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Is There Any Hope for Calcium Use in Allergic Diseases?

Czy stosowanie wapnia w chorobach alergicznych jest uzasadnione?

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Abstract

In light of the available literature, calcium use in allergic diseases is currently very controversial. This paper presents a review of studies evaluating the effectiveness of calcium preparations in inhibiting the type I allergic reaction induced in healthy volunteers and in the therapy of allergic diseases. Additionally, the risk of calcium deficiency in allergy patients on elimination diets and current knowledge on the potential effect of calcium intake volume on the prevalence of allergic diseases are discussed (*Adv Clin Exp Med* 2009, 18, 5, 507–512).

Keywords: calcium, atopy, asthma.

Streszczenie

Stosowanie wapnia w schorzeniach o podłożu alergicznym budzi w świetle dostępnej literatury naukowej duże kontrowersje. W pracy przedstawiono przegląd piśmiennictwa oceniającego skuteczność preparatów wapnia w hamowaniu indukowanej reakcji alergicznej typu pierwszego u zdrowych ochotników oraz w leczeniu schorzeń alergicznych. Omówiono ryzyko występowania niedoborów wapnia u pacjentów ze schorzeniami alergicznymi stosujących diety eliminacyjne. Przedstawiono także obecny stan wiedzy na temat potencjalnego wpływu ilości spożywanego wapnia na częstość występowania chorób alergicznych (*Adv Clin Exp Med* 2009, 18, 5, 507–512).

Słowa kluczowe: wapń, atopia, astma.

Calcium is a mineral element necessary for the proper functioning of numerous tissues and organs. Among others, it is responsible for regular muscle contraction, nerve conductivity, hormone release, and blood clotting. It is a significant intracellular mediator necessary for phospholipase A₂ activation and, therefore, the production of prostaglandin E₂, having modulating effect on cytokines and the profile of IgG immunoglobulin [1]. Moreover, calcium is important for the function of many enzymes [2]. Therapeutically, calcium is currently administered in deficiency conditions caused by insufficient supply of this macroelement in the diet or by its malabsorption and in calcium deficiency prophylaxis, osteoporosis, and hypoparathyroidism. Calcium is also a constituent of antacids, currently less frequently used for gas-

tric hyperacidity and peptic ulcer [3]. The FDA also approved calcium use in dermatitis exudativa, hyperkalemia, lead poisoning, magnesium overload, non-thrombocytopenic diathesis, hypocalcemia-related tetany, hyperphosphatemia in the course of renal insufficiency, bite of the *Latrodectus mactans* spider, and as an adjunctive in osteomalacia and rickets. The FDA also approved the use of calcium in allergic diseases in the form of intravenous infusion of 10% calcium gluconate at doses of 0.5–2.0 g with a rate below 0.2 g/minute to reduce capillary permeability. In the same indication in children it is recommended to administer 10% calcium gluconate at a dose of 0.2–0.5 g and in newborns up to 0.2 g with an infusion rate below 0.2 g/minute [4]. The use of calcium in the last of the above indications, i.e. allergic disorders,

is very controversial in light of the available literature.

In Poland, calcium preparations are very commonly used in allergic diseases, especially in allergic dermatological conditions such as urticaria. Many patients report to a physician previously self-administered calcium because of developing signs and symptoms of allergy. Many physicians also recommend the use of these preparations. A similar practice was observed in other countries, including Germany [5]. However, in the scientific literature only single studies can be found indicating an effectiveness of calcium preparations in the therapy of allergic conditions. Polish and European allergological and pharmacological associations do not recommend the use of calcium preparations in allergic diseases. Also, in available textbooks on allergology and pharmacology the validity of their use is questioned or there is no information on calcium use in allergic diseases [3].

In the available data bases and medical reviews (e.g. Medline, Cochrane Library, Micromedex, Martindale Complete Reference), the present authors found only two reports confirming the effectiveness of calcium in inhibiting a rapid, induced type I allergic reaction in healthy volunteers and only one report indicating a potential effectiveness of a calcium preparation in the therapy of allergic rhinitis. In a randomized double-blind placebo-controlled clinical trial, Debelic evaluated the effect of orally administered calcium on the course of a local rapid allergic reaction caused by a histamine and grass pollen mixed extract administered as a prick test to 20 healthy adult volunteers. The study indicated a statistically significant ($p < 0.001$) reduction of the induced wheal following oral administration of a preparation composed of 3 g of calcium gluconate, 2.1 g of calcium lactate, and 75 µg of ergocalciferol (3000 IU of vitamin D₂) [6]. In another double-crossed randomized double-blind placebo controlled trial, Haas et al. induced itching symptoms, erythema, and wheal with a magnetic oscillation system in 20 healthy volunteers. It was shown that oral administration of a complex combined preparation composed of 2.5 g of calcium gluconate, 1.75 g of calcium lactate, 12.5 µg of ergocalciferol (500 IU of vitamin D₂), and 0.5 g of ascorbic acid (vitamin C) caused statistically significant ($p < 0.001$) reduction of urticaria and wheal and signs of itching compared with a control group of participants who did not receive the treatment and a group receiving placebo [7]. It should be noted, however, that the dose of calcium used in both of the above trials significantly exceeded the doses usually administered in Poland to patients with allergic reactions. Moreover, in both cases the

allergic reactions were induced in healthy volunteers, not in allergy-affected patients.

In another placebo-controlled double-blind trial, Bachert et al. evaluated the anti-allergy effect of intravenously administered calcium in 25 patients with symptoms of allergic rhinitis during the clinical symptom-free season. The evaluated parameter was reduction of air flow through the nose by 50% after administration of the timothy-grass (*Phleum pratense*) allergen. Before nasal challenge with the allergen, administered in increasing doses, the patients received intravenous calcium at a dose of 9 mmol or placebo. In the group receiving calcium, the serum concentration of the element increased by 0.45 ± 0.055 mmol/l. The trial indicated a protective effect of the administered calcium on the development of allergic reaction. In the calcium-receiving group, achievement of a 50% reduction of nasal air flow required the administration of a statistically significant ($p = 0.021$) dose of allergen, i.e. 20,433 units compared with the placebo group's 7494 units [8]. According to the authors' knowledge, that is the only trial available in the literature confirming a positive effect of calcium in patients with allergic conditions.

On the other hand there are only single studies proving a lack of calcium effectiveness in the therapy of allergy. According to Hiddemann, the broadly propagated opinion of a "vessel-tightening" effect of calcium is groundless. Also, *in vitro* calcium-mediated inhibition of histamine release from mastocytes requires very high concentrations, which are not possible to achieve *in vivo* even following intravenous administration [5]. In a placebo-controlled study, Prokropp et al. also proved a lack of effect of intravenous calcium on histamine-induced wheal, erythema, and itch [9].

At the same time there is another, very important aspect of calcium use in allergic diseases. Numerous studies indicate a risk of calcium deficiency in patients with allergic conditions on elimination diets. There are also single epidemiological studies indicating a negative correlation between the prevalence of allergic disorders, including asthma and allergic rhinitis, and calcium blood level.

Regular calcium intake is very important for skeletal development in children. Dairy products are the basic calcium source in Western Europe. Seventy to eighty percent of the recommended daily calcium dose in children comes from dairy products [10–12]. At the same time it is estimated that an alimentary allergy develops in 6 to 8% of children under 3 years of age [13]. Allergy to cow's milk is currently the most common alimentary allergy developing in small children [14]. According to studies completed in 1990, 2.2% of

children develop allergy or cow's milk intolerance before they turn 2 years old. Thirteen percent of these children still do not tolerate milk at the age of 3 and older [15, 16]. According to another study, 2.5% of children have allergy to cow's milk or milk intolerance [12].

Although in the majority of the children the allergy to milk and other dietary elements recedes at the age of 3 to 5, the period of an elimination diet is simultaneously a critical period for their regular development [13, 15, 17]. Alimentary deficiencies caused by a milk-depleted elimination diet can lead to disturbance in the children's regular development. Single cases of severe alimentary deficiencies were described in 22- and 17-month-old children in whom rice and soybean milk-replacement preparations were used, respectively, leading to severe protein-calorie malnutrition and advanced rickets in the first case and to almost complete inhibition of weight and height gain in the other [18]. David et al. found insufficient calcium intake in 13 of 23 children in ages ranging between 6 months and 13 years (mean age: 2 years) treated with elimination diets because of atopic eczema. In 10 patients the intake was below 75% and in 3 below 50% of the recommended value. On the other hand, regular daily calcium intake was found in all 23 healthy children of corresponding age in the control group. The results of the study suggest the necessity of calcium supplementation in patients receiving an elimination diet [19]. In another study on 48 children at ages between 8 months and 14 years with symptoms of atopic eczema, insufficient calcium supply was shown in 15 of 20 patients treated with a cow-milk elimination diet who were not simultaneously given any milk-replacement preparations and in 3 of 26 patients on the same diet who were additionally given soybean preparations or casein hydrolysates [20].

Christie et al. studied the effect of elimination diet in 98 children aged 3.7 ± 2.3 years because of alimentary allergy on growth and the supply of nutritional dietary components. In 26 individuals in the group, allergy to cow's milk was diagnosed. The control group was 99 children without alimentary allergy. It was found that in both groups, test and control, daily calcium consumption was below 67% of the recommended value in 25% of the children. It was also shown that significantly ($p < 0.05$) more children with allergy to cow's milk protein (58%) compared with the control group (46%) consumed insufficient quantities of calcium in their diet. Of 11 children with allergy to cow's milk protein who received a safe infant/toddler formula or fortified soy beverage in their diet, 10 (91%) had normal calcium consump-

tion levels. The possibility of daily calcium consumption below the recommended value was less if the children received nutrition counseling ($p < 0.05$) [17].

McGowan et al. examined 323 patients with alimentary allergy, of whom 38 reported hypersensitivity to cow's milk protein. Only these 38 patients were further analyzed compared with a control group composed of individuals of the same sex, age, and profession without signs of alimentary allergy. Statistically lower daily calcium intake was found in the patients with allergy than in the control group ($p < 0.002$). Thirty-four percent of the patients with allergy to cow's milk protein who completely avoided milk consumption supplemented their diet with calcium, but also in that group the mean daily calcium intake was clearly below the normal range (441 mg/day) [21].

In another study, Adamska et al. evaluated calcium intake in a Polish population of 40 children with hypersensitivity to cow's milk protein at ages ranging from 1 month to 2 years treated with elimination diet. The control group consisted of 20 healthy children of the same age. It was found that in 72.5% of the children treated with an elimination diet, daily calcium intake was below the recommended standard. At the same time, 35% of the children in the group with hypersensitivity to cow's milk protein received only 40–64% of the recommended daily calcium intake in their diets. Statistically reduced mean calcium intake was found in the study group compared with the controls at ages between 13 and 24 months, but not at ages from 1 to 6 months and 7 to 12 months. The authors link these results with the reduction of milk-replacement preparations in the children's diet at post-infant age in favor of a calcium-depleted meat-cereal-vegetable diet [22].

In a study of 10 children with allergy to cow's milk protein aged 31–37 months selected from a population of 3289 children, Henriksen et al. found insufficient calcium consumption even if milk-replacement preparations were used. Calcium consumption below the normal range was found (< 300 mg/day) in all the children with allergy to cow's milk protein. Moreover, in 2 of 4 children given calcium supplements, the daily intake of the element was still below the normal range. In all the healthy children of the control group, calcium intake was normal. Concluding, Henriksen et al. pointed out the necessity of supplying calcium preparations to children with allergy to cow's milk protein, recommending a dose of 500 mg/day for patients aged 1–3 years [23].

In another study, Barth et al. analyzed the diets of 116 patients with atopic eczema aged 17–62 years.

They showed insufficient consumption of numerous nutrients, including dairy products and calcium in patients who had symptoms of the disease. The mean daily consumption of dairy products in the group of individuals without atopic eczema symptoms was 23.0 g (range: 2.5–106.8) compared with 1.4 g (0–14.0) in the symptomatic patients ($p = 0.0054$). The authors pointed out the necessity of calcium and other nutrient supplementation in the patients with symptoms of atopic eczema [24]. This is particularly important in light of the increasing prevalence of atopic eczema in Western Europe. It is estimated that 10–20% of children have symptoms of atopic eczema at some stage of their development. A diet implemented because of this condition may therefore lead to serious nutritional deficiencies in many cases. This was confirmed by the results obtained by Mabin et al., who analyzed 45 patients with atopic eczema treated with two different elimination diets, finding significantly reduced calcium consumption in both groups [25].

Reports on significant bone mass reduction and numerous bone fractures in children with allergy to cow's milk protein resulting from insufficient supply of calcium and vitamin D are found in literature, which confirms the necessity of their supplementation [26]. Infante et al. showed that patients with allergy to cow's milk protein treated with an elimination diet for over two years belong to a group at risk of bone mineralization impairment, leading to osteopenia and osteoporosis [27]. Monti et al. described the case of an 8-year-old child with allergy to cow's milk protein who sustained four bone fractures and severe bone mass reduction resulting from long-standing and insufficient calcium supply, despite the administration of appropriate doses of vitamin D; other endocrine and orthopedic causes of the described pathology were excluded [28]. In another study, Goulding et al. compared the prevalence of bone fractures in a group of 50 children receiving milk-depleted diets aged 3 to 13 years with a control group of over one thousand milk-consuming children. The frequency and severity of fractures were retrospectively analyzed during the whole lifetimes of the children. It was shown that the milk-free diet children did not receive sufficient calcium supplementation and the daily calcium intake was below the normal range. A reduction of mean bone mineral density was also found in the group. Bone fractures were statistically more frequent compared with controls. They were found in 16 of 50 tested children on a milk-free diet, usually accompanied by a minor injury. Eighty-two percent of diagnosed fractures in the tested group occurred in children below the age of 7 [10]. In another study,

Kalkwarf et al. also showed a relationship between low milk consumption during childhood and the frequency of bone fractures in adulthood in the course of osteoporosis [29].

Many children with allergy to cow's milk protein also suffer from bronchial asthma. Jensen et al. studied 9 children with allergy to cow's milk protein persisting for over 4 years. Moreover, all the tested patients had confirmed bronchial asthma and used corticosteroids for treatment. The large reference population consisted of 343 healthy children. In the children with allergy to cow's milk protein and asthma, a statistically significant reduction in bone mineral content (BMC) and bone mineral density (BMD) was found compared with the control group (BMD, $p < 0.01$). The extreme BMC per bone surface value reduction ($p = 0.05$) could indicate a reduction of bone mineralization in the allergic patients. Moreover, a statistically significant reduction of body height appropriate for the age was found ($p < 0.01$) along with body height reduction compared with parents and siblings ($p < 0.01$) and a bone age delay by an average of 1.4 years ($p < 0.01$). Analyzing daily calcium consumption in the food consumed by the patients it was found that the average content of the element was 217 mg, which was only 25% of the recommended dose. The authors pointed out the necessity of supplementary calcium intake by these patients. This may be of importance for the prevention of any future osteoporosis in these patients [12].

The above studies clearly confirm the purposefulness of adjunctive administration of calcium preparations supply in the therapy of allergic diseases such as allergy to cow's milk protein and atopic eczema in which elimination diets are used involving a reduction of dairy product consumption.

The next very interesting aspect of calcium preparation use in allergic conditions is the potential effect of calcium intake volume on their prevalence. Numerous studies indicate a possible effect of diet change on increased prevalence of asthma and atopy in industrialized countries. An association was shown, among others, between reduced consumption of antioxidants and bronchial hyperactivity or a protective effect of a low consumption of saturated and monounsaturated fatty acids on the risk of bronchial hyperactivity development [30]. At the same time, only a few studies analyzed daily calcium intake and its effect on the occurrence and course of allergic diseases. The potential mechanism by which a regular or increased calcium intake would reduce the risk of allergic diseases is unknown. Hijazi et al. compared the diets of 114 children with asthma and

wheezing confirmed during the last 12 months with a control group of 202 who had never had those symptoms. Using single-factor analysis they found a statistically significant association between the volume of calcium consumption and the prevalence of asthma ($p < 0.001$). Analysis by multi-variable logistic regression confirmed that trend. It was, however, not statistically significant ($OR = 1.88$; 95% CI : 0.91–3.89) [31].

Two other clinical trials also indicated the effectiveness of high calcium intake in the prevention of allergic diseases such as atopic eczema and allergic rhinitis. In a prospective clinical trial, Laitinen et al. evaluated 159 children with a positive family history of atopic eczema (e.g. atopic eczema, allergic rhinitis, or asthma in the mother, father, and/or older siblings) from birth to the age of 4. Control tests evaluating the patients' diets were performed at the ages of 6, 12, and 48 months. It was found that increased calcium intake reduced the risk of atopic eczema development in the patients. At both the ages of 12 and 48 months, calcium consumption in the group of children with symptoms of atopic eczema was lower compared with a group in which there were no symptoms of atopic eczema [32]. The results of Miyake's et al. study indicated a possible association between high calcium consumption and rarer occurrence of allergic rhinitis. In a cross-sectional study involving 1002 pregnant Japanese women, the effect of traditional Japanese diet on the prevalence of allergic rhinitis was studied. A statistically significant, negative, dose-dependent relationship was found between calcium intake and the prevalence of allergic rhinitis. Mean daily calcium intake in the study group was 556.0 ± 182.9 mg. The relationship was still valid and statistically significant in analysis considering the effect of interfering factors and was not statistically significant in analysis by multivariable logistic regression [33].

Summarizing, it should be stated that there are too few studies available to determine whether calcium is an effective agent in the therapy of allergic diseases. Based on published studies it seems, however, that its routine administration is groundless and that the popularity of calcium salt is rather an effect of habit and a not fully proven thesis that it reduces the permeability of blood vessels. When analyzing the results of these studies it is also worth noting that the doses of calcium salt that could have any effect (probably resulting from the inhibition of histamine release from mast cells) would have to be very high, exceeding by far the generally recommended daily doses.

The results of studies on the usefulness of calcium preparations in elimination diets seem, however, to be clear. Nutritional deficiencies, including calcium deficiencies caused by, among others, a milk-free elimination diet, may lead to disorders in children's development. An elimination diet is most frequently applied in children with allergic disease, including allergy to cow's milk protein and atopic eczema. It is generally known that children allergic to cow's milk protein also frequently suffer from bronchial asthma. Patients with low calcium level should supplement the macro-element. This is even more important as a negative relationship was found between calcium intake volume and the prevalence of asthma. It seems that the lower the calcium serum level, the higher the prevalence of bronchial asthma, atopic eczema, and allergic rhinitis. Therefore, if the effectiveness of calcium in the therapy of allergic diseases is doubtful, supplementation of the element to prevent these diseases in patients with calcium deficiency seems promising, although more studies are needed. Calcium substitution is unquestionably recommended in patients with allergic diseases using milk-free elimination diets to prevent deficiency of this element.

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