







Effect of exclusion diet on the nutritional status of children and adolescents with cow's milk protein allergy: a retrospective study

Efeito da dieta de exclusão sobre o estado nutricional de crianças e adolescentes com alergia à proteína do leite de vaca: um estudo retrospectivo

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ABSTRACT

Objective: To describe the anthropometric parameters of patients with cow's milk protein allergy (CMPA) followed up at a tertiary-care hospital before and after the initiation of a cow's milk exclusion diet. **Methods:** Observational retrospective study of patients aged zero to 18 years with a diagnosis of CMPA who started specialized follow-up from 2015 until the first semester of 2021 at the food allergy outpatient clinic in a tertiary hospital in the interior of São Paulo. **Results:** The study included 278 patients, 3,629 weight measurements and 2,983 length/height measurements, allowing for the calculation of 2,985 Body Mass Index (BMI), with a mean age of symptom onset of 6.4 [± 11.7] months, mean age of cow's milk exclusion diet start of 9.6 [± 14.2] months, and mean age of specialized care start of 3.1 [± 2.8] years. A significant decrease in Z-scores for weight, height, and BMI for age occurred after birth, with progressive recovery after the cow's milk exclusion diet. The exclusion diet appears to have a greater impact on growth recovery than the initiation of specialized follow-up. In the long term, the same patients had a trend toward overweight and obesity. **Conclusions:** Children with CMPA showed progressive growth impairment up to the initiation of the cow's milk exclusion diet, after which they exhibited recovery of all parameters. In the long term, there is an increase in the proportion of patients with overweight and obesity.

Keywords: Food allergy, Milk hypersensitivity, Child nutrition disorders, Growth and development.

RESUMO

Objetivo: Descrever os parâmetros antropométricos dos pacientes com alergia à proteína do leite de vaca (APLV) em seguimento em um hospital terciário, antes e depois do início do tratamento com dieta de exclusão do leite de vaca (LV). **Métodos:** Estudo observacional retrospectivo de zero a 18 anos com diagnóstico de APLV que iniciaram seguimento de 2015 até o primeiro semestre de 2021 no ambulatório de alergia alimentar de um hospital terciário do interior paulista. **Resultados:** O estudo incluiu 278 pacientes e 3.629 medidas de peso e 2.983 medidas de comprimento/estatura, permitindo o cálculo de 2.985 índices de massa corporal (IMC), com idade média do início dos sintomas de 6,4 [± 11,7] meses, idade média de início da dieta de exclusão do LV de 9,6 [± 14,2] meses, e idade média à primeira consulta especializada de 3,1 [± 2,8] anos. Ocorreu uma queda significativa dos escores Z do peso, estatura e IMC para idade após o nascimento com recuperação progressiva após o início da dieta de exclusão do LV. A dieta de exclusão parece ter maior

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repercussão sobre a recuperação do crescimento do que o início do seguimento especializado. Em longo prazo, os mesmos pacientes parecem ter uma tendência a sobrepeso e obesidade. Conclusões: Crianças com APLV apresentaram déficit de crescimento progressivo até o início da dieta de exclusão do LV, após o que apresentaram recuperação de todos os parâmetros. Em longo prazo, há aumento da proporção de pacientes com sobrepeso e obesidade.

Palavras-Chave: Alergia a alimentos, Hipersensibilidade a leite, Transtornos da nutrição infantil, Crescimento e desenvolvimento.

INTRODUCTION

Cow's milk protein allergy (CMPA) is the most common food allergy in children under three years, whereas symptoms suggestive of the disease can be found in 5 to 15% of pediatric patients¹. It clinically manifests with gastrointestinal, mucocutaneous, and respiratory symptoms, which can occur immediately or later after cow's milk protein consumption. The disease can trigger immunoglobulin E (IgE)-mediated or non-IgE-mediated reactions¹. Diagnosis is based on the clinical history and, in the case of suspected IgE-mediated CMPA, with the assistance of complementary tests such as skin tests or serum-specific IgE levels. An exclusion diet is also essential for diagnosing suspected cases of non-IgE-mediated CMPA. The primary treatment involves excluding cow's milk protein from the child's or the mother's diet if exclusively breastfeeding¹.

Children with food allergies have an altered intestinal barrier, possibly caused by a secondary hypersensitivity². This local reaction increases the mucous membrane permeability and reduces the utilization of nutrients³. This functional alteration adds difficulty in implementing an exclusion diet that also meets the child's nutritional needs. These factors can negatively impact the nutritional status, growth, and development of children with CMPA, even after diagnosis and the initiation of the exclusion diet.

However, European studies have observed that children with CMPA have impaired growth only before treatment, with good recovery after the cow's milk exclusion diet^{4,5}. In another study conducted in Brazil,

a high prevalence of nutritional deficits was found in infants with CMPA in the initial assessment: about 15% had low weight for age, and 24% had low height for age⁶. Besides, early disease onset was more closely related to growth delay⁷. Therefore, exclusion diets should be prescribed not only to control the allergic symptoms but also to prevent malnutrition. Therefore, once CMPA is diagnosed, initiation of treatment is essential. The exclusion of cow's milk should be carried out appropriately with nutritionally adequate substitutions⁸. For a successful treatment, these children require intensive nutritional and growth monitoring⁹.

However, there are few comprehensive studies of the effects of the disease on the nutritional status of these patients, and it is unclear whether the initiation of treatment promotes growth recovery.

Therefore, this study aims to describe the anthropometric parameters of patients with CMPA followed up at a tertiary hospital before and after the initiation of the cow's milk exclusion diet.

METHODS

This is a retrospective observational study. Ethical aspects of the study were conducted following Brazilian regulations (Resolution CNS 466/2012) and were approved by the Research Ethics Committee (CAAE: 50901521.2.0000.5440, Approval Number: 4.943.343, issued on 08/31/2021), and informed consent was waived. The study was conducted at a tertiary-care university hospital in the countryside of São Paulo state. Patients with suspected or

confirmed CPMA who started receiving specialized care at the food allergy outpatient clinic between January 2015 and June 2021 were eligible. A search for the ICD-10 code for CPMA (T78.1) was used to identify the eligible patients. Then, their electronic medical charts were reviewed by allergy specialists to confirm the diagnosis. Patients were excluded when CPMA was ruled out.

The following variables were collected from electronic medical charts: name, gender, date, age at the first appointment at the food allergy outpatient clinic, date of birth, birth weight and length, signs and symptoms that led to CPMA suspicion, duration of exposure to cow's milk protein before symptoms, duration of dietary exclusion before the consultation at the food allergy outpatient clinic, alternative diet, levels of specific IgE for cow's milk, comorbidities, other associated food allergies, and all the patient's height and weight measurements throughout the follow-up. The anthropometric indices used were weight, height, and body mass index (BMI), calculated by dividing weight (in kilograms) by the square of height (in meters). Google® Sheets (Alphabet Inc., Mountain View, USA) spreadsheets were used for data collection.

Weight and length or height measurements were digitally extracted from the electronic medical records for all patient visits, covering the period from birth to the most recent visit. The number of anthropometric measurements varied for each patient, as well as the follow-up time and number of consultations performed. The data were reviewed for inconsistencies in units (grams versus kilograms, centimeters versus meters) and implausible values (outliers), which were corrected or excluded from the database. Z-scores for weight for age, length or height for age, and BMI for age were calculated according to the 2006 WHO standard curves (0 to 5 years) or the

2007 WHO reference curves (5 to 19 years). For the analysis of BMI, patients were categorized as underweight (Z-score < -2), eutrophic (Z-score between -2 and +2 up to 5 years, and between -2 and +1 after 5 years), overweight (Z-score between +2 and +3 up to 5 years, and between +1 and +2 after 5 years), or obese (Z-score > +3 up to 5 years, and > +2 after 5 years).

All anthropometric measurements were grouped as follows: measurements at birth, measurements before the start of specialized care or the cow's milk exclusion diet (split at the median), and measurements after the start of specialized care or cow's milk exclusion diet (split into quartiles). By using this approach, some patients could have more than one measurement in each of these time periods.

Statistical Analysis

The results were summarized as mean [standard deviation] or absolute frequency (percentage) as appropriate. StataSE 14.0 (StataCorp, College Station, USA) and SAS 9.4 (The SAS Institute, Cary, USA) softwares were used for the statistical analysis. For Z-scores calculation, the zanthro Stata package was used¹⁰. Comparisons between proportions were performed using the chi-squared test. Comparisons of the same measurements at different time points were conducted using a linear mixed-effects model. A significance level of 5% was adopted.

RESULTS

A total of 278 patients were included (Figure 1), along with 3,629 weight measurements and 2,983 length/height measurements (allowing for the calculation of 2,985 BMIs). The demographic data of the patients are summarized in Table 1.

Figure 1. Patient selection flowchart.

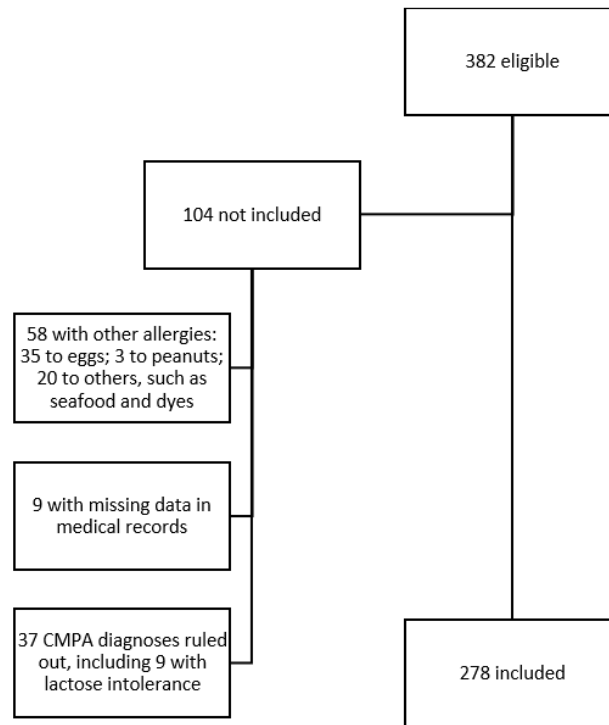


Table 1. Demographic and clinical data (n=278)

Characteristic	Result
Sex	
Male	165 (59%)
Female	113 (41%)
Age at symptom onset (months)	6.4 [11.7]
Clinical presentation	
Anaphylaxis	30 (10.8%)
Gastrointestinal manifestations	189 (68.0%)
Cutaneous manifestations	123 (44.2%)
Respiratory manifestations	36 (13.0%)
Exposure time	
Immediate	124 (44.6%)
Late	153 (55.0%)
Immediate and late	1 (0.4%)
Comorbidities	
Allergic rhinitis	146 (52.5%)
Atopic dermatitis	42 (15.1%)
Asthma or wheezing	66 (23.7%)
Gastroesophageal reflux disease	17 (6.1%)
Other*	38 (13.7%)
Associated allergies	
Egg	62 (22.3%)
Soy	26 (9.4%)
Peanut	13 (4.7%)
Other**	44 (15.8%)
Age at the start of cow's milk exclusion	9.6 [14.2]

(months)	
Age at the start of follow-up at the food allergy outpatient clinic (years)	3.1 [2.8]
Specialized follow-up time (months)	25.5 [25.2]
Alternative diet	
Soy formula	82 (29.5%)
Amino acid-based formula	77 (27.7%)
Extensively hydrolyzed formula	45 (16.2%)
Breastfeeding	40 (14.4%)
None	19 (6.8%)
Rice milk	4 (1.4%)
Calcium supplementation	4 (1.4%)
Almond milk	3 (1.1%)
Coconut milk	2 (0.7%)
Oat milk	1 (0.4%)
Goat milk	1 (0.4%)

Legend: The data is expressed as frequency (percentage) or mean [standard deviation]. * Constipation, chronic urticaria, humoral immunodeficiencies, autism, bronchiolitis obliterans, congenital kidney and urinary tract anomalies, congenital heart disease, diabetes mellitus, eosinophilic esophagitis, microcephaly, epilepsy, osteogenesis imperfecta type 1, cerebral palsy, Noonan syndrome, Down syndrome, Edwards syndrome, and inflammatory bowel disease; ** Meats, fruits, tubers, legumes, nuts, seafood, fish, latex, and pharmaceuticals.

Analysis regarding the time of cow's milk exclusion

All patients in the study began the cow's milk exclusion diet before the start of specialized care, except for one patient. On average, patients started the exclusion diet 28 [± 30] months before their first appointment in the food allergy outpatient clinic. The Z-scores for weight for age, BMI for age, and length/height for age showed a significant decline after birth until the start of cow's milk exclusion, when there was a significant recovery over time. The recovery

of BMI seemed to start just before cow's milk exclusion.

Analysis regarding specialized follow-up

The Z-scores for weight for age, before and after the start of follow-up in the specialized food allergy outpatient clinic, showed significant variations over time, with a drop after birth and significant recovery that began even before the start of specialized care.

As for the Z-scores for BMI for age, before and after the start of follow-up in the specialized food allergy outpatient clinic, a smaller but significant variation over time was observed, with a progressive increase even before the start of specialized follow-up.

Likewise, the Z-scores for length/height for age, before and after the start of follow-up in the specialized food allergy outpatient clinic, showed a slight but significant variation over time, especially a drop shortly after birth and a slow recovery.

Comparison between the two approaches

Figure 2 displays the average Z-

scores for weight, length/height, and body mass index (BMI) for age at birth and at different times before and after the initiation of cow's milk exclusion from the diet. This figure shows a decline in all parameters between birth and the start of cow's milk exclusion from the diet, with progressive recovery afterward. Although less pronounced, the same pattern can be seen in Figure 3, which presents the same parameters but in relation to the beginning of the specialized care, nutritional recovery seems to occur even before the start of follow-up at the food allergy outpatient clinic (3.1 ± 2.8 years), suggesting that it is associated with the initiation of cow's milk exclusion, which occurred earlier, on average (9.6 ± 14.2 months).

Figure 2. Mean Z-scores for weight, length/height, and body mass index (BMI) by age at birth and at different time points (months) before and after the start of cow's milk exclusion from the diet.

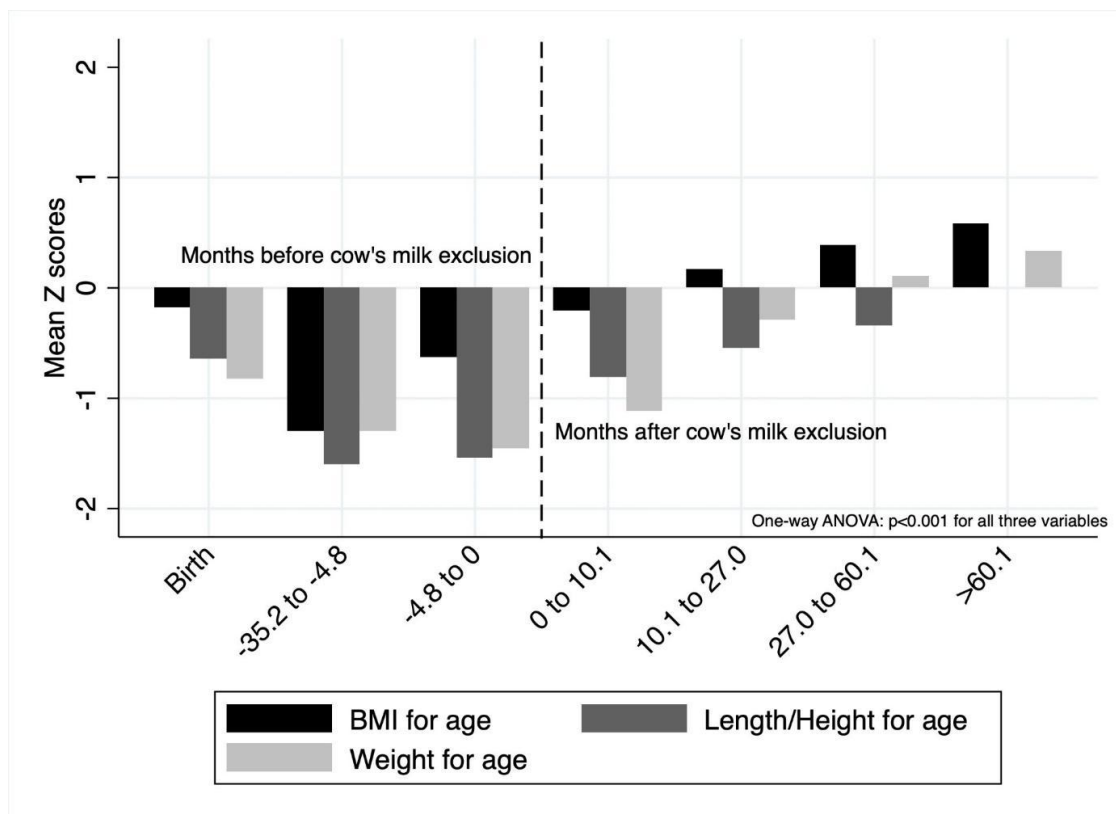
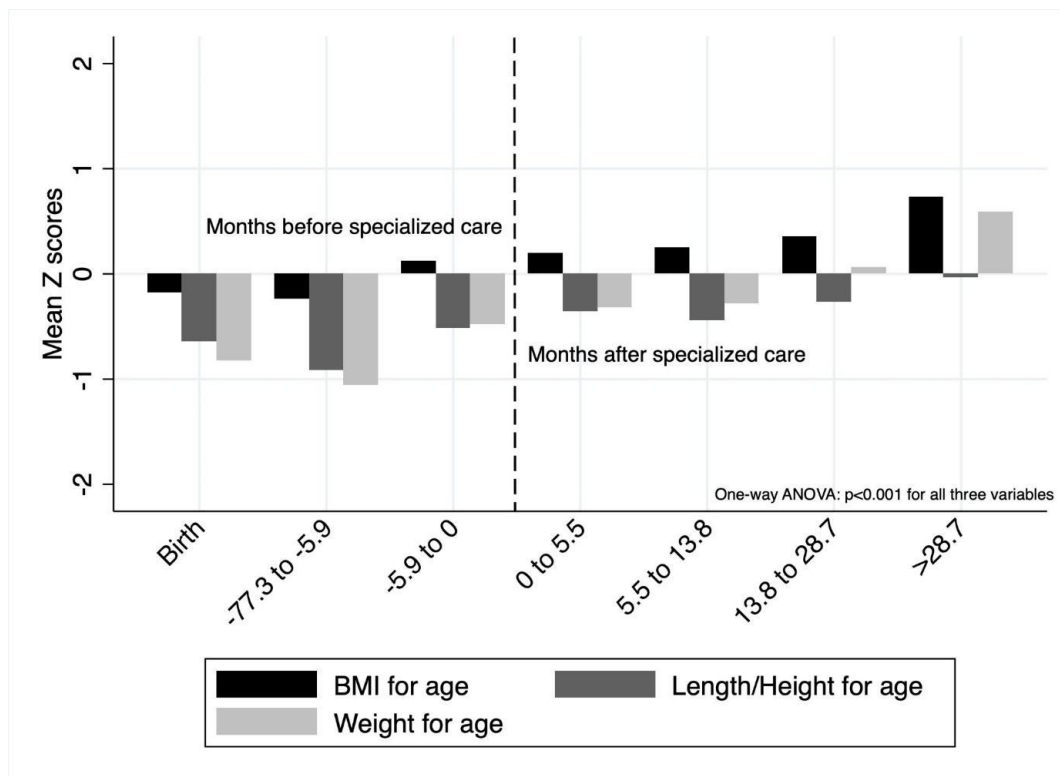


Figure 3. Mean Z-scores for weight, length/height, and body mass index (BMI) for age at birth and at different time points (months) before and after the start of specialized follow-up at the food allergy outpatient clinic.

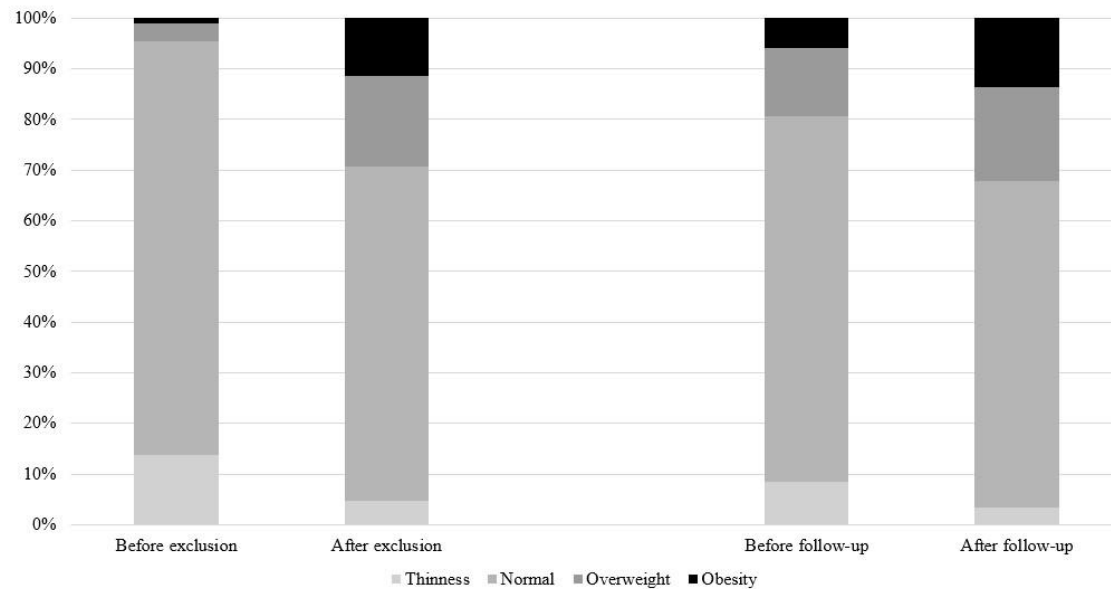


Analysis of categorized nutritional diagnosis

Figure 4 shows the proportions of the main categories of BMI (underweight, eutrophy, overweight, and obesity) before and after the cow's milk exclusion diet and

before and after the follow-up in the food allergy outpatient clinic. There was a significant decrease in the proportion of underweight patients and an increase in the proportion of overweight and obese patients ($p < 0.001$ for both comparisons).

Figure 4. Proportion of Z-scores for body mass index categorized as underweight, normal weight, overweight, and obesity before and after the start of cow's milk exclusion from the diet and before and after the start of specialized follow-up at the food allergy outpatient clinic.



DISCUSSION

This study revealed that patients with CMPA had failure-to-thrive prior to the initiation of the cow's milk exclusion diet, followed by clear catch-up growth once the diet was implemented. The exclusion diet appears to have a more significant impact on growth recovery than the initiation of specialized follow-up. In the long term, these patients seem to have a trend towards excess weight.

Most of the studied patients were male and predominantly presented with gastrointestinal symptoms. Comorbidities such as allergic rhinitis and other atopic diseases were observed in over half of the patients. Concerning nutritional status, the mean Z-scores of weight and height for age at birth were below zero, indicating that the studied patients were born smaller and lighter than expected. Nevertheless, the BMI for age at birth remained close to zero, indicating proportionality in the measurements presented.

The studied patients showed a

progressive decrease in weight and height Z-scores after birth, possibly starting around the onset of CMPA symptoms. Most patients were not undernourished before treatment initiation, but the cow's milk exclusion diet led to a significant increase in weight and height gain. This recovery occurred within the first few months of the cow's milk exclusion diet, even before specialized care was offered. This indicates that excluding cow's milk from the diet of patients with CMPA is generally effective in restoring weight and height, especially when started early. It also highlights the significance of proper diagnosis and treatment, irrespective of the availability of specialized follow-up.

We found an important difference between the age at symptom onset and the age at the start of follow-up at the food allergy outpatient clinic of the tertiary hospital. The difference is likely attributed to the delayed access of these patients to an allergy specialist through the public healthcare system. Consequently, most patients initially receive care from a pediatrician, who suspects the possibility of

CMPA and initiates an exclusion diet before being referred to a specialist for diagnostic confirmation and clinical follow-up.

When each anthropometric measurement obtained during the follow-up was separately analyzed, there was a significant reduction in the proportion of underweight after the cow's milk exclusion diet (from 13.8% to 4.6%) and specialized follow-up (from 8.5% to 3.4%). Furthermore, the proportion of measurements categorized as overweight and obesity increased significantly after the cow's milk exclusion diet, from 3.5% to 17.8% overweight and from 1.1% to 11.5% obesity. These data suggest the importance of looking at the nutritional quality of these patients' diets, which may involve inappropriate food substitution.

A cross-sectional study conducted in the metropolitan region of São Paulo found that a group of patients who had been following a cow's milk exclusion diet for at least one month had worse nutritional status compared to children without dietary restrictions despite being fed larger quantities of energy and macro and micronutrients¹¹. This contrast could be explained, firstly, by the static analysis of the measurements in the study, which does not show the trends of anthropometric measurements over time. Another explanation could be the pathophysiology involved in CMPA, where sustained allergic inflammation and increased intestinal permeability lead to reduced nutrient utilization. In this sense, strict adherence to the cow's milk exclusion diet leads to the elimination of the antigen from the intestine, and intestinal inflammation can be controlled. This phenomenon can explain the trend toward normalization of weight and BMI for age Z-scores after treatment initiation.

On the other hand, a study conducted in Poland found no significant differences in excessive caloric intake and nutritional status between patients following a cow's milk exclusion diet and those with

unrestricted diets¹². This discordant result can be explained by the inclusion of patients who had been following the cow's milk exclusion diet for more than six months. This longer period of cow's milk exclusion may have allowed for better dietary adaptation in patients with dietary restrictions in the context of better socioeconomic conditions, as in Europe. Some other studies involving CMPA patients also did not show changes in growth and nutritional status during clinical follow-up^{13,14}.

On the other hand, Meyer et al. demonstrated that the exclusion diet of cow's milk protein led to lower weight-for-height Z-scores than the elimination of other foods and that patients with non-IgE-mediated allergies had lower weight-for-height and BMI¹⁵.

In the United Kingdom, a nutritional survey of CMPA patients showed a less varied overall diet and increased consumption of baby food products despite the lower overall dietary variety and lower variety of meat and sweet foods consumed¹⁶. This result may reflect excessive dietary restriction due to the lack of nutritional guidance or the high prevalence of milk in processed foods. Furthermore, it was found that parents do not seem to compensate for the restriction on cow milk by increasing the variety and consumption of fruits and vegetables. These results can be corroborated by other studies showing a higher frequency of feeding difficulties and selective eating in patients following cow's milk exclusion diets^{17,18}.

In China, a study demonstrated that CMPA patients can achieve normal nutritional status, except for relatively low plasma leptin levels at two years of age¹⁹. This hormonal alteration could not be related to body fat levels, as at this age, the children already had similar amounts of body fat as healthy children. Salmivesi et al. reported a significant increase in plasma leptin in CMPA children after six months of treatment with oral immunotherapy²⁰. This suggests the disease itself could be implicated in the

mechanism of reduced plasma leptin. This hormonal alteration could be involved in the progressive increase in weight and BMI for age found in the studied patients over time.

In our study, we demonstrated a significant improvement in the Z-scores for weight, height, and BMI for age of CMPA patients after the initiation of the cow's milk exclusion diet. This disagrees with studies that showed little or no change in nutritional status with CMPA diagnosis and treatment¹²⁻¹⁴. However, unlike most other studies, our study had a large study population and provided a substantial amount of data over an extended period. We also demonstrated a trend for these patients to become overweight and obese over time, which has not been found in any other study to our knowledge. This highlights the need for further studies on the long-term effects of CMPA and exclusion diets and possible interventions to improve nutritional outcomes.

Several limitations can be recognized in this study, including the lack of a control group to compare the data and the fact that specialized follow-up only began after the initiation of the exclusion diet in nearly all cases due to being conducted in a tertiary-care hospital. This limited the standardization of alternative diet choices and delayed the standardization of nutritional guidance. Additionally, the diagnosis of CMPA was not confirmed through a double-blind, placebo-controlled oral food challenge test, which may have led to an overestimation of the CMPA rate in our study. Another limitation was the lack of information on gestational age, which prevented the correction of anthropometric measurements on reference curves and may have reduced the average Z-scores at birth and in the first months of life. Anthropometric measurements were taken by adequately trained healthcare professionals, but as they were not performed by the same person,

there is also the possibility of small variations in the measurements. Another consideration is that the comparisons were made between all anthropometric measurements obtained in our study without individual patient comparisons. Nevertheless, the number of measurements among patients was similar and representative. This method could create a bias by valuing measurements of patients with more frequent follow-up and, therefore, possibly more comorbidities. However, we believe that these limitations do not compromise our results, as we have a large study population, and our data comprises a period of 6.5 years.

CONCLUSION

Patients with CMPA presented progressive growth impairment (weight, height, and BMI for age) up to the initiation of the cow's milk exclusion diet, after which they exhibited recovery in all parameters. In the long term, there was an increase in the proportion of overweight and obese patients.

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Author's contributions:

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- 3- Involvement in the review and approval of the final version: FC, PSS, PRJ, LDN, GSPLM
- 4- Agreement to be accountable for the accuracy or integrity of any part of the study: LCB, PSS, FC, PRJ, LDN

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