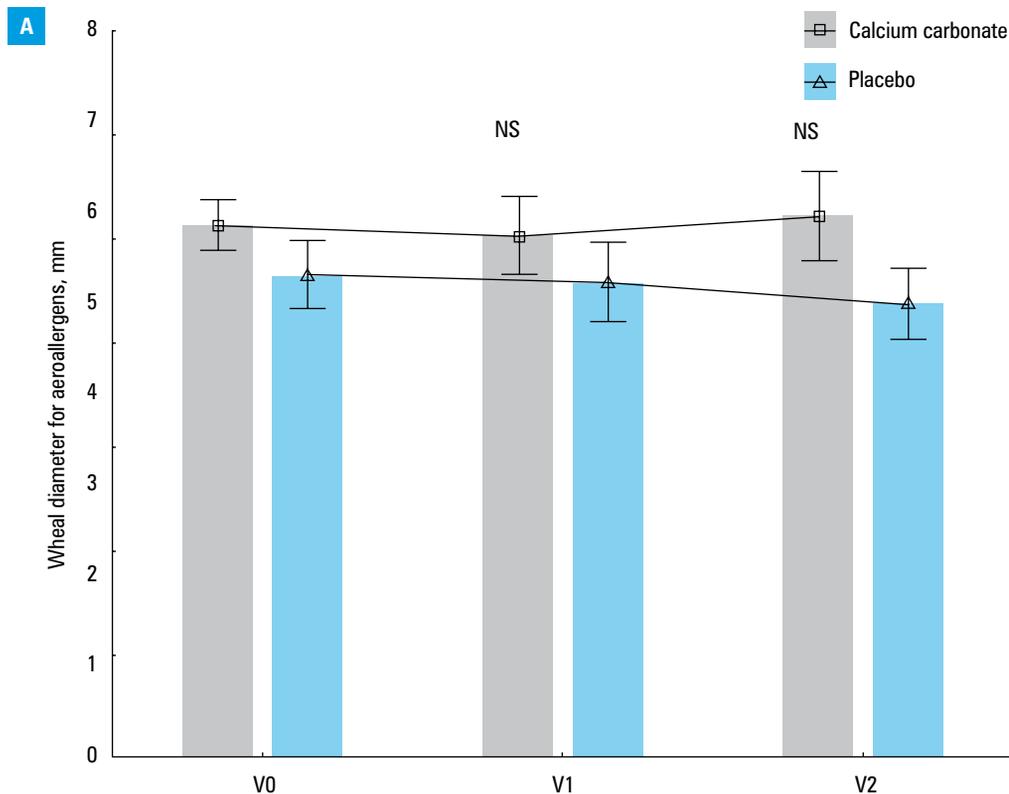
Calcium carbonate was well tolerated when used at high doses, and no drug-induced adverse effects were observed.

**DISCUSSION** The use of calcium in allergic diseases is controversial. Despite the lack of evidence, its application in allergy-related skin reactions is relatively common in Central and Eastern Europe, especially in Poland, Czech Republic, Germany, Hungary, Bulgaria, Slovenia, and Ukraine (a social-media based survey prior to the study initiation; data not shown). On the other hand, calcium salts were found to interact with many drugs, both by alterations in gastric pH and by formation of nonabsorbable complexes.<sup>8,18</sup> These compounds were found to impair the absorption of prednisone and probably other corticosteroids used to treat symptoms of allergic reactions; therefore, their extensive use may significantly decrease corticosteroid activity.<sup>5,6</sup> In this study, we addressed the question of the usefulness of calcium preparations in allergy-related skin reactions by using objective and restrictive principles of a randomized controlled trial in a reliable research model.<sup>19</sup> We found that calcium supplements given at a single dose or as a 3-day treatment did not reduce the size of the wheal or pruritus compared with placebo in a human SPT model.

Of note, the levels of calcium in intracellular compartments are 20 000 times lower than those in extracellular compartments.<sup>20</sup> Therefore, in vitro experiments showing calcium-mediated inhibition of histamine release are not reproducible in vivo, since very high intracellular concentrations are unlikely to be obtained, even following an intravenous administration.<sup>10</sup>

Our results are inconsistent with those of previous studies conducted in the 1970s and 1980s, in which the authors observed the efficacy of calcium in inhibiting type I allergic reactions. In the first report, Debelic<sup>21</sup> evaluated the effects of oral calcium gluconate and calcium lactate combined with vitamin D<sub>2</sub> on SPT results in 20 pollen-allergic volunteers in a double-blind randomized controlled study, indicating a significant wheal reduction (20%). A double-blind randomized study by Haas<sup>22</sup> revealed that the same mixture of ingredients fortified with ascorbic acid was effective in reducing the wheal area and

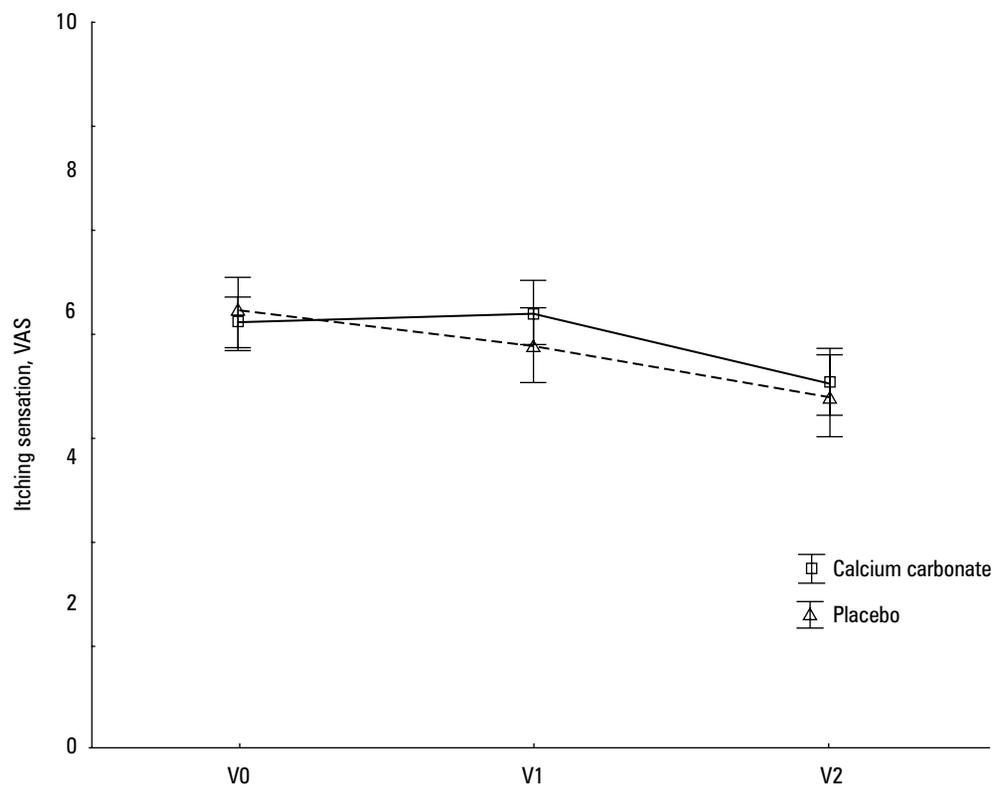
**FIGURE 2** Mean (SEM) wheal diameter for aeroallergens (A) and histamine (B) at screening visit (V0), 4 hours after the intake of the first dose of the drug (V1), and at 72 hours (V2) in patients treated with calcium carbonate or placebo. Abbreviations: NS, not significant



itching intensity. However, the methodology of both studies raises some concerns. The authors of both papers did not adequately address SPT reproducibility in their reports. There are many factors known to modulate the SPT readout, which are required to obtain reproducible results, and in our study, we strictly conformed to those criteria.<sup>23</sup> Moreover, considering calcium pharmacokinetics and bioavailability, the maximum serum

calcium levels occur 2 to 6 hours after calcium ingestion,<sup>24,25</sup> while in the above reports, calcium-induced responses were recorded 10 and 30 minutes after administration.<sup>21,22</sup> Based on the antihistamine model, even when the maximum plasma level of the drug is reached by 30 minutes, it takes another 1.5 hours for the drug to diffuse into the extravascular space to observe clinical effect.<sup>26</sup>

**FIGURE 3** Mean (SEM) itching sensation during skin prick test assessed by the visual analogue scale (VAS, 1–10 points) at screening visit (V0), 4 hours after the intake of the first drug dose (V1), and at 72 hours (V2) in patients treated with calcium carbonate or placebo



**TABLE 1** Percentage change in wheal responses 4 hours after the first dose (V1) and after 72 hours of treatment (V2) versus baseline (V0) in patients treated with calcium carbonate or placebo

	Time	Mean % change in wheal diameter (vs V0)		P value (calcium carbonate vs placebo)
		Calcium carbonate	Placebo	
Histamine SPTs	V1	-3.33	-4.58	0.9
	V2	-4.79	-2.08	0.6
Aeroallergen SPTs	V1	1.48	-0.54	0.8
	V2	-0.88	4.99	0.5

Abbreviations: SPTs, skin prick tests

**TABLE 2** Percentage change in itching sensation 4 hours after the first dose (V1) and after 72 hours of treatment (V2) versus baseline (V0) in patients treated with calcium carbonate or placebo

	Time	Mean % change in itching sensation (vs V0)		P value (calcium carbonate vs placebo)
		Calcium carbonate	Placebo	
SPTs	V1	-3.93	4.08	0.4
	V2	13.79	17.78	0.7

Abbreviations: see TABLE 1

Our results are also in contrast to 2 studies conducted by Bachert et al,<sup>27,28</sup> who analyzed the effects of intravenous and oral calcium on nasal allergen provocation tests. The authors observed decreased swelling of the nasal mucosa and improved nasal flow after calcium application, but interestingly, those effects were associated with only a minimum (4.5%) increase in serum calcium levels. The discrepancy between these studies and our findings is probably related to the study model. It may be speculated that calcium activity in allergic rhinitis most probably relies on the reduction in the permeability of blood vessel walls,

an effect resulting from the inhibition of histamine release from mast cells.<sup>29-31</sup>

In the 3 studies discussed above, calcium preparation was administered in a single oral dose, much higher than that used in our study or than doses commonly administered to patients in order to mitigate the symptoms of allergy. It is worth noting that calcium absorption is a saturable process, which means that a dose of about 500 mg of elemental calcium results in a significantly reduced absorption.<sup>32</sup> Furthermore, during our 3-day study, the total dose administered in participants was 3.6-fold higher than the dose

in the Bachert's study,<sup>27</sup> and no antiallergic effects were observed, which makes this discrepancy even more intriguing.

A few more studies on this subject can be found in non-English literature. They evaluated the efficacy of oral or intravenous calcium preparations in allergic diseases such as allergic rhinitis, urticaria, and allergic bronchial asthma; however, their results are inconsistent.<sup>33-35</sup>

Our study has several limitations. Firstly, this was not a clinical trial, but rather a human-model study. The suppression of histamine-induced skin wheals has been well established as an objective *in vivo* model for evaluating peripheral H<sub>1</sub>-blockade<sup>19</sup>; however, it does not necessarily reflect the overall antiallergic activity. Mediators other than histamine also play an important role in allergic cutaneous responses, including mediators involved in cellular late-phase responses.<sup>36</sup> Therefore, SPT findings should be interpreted with caution and with consideration of the clinical situation since they may not necessarily correlate with clinical responses.<sup>37</sup>

The advantage of these tests is that they are easy to perform, fast, inexpensive, and safe. The SPT is used as an objective assessment of the efficacy and pharmacodynamics of antihistaminic drugs; however, its readout is still prone to errors.<sup>38</sup> Therefore, another limitation of our study was the subjective and manual method for SPT readouts, even though this part was performed by investigators blinded to the study groups. An automatic wheal measurement might be more accurate, but it is not available yet.<sup>39</sup>

**Conclusions** To our knowledge, this is the only reliable report investigating the activity of calcium preparations in allergic reactions. In this paper, we ultimately question any applicability of calcium preparations in the treatment of allergy. Our results show that neither single doses nor long-term treatment with calcium supplements reduces allergic cutaneous reactions (measured as the wheal response and symptoms of pruritus), as compared with placebo.

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**Contribution statement** KM and WF conceived the idea for the study. KM and WF contributed to the design of the research. KM and MM were involved in data collection. KM and WF analyzed the data. MD generated the random allocation sequence and assigned participants to interventions. All authors enrolled participants. WF coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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