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ORIGINAL ARTICLE

Calcium preparations do not inhibit allergic reactions. A randomized controlled trial

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Abstract

Introduction Massive consumption of dietary supplements, including vitamins and minerals, has recently become a serious public issue in Europe. When ingested, they may negatively affect pharmacological activity of various medications, including anti-allergic drugs. Calcium preparations are well-known and 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, their action has not been reliably proven yet.

Objectives The aim of this study is to investigate the efficacy of calcium salts in allergic reactions using the allergen-induced skin prick test (SPT) in a randomized, double-blind, placebo-controlled approach.

Patients and methods Forty adult volunteers with allergic rhinoconjunctivitis and/or asthma were recruited and received oral calcium carbonate (1000 mg) or placebo t.i.d. for 3 days. SPTs were performed with 11 aeroallergen extracts at baseline, 4 and 72 hours after drug administration. The diameter of wheal was measured. We also evaluated pruritus intensity based on the visual analog scale (VAS).

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 anti-allergic medications.

Key words

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

INTRODUCTION

Consumption of dietary supplements in Europe has recently become a serious public issue [1].

Vitamins, minerals and dietary supplements, commonly considered to be harmless when ingested, may negatively affect the pharmacological activity of various prescription medications.

A combination of minerals or dietary supplements has 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 [2-4]. Calcium preparations can impair intestinal absorption of some compounds, including corticosteroids, which are used in the treatment of allergy [5, 6].

Calcium is an essential mineral element necessary to maintain the 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 [7, 8]. Calcium is also a component of antacids, currently less commonly used for gastric hyperacidity and peptic ulcer [8].

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

Despite the widespread use of calcium in allergy-related skin reactions, its application remains controversial. Its possible mechanism of action has not been explained so far, and there are no well-designed, controlled studies [10]. Despite the lack of evidence, the Polish

Summary of Product Characteristics recommends calcium preparations as an additional treatment in allergic diseases. However, this treatment is not recommended by any Polish or International guidelines or recommendations [11-13]. 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) model.

PATIENTS AND METHODS

This was a randomized, double-blind, parallel-group, placebo-controlled study performed according to the CONSORT statement guidelines [14]. It was conducted at the *Department of Pediatric Pneumology and Allergy The Medical University of Warsaw* between October 2015 and March 2016.

The study group included adult subjects suspected of pollen-induced AR and/or allergic rhinoconjunctivitis with or without asthma. Patients with at least one positive skin prick test (SPT) (wheal diameter ≥ 3 mm) to aeroallergen were included in the study.

Exclusion criteria were as follows: an intake of medication that interferes with skin reactivity (oral antihistamines, anxiolytics and antidepressants) and other issues that might reduce the safety of SPT or calcium supplementation or interfere with SPT results (according to European Academy of Allergy and Clinical Immunology), including hypercalcemia, hypercalciuria, the use of cardiac glycosides or calcium channel blockers, lactose intolerance, kidney failure, pregnancy and breast-feeding [15]. Topical application of corticosteroids or calcineurin inhibitors on the volar forearms had to be discontinued for at least two weeks before testing. None of these agents was permitted during the study. Furthermore, subjects with active skin disease, urticaria, dermographism, UV light treatment were also excluded. After a 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 consecutive and ascending order.

Blinding of the patients and the investigators was ensured by the identical size, shape, weight, color, taste and smell of the study medication and packaging.

After the V0 visit, the subjects received oral calcium capsules or placebo to be taken three times a day for 3 days (Figure S1). Calcium carbonate (*Calperos 1000*, containing 1000 mg of calcium carbonate, including 400 mg of elemental calcium) or placebo (lactose) were given to the study subjects, with the first dose administered shortly after completion of the first series of SPT followed by 3 capsules a day for 3 days, according to the manufacturer's maximum recommended dosage.

We chose calcium carbonate since it contains the highest proportion of calcium element and is generally well tolerated, although with a lesser bioavailability [16, 17].

At visits V0, V1 and V2, all participants were subjected to SPTs, performed according to the EAACI guidelines, using 11 standard common aeroallergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog allergens, alder, birch, hazel, grass and cereals, artemisia, *Alternaria alternata*, *Cladosporium herbarum*) [15]. Fifteen minutes after inoculation of 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 or greater than 3 mm. SPTs were conducted by two trained investigators blinded to the study groups. Histamine (1.7 mg/mL histamine hydrochloride; equal to 1mg/mL histamine) was a positive control, and a diluent was a negative control (both Allergopharma J. Ganzer KG, Reinbeck, Germany).

Visits V0 and V2 took place in the morning (8-11AM), and visit V1 was 4 hrs 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 visual analog scale (VAS) to assess pruritus intensity. The VAS consisted of a 10-cm line marked at one end by the label 'no itch', and by the label 'very strong itch, as bad as could possibly be' at the opposite end. Pruritus was scored from 0 (no pruritus) to 10 (maximal pruritus). Participants were asked to assess pruritus intensity 15 minutes after each SPT.

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

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

The values obtained for each measurement at 4 hrs and 72 hrs 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 ($\% \text{ change} = ((\text{baseline wheal diameter} - \text{wheal diameter time } t) / \text{wheal diameter baseline}) * 100$) for each test group for all time periods and compared with each other. The same method was used to calculate the percentage change of itching.

Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA). A *P* value less than 0.05 was considered statistically significant. The data are presented as the means $\pm$ standard error (all computed with Statistica Version 13.2, Statistica, Tulsa, Oklahoma, USA).

This study was conducted in accordance with the Declaration of Helsinki, good clinical practice (GCP) guidelines and the requirements of national laws. All study documents were

approved by an independent ethical committee (primary responsible ethics committee: *Medical University in 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 who met all inclusion criteria were enrolled and randomized, and all of them completed the study. No dropouts were recorded. Patients' baseline characteristics are presented in Table S1. There was no significant difference among the baseline groups in mean wheal SPTs responses and itching sensation. Neither mean SPT wheal diameters nor itching perception changed in any of the groups throughout the study compared to the baseline values (Figure S2a and Figure S2b, Figure S3, Table S2). There was no significant difference in the percentage change from baseline in wheal response in any time point (V1, V2) between calcium and placebo groups ($P>0.05$) (Table S2). Also, there were no significant differences in itching scored in VAS between the study agent and placebo ($P>0.05$) (Table S2).

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 lacking evidence, its use in allergy-related skin reactions in Central and Eastern Europe is relatively common, 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 non-absorbable complexes [8, 18]. 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 [5, 6]. In this report, we have ultimately solved the problem 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 [19]. Using a human SPT model, we found that calcium supplements given in a single dose or as a three-day treatment did not reduce the size of the wheal or pruritus compared to placebo.

Noteworthy, the levels of calcium in intracellular compartments are 20,000 times lower than those in extracellular compartments [20]. Therefore, *in vitro* experiments showing calcium-mediated inhibition of histamine release are not reproducible *in vivo*, since very high intracellular concentrations are unlikely to achieve, even following intravenous administration [10].

Our results are inconsistent with previous studies conducted in the 70' and 80-'s, in which the authors observed the efficacy of calcium in inhibiting type I allergic reactions. In the first report, Debelic and colleagues evaluated the effects of oral calcium gluconate and calcium lactate combined with vitamin D2 on SPT in 20 pollen-allergic volunteers in a DBRCT, indicating a significant wheal reduction (20%) [21]. Another DBRCT by Haas and colleagues revealed that the same mixture of ingredients fortified with ascorbic acid was effective in reducing wheal area and itching intensity [22].

Furthermore, the methodology of both studies raises some uncertainties. 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. Those factors have been strictly conformed to in our study [23]. Moreover, considering calcium pharmacokinetics and bioavailability, the maximum serum calcium levels occur 2-6 hrs after calcium ingestion [24, 25], while in the above quoted reports, calcium-induced responses

were recorded 10 and 30 minutes after administration [21, 22]. Based on the antihistamine model, even when maximum plasma level of the drug is reached by 30 min, it takes another 1½ hrs for the drug to diffuse into the extravascular space to observe clinical effect [26].

Our results are also in contrast with two studies conducted by Bachert et al., who analyzed the effects of intravenous and oral calcium on nasal allergen provocation tests [27, 28]. The authors observed decreased swelling of nasal mucosa and improved nasal flow after calcium application, but interestingly these effects were associated with only a minimal (4.5%) increase in serum calcium levels.

The discrepancy between these studies and our findings is probably related with the study model. It may be speculated that calcium activity in AR 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 [29-31].

In the three above mentioned papers, calcium preparation was administered in a single oral dose, much higher than that used in our study or doses commonly administered to patients in order to mitigate the symptoms of allergy. It is worth noticing, that the mechanism of calcium absorption is a saturable process, which means that a dose of about 500 mg elemental calcium results in significantly reduced absorption [32]. Furthermore, during our three-day study, the total dose administered in the subjects was 3.6-fold higher than the dose in Bachert's study, and no anti-allergic effects were observed, which renders this discrepancy even more intriguing.

A few more studies on this subject can be found in non-English literature. These evaluated the efficacy of oral or intravenous calcium preparations in allergic diseases such as AR, urticaria, allergic bronchial asthma, however, the results are inconsistent [33-35].

Several limitations can be also found in our study. 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 H1-blockade [19], however, it does not necessarily reflect the overall anti-allergic activity. Mediators other than histamine also play important roles in allergic cutaneous responses, including mediators involved in cellular late-phase responses [36]. Therefore, SPT findings should be interpreted with caution and considering the clinical situation since they may not necessarily correlate with clinical responses [37].

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 [38]. 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 in academic research, however, it is not available yet [39].

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 either single doses or long-term treatment with calcium supplements does not reduce allergic cutaneous reactions (measured as the wheal response and symptoms of pruritus) as compared with placebo.

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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Conflict of interest

The authors have no conflicts of interest or competing financial interests with regards to this manuscript.

References

1. Zelig R, Rigassio Radler D. Understanding the properties of common dietary supplements: clinical implications for healthcare practitioners. *Nutr Clin Pract*. 2012; 27: 767-776.
2. Trivedi R, Salvo MC. Utilization and Safety of Common Over-the-Counter Dietary/Nutritional Supplements, Herbal Agents, and Homeopathic Compounds for Disease Prevention. *Med Clin North Am*. 2016; 100: 1089-1099.
3. Navarro VJ, Khan I, Bjornsson E, et al. Liver injury from herbal and dietary supplements. *Hepatology*. 2017; 65: 363-373.
4. Hamishehkar H, Ranjdoost F, Asgharian P, et al. Vitamins, Are They Safe? *Adv Pharm Bull*. 2016; 6: 467-477.

5. Sadowski DC. Drug interactions with antacids. Mechanisms and clinical significance. *Drug Saf.* 1994; 11: 395-407.
6. Uribe M, Casian C, Rojas S, et al. Decreased bioavailability of prednisone due to antacids in patients with chronic active liver disease and in healthy volunteers. *Gastroenterology.* 1981; 80: 661-665.
7. Krela-Kazmierczak I, Szymczak A, Tomczak M, et al. Calcium and phosphate metabolism in patients with inflammatory bowel diseases. *Pol Arch Med Wewn.* 2015; 125: 588-590.
8. Sweetman SC. Calcium. In: Sweetman SC, ed. *Martindale The Complete Drug Reference.* London: Pharmaceutical Press; 2009: 1675-1678.
9. Unger R. Erfahrungen mit parenteraler Calciumtherapie. *Ther Ggw.* 1935; 76: 69.
10. Sozanski T, Magdalan J, Sozanska B, et al. Is there any hope for calcium use in allergic diseases? *Adv Clin Exp Med.* 2009; 18: 507-512.
11. Nittner-Marszalska M, Cichocka-Jarosz E. Insect sting allergy in adults: key messages for clinicians. *Pol Arch Med Wewn.* 2015; 125: 929-937.
12. Nowicki R. Leczenie pokrzywek: zalecenia ogólne. In: Kruszewski J, Śpiewak R, Nowicki R, eds. *Pokrzywki - rozpoznawanie i leczenie: stanowisko Panelu Ekspertów Polskiego Towarzystwa Alergologicznego.* Warszawa: Medycyna Praktyczna; 2011: 65-68.
13. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy.* 2014; 69: 868-887.
14. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med.* 2010; 8: 18.
15. Bousquet J, Heinzerling L, Bachert C, et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy.* 2012; 67: 18-24.

16. Levenson DI, Bockman RS. A review of calcium preparations. *Nutr Rev.* 1994; 52: 221-232.
17. Weisman SM. The calcium connection to bone health across a woman's lifespan: a roundtable. *J Reprod Med.* 2005; 50: 879-884.
18. Palleria C, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *J Res Med Sci.* 2013; 18: 601-610.
19. Simons FE, Simons KJ. Peripheral H1-blockade effect of fexofenadine. *Ann Allergy Asthma Immunol.* 1997; 79: 530-532.
20. Clapham DE. Calcium signaling. *Cell.* 2007; 131: 1047-1058.
21. Debelic M. Antiallergic effect of a calcium preparation administered orally, a controlled double-blind study. *Fortschr Med.* 1979; 97: 1537-1540.
22. Haas PJ. Drug effects against mechanically stimulated itch with concomitant erythemas and wheals of the skin. *Fortschr Med.* 1983; 101: 1939-1943.
23. Nelson HS, Knoetzer J, Bucher B. Effect of distance between sites and region of the body on results of skin prick tests. *J Allergy Clin Immunol.* 1996; 97: 596-601.
24. Wang H, Bua P, Capodice J. A comparative study of calcium absorption following a single serving administration of calcium carbonate powder versus calcium citrate tablets in healthy premenopausal women. *Food Nutr Res.* 2014; 58.
25. Chaturvedi P, Mukherjee R, McCorquodale M, et al. Comparison of calcium absorption from various calcium-containing products in healthy human adults: a bioavailability study. *FASEB J.* 2006; 20: A1063-A1064.
26. Church MK, Church DS. Pharmacology of Antihistamines. *Indian J Dermatol.* 2013; 58: 219-224.
27. Bachert C, Drechsler S, Hauser U, et al. Influence of oral calcium medication on nasal resistance in the nasal allergen provocation test. *J Allergy Clin Immunol.* 1993; 91: 599-604.

28. Bachert C, Drechsler S, Keilmann A, et al. [Reduction of reactivity to allergic rhinitis with intravenous administration of calcium. Clinical-experimental study on the effect of changes of local airway resistance after nasal allergen provocation]. *Arzneimittelforschung*. 1990; 40: 984-987.
29. West GB. Further thoughts on mast cells, calcium channels and histamine release. *Int Arch Allergy Appl Immunol*. 1990; 91: 214-216.
30. Busch L, Tessler J, Bazerque PM. Effects of calcium and EDTA on rat skin capillary permeability and on its response to histamine, serotonin and bradykinin. *Acta Physiol Pharmacol Latinoam*. 1989; 39: 227-234.
31. Dhar HL. Role of Calcium Channel Antagonists in Allergy and Asthma. *Indian J Allergy Asthma Immunol*. 2001; 15: 107-110.
32. Heaney RP, Weaver CM, Fitzsimmons ML. Influence of calcium load on absorption fraction. *J Bone Miner Res*. 1990; 5: 1135-1138.
33. Beiteke U. Die polymorphe Lichtdermatose. *Sandorama*. 1992; 2: 17 – 18.
34. Petersen LJ, Church MK, Skov PS. Histamine is released in the wheal but not the flare following challenge of human skin in vivo: a microdialysis study. *Clin Exp Allergy*. 1997; 27: 284-295.
35. Pokropp A, Czarnetzki B. Untersuchungen zur Wirkung von intravenosem Kalzium auf experimentell Quaddel- und Erythembildung. *Allergologie*. 1983; 6: 82-83.
36. Meltzer EO, Gillman SA. Efficacy of fexofenadine versus desloratadine in suppressing histamine-induced wheal and flare. *Allergy Asthma Proc*. 2007; 28: 67-73.
37. Monroe EW, Daly AF, Shalhoub RF. Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines. *J Allergy Clin Immunol*. 1997; 99: 798-806.

38. van der Valk JP, Gerth van Wijk R, Hoorn E, et al. Measurement and interpretation of skin prick test results. Clin Transl Allergy. 2015; 6: 8.
39. Justo X, Diaz I, Gil JJ, et al. Prick test: evolution towards automated reading. Allergy. 2016; 71: 1095-1102.

Table S1. Characteristics of study populations	
Number of subjects	40
gender male/female	12/28
age, years	19-32
mean age, years	25

Table S2. Percentage change in wheal responses and itching sensation 4 hrs after the first dose (V1) and after 3 days (72h) of treatment (V2) versus baseline in patients treated with calcium carbonate (verum) or placebo.				
	Time	Mean % change in wheal diameter (vs V0)		P (verum vs placebo)
		verum	placebo	
histamine SPTs	V1	-3.33%	-4.58%	0.9
	V2	-4.79%	-2.08%	0.6
aeroallergens SPTs	V1	1.48%	-0.54%	0.8
	V2	-0.88%	4.99%	0.5

	Time	Mean % change of itching (vs V0)		P (verum vs placebo)
		verum	placebo	
SPTs	V1	-3.93%	4.08%	0.4
	V2	13.79%	17.78%	0.7
Abbreviations: SPTs, skin prick tests; V0, SPTs performed pretreatment; V1, SPTs performed 4 hours after the intake of the first dose of drug; V2, SPTs performed 72 hours (3 days) after V0.				

Figure S1. The study diagram: Calcium carbonate (1000 mg) or placebo were given to the volunteers three times daily for 3 days. Skin prick tests were performed pretreatment at screening visit (V0), 4 hours after the intake of the first dose of the drug (V1) and 3 days (72 hours) later (V2), when all doses of drugs were administered.

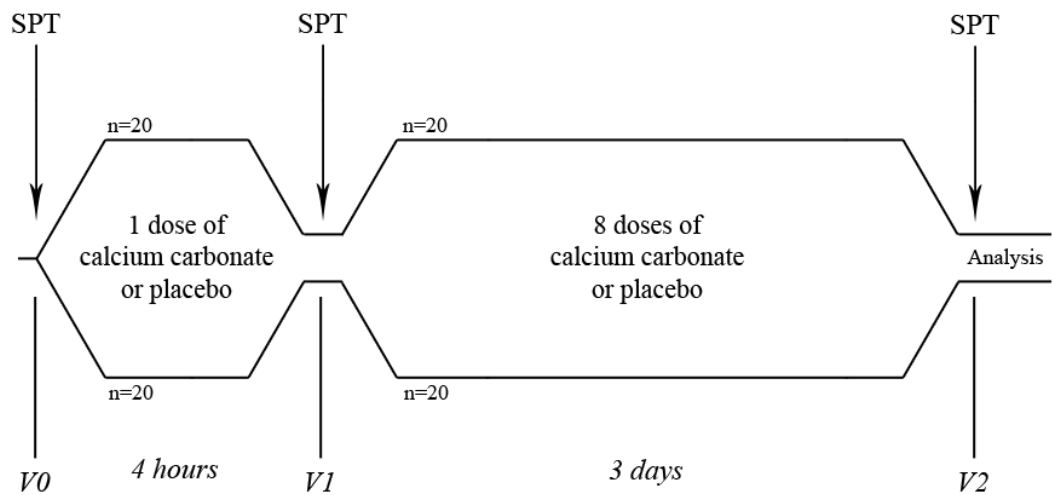
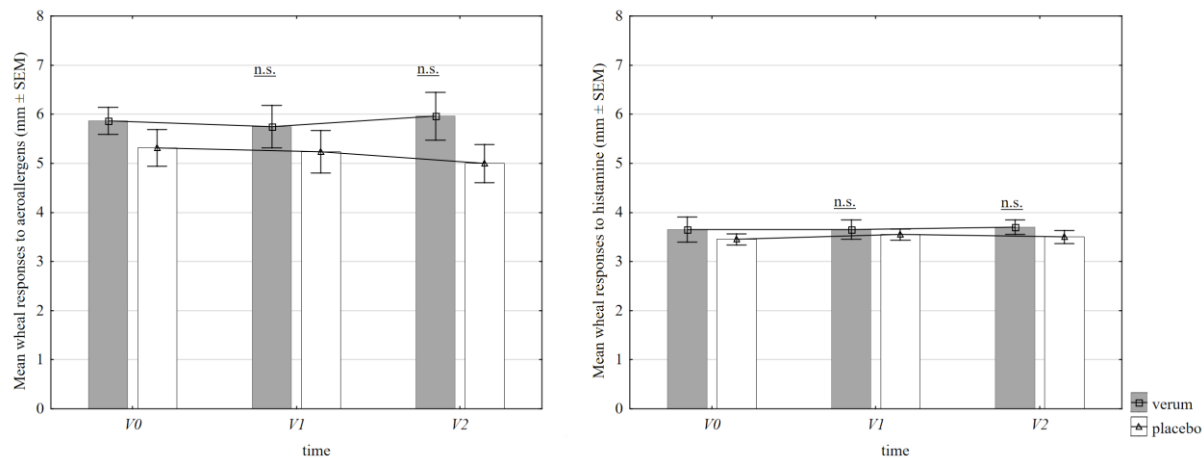


Figure S2. A) Mean diameter of wheal for histamine at *V0*, *V1* and *V2* in patients treated with calcium carbonate (verum) or placebo. B) Mean diameter of wheal for aeroallergens at *V0*, *V1* and *V2* in patients treated with calcium carbonate or placebo.



Figures S3. Mean sensation of itching during skin prick tests at *V0*, *V1* and *V2* in patients treated with calcium carbonate (verum) or placebo.

