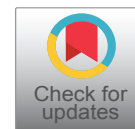**International Journal of**
Allergy Medications

Diet and Nutritional Status of Children with Cow's Milk Protein Allergy, Treated with a Milk-Free Diet

Grażyna Rowicka*, Małgorzata Strucińska, Agnieszka Riahi and Halina Weker

Department of Nutrition, Institute of Mother and Child in Warsaw, Poland

*Corresponding author: *Grażyna Rowicka, Department of Nutrition, Institute of Mother and Child, Kasprzaka 17a, 01-211 Warsaw, Poland, Tel: +48-22-32-77-366, E-mail: grazyna.rowicka@imid.med.pl*

Abstract

Children with Cow's Milk Protein Allergy (CMPA), treated with a milk-free diet, may be at risk of deficiency of nutrients important for appropriate development. The aim of the study was to evaluate the diets and the nutritional status of children with CMPA.

The study included 48 children, aged 4-6 years, with CMPA treated with a milk-free diet. The principles of the milk-free diet were defined and the compliance with the diet by children was monitored by a physician and a dietician. The control group consisted of 30 healthy controls, aged 4-6 years, on a traditional diet containing milk and milk products. The energy and nutritional value of the diets was determined on the basis of 3-day dietary records. Children's nutritional status was evaluated based on the normalised Body Mass Index (BMI z-score) and selected biochemical indices. The energy value of the diets of children with CMPA was higher compared to recommendations and significantly higher than the energy value of the diets of healthy controls. The intake of protein in both groups exceeded approximately three times the daily requirement. Children with CMPA consumed significantly more long-chain poly-unsaturated fatty acids, carbohydrates, iron, iodine, copper and vitamins D, E, B1, B6 and PP. Vitamin D deficiency was found in the diets of children from both groups. Calcium deficiency was recorded in the diets of 93.8% of children with CMPA and 90% of the controls. The evaluated biochemical indices in both groups did not different significantly and, except for the concentration of 25(OH) vitamin D in blood serum of children with allergy, were within the reference range. Milk-free diets in children with CMPA were adequate for most nutrients, but the children are at risk of vitamin D insufficiency despite the higher vitamin D content of their diets compared to the group of healthy children. The better balancing of the diets of children with allergy was probably due to continuous medical and nutritional care provided by paediatricians and dieticians.

Keywords

Cow's milk protein allergy, Milk-free diet, Dietary intake, Nutritional status, Children

Introduction

Milk and milk products play an important role not only in the diet of non-breastfed infants, but also in the diet of children in subsequent years of life. Those products are a source of complete protein, calcium, phosphorus, vitamins from B group (mainly B2) and contain also fat-soluble vitamins A and D. Milk sugar (lactose) is conducive to colonisation of intestines with beneficial bacterial flora and facilitates the absorption of calcium from the small intestine. The fat in milk consists primarily of short- and medium-chain fatty acids, which makes it easily digestible. However, milk and its products are among the most common food allergens in the population of children. Cow's milk contains more than 25 different proteins and some of them are known to be allergenic. The proteins that are most often responsible for causing allergies include casein, as well as α-lactalbumin and β-lactoglobulin of the whey fraction [1].

The prevalence of Cow's Milk Protein Allergy (CMPA) among children in the first year of age is approximately 2-3%, and below 1% in children aged above 6 years [2]. The main treatment for CMPA is an elimination diet consisting in temporary or permanent exclusion of milk and its products from the mother's diet, if the child is breastfed, or from the child's diet, if the child is formula-fed. A properly balanced milk-free diet ensures optimal psychophysical and intellectual development of the child, even if it is followed for several months or several years [3]. Nevertheless, it is sometimes difficult to balance such diet, and thus children treated with a milk-free diet may be at risk of nutritional deficiencies [4,5].

According to the nutritional programming theory, a

non-balanced diet may, due to both deficiency and surplus of nutrients, permanently change metabolism and course of physiological processes and thus increase predispositions to numerous diseases, such as cardiovascular diseases, osteoporosis, obesity, cancers in later life. Therefore, appropriately early detection of abnormalities in the diet of the child and prompt introduction of proper nutritional intervention are important not only for the current health status of the child, but also for its health in adulthood [6].

The aim of the study was to evaluate the energy and nutritional value of the diets of children aged 4-6 years treated for allergy to cow's milk protein, and to link their diets intake with selected indices of the nutritional status.

Materials and Methods

The study covered 48 children aged 4-6 years with CMPA who were treated with a milk-free diet for at least a year and for this reason were under care of both a physician and a dietician from the Gastroenterological Outpatient Clinic of the Institute of Mother and Child in Warsaw. After the diagnosis of CMPA in a child, its parents/caregivers received nutritional counseling from a dietician on the principles of the milk-free diet with the use of the milk substitutes ordered by a physician. Then, the compliance with the milk-free diet was monitored by a physician and a dietician. The diagnosis of cow's milk protein allergy in children was made based on clinical symptoms, evidence of sensitization (food-specific IgE antibodies, skin prick tests) and was confirmed with the open food challenge. The control group consisted of 30 age-matched healthy children on a traditional diet with the share of milk and milk products.

Assessment of the diet

The dietary intake was assessed using children's food diaries recorded according to instructions by parents/carers for three days [7].

The dietary records were used for estimating the intake of individual products using the Photo Album of Products and Meals [8] and the energy and nutritional value of the children's diets was calculated using the Dieta 5 software [9]. The energy and nutrients intake were compared to the nutritional standards for Polish children population aged 4-6 years [10]. Furthermore, the dietary records were used for estimating the amount of milk substitutes and milk-free

fortified products consumed by children, and the amount of milk and milk products consumed by the control group. The amount of calcium and vitamin D consumed with milk substitutes and milk-free fortified products, as well as with milk and milk products, was calculated using the Dieta 5.0 dietary software

Assessment of nutritional status

The nutritional status of the children was assessed using anthropometric data (current body weight and height), the BMI (body weight [kg], divided by height squared [m²]), standardised with respect to WHO growth charts, thus receiving the BMI z-score independent from gender and age [11,12]. The nutritional status was also assessed using selected biochemical indices. Fasting peripheral blood samples (3 ml) were taken in the summer season (from June to September 2015) in the morning hours from all children. Blood in EDTA-containing tubes was analysed immediately for the determination of erythrocytes, Haemoglobin (Hb) and Mean Corpuscular Volume (MCV) using a haematology analyser (Pentra, HORRIBA ABX, and France). In order to obtain serum, the blood was centrifuged at 2500 × g, at 4 °C for 10 minutes and stored in small portions at -25 °C for subsequent biochemical analysis. Serum iron, ferritin, transferrin as well as calcium, phosphate, magnesium were determined using commercially available kits on a biochemical analyser (COBAS INTEGRA, ROCHE, Switzerland). The 25(OH) vitamin D concentrations in blood serum were determined by chemiluminescence method using DiaSorin (USA) kits.

The study was performed in accordance with the Helsinki Declaration for Human Research and the study protocol was approved by the Ethics Committee of the Institute of Mother and Child in Warsaw, Poland.

All parents of participating children were informed of the study objectives and written consent was obtained for analysis of blood samples before their participation in the study.

Statistical analyses

The t-student test for normally distributed variables and U Mann-Whitney test for variables with non-normal distribution were used to analyse differences in anthropometric and haematological and biochemical parameters as well as energy and nutritional value of diets between children with CMPA and healthy controls. Data are presented

Table 1: Clinical and anthropometric data in children with CMPA and healthy controls.

Variables	Children with CMPA (n = 48) Median (1-3 quartile)	Healthy controls (n = 30) Median (1-3 quartile)	P value for U Mann-Whitney test
Sex [%]*	39.6/60.4	46.7/53.3	-
Age [years]	5.3 (4.8-5.7)	5.4 (4.9-5.9)	0.5
Body weight [kg]	18.9 (17.2-20.2)	18.1 (17.4-20.3)	0.9
Body height [cm]	112.3 (107.3-117.0)	111.5 (108.7-118.5)	0.9
BMI [kg/m²]	14.9 (14.5-15.7)	14.9 (14.2-15.8)	0.9
BMI z-score	-0.5 (-0.9 - -0.1)	-0.6 (-0.8-0.01)	0.8

*Data presented as percent of girls/percent of boys.

as means and standard deviations for normally distributed variables and medians and interquartile ranges for non-normally distributed variables. An assessment of the normality of data was performed with Shapiro-Wilk test. The Chi^2 test was used for analysing differences in percentages of children with nutrients intake below EAR (Estimated Average Requirement) or AI (Adequate Intake). Dependencies between biochemical parameters and dietary intake of selected minerals and vitamins were assessed using the Pearson's r correlation coefficient.

For all types of tests, α = 0.05 was adopted as the statistical significance level. Statistical analyses were performed using the Statistica 12 PL package.

Results

In 41.6% (N = 20/48) of the children with CMPA symptoms of allergy from the gastrointestinal tract were present (loose stools, constipation, stomach pain, abdominal bloating), in 16.6% (N = 8/48) it was atopic dermatitis, in 12.5% (N = 6/48) respiratory tract symptoms, while 29.1% (N = 16/48) of children had symptoms from more than one system.

The characteristics of the both groups of children are presented in (Table 1).

There were no significant differences in terms of age, body weight, height, BMI and BMI z-score between

Table 2: The energy and nutrients intake in children with CMPA and healthy controls in reference to Polish nutritional standards 2012 [10].

Energy and nutrients	Nutritional standards (EAR/AI[#])	Energy and nutritional value of diets			Percent of children with energy/ nutrients intake below EAR/AI		
		Children with CMPA (n = 48)	Healthy controls (n = 30)	P value[c]	Children with CMPA (n = 48)	Healthy controls (n = 30)	P value[d]
Energy[a] [kcal]	1400	1601.8 (340.2)	1350.5 (360.0)	0.003[*]	29.2	50.0	0.06
Protein[a] [g]	16	46.6 (13.3)	47.4 (14.9)	0.8	0.0	0.0	0.9
Total fat[b] [g]	54	50.7 (41.2-68.3)	49.1 (35.6-57.9)	0.2	56.3	53.7	0.9
LC-PUFA[b] [mg]	250[#]	72.2 (26.2-196.2)	36.9 (21.8-64.3)	0.02[*]	79.2	93.3	0.09
Total carbohydrates[a] [g]	-	243.8 (66.6)	191.1 (53.9)	0.0004[*]	-	-	-
Digestible carbohydrates[a] [g]	100	227.9 (62.3)	178.3 (50.2)	0.0004[*]	2.1	3.3	0.7
Fiber [g][b]	14[#]	15.6 (12.4-19.3)	13.2 (9.2-16.6)	0.03[*]	37.8	60.0	0.052
Percent of energy from protein [%][a]	-	11.8 (2.2)	14.2 (2.4)	0.0001[*]	-	-	-
Percent of energy from fat [%][b]	-	28.9 (24.7-36.7)	30.3 (28.4-35.4)	0.2	-	-	-
Percent of energy from carbohydrates [%][b]	-	59.0 (51.3-63.5)	55.7 (51.2-58.3)	0.03[*]	-	-	-
Calcium[b] [mg]	800	321.9 (229.7-505.5)	408.6 (259.9-588.4)	0.2	93.8	90.0	0.5
Phosphorus[b] [mg]	410	733.5 (589.5-827.8)	781.8 (614.8-961.3)	0.2	4.2	10.0	0.3
Magnesium[b] [mg]	110	204.3 (168.3-246.4)	191.0 (143.6-232.4)	0.2	0.0	13.3	0.009[*]
Iron[a] [mg]	4	9.1 (2.4)	7.2 (2.4)	0.001[*]	0.0	10.0	0.02[*]
Zinc[a] [mg]	4	6.5 (1.7)	5.9 (1.8)	0.1	4.2	13.3	0.1
Copper[b] [mg]	0.3	0.9 (0.8-1.1)	0.8 (0.6-1.1)	0.046[*]	0.0	6.7	0.07
Iodine[b] [μg]	65	79.1 (57.0-113.8)	69.2 (42.4-92.1)	0.03[*]	27.1	50.0	0.04[*]
Sodium[b] [mg]	1000[#]	1950.6 (1626.8-2751.5)	1768.8 (1245.0-2399.0)	0.057	2.1	13.3	0.04[*]
Potassium[b] [mg]	3100[#]	2274.7 (1774.4-2758.6)	2145.4 (1635.1-2450.8)	0.1	83.3	96.7	0.07
Vitamin A[b] [μg]	300	750.7 (560.9-1043.1)	696.8 (533.8-1135.0)	0.7	0.0	10.0	0.02[*]
Vitamin E[a] [mg]	6[#]	10.3 (3.4)	6.3 (3.3)	0.000002[*]	12.5	46.7	0.0008[*]
Vitamin B1[b] [mg]	0.5	1.0 (0.8-1.2)	0.7 (0.5-1.0)	0.002[*]	2.1	20.0	0.007[*]
Vitamin B2[a] [mg]	0.5	1.1 (0.3)	1.1 (0.4)	0.4	2.1	3.3	0.7
Vitamin PP[b] [mg]	6	11.9 (9.0-14.3)	9.6 (6.3-11.0)	0.002[*]	2.1	23.3	0.003[*]
Vitamin B6[b] [mg]	0.5	1.4 (1.1-1.8)	1.2 (0.9-1.5)	0.02[*]	0.0	6.7	0.07
Vitamin B12[b] [μg]	1	2.1 (1.4-2.7)	2.1 (1.3-3.1)	0.9	14.6	16.7	0.8
Vitamin C[b] [mg]	40	81.6 (65.1-116.3)	67.5 (42.8-102.6)	0.09	10.4	20.0	0.2
Vitamin D[b] [μg]	10	3.7 (2.1-6.3)	1.7 (0.9-2.3)	0.00001[*]	100.0	100.0	0.9
Folate[b] [μg]	160	178.3 (135.8-228.3)	172.0 (131.1-222.3)	0.5	37.5	46.7	0.4

[*]Statistically significant differences, p < 0.05; [a]Normally distributed variables; energy and nutrients intake presented as means and standard deviations; [b]Non-normally distributed variables; energy and nutrients intake presented as medians and interquartile ranges (1-3 quartile); [c]p value for t Student test/U Mann-Whitney test according to variable distribution (normal/non-normal); [d]p value for Chi^2 test; EAR: Estimated Average Requirement; AI[#]: Adequate Intake; LC-PUFA: Long-Chain Polyunsaturated Fatty Acids.

CMPA and healthy children. The value of BMI z-score pointed to appropriate nutritional status of children from both groups (BMI z-score < -1; +1 >)

The energy and nutritional value of the diets of children from both groups in reference to Polish nutritional standards (2012) are presented in (Table 2).

The energy value of the diets of children with CMPA was higher in comparison to recommendations and significantly higher compared to the energy value of the diets of healthy controls. The protein and fat intake did not differ significantly between the two groups. The protein intake was almost three times higher than EAR, while fat intake was close to recommended level. A similar percentage of children from both groups (56.3% vs. 53.7%) did not comply with the standard for fat, while the diets of children with CMPA included significantly more long-chain poly-unsaturated fatty acids (p < 0.05). The diets of children with allergy contained more carbohydrates (p < 0.05) than the traditional diets of healthy ones, and the majority of children from both groups exceeded recommended intake of digestible carbohydrates (97.9% in CMPA group and 96.7% in controls). Calcium intake in the diets of children from both groups did not differ and was lower than recommended. The percent of children with this nutrient intake below EAR was similar of children on a milk-free and a traditional diet (93.8% vs. 90.0%). Iron content in the diets of children with allergy was significantly higher compared to its content in the diets of healthy children (p < 0.05). In all children with CMPA, the standard for this nutrient was met. Iodine intake was significantly higher in the group of children with allergy (p < 0.05). Also in this group, a lower percentage of children did not achieve the EAR recommended level for this nutrient (27.1% vs. 50.0% in healthy controls; p < 0.05). The diets of children with allergy were better balanced in terms of vitamins content, apart from vitamin D, the intake of which in the diets of all children was deficient. Vitamin D deficiency was significantly higher in the group of children on a traditional diet (p < 0.05).

The diets of 75% (N = 36/48) of children with allergy included milk substitutes (e.g. extensively hydrolysed formulas and soy, oat, almond, rice or other grain beverages and dairy substitute) fortified among others with minerals and vitamins.

From among the children with allergy, 10.4% (N = 5/48) received extensively hydrolysed formulas of whey or casein, 12.5% (N = 6/48)-extensively hydrolysed formulas and fortified milk substitutes and 52.0% (N = 25/48) -only fortified milk substitutes. Due to the lack of organoleptic acceptance, 25.0% (N = 12/48) of children with allergy did not consume such foods at all. The diets of all children from the control group included milk and milk products.

The amounts of extensively hydrolysed formulas and/or fortified milk substitutes consumed by children with CMPA, as well as the amount of milk and milk products consumed by controls are presented in (Table 3).

The median and interquartile ranges of the amounts

Table 3: Comparison of amounts of calcium and vitamin D derived from selected dietary sources in diets of children with CMPA and healthy controls.

Variables	Children with CMPA (n = 36)[*]	Healthy controls (n = 30)
Selected dietary sources	Extensively hydrolysed formulas and/or fortified milk substitutes	Milk and milk products
Daily amounts of selected dietary sources consumed by children [ml] (median and interquartile range)	201.0 (88.7-413.2)	368.1 (176.4-600.2)
Daily intake of calcium from selected dietary sources [mg] (median and interquartile range)	154.0 (63.3-328.8)	400.3 (168.2-634.0)
Daily intake of vitamin D from selected dietary sources [μg] (median and interquartile range)	1.7 (0.9-3.7)	0.1 (0.1-0.3)

[*]Only children who consumed extensively hydrolysed formulas and/or fortified milk substitutes (N = 36/48).

Table 4: Haematological and biochemical parameters in children with CMPA and healthy controls.

Variables	Children with CMPA (n = 48)	Healthy controls (n = 30)	P value
Red Blood Cells (RBC) [mln/m^3][a]	4.6 (0.2)	4.4 (0.3)	0.06
Haemoglobin (Hgb) [g/dl][a]	12.6 (0.7)	12.4 (0.9)	0.3
Haematocrit (HT) [%][a]	37.3 (1.9)	36.4 (2.3)	0.1
Mean Corpuscular Volume (MCV) [fL][a]	81.6 (3.6)	82.5 (3.7)	0.3
Iron (Fe) [μmol/l][b]	14.1 (9.7-16.4)	13.3 (10.1-16.8)	0.9
Ferritin [ng/ml][b]	30.0 (23.4-42.8)	32.1 (22.4-56.4)	0.6
Transferrin [mg/dl][a]	302.7 (36.7)	296.2 (30.7)	0.5
Calcium (Ca) [mmol/l][b]	2.3 (2.2-2.4)	2.3 (2.2-2.4)	0.9
Phosphate (P) [mmol/l][b]	1.7 (1.5-1.9)	1.8 (1.5-1.9)	0.9
Magnesium (Mg) mmol/L[b]	0.9 (0.8-1.0)	0.9 (0.7-0.9)	0.2
25(OH) vitamin D [ng/ml][a]	26.6 (8.5)	30.5 (6.8)	0.1

[a]Normally distributed variables; data presented as means and standard deviations; [b]Non-normally distributed variables; data presented as medians and interquartile ranges (1-3 quartile).

(ml) of extensively hydrolysed formulas and/or fortified milk substitutes consumed by children with CMPA equalled 201.0 ml (88.7-413.2), whereas the amount of milk and milk products consumed by children from the control group totalled 368.1 ml (176.4-600.2).

The median daily intake of calcium derived from extensively hydrolysed formulas and/or fortified milk substitutes in children with CMPA was 154.0 mg (interquartile range 63.3-328.8 mg) versus 400.3 mg (interquartile range 168.2-634.0 mg) derived from milk and dairy products in the diets of healthy controls. The content of vitamin D derived from the median amount of extensively hydrolysed formulas and/or fortified milk substitutes consumed daily by children with CMPA was 1.7 µg (interquartile range 0.9-3.7 µg), whereas the median amount of 368.1 ml of milk and its products consumed daily by healthy children provided only 0.1 µg (interquartile range 0.1-0.3 µg) of vitamin D.

In 50% (N = 24/48) children with CMPA and 10% (N = 3/30) on a traditional diet, supplementation of vitamin D was used. Calcium supplementation was used in only 15% (N = 7/48) of children with allergy.

Biochemical and haematological parameters in both groups of children are presented in (Table 4).

Haematological and biochemical parameters did not differ significantly in both groups of children and were within the reference range, except for 25(OH) vitamin D concentrations in blood serum in the group of children with CMPA, indicating suboptimal status of this vitamin [13]. The correlations between the content of selected diet components and their concentration in blood serum of children with CMPA are presented in (Table 5).

In the group of children with CMPA, we found a significant positive correlation between dietary intake of vitamin D and concentration of 25(OH) vitamin D in blood serum (r = 0.53, p < 0.05).

Discussion

The child's diet, regardless of its type, should provide an adequate amount of energy and building components necessary for appropriate development of the growing body. The study of Mowszet, et al. demonstrated that food allergy was the most common reason for malnutrition in children aged up to 5 years [14]. Similarly, Gębala, et al. in the study on 571 children aged 1-18 years (mean age of 4.5 years), found that 21.7% (N = 124) of these subjects were underweight of whom in 22.6% (N = 28) the identified reduced body weight resulted from food allergy [15]. Meyer, et al. also found, in the study conducted in the UK, that children with allergy were more often underweight than the entire population of children in England, also noting that it was dependent not only on adequacy of dietary intake, but also on the course of allergy [16]. Interesting results were obtained by Tuokkola, et al. in a study on children with CMPA treated with a milk-free diet, where nutritional intake at age 1, 2 and 3 was assessed and anthropometric measurements were made once a year until the age of 5. The authors found that, despite the balanced diets, the growth of these children was slower compared to healthy children on a traditional diet [17]. Similarly, Flammarion, et al. proved that children with allergy (mean age 4.7 ± 2.5 years) were smaller for their age than controls even when they received similar nutrient intakes [18]. Our work seems to confirm these observations, since the energy value of the diets of children with CMPA was higher not only compared to recommendations, but also compared to the diet of children from the control group. Nevertheless, the nutritional status of children from both groups, assessed on the basis of anthropometric parameters, was not only appropriate, but also not significantly different. Paganus, et al. believe that children with CMPA require increased energy intake due to inflammation, i.e. skin or gastrointestinal [19]. In our study, 41.6% of children with CMPA had gastrointestinal symptoms, 16.6% atopic dermatitis, and 12.5% respiratory symptoms, while 29.1% had symptoms from more than one system.

Children with CMPA or multiple allergies are at risk of consuming less than recommended amount of calcium and vitamin D. Vitamin D deficiencies in the diets of children with food allergies (mean age 4.7 years), but also in a control group, were found by Flammarion, et al. [18]. In the work of Christie, et al. covering 98 children with food allergy, with mean age of 3.7 ± 2.3 years, and 99 controls at a similar age, dietary records obtained in 66% and 64%, respectively, showed that more than 25% of children in both groups consumed less than 67% of RDA/RDI (Recommended Dietary Allowances/Recommended Dietary Intake) for calcium and vitamin D. The authors also point out that the nutritional counselling and introduction a safe infant/toddler formula or fortified soy beverages into the diet decrease the risk of insufficient intake of calcium and vitamin D in children with food allergy [20]. Our study proved that consumption of vitamin D in both groups of children did not meet the EAR, but the children with allergy consumed significantly more of this vitamin, which could be due to consumption of fortified foods by 75% of these children. Such foods provided 1.7 µg of vitamin D to those children, while milk and milk products supplied only 0.1

Table 5: Correlations between dietary intake of selected components and their concentration in blood serum of children with CMPA.

Correlation between intake and concentration in blood serum	R	P value
Calcium (Ca)	-0.30	0.08
Phosphorus (P)	-0.18	0.3
Magnesium (Mg)	0.04	0.8
Iron (Fe)	-0.06	0.7
Vitamin D	0.53	0.001*

R: Pearson's correlation coefficient; *p < 0.05.

µg of this vitamin in the control group. Therefore, our study, similarly to the study by Sidnell, et al., shows that fortified foods contributed to the better balancing of the children's diets in terms of vitamin D [21]. Canani, et al. also observed a positive impact of supervision of a physician and a dietician on the balancing of the diets of children with food allergies. The authors argue that such supervision also results in a significant improvement of anthropometric and laboratory biomarker of nutritional status of those children [22]. This is further confirmed by the results of the study by Medeiros, et al. [23]. The concentration of 25(OH) vitamin D in blood serum of children with CMPA was 26.6 ng/l and was within the range of suboptimal values, although the study was performed in summer months during which skin synthesis of vitamin D is the most effective. In addition, it should be emphasized that approximately 50% of the children received vitamin D supplements. According to "Practical guidelines for the supplementation of vitamin D and the treatment of its deficits in Central Europe", blood serum concentration of 25(OH) vitamin D within the range of 0-50 nmol/l (0-20 ng/ml) is considered to indicate deficiency of the vitamin, the concentration > 50-75 nmol/l (> 20-30 ng/ml) is considered suboptimal, > 75-125 nmol/l (> 30-50 ng/ml)-optimal, while > 125-250 nmol/l (> 50-100 ng/ml)-high [13]. The concentration of 25(OH) vitamin D in blood serum of children from the control group amounted to 30.5 ng/ml on average and was within optimal range, and vitamin D supplementation was received by only around 10% of the children. The lower concentration of 25(OH) vitamin D in blood serum of children with allergy, combined with a higher content of this vitamin in the diet, could result from its impaired bioavailability due to gastrointestinal inflammation caused by allergy. It is possible that the observed differences in the status of vitamin D in children from both groups could also result from different exposure to sun rays and application or non-application of creams with SPF filters during the exposure, which was not analysed in this work. In the group of children with CMPA, there is also a positive correlation between the vitamin D intake in the diet and the concentration of 25(OH) vitamin D in blood serum. The observed correlation may indicate that the compliant with recommendations vitamin D dietary intake in children with CMPA is important for optimal vitamin D status, although its main source is skin synthesis. The importance of consumption of foods fortified with vitamin D for achieving an appropriate concentration of 25(OH) vitamin D in blood serum of children is also confirmed by the study of Houghton, et al. [24].

The calcium intake in the diets of children from both groups did not differ significantly and was lower than recommended. In a similar percentage of children on a milk-free and traditional diet (93.8% vs. 90.0%) the intake of calcium was below EAR. The diet of children with CMPA, although insufficient in calcium, is more diversified in terms of dietary sources of this nutrient than the diet of healthy children where dairy products are almost the only source of calcium. It is possible that the lack of differences in calcium concentration, despite the suboptimal vitamin D status in children with CMPA could result from calcium supplementation used in 15% of these children, but also mobilization of calcium stores out from bones. Insufficient supply of calcium and vitamin D, in particular in childhood, may result in disturbances of calcium metabolism and in consequence in development of such diseases as rickets, osteopenia, or osteoporosis which lead to disability [25,26]. Ambroszkiewicz, et al. note that children with CMPA, despite the correct values of basic parameters of calcium and phosphorus balance, have a lower level of sclerostin and increased cytokine ratio RANK/OPG, which may point to disturbances of the balance between bone formation and resorption [27]. The results of the study by Mailhot, et al. of pre-puberty children with persistent CMPA allergy showed that in the group of these children lumbar spine BMD (Bone Mineral Density) z-scores were significantly lower compared to the control group. Low bone mass was detected in 6% of children from this group compared with none in the controls. At the same time, the vitamin D status assessed based on concentration of 25(OH) vitamin D in blood serum of children with allergy was not reduced compared with control subjects, but this group had a lower calcium intake. Furthermore, in approximately 50% of children with allergy, the use of calcium and vitamin D supplements was declared [28]. Numerous authors point to adverse effects of long-term milk-free diet in children with allergy. The studies by Infante, et al. show that approximately 50% of children (2-14 years, mean age 7 years) treated with a milk-free diet had osteopenia or osteoporosis [29]. Hidvegi, et al. found low bone density in approximately 30% of children with CMPA [30]. Black, et al. also note that in growing children (3-10 years) long term avoidance of cow's milk is associated with short stature and poor bone health assessed based on bone mineral density with dual-energy X-ray absorptiometry [26].

Bone health requires adequate intake of i.a. protein, magnesium, phosphorus, zinc and vitamin C. The intake of those nutrients was not deficient in the diets of children from both groups and did not differ significantly. Blood serum concentration of phosphate and magnesium did not reveal any differences and was within the reference range.

The diets of children with CMPA allergy may be deficient in iron. In the study by Salman, et al. in children with allergy, aged 1-9, iron consumption was below 67% of RDA (Recommended Dietary Allowances) [31]. In our observation, iron intake in the diets of children with CMPA was higher than recommended (EAR - Estimated Average Requirement) and also significantly higher than the intake in the diets of children from the control group. Furthermore, in all children with CMPA the rec-

ommended level of intake for this nutrient was achieved. This could be due to consumption of fortified foods; the children could also consume different types of meat, including veal and beef which are a good source of easily absorbed hem iron. Adequate iron intake is necessary for erythropoiesis. Iron is a component of haemoglobin, myoglobin, it is present in tissue enzymes, participates in immune processes, is co-responsible for integrity of intestinal barrier. Children from both groups received adequate amounts of this dietary component, since none of them was diagnosed with iron deficiency or iron deficiency anemia.

Oh, et al. suggest that the increased risk of development of allergies is due to insufficient intake of foods being the source of antioxidants in the diet. They argue that in children with allergy (mean age 5.3 ± 0.9 y) risk of Atopic Dermatitis (AD) was associated negatively with intakes of antioxidant related nutrients and AD was predicted better by the intake measure than the corresponding blood biomarkers regarding vitamin E and beta-carotene [32]. Patel, et al. observing an unselected cohort of 861 children from birth until the age of 8, found that increased beta-carotene intake was associated with a reduced risk of allergic sensitization and lower IgE levels in 5 and 8-year-old children [33].

Our study found that the dietary intake of vitamin E in allergic children was significantly higher, compared to the control group. We also did not observe the risk of vitamin E, A and C deficiency in group of children with CMPA.

It should also be noted that the diets of children with CMPA contained significantly more LCPUFA, and the percentage of children who did not achieve the nutritional standard for this diet component determined at AI (Adequate Intake) was lower than in control group, though insignificantly. It is important, since LCPUFA hamper excessive immune reaction and have anti-inflammatory and anti-allergic properties [34]. Adequate intake of long-chain polyunsaturated fatty acids LCPUFA is one of dietary factors affecting the skin condition. In the group of children with allergy, in 16.6% of children atopic dermatitis was the only clinical manifestation of allergy or accompanied its other symptoms [35]. The study by Kim, et al. on children with atopic dermatitis shows that 4-month individualised elimination diet, by improving the nutrient intake, is useful for alleviating the severity of atopic dermatitis and improving the growth status [36].

Conclusion

Milk-free diets in children with CMPA were adequate for most nutrients, but the children are at risk of vitamin D insufficiency, despite the higher vitamin D content of their diets compared to the group of healthy children. The better balancing of the diets of children with allergy was probably due to continuous medical and nutritional care provided by paediatricians and dieticians.

Conflict of Interest

The authors declare no conflict of interest.

Authors Contributions

According to the order of the authorship.

Acknowledgment

References

1. Hochwallner H, Schulmeister U, Swoboda I, Spitzauer S, Valenta R (2014) Cow's milk allergy: From allergens to new form of diagnosis, therapy and prevention. Methods 66: 22-33.

2. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, et al. (2012) Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 55: 221-229.

3. Kaczmarski M, Maciorowska E, Semeniuk J, Daniluk U, Gorał M (2004) Dieta eliminacyjna w alergii pokarmowej. Prz Alergol 1: 30-34.

4. Henriksen C, Eggesbø M, Halvorsen R, Botten G (2000) Nutrient intake among two-year-old children on cows' milk-restricted diets. Acta Paediatr 89: 272-278.

5. Barreto-Chang OL, Pearson D, Shepard WE, Longhurst CA, Greene A (2010) Vitamin D - deficient rickets in a child with cow's milk allergy. Nutr Clin Pract 25: 394-398.

6. Barker DJ (1995) Fetal origins of coronary heart disease. BMJ 311: 171-174.

7. Gronowska-Senger A (2013) Przewodnik metodyczny badań sposobu żywienia. Komitet Nauki o Żywieniu Człowieka Polskiej Akademii Nauk, Warszawa.

8. Szponar L, Wolnicka K, Rychlik E (2011) Photograph Album of Food Products and Dishes. National Food and Nutrition Institute, Warsaw.

9. Wajszczyk B, Chwojnowska Z, Nasiadko D, Rybaczuk M (2015) Dieta 5.0 software for individual and group nutrition assessment and diet planning. National Food and Nutrition Institute, Warsaw.

10. Jarosz M (2012) Normy żywienia dla populacji polskiej-nowelizacja. Instytut Żywności i Żywienia, Warszawa.

11. WHO (2006) The WHO child growth standards.

12. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, et al. (2007) Development of a WHO growth reference for school-aged children and adolescents. Bulletin of the World Health Organization 85: 660-667.

13. Płudowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokół D, et al. (2013) Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe - recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol 64: 319-327.

14. Mowszet K, Piasecka A, Reich M, Iwańczak F (2005) Causes of malnutrition in children under the age of 5 years in own material. Adv Clin Exp Med 14: 315-322.

15. Gębala A, Czaja-Bulsa G, Korlatowicz-Bilar A, Woźniak-Prajwowska A, Ogrodowska M, et al. (2008) Ocena stanu odżywienia u dzieci hospitalizowanych z różnych przyczyn pediatrycznych. Pediatr Współcz Gastroenterol Hepatol Żywienie Dziecka 10: 133-136.

Rowicka et al. Int J Aller Medications 2017, 3:025

• Page 7 of 8 •

16. Meyer R, De Koker C, Dziubak R, Venter C, Dominguez-Ortega G, et al. (2014) Malnutrition in children with food allergies in the UK. J Human Nutr Diet 27: 227-235.

17. Tuokkola J, Luukkainen P, Nevalainen J, Ahonen S, Toppari J, et al. (2017) Eliminating cows' milk, but not wheat, barley or rye, increases the risk of growth deceleration and nutritional inadequacies. Acta Paediatr 106: 1142-1149.

18. Flammarion S, Santos C, Guimber D, Jouannic L, Thumerelle C, et al. (2011) Diet and nutritional status of children with food allergies. Pediatr Allergy Immunol 22: 161-165.

19. Paganus A, Juntunen-Backman K, Savilahti E (1992) Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatr 81: 518-521.

20. Christie L, Hine RJ, Parker JG, Burks W (2002) Food allergies in children affect nutrient intake and growth. J Am Diet Assoc 102: 1648-1651.

21. Sidnell A, Pigat S, Gibson S, O'Connor R, Connolly A, et al. (2016) Nutrient intakes and iron and vitamin D status differ depending on main milk consumed by UK children aged 12-18 months-secondary analysis from the Diet and Nutrition Survey of Infants and Young Children. J Nutr Sci 5: e32.

22. Canani BR, Leone L, D'Auria E, Riva E, Nocerino R, et al. (2014) The effects of dietary counseling on children with food allergy: A prospective, multicenter intervention study. J Acad Nutr Diet 114: 1432-1439.

23. Medeiros LC, Speridião PG, Sdepanian VL, Fagundes-Neto U, Morais MB (2004) Nutrient intake and nutritional status of children following a diet free from cow's milk and cow's milk by-products. J Pediatr 80: 363-370.

24. Houghton LA, Gray AR, Szymlek-Gay EA, Heath AL, Ferguson EL (2011) Vitamin D-fortified milk achieves the targeted Serum 25-Hydroxyvitamin D concentration without affecting that of Parathyroid Hormone in New Zealand Toddlers. J Nutr 141: 1840-1846.

25. Morris HA, Turner AG, Anderson PH (2012) Vitamin-D regulation of bone mineralization and remodelling during growth. Front Biosci (Elite Ed) 4: 677-689.

26. Black RE, Williams SM, Jones IE, Goulding A (2002) Children who avoid drinking cow milk have low dietary calcium intakes and poor bone health. Am J Clin Nutr 76: 675-680.

27. Ambroszkiewicz J, Rowicka G, Chełchowska M, Gajewska J, Strucińska M, et al. (2013) Serum concentrations of sclerostin and bone turnover markers in children with cow's milk allergy. Med Wieku Rozwoj 17: 246-252.

28. Mailhot G, Perrone V, Alos N, Dubois J, Delvin E, et al. (2016) Cow's milk allergy and bone mineral density in prepubertal children. Pediatrics 137: e20151742.

29. Infante D, Tormo R (2000) Risk of inadequate bone mineralization in diseases involving long-term suppression of dairy products. J Pediatr Gastroenterol Nutr 30: 310-313.

30. Hidvégi E, Arató A, Cserháti E, Horváth C, Szabó A, et al. (2003) Slight decrease in bone mineralization in cow milk-sensitive children. J Pediatr Gastroenterol Nutr 36: 44-49.

31. Salman S, Christie L, Burks W, Mccabe-Sellers B (2002) Dietary intakes of children with food allergies: Comparison of the food guide pyramid and the recommended dietary allowances 10th ed. J Allergy Clin Immunol 109: S214.

32. Oh SY, Chung J, Kim MK, Kwon SO, Cho BH (2010) Antioxidant nutrient intakes and corresponding biomarkers associated with the risk of atopic dermatitis in young children. Eur J Clin Nutr 64: 245-252.

33. Patel S, Murray CS, Woodcock A, Simpson A, Custovic A (2009) Dietary antioxidant intake, allergic sensitization and allergic diseases in young children. Allergy 64: 1766-1772.

34. Kelley DS (2001) Modulation of human immune and inflammatory response by dietary fatty acids. Nutrition 17: 669-673.

35. Bojarowicz H, Woźniak B (2008) Wielonienasycone kwasy tłuszczowe oraz ich wpływ na skórę. Probl Hig Epidemiol 89: 471-475.

36. Kim SH, Lee JH, Ly SY (2016) Children with atopic dermatitis in Daejeon, Korea: Individualized nutrition intervention for disease severity and nutritional status. Asia Pac J Clin Nutr 25: 716-728.