

## ORIGINAL ARTICLE

## Nutrition

# Growth pattern of paediatric patients affected by cow milk protein allergy fed with rice hydrolyzed formula

Rita Nocerino<sup>1,2</sup> | Serena Coppola<sup>1,2</sup> | Laura Carucci<sup>1,2</sup> | Franca Oglio<sup>1,2</sup> |  
Marica Cozzolino<sup>1,2</sup> | Antonio Masino<sup>1,2</sup> | Gulsum Ozen<sup>3</sup> |  
Margherita Farnetano<sup>1,2</sup> | Roberto Berni Canani<sup>1,2,4,5</sup>

<sup>1</sup>Department of Translational Medical Science, University of Naples Federico II, Naples, Italy

<sup>2</sup>ImmunoNutritionLab at CEINGE Advanced Biotechnologies, University of Naples Federico II, Naples, Italy

<sup>3</sup>Department of Pediatrics, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey

<sup>4</sup>European Laboratory for the Investigation of Food-Induced Diseases, University of Naples Federico II, Naples, Italy

<sup>5</sup>Task Force on Microbiome Studies, University of Naples Federico II, Naples, Italy

## Correspondence

Rita Nocerino, Pediatric Allergy Program at the Department of Translational Medical Science, ImmunoNutritionLab at CEINGE—Advanced Biotechnologies, University of Naples “Federico II,” Via S. Pansini 5 80131 Naples, Italy.

Email: [rita.nocerino@unina.it](mailto:rita.nocerino@unina.it)

## Funding information

The study was supported by the Department of Translational Medical Science of the University of Naples “Federico II,” Naples, Italy, which received funding from the National Recovery and Resilience Plan, European Union—NextGenerationEU (On Foods—Research and Innovation Network on Food and Nutrition Sustainability, Safety and Security—Working on Foods), Grant/Award Number: PE0000003

## Abstract

**Objectives:** Formulas made from hydrolyzed rice proteins (HRPF) are well-tolerated plant-based alternatives to cow's milk protein (CMP)-based formulas for the dietary management of paediatric patients with CMP allergy (CMPA). Growth in patients with CMPA fed with HRPF has been evaluated in several studies with conflicting results. The aim was to evaluate the growth pattern of children with CMPA over a 12-month follow-up period.

**Methods:** Prospective cohort study evaluating growth patterns in challenge proven CMPA paediatric patients receiving HRPF for 12 months. Outcomes were anthropometry (body weight, body length, head circumference), adherence to the study formula and occurrence of adverse events (AEs).

**Results:** Sixty-six children were included and completed the 12-month study. At baseline, all CMPA patients were weaned. For the entire CMPA pediatric patients' cohort, from baseline to the end of the study period, the growth pattern resulted within the normal range of World Health Organization (WHO) growth references. The formula was well tolerated. Adherence was optimal and no AEs related to HRPF use were reported.

**Conclusions:** HRPF is well tolerated and can help support healthy growth and development in infants and young children with CMPA. These type of formula can be given with complementary foods in the dietary management of CMPA.

## KEYWORDS

anthropometric measurements, food allergy, malnutrition

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Authors. *Journal of Pediatric Gastroenterology and Nutrition* published by Wiley Periodicals LLC on behalf of European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition.

# 1 | INTRODUCTION

Cow's milk protein allergy (CMPA) is a relevant problem worldwide with lifelong implications for health.<sup>1</sup> With an estimated prevalence of up to 3%, it is one of the most common food allergies and one of the main causes of food-induced anaphylaxis in the paediatric age.<sup>1</sup>

Management of CMPA includes elimination of cow's milk proteins from the diet and identification of suitable alternatives for a nutritionally balanced diet.<sup>2</sup> When breastfeeding is not possible, there are a variety of special formulas for infants and children with CMPA that can be selected based on the patient's age, disease features, and local availability.<sup>2-5</sup>

It has been suggested that compared with breastfeeding, formula feeding is more likely to cause malnutrition in children with CMPA.<sup>6,7</sup>

Formulas for the dietary management of paediatric CMPA contain different protein sources.<sup>4</sup> Regardless of the protein source, these formulas must comply with relevant food regulations, be nutritionally complete to support normal growth and development in infants, and have to undergo clinical trials to support efficacy.<sup>8</sup>

Formulas made from hydrolyzed rice proteins (HRPFs) have been developed and marketed in Europe over the last two decades.<sup>8,9</sup> They are well-tolerated plant-based alternatives to cow milk proteins (CMP)-based extensively hydrolyzed formulas (EHF) for the dietary management of paediatric patients affected by CMPA.<sup>8-14</sup>

Growth in paediatric patients with CMPA fed with HRPFs has been evaluated in several studies with conflicting results. Many studies were focused on small cohorts of patients and were of relatively short duration.<sup>15-18</sup>

In a prospective, nonrandomised, open single-centre study evaluating the growth of infants treated with different formulas during the first 2 years of life, growth was significantly lower in 15 infants (mean age of 2.42 months) fed with HRPF at different time points.<sup>15</sup> Similar results were reported in a randomised trial designed to investigate whether the type of formula used in the complementary feeding period affects growth in infants with CMA. In this study, 30 infants aged from 3 to 6 months, treated with HRPF up to 12 months of age showed negative values for both weight-for-age and length-for-age z-scores at different study points.<sup>16</sup> In contrast, in a study designed to assess whether an HRPF allows normal growth and adequate metabolic balance during a 6-month treatment period in 8 CMPA patients (mean age of 10.7 months), weight and height z-scores remained within expected ranges.<sup>17</sup> In a study aimed to evaluate the hypoallergenicity and safety of a new HRPF for 6 months in 36 CMPA infants of mean age of 3.4 months, weight-for-age and weight-for-length increased significantly towards full normalization during the study.<sup>14</sup> Similarly, in a randomised trial aimed to assess growth, tolerance and plasma biochemistry, 32 infants

## What is Known

- The management of cow's milk protein allergy (CMPA) includes the elimination from the diet of cow's milk protein sources and identifying suitable alternatives for a nutritionally balanced diet.
- Growth in paediatric patients with CMPA fed with rice hydrolysed formula has been evaluated in several studies with conflicting results.

## What is New

- Rice hydrolyzed formula is well tolerated and can help support healthy growth and development in infants and young children with CMPA.
- Rice hydrolyzed formulas can be given with complementary foods in the dietary management of CMPA.

(mean age of 1.8 days) treated with HRPF for 16 weeks showed growth patterns similar to healthy controls treated with CMP-based formula.<sup>18</sup>

Based on this evidence, the present study was designed to evaluate the growth pattern of children with CMPA receiving HRPF for a treatment period of 12 months.

# 2 | METHODS

## 2.1 | Study design and ethics

A prospective cohort study was conducted from September 2020 to December 2022 in a tertiary Centre for Paediatric Allergy.

The study was approved by the Ethics Committee of the University Federico II of Naples and was conducted in accordance with the Helsinki Declaration (Fortaleza revision, 2004), the standards of Good Clinical Practice (CPMP/ICH/135/95), and the pertinent European and Italian regulations on data protection.

## 2.2 | Participants

Non-breastfed paediatric patients (aged 2–24 months) with suspected immunoglobulin E (IgE)-mediated or non-IgE-mediated CMPA were eligible for the study. Patients were referred to the Center by family paediatricians to confirm CMPA diagnosis.

Exclusion criteria were age < 2 or > 24 months at the first evaluation; breastfed infants; concomitant

presence of celiac disease or other chronic gastrointestinal diseases; other allergic diseases; chronic systemic diseases; chronic infectious diseases; autoimmune diseases; immunodeficiencies; malformations; malignancies; genetic and metabolic diseases; cardiac diseases; chronic respiratory tract diseases; cystic fibrosis; history of gastrointestinal tract surgery; treatment with antibiotics in the previous 4 weeks; participation in other studies.

## 2.3 | Patients' evaluation

At baseline, after written informed consent was obtained from the parents/caregivers of all study subjects, the patients were evaluated by a Multidisciplinary Paediatric Allergy Team (MPAT) formed by paediatric allergists, dietitians, and nurses. For all patients the MPAT performed a complete medical history (i.e., type of delivery, gestational age, birth weight, breastfeeding, weaning age, family history of allergy, exposure to passive smoking/maternal smoking during pregnancy) and clinical assessment collecting of all demographic, anthropometric, and clinical data.

Anthropometric measurements were collected according to standardized procedures by calculating the mean of two measurements with the mean of the two closest measurements recorded (see Supporting Information: Appendix 1 for diagnostic study procedures).

Skin prick tests and atopy patch tests with fresh cow's milk were also performed (see Supporting Information: Appendix 1 for diagnostic study procedures).

If the suspected diagnosis of CMPA was confirmed on the basis of the medical history and clinical evaluation, an elimination diet period of 2–4 weeks was started with the use of HRPF (BLEMIL RISO® 1 or 2, Laboratorios Ordesa S. L). The composition of the study formulas is reported in the Supporting Information: Table S1.

In patients with complete resolution of CMPA-related signs and symptoms on the exclusion diet with HRPF, the oral food challenge (OFC) was performed after 2–4 weeks to confirm the diagnosis of IgE- or non-IgE-mediated CMPA, as previously described<sup>19–22</sup> (see Supporting Information: Appendix 1 for diagnostic study procedures). Subjects with a diagnosis of CMPA confirmed by OFC were invited to participate in the study.

Parents/caregivers were instructed on how to follow an adequate CMP-free diet with verbal and written instructions on how to prepare, use and weigh HRPF and solid foods, and how to record daily formula and solid food intake in the standardised a 3-day food record (2 weekdays and 1 weekend day).<sup>23</sup>

It was recommended that patients follow a normocaloric diet (daily energy intake was based on the patient's age and sex), consisting of proteins (population reference intake: 1.00–1.32 g/kg/die), carbohydrates (45%–60% of energy intake [En]), fat (35–40% En; <10% En from saturated fatty acids, 5–10% En from polyunsaturated fatty acids), and fiber (8.4 g/1000 kcal) according to the reference values recommended by the Italian Society of Human Nutrition.<sup>24</sup> Supplementation with calcium and vitamin D was evaluated in case of deficiency and/or inadequate dietary intake.<sup>5</sup> Dietary assessment of energy and nutrient intakes was performed by analyzing the 3-day food records using an ad hoc software (Winfood 3; Medimatica Srl) at each study visit by independent experienced registered dietitians not directly involved in the study and in the patient care.

Then, according to the standard care procedures for patients with CMPA, two visits after 6 and 12 months were planned. During the visits, the MPAT assessed clinical status, the compliance to the CMP-free diet, the growth, the adherence, and the compliance with the HRPF by analysing the 3-day food records administered by the study dietitian and reviewing the notes regarding the HRPF use in the diary recorded by parents. Compliance was judged acceptable if 80% of the recommended HRPF intake was achieved.

Unscheduled visits were made, when necessary, for allergic symptoms or other morbidity.

Adverse events (AEs), serious and nonserious, during the 12-month study period were notified by the investigators and coded according to diagnosis, severity, date of onset, and resolution. They were reported and classified by the investigators as related (definitely, probably, or possibly related) or unrelated (unlikely or not related) to the use of the study formula. All data were recorded in the specific clinical chart.

## 2.4 | Study outcomes

The main study outcome was the weight-for-age z-score (WAZ) of children with CMPA receiving HRPF over a 12-month treatment period compared with the WHO Child Growth Standards.<sup>25</sup>

Explorative analyses were: the WAZ at 6 m from baseline; additional anthropometric measures (weight, g; length, cm; head circumference, cm; weight-to-length ratio) and their Z-scores compared with WHO Standards after 6 and 12 m from baseline; formula intake; and AEs reported throughout the study.

## 2.5 | Sample size

The sample size calculation determined that 63 infants were needed to demonstrate a mean WAZ significantly greater than the non-inferiority margin of  $-0.5$  SD (primary outcome) with a standard deviation of  $1.2$  SD at the  $\alpha$  level of  $0.025$  with  $90\%$  power in a one-tailed  $t$ -test.

The non-inferiority margin of  $-0.5$  SD corresponds to a difference in weight gain of  $3$  g/day, which is considered clinically relevant by the American Academy of Pediatrics.<sup>26</sup> With an estimated dropout rate of up to  $5\%$ , an enrolment target of  $66$  subjects was planned.

## 2.6 | Statistical analysis

A clinical trial monitor reviewed the clinical forms for completeness, clarity, consistency, and accuracy. All the data were collected anonymously and entered into the study database using a single data entry method. The study database was cleaned according to standard procedures and was locked before statistical analysis by the statistical team. The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed, in which case they were reported as mean (SD). Continuous variables that were not normally distributed were reported as median and interquartile range (IQR). Categorical variables were reported as the number and proportion of subjects with the characteristic of interest. Estimated means and  $95\%$  confidence intervals (CIs) of the  $z$ -score at each visit were calculated. According to sample size calculation, a CI approach was used to assess the non-inferiority of the primary outcome, compared to the WHO standards. The estimated mean WAZ and  $95\%$  CI were compared with the non-inferiority margin of  $-0.5$  SD; non-inferiority was demonstrated if the lower limit of the  $95\%$  CI of WAZ was above  $-0.5$  SD. Data between enrolment and after  $6$  and  $12$  months from baseline were compared using paired Student's  $t$ -test. Individual growth trajectories were plotted and examined to gain a better insight into the interindividual variability of growth. The level of significance for all statistical tests was two-sided,  $p < 0.05$ . All analyses were performed using SPSS for Windows (SPSS Inc, version 23.0).

## 3 | RESULTS

A total of  $86$  subjects were assessed for eligibility. Four subjects were excluded due the presence of at least one exclusion criterion,  $5$  due to other diagnoses, and  $11$  were excluded due to negative OFC

leaving a total of  $66$  children ( $54.5\%$  male, mean  $\pm$  SD age of  $9.4 \pm 4.5$  months).

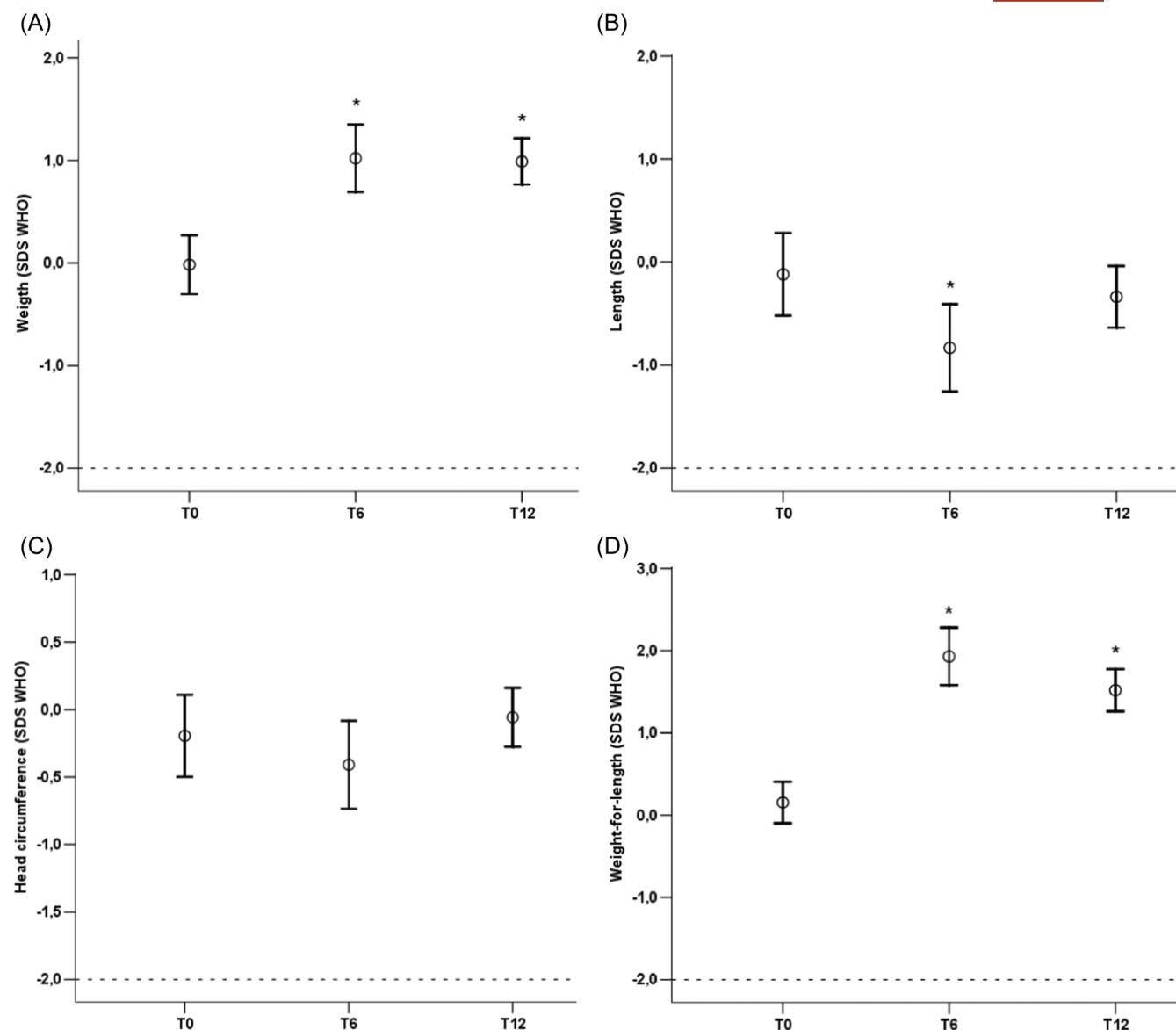
Baseline medical history, demographic, and clinical features of the study population are reported in Supporting Information: Table S2. All patients completed the study without any protocol violations. All children were compliant.

Figure 1 shows the mean ( $95\%$  CI) of the standard deviations score of body weight (panel A), body length (panel B), head circumference (panel C) and weight-for-length ratio (panel D) at baseline, at  $6$  months and at  $12$  months from baseline. The estimated mean ( $95\%$  CI) WAZ after  $12$  m-treatment period from baseline was  $0.99$  ( $0.76$ – $1.21$ ), and the lower limit of the  $95\%$  CI was above the non-inferiority margin of  $-0.5$  SD. Also after  $6$  m-treatment period from baseline the lower limit of the  $95\%$  CI was above the  $-0.5$  SD non-inferiority margin, with a mean ( $95\%$  CI) WAZ of  $1.02$  ( $0.69$ – $1.35$ ). The mean of WAZ increased over the course of the study (Figure 2, panel A). The results for other anthropometric  $z$ -scores were similar to those for WAZ. At  $6$  months from baseline was observed a significant decrease of length; however, the mean value was not  $\leq 2$  SDS, and returned at T12 similar to that at baseline. No significant difference was observed in the standard deviation score of head circumference compared the study points. A significant increase in the standard deviation score of weight-for-length ratio was observed during the study.

In Supporting Information: Table S3 all anthropometric measurements of the study population are also reported by sex. At  $6$  months and at  $12$  months from baseline the lower limit of the  $95\%$  CI of the WAZ was above the non-inferiority margin of  $-0.5$  SD for both males and females. The only significant difference between the two groups was observed for the head-circumference-for-age  $z$ -score at  $6$  and at  $12$  months from baseline.

Figure 2 plots the mean of body weight (panel A), body length (panel B) and head circumference (panel C) at baseline, at  $6$  months and at  $12$  months from baseline. A significant increase in body weight, body length and head circumference was observed during the study.

Figure 3 shows the individual changes in the standard deviation scores for body weight (panel A), body length (panel B), head circumference (panel C) and weight-for-length (panel D) at baseline, at  $6$  and  $12$  months from baseline. At baseline, some subjects presented with  $< -2$  SDS for WAZ ( $n = 2$ ), length-for-age ( $n = 4$ ) and weight-for-length ( $n = 1$ ), indicating malnutrition. However, at  $12$  months from baseline all subjects had SDS higher than  $-2$  for all anthropometric measurements. Furthermore, already after  $6$  months from the enrolment, no infant had a weight or a weight-for-length  $< -2$  SDS, confirming that the subjects achieved normal growth early on. In



**FIGURE 1** Mean (95% CI) of weight-for-age (panel A), length-for-age (panel B), head circumference-for-age (panel C) and weight-for-length (panel D) z-scores at baseline, at 6 months and 12 months from baseline. \* $p < 0.05$  versus T0.

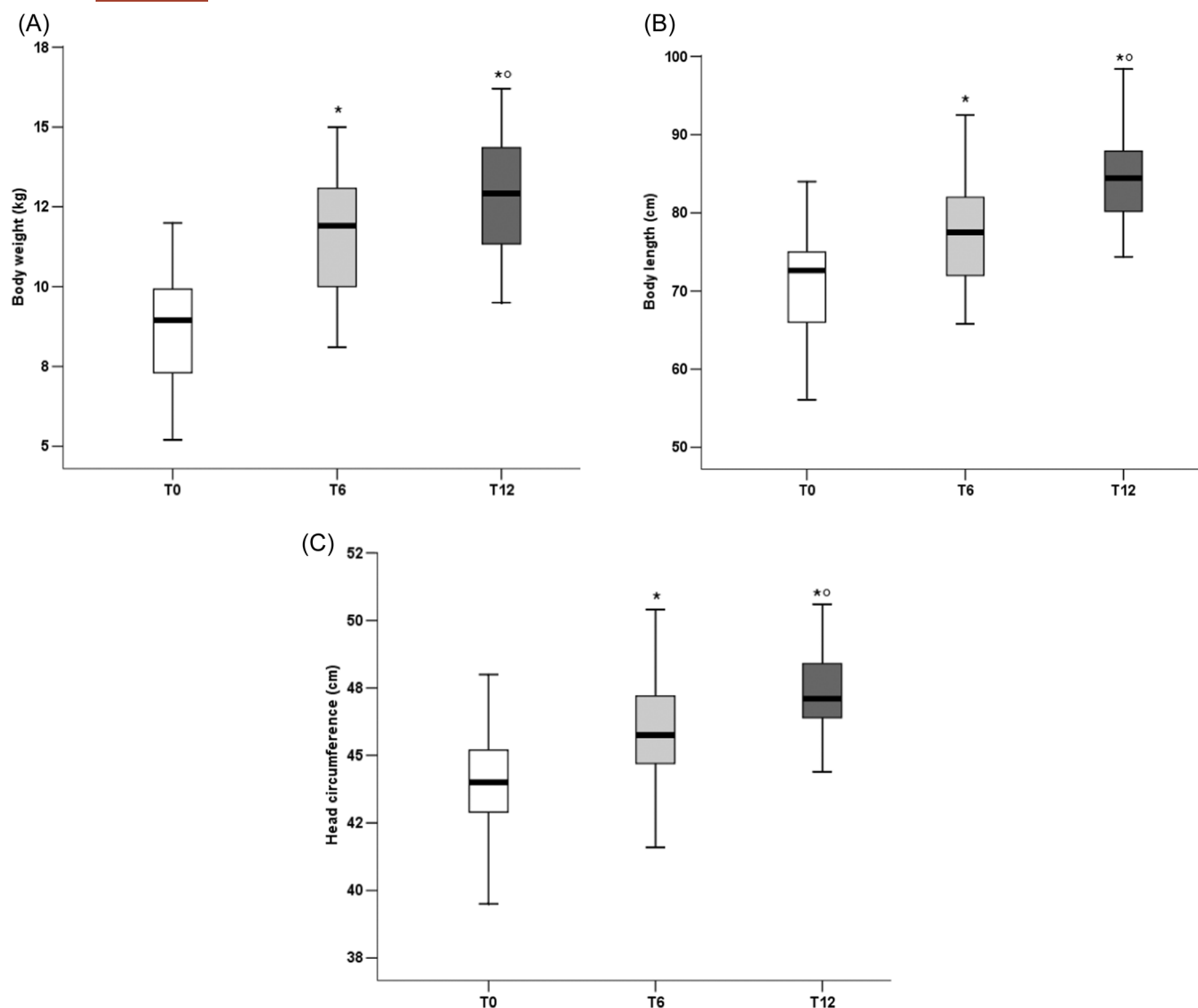
addition, we examined patterns of weight/length/head circumference velocity of patients throughout the study period, by using the WHO reference for growth standards. As the WHO reference standards for growth velocity are available up to 24 months of age, we evaluated the weight/length/head circumference velocity for age standard deviation score at 6 months and at 12 months from baseline in patients up to 18 months of age at enrolment and after 6 months of treatment. From 6 months to 12 months the vast majority of subjects presented a weight/length/head circumference velocity for age standard deviation score between  $-1$  and  $1$  (Supporting Information: Table S4). Finally, the mean weight gain was 2983.63 g at T6 compared to T0, and 1253.18 g at

12 months from baseline compared to T6. Similarly, the mean length gain was 5.97 cm at 6 months from baseline to T0, and 6.98 cm at 12 months from baseline compared to 6 months from baseline.

At 6 months and at 12 months from baseline, the mean ( $\pm$ SD) daily formula intake was 350.8 ( $\pm$ 60.4) mL, and 282.6 ( $\pm$ 67.6) mL respectively. Total daily energy and nutrient intakes were within the recommended reference values for gender and age for all study subjects at each study visit (data not shown).

Regarding safety data, there were 29 nonserious AEs due to acute gastroenteritis ( $n = 8$ ), respiratory infections ( $n = 9$ ), and febrile illness/viral infections ( $n = 12$ ). All AEs were considered to be unrelated to the HRPf use.



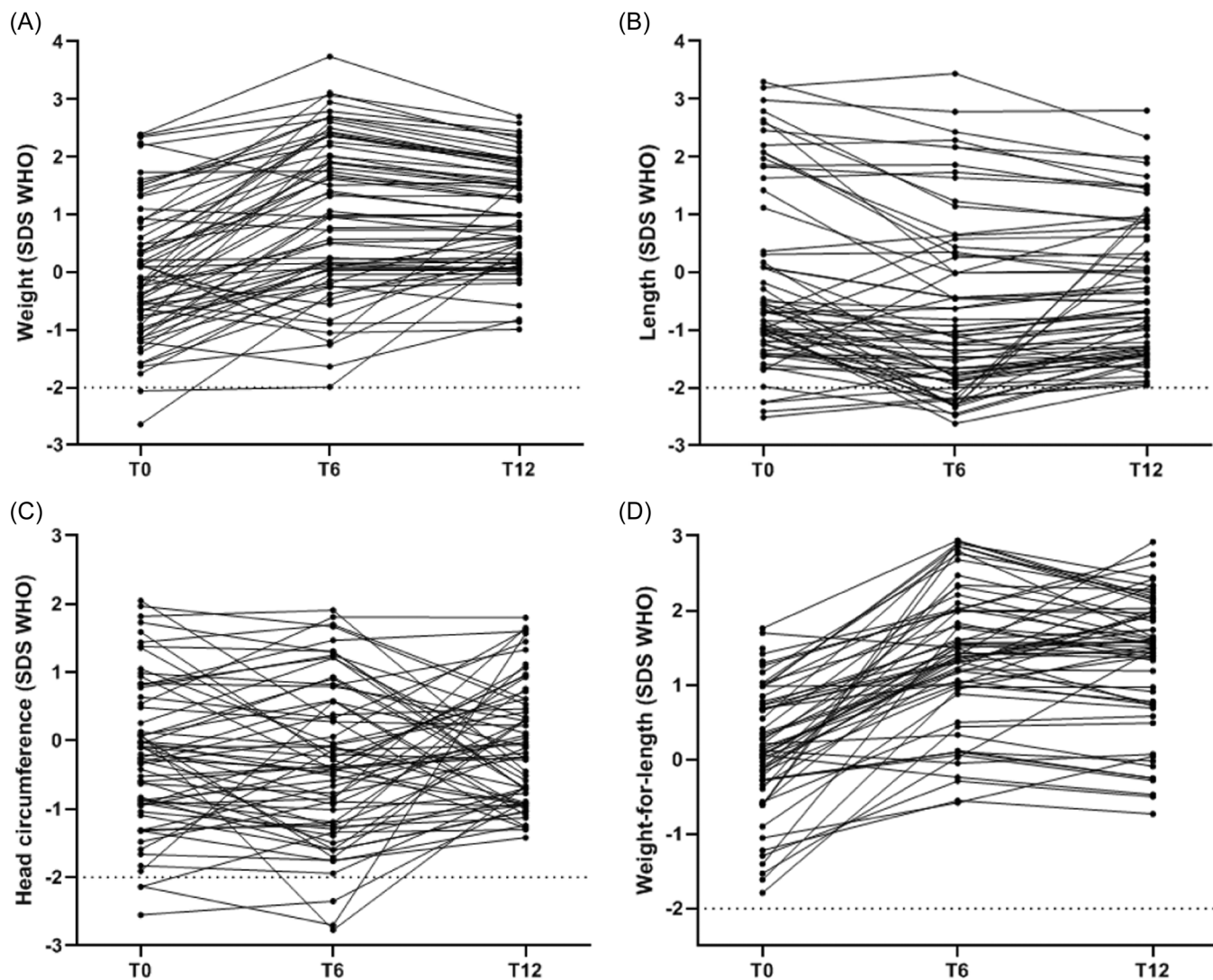


**FIGURE 2** Mean of body weight (panel A), body length (panel B), head circumference (panel C) at baseline, at 6 months and 12 months from baseline. \* $p < 0.05$  versus T0; ° $p < 0.05$  versus T6.

## 4 | DISCUSSION

The results of this study suggest that the 12-month dietary treatment with HRPF is well tolerated and can help support healthy growth and development in infants and young children with IgE- or non-IgE mediated CMPA. These results are well in line with previous evidence reporting that HRPFs exhibit good efficacy and tolerance and appear to be adequate in promoting normal growth in both healthy children and paediatric patients affected by CMPA.<sup>14,17,18,27</sup> Based on the current evidence, the commercially available HRPFs seem to be adequate to restore a normal growth and ensure metabolic balance and they are considered an appropriate strategy for the dietary management of paediatric CMPA.<sup>9</sup> The strengths of our study, when compared with the available literature

on this topic,<sup>14-18</sup> are related to the fact that the investigation was conducted with an adequate sample size, calculated on the non-inferiority margin of  $-0.5$  SD, which was considered clinically relevant. In addition, the study was conducted in a well-characterised population of children with challenge-proven CMPA who were followed at a tertiary center for paediatric allergy. The study methodology was rigorous, with diet and formula intake systematically assessed using standardized procedures. Lastly, the 12-month follow-up period adopted in our study was longer than other previous studies available in the literature,<sup>14,16-18</sup> suggesting that HRPF may help to support healthy growth in CMPA children even in the long term. However, to better assess this aspect, future studies are advocated. Nonetheless, this study has limitations. Our data cannot be generalised to



**FIGURE 3** Individual changes of the standard deviation score of weight-for-age (panel A), length-for-age (panel B), head circumference-for-age (panel C) and weight-for-length (panel D) at baseline, 6 months and 12 months from baseline.

children with conditions that were reasons for exclusion from the study.

Our findings are well in line with those outlined in the Diagnosis and Rationale for Action against Cow's Milk Allergy guidelines. In fact, it has been stated that HRPF has proven hypoallergenicity and is suitable for dietary management, and it has been shown to support infant growth compared to other hypoallergenic formulas and where available, it can be therefore recommended as a first-line alternative for feeding infants and children with CMPA.<sup>28</sup>

In addition, a recent survey of Spanish paediatricians on this topic showed that HRPF was indicated as the second preferred alternative formula after EHF, and that more than 80% of paediatricians believed that HRPF was better accepted by infants in terms of organoleptic qualities compared to EHF, as far as taste preferences are concerned.<sup>29</sup> Another important point

is the cost-effectiveness of HRPF; in fact, in a recent study, hypoallergenic formulas accounted for the largest proportion of the total cost of managing CMPA, averaging 69% across all comparators, with a minimum of 58% for HRPF and a maximum of 87% for amino acid-based formulas.<sup>30</sup>

However, according to the ESPGHAN position paper,<sup>31</sup> it is important to consider the arsenic content of HRPFs, as this is not stated for all commercial HRPFs.<sup>32</sup> Therefore, only HRPFs whose the arsenic content is known and within the recommended limits should be used.<sup>33</sup>

To date, evidence is lacking on the effects of HRPFs long-term consumption in infants and children on bone mineralization, on the acquisition of immune tolerance, and on their exact place in complex conditions associated with CMPA, such as allergy to hydrolysates, multiple food allergies and neonates.

Thus, more data are needed to better support the use of HRPFs in these specific settings.

In conclusion, among the special formulas already available, HRPFs where accessible, may be a suitable alternative as an adjunct to complementary foods for the dietary management of infants and children with CMPA that can help to meet nutritional requirements and can help support healthy growth in paediatric patients affected by CMPA.

## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## REFERENCES

- Carucci L, Coppola S, Luzzetti A, et al. Immunonutrition for pediatric patients with cow's milk allergy: how early interventions could impact Long-Term outcomes. *Front Allergy*. 2021; 2:676200. doi:10.3389/falgy.2021.676200
- Berni Canani R, Caffarelli C, Calvani M, et al. Diagnostic therapeutic care pathway for pediatric food allergies and intolerances in Italy: a joint position paper by the Italian society for pediatric gastroenterology hepatology and nutrition (SIGENP) and the Italian society for pediatric allergy and immunology (SIAIP). *Ital J Pediatr*. 2022;48:87. doi:10.1186/s13052-022-01277-8
- Meyer R, Groetch M, Venter C. When should infants with cow's milk protein allergy use an amino acid formula? A practical guide. *J Allergy Clin Immunol Pract*. 2018;6:383-399. doi:10.1016/j.jaip.2017.09.003
- Paparo L, Picariello G, Bruno C, et al. Tolerogenic effect elicited by protein fraction derived from different formulas for dietary treatment of cow's milk allergy in human cells. *Front Immunol*. 2021;11:604075. doi:10.3389/fimmu.2020.604075
- Fiocchi A, Dahda L, Dupont C, Campoy C, Fierro V, Nieto A. Cow's milk allergy: towards an update of DRACMA guidelines. *World Allergy Organizat J*. 2016;9:35. doi:10.1186/s40413-016-0125-0
- Yang QH, Zheng BS, Zhou SM, Dai DL. Clinical features of cow's milk protein allergy in infants presenting mainly with gastrointestinal symptoms: an analysis of 280 cases. *Zhongguo Dang Dai Er Ke Za Zhi*. 2019;21:271-276. doi:10.7499/j.issn.1008-8830.2019.03.016
- Meyer R, Venter C, Fox AT, Shah N. Practical dietary management of protein energy malnutrition in young children with cow's milk protein allergy. *Pediatr Allergy Immunol*. 2012;23:307-314. doi:10.1111/j.1399-3038.2012.01265.x
- Dupont C, Bocquet A, Tomé D, et al. Hydrolyzed rice protein based formulas, a vegetal alternative in cow's milk allergy. *Nutrients*. 2020;12:2654. doi:10.3390/nu12092654
- D'Auria E, Salvatore S, Acunzo M, et al. Hydrolysed formulas in the management of cow's milk allergy: new insights, pitfalls and tips. *Nutrients*. 2021;13(8):2762. doi:10.3390/nu13082762
- Bocquet A, Dupont C, Chouraqui JP, et al. Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow's milk protein allergy. *Archives de Pédiatrie*. 2019;26:238-246. doi:10.1016/j.arcped.2019.03.001
- Reche M, Pascual C, Fiandor A, et al. The effect of a partially hydrolysed formula based on rice protein in the treatment of infants with cow's milk protein allergy. *Pediatr Allergy Immunol*. 2010;21(4 Pt 1):577-585. doi:10.1111/j.1399-3038.2010.00991.x
- Terracciano L, Bouygue GR, Sarratud T, Veglia F, Martelli A, Fiocchi A. Impact of dietary regimen on the duration of cow's milk allergy: a random allocation study. *Clin Experim Allergy*. 2010;40:637-642. doi:10.1111/j.1365-2222.2009.03427.x
- Vandenplas Y, Brough HA, Fiocchi A, et al. Current guidelines and future strategies for the management of cow's milk allergy. *J Asthma Allergy*. 2021;14:1243-1256. doi:10.2147/JAA.S276992
- Vandenplas Y, De Greef E, Hauser B, et al. Safety and tolerance of a new extensively hydrolyzed rice proteinbased formula in the management of infants with cow's milk protein allergy. *Eur J Pediatr*. 2014;173:1209-1216. doi:10.1007/s00431-014-2308-4
- Savino F, Castagno E, Monti G, et al. Z-score of weight for age of infants with atopic dermatitis and cow's milk allergy fed with a rice-hydrolysate formula during the first two years of life. *Acta Paediatr (Stockholm)*. 2005;94:115-119. doi:10.1111/j.1651-2227.2005.tb02166.x
- Agostoni C, Fiocchi A, Riva E, et al. Growth of infants with IgE-mediated cow's milk allergy fed different formulas in the complementary feeding period. *Pediatr Allergy Immunol*. 2007;11:1-8. doi:10.1111/j.1399-3038.2010.00987.x
- D'Auria E, Sala M, Lodi F, Radaelli G, Riva E, Giovannini M. Nutritional value of a rice-hydrolysate formula in infants with cows' milk protein allergy: a randomized pilot study. *J Int Med Res*. 2003;31:215-222. doi:10.1177/147323000303100308
- Lasekan JB, Koo WWK, Walters J, Neylan M, Luebbbers S. Growth, tolerance and biochemical measures in healthy infants fed a partially hydrolyzed rice protein-based formula: a randomized, blinded, prospective trial. *J Am Coll Nutr*. 2006; 25(1):12-19. doi:10.1080/07315724.2006.10719509
- Berni Canani R, Nocerino R, Terrin G, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. *J Pediatr*. 2013;163:771-777.e1. doi:10.1016/j.jpeds.2013.03.008
- Berni Canani R, Buongiovanni A, Nocerino R, Cosenza L, Troncone R. Toward a standardized reading of the atopy patch test in children with suspected cow's milk allergy-related gastrointestinal symptoms. *Allergy*. 2011;66:1499-1500. doi:10.1111/j.1398-9995.2011.02674.x
- Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo controlled oral food challenges: American academy of allergy, asthma & Immunology-European academy of allergy and clinical immunology PRAC-TALL consensus report. *J Allergy Clin Immunol*. 2012;130: 1260-1274. doi:10.1016/j.jaci.2012.10.017
- Nowak-Węgrzyn A, Assa'ad AH, Bahna SL, et al. Adverse reactions to food committee of American academy of allergy, asthma & immunology. work group report: oral food challenge testing. *J Allergy Clin Immunol*. 2009;123:S365-S383. doi:10.1016/j.jaci.2009.03.042
- Crawford PB, Obarzanek E, Morrison J, Sabry ZI. Comparative advantage of 3-day food records over 24-hour recall and 5-day food frequency validated by observation of 9- and 10-year-old girls. *J Am Diet Assoc*. 1994;94(6):626-630. doi:10.1016/0002-8223(94)90158-9
- Italian Society of Human Nutrition (SINU). *Recommended Levels of Intake of Energy and nutrients for the Italian Population (LARN). Fourth Revision*. SICS Editor; 2014.
- WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development*. World Health Organization; 2006.



26. American Academy of Pediatrics. Clinical testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants; report to FDA; American Academy of Pediatrics, Committee on Nutrition: Elk Grove Village. 1988.
27. Anania C, Martinelli I, Brindisi G, et al. Hydrolyzed rice formula: an appropriate choice for the treatment of cow's milk allergy. *J Clin Med*. 2022;11(16):4823. doi:10.3390/jcm11164823
28. Fiocchi A, Barrio-Torres J, Dupont C, et al. Hydrolyzed rice formula for dietary management of infants with cow's milk allergy. *World Allergy Organ J*. 2022;15(12):100717. doi:10.1016/j.waojou.2022.100717
29. Martín-Masot R, Díaz-Martín JJ, Santamaría-Orleans A, Navas-López VM. Spanish pediatricians' positions regarding prevention, diagnosis, nutritional management, and challenges in cow's milk protein allergy. *Nutrients*. 2023;15(16):3586. doi:10.3390/nu15163586
30. Paquete AT, Martins R, Connolly MP, et al. Cost-effectiveness of infant hypoallergenic formulas to manage cow's milk protein allergy in France. *J Mark Access Health Policy*. 2022;11(1):2154418. doi:10.1080/20016689.2022.2154418
31. Vandenplas Y, Broekaert I, Domellöf M, et al. An ESPGHAN position paper on the diagnosis, management and prevention of cow's milk allergy. *J Pediatr Gastroenterol Nutr*. 2023. doi:10.1097/MPG.0000000000003897
32. Hojsak I, Braegger C, Bronsky J, et al. Arsenic in rice: a cause for concern. *J Pediatr Gastroenterol Nutr*. 2015;60:142-145. doi:10.1097/MPG.000000000000050
33. Meyer R, Carey MP, Turner PJ, Meharg AA. Low inorganic arsenic in hydrolysed rice formula used for cow's milk protein allergy. *Pediatr Allergy Immunol*. 2018;29:561-563. doi:10.1111/pai.12913

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Nocerino R, Coppola S, Carucci L, et al. Growth pattern of paediatric patients affected by cow milk protein allergy fed with rice hydrolyzed formula. *J Pediatr Gastroenterol Nutr*. 2024;78:909-917. doi:10.1002/jpn3.12161