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Trabajo Original

Pediatría

Behavior of weight z-score in preterm infants who are small for gestational age

Comportamiento de la puntuación z del peso en los bebés prematuros pequeños para la edad gestacional

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Abstract

Introduction: the follow-up of small for gestational age (SGA) preterm infants is critical due to their differentiated postnatal growth pattern.

Objective: to investigate the weight z-score behavior in SGA preterm infants during a four-week stay in a Neonatal Intensive Care Unit.

Methods: a retrospective longitudinal study with data from nutritional anamneses of 190 preterm infants admitted to a Neonatal Intensive Care Unit between January/2017 and December/2019, classified according to nutritional status at birth as either SGA or appropriate for gestational age (AGA). Linear regression was used to verify association between weight z-score with gestational age, birth weight, initiation of enteral nutrition and relative amount of energy and protein administered.

Results: SGA preterm infants accounted for 23 % of the study participants. In SGA, the difference in weight score was observed at week 1 when compared to admission ($p < 0.05$), while in AGA there was a difference sustained during the whole period ($p < 0.05$). In SGA, the linear regression analysis showed that the change in z-score was explained by time to start of enteral nutrition ($p = 0.033$), gestational age ($p = 0.003$) and birth weight ($p = 0.001$). In AGA the change was explained by gestational age ($p = 0.000$) and birth weight ($p = 0.000$).

Conclusion: the weight z-score behavior in preterm infants was downward compared to admission, stable at the end of 4 weeks, and different according to nutritional status at birth. In the AGA group the decline in nutritional status was not recovered throughout hospitalization and in the SGA group the unfavorable nutritional status was maintained.

Keywords:

Premature infant. Newborn. Weight gain. Growth. Intensive care unit.

Resumen

Introducción: el seguimiento de los prematuros pequeños para la edad gestacional (PEG) es crítico debido al patrón de crecimiento posnatal diferenciado.

Objetivo: investigar el comportamiento de la puntuación z del peso en recién nacidos prematuros PEG durante cuatro semanas de estancia en una unidad de cuidados intensivos neonatales.

Métodos: estudio longitudinal retrospectivo con datos de anamnesis nutricionales de 190 prematuros ingresados en una unidad de cuidados intensivos neonatales entre enero/2017 y diciembre/2019, clasificados según el estado nutricional al nacer como PEG o como adecuado para la edad gestacional (AEG). Se utilizó la regresión lineal para verificar la asociación entre la puntuación z del peso con la edad gestacional, el peso al nacer, el inicio de la nutrición enteral y la cantidad relativa de energía y proteínas administradas.

Resultados: los bebés prematuros PEG representaron el 23 % de los participantes en el estudio. En el grupo PEG, la diferencia de la puntuación z del peso se observó en la semana 1 en comparación con el ingreso ($p < 0,05$), mientras que en el grupo AEG hubo diferencia durante todo el período evaluado ($p < 0,05$). En los PEG, el análisis de regresión lineal mostró que el cambio de la puntuación z se explicaba por el tiempo transcurrido hasta el inicio de la nutrición enteral ($p = 0,033$), la edad gestacional ($p = 0,003$) y el peso al nacer ($p = 0,001$). En el caso de la AEG, el cambio se explicaba por la edad gestacional ($p = 0,000$) y el peso al nacer ($p = 0,000$).

Conclusión: el comportamiento de la puntuación z del peso en los prematuros fue descendente en comparación con la admisión, estable al final de 4 semanas y diferente según el estado nutricional al nacer. En el caso de los AEG, el estado nutricional no se recuperó a lo largo de la investigación y, en el caso de los PEG, el estado nutricional desfavorable se mantuvo.

Palabras clave:

Prematuro. Recién nacido. Aumento de peso. Crecimiento. Unidad de cuidados intensivos.

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INTRODUCTION

The nutritional pattern considered ideal for premature infants is one in which it is possible to provide growth similar to that which normally occurs in the uterus at a rate of approximately 15-20 g/kg/day (1). On the other hand, recent data indicate that the growth of these babies should not be compared to that of healthy fetuses because in practice this hardly happens, especially in those who are very premature (2). The justification is that the growth pattern is very different, since the manner in which intrauterine and extrauterine weight gain occurs is influenced by distinct biological processes and conditions related to nutrition and environment (2).

The growth process in the neonatal period is represented by two phases, the first characterized by an initial loss of birth weight and the second by recovery. However, it should be noted that both the intensity and duration of these phases are directly related to the degree of prematurity, nutritional status at birth, clinical evolution during hospitalization, and adequate intake of nutrients and energy (3-5).

Worldwide, about 3 to 10 % of all live newborns are small for gestational age (SGA) (6). These babies have higher rates of morbidity and mortality when compared to those appropriate for gestational age (AGA) because they have a higher risk of hypoglycemia, inadequate thermoregulatory response and thrombocytopenia, for example (7). Most overcome such complications and go on to have catch-up (spontaneous growth recovery) (8).

Although the correct period at which catch-up growth occurs in premature infants is not known, it is known that achieving catch-up growth between 6-9 months of corrected age provides better neurodevelopmental outcomes (9). However, care must be taken to ensure that this happens properly, because when it occurs rapidly and excessively there is an increased risk of insulin resistance and type-2 diabetes *mellitus* in adulthood, and when it occurs slowly and insufficiently there is also an increased risk of adverse outcomes such as impaired cognitive development and short stature (8).

Growth is a global indicator of well-being from fetal life to adolescence, which can be assessed by easily obtained anthropometric measurements such as weight (10). The z-score of an anthropometric measurement is commonly used to measure the level of growth, indicating how far and in which direction it departs from a central value of the reference population, and can be negative when below, positive when above, or zero when equal to the reference population mean (11).

The follow-up of SGA preemies is a critical issue because of the differential postnatal growth pattern. Thus, it is important to better understand the characteristics and outcomes of this frail population in order to provide better care that provides a favorable environment for timely catch-up growth, avoiding short- and long-term health complications. Therefore, the objective of the present study was to investigate the behavior of weight z-score in small-for-gestational-age premature newborns during a four-week stay in a neonatal intensive care unit.

MATERIALS AND METHODS

A retrospective longitudinal study was conducted with data from anamneses used by the Clinical Nutrition Unit at School Hospital, Universidade Federal de Pelotas/Empresa Brasileira de Serviços Hospitalares (HS-UFPEL-EBSERH), Pelotas, Rio Grande do Sul, Brazil.

The study population was composed of premature newborns admitted to the neonatal intensive care unit (NICU) of HS-UFPEL-EBSERH between January 2017 and December 2019. Premature newborns with gestational age (GA) at birth ≥ 24 and < 37 weeks, of both sexes, non-twin, admitted up to 48 hours after birth, classified according to nutritional status at birth as SGA or AGA, and who did not have conditions interfering with growth and anthropometry (microcephaly, hydrocephalus, fetal hydrops, chromosomopathies, and/or congenital malformations) were included. Of the 518 preterm infants admitted to the NICU, 190 were eligible for the study. Of these, 155, 93, 59, and 36 remained in the first, second, third, and fourth week of hospitalization, respectively. The reasons for the decrease in participants over the course of the study were due to NICU discharge, death, and loss to follow-up (Fig. 1).

Demographic, clinical, nutritional and anthropometric variables were obtained from the NICU records by nutritionists and recorded in the anamneses of the nutrition service.

The anthropometric evaluation was based on weight, length, and cephalic perimeter, which were measured on admission, and on the 7th, 14th, 21st, and 28th day of hospitalization. Anthropometric measurements were performed by nurses or nursing technicians of the NICU, who were previously trained by the nutrition service, following the recommendations described by the World Health Organization (WHO) in the Anthropometry Handbook (12). Weight was measured on a Filizola Baby® scale (to the nearest 5 g) and, after weighing, discounting any equipment attached to the newborn. length was obtained with a SECA 210 portable anthropometer (with 5 mm graduation) with the newborn in the dorsal decubitus position, in Frankfort's horizontal plane, with one end fixed (cephalic) and the other mobile (podalic), with the help of another person holding the newborn. Head circumference was measured with an inextensible measuring tape (to the nearest 0.1 cm), taking into account the largest occiptofrontal diameter. The classification of preterm infants according to birth weight was based on the reference curves for GA according to INTERGROWTH-21st, considering as SGA those with weight below the 10th percentile and SGA those with weight between the 10th and 90th percentiles (13).

The outcome variable was the weight z-score value according to sex and GA, obtained using the INTERGROWTH-21st manual online calculator for preterm infant body dimensions, available at: http://intergrowth21.ndog.ox.ac.uk/pt/ManualEntry.

The exposure variables were: GA at birth (weeks), APGAR value at the fifth minute of life (1-10 points), weight (grams), length (centimeters), and head circumference (centimeters) at birth, start of enteral nutrition (hours), start of parenteral nutrition (hours), end of parenteral nutrition (days), relative amount of en-

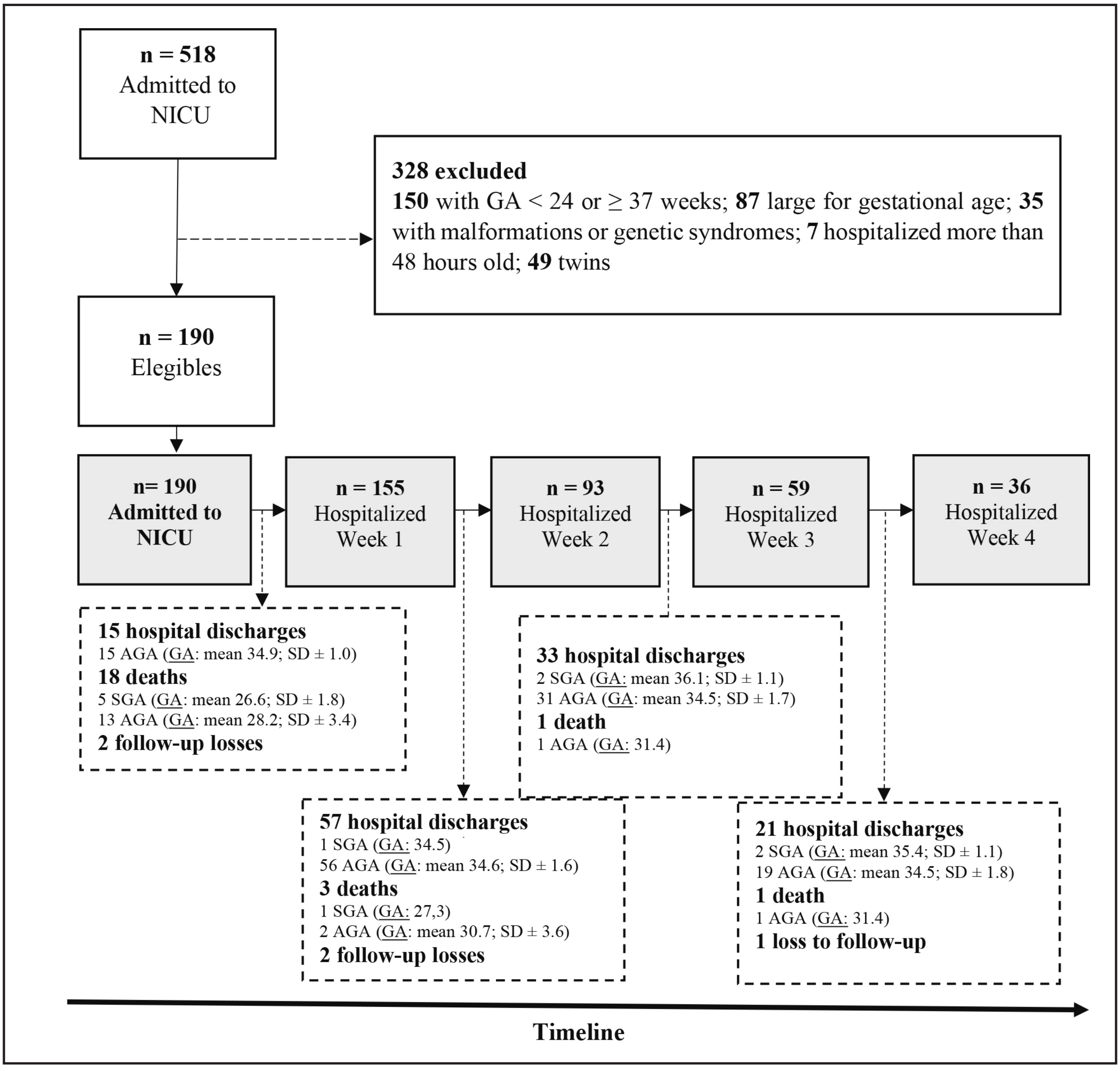

Figure 1.

Recruitment and follow-up of the premature newborns in the study. Neonatal intensive care unit. HS-UFPEL/EBSERH, Pelotas, 2017-2019.

ergy (kcal/kg/day) and protein (g/kg/day) administered, and rate of weight gain (g/kg/day). For the calculation of GA the following was used in order of priority: a) maternal information on the date of the last menstrual period (Naegele's rule, which considers the normal gestation period to be 280 days), when it differed by a maximum of two weeks from the age provided by fetal ultrasound up to 13 weeks and 6 days of gestation; b) ultrasonography performed up to 13 weeks and 6 days of gestation, in cases in which the maternal GA was not considered reliable and the difference between the ages calculated by ultrasonographic methods and the New Ballard (analysis of neurological and physical parameters at birth) was less than two weeks; and c) postnatal GA calculated by the New Ballard method when it differed by more than two weeks from maternal and ultrasonographic GAs (14,15). The daily intake of energy and protein administered was calculated considering the total supply of nutrients from breast milk, infant formulas, breast milk additives, medium chain triglycerides, and parenteral nutrition solution, considering the volume effectively administered in 24 hours provided by parenteral and/or enteral nutrition. The calculation was based on the product labels and the estimate of the protein and calorie intake of the milked breast milk was calculated considering the chemical composition values of premature breast milk, as informed by the Ministry of Health (16). The relative calorie and protein supply was obtained by dividing the average energy (kcal) and protein (g) administered by the weight (kg) in each follow-up period of the study. The result was expressed as kcal/kg/day or g/kg/day. The rate of weight gain (g/kg/day) was obtained using the following equation: [(current weight - previous weight) / ([(previous weight + current weight) / 2] / 1000) / number of days], considering the weight from the lowest weight recorded during the neonatal period and calculated until the fourth week of hospitalization (17).

The data were entered in duplicate in Excel® software and then transferred to and analyzed with the Stata® version 12 software. Data were described as mean and standard deviation, median and interquartile range (IIQ, P25-75) for quantitative variables and absolute and relative frequency for qualitative variables. Since the outcome variable had a symmetrical distribution, the comparison between the two categories was performed using Student's t-test. The comparison between SGA and AGA over the length of stay was performed using repeated measures ANOVA (MR), followed by Bonferroni post hoc. To this end, the assumptions of homoscedasticity, independence, and sphericity of the residuals were analyzed. Linear regression was used to evaluate the association between z-score birth weight and GA at birth, birth weight, initiation of enteral nutrition, and daily energy and protein intake. Only variables associated with a statistically significant change in the β-value were kept in the regression model. The level of statistical significance adopted was $p < 5$ %.

The present study was inserted in the Umbrella Project entitled "Specific and Multiprofessional Action in a Residency Program in Child Health Care", approved by the Ethics and Research Committee of the Faculty of Medicine of Universidade Federal de Pelotas, under number 1.639674, via Platform Brazil.

RESULTS

Of the 190 premature newborns participating in the study, 58 % were male and 23 % were classified as SGA. Most (78 %) had newborn respiratory distress syndrome and 11 % had neonatal sepsis. Fifty-five percent were children of mothers who had

Table I. Characteristics of premature newborns according to nutritional status at birth. Neonatal intensive care unit. HS-UFPEL/EBSERH, Pelotas, 2017-2019 (n = 190)

	ALL		SGA		AGA		
	n	Mean (± SD)	n	Mean (± SD)	n	Mean (± SD)	p-value
Gestational age (weeks)	190	32.0 (2.8)	44	31.2 (3.1)	146	32.6 (2.6)	0.004†
APGAR[a]	187	8.0 (1.0)	43	8.0 (1.0)	144	8.0 (1.0)	0.180†
Birth weight (g)	190	1,673.5 (588.9)	44	1,157.5 (460.3)	146	1,829.0 (533.0)	< 0.001†
Birth length (cm)	189	40.1 (4.9)	44	36.0 (5.4)	145	42.3 (4.0)	< 0.001†
Birth cephalic perimeter (cm)	189	28.9 (3.2)	44	27.0 (3.3)	145	29.6 (2.8)	< 0.001†
Nutritional care							
Start of enteral nutrition (h)	173	16.4 (22.7)	32	12.2 (16.0)	141	17.4 (24.0)	0.252†
Start of parenteral nutrition (h)	71	12.5 (2.5)	14	11.7 (10.5)	57	12.7 (13.0)	0.793†
End of parenteral nutrition (days)	71	9.5 (5.4)	14	8.3 (5.3)	57	9.8 (5.6)	0.356†
Energy (kcal/kg/dia)							0.086††α 0.411††β
Admission	149	13.3 (18.6)	29	18.2 (25.3)	120	8.4 (11.8)	
Week 1	147	78.2 (22.5)	33	85.1 (19.9)	114	71.2 (25.0)	
Week 2	89	97.0 (22.5)	27	96.8 (19.6)	62	97.1 (23.8)	
Week 3	23	114.1 (38.4)	7	124.8 (23.9)	16	109.5 (43.1)	
Week 4	11	119.4 (32.0)	5	133.9ω (28.1)	6	107.3 (32.1)	
Protein (g/kg/dia)							0.537††α 0.138††β
Admission	149	0.5 (0.9)	29	0.7 (1.2)	120	0.3 (0.6)	
Week 1	147	3.1 (1.1)	33	3.6 (0.9)	114	2.6 (1.2)	
Week 2	89	2.9 (1.0)	27	3.0 (1.1)	62	2.9 (0.9)	
Week 3	23	3.2 (1.2)	7	2.9 (0.6)	16	3.3 (1.4)	
Week 4	11	3.5 (1.3)	5	3.3 (1.5)	6	3.7 (1.1)	

SGA: birth weight classified as small for gestational age; AGA: birth weight classified as appropriate for gestational age; SD: standard deviation. [a]APGAR index at the fifth minute of life; †Student's t-test; ††αcomparison between weeks, ANOVA-MR; ††βcomparison between SGA and AGA, ANOVA-MR; ω$p < 0.05$ for comparison at week 4 between SGA and AGA, ANOVA-MR.

complications during pregnancy, with preeclampsia (32 %) and gestational diabetes (25 %) being the most prevalent.

Mean birth GA, birth weight, birth length, and head circumference were statistically significantly lower in SGA preterm infants (31.2 weeks, 1,157.5 g, 36 cm, and 27 cm, respectively) compared to AGA (32.6 weeks, 1,829.0 g, 42.3 cm, and 29.6 cm) (Table I). The mean time to start enteral and parenteral nutrition between the groups was 16.4 and 12.5 hours, respectively, and the mean time to stay on parenteral nutrition was 9.5 days. The energy intake given to SGA preterm infants at the fourth week of hospitalization was higher (133.9 ± 28.1 kcal) when compared to AGA (107.3 ± 32.1 kcal; $p < 0.05$). There was no difference in the other periods evaluated. The protein intake did not differ between SGA and AGA preterm infants during four weeks of hospitalization.

Most preterm infants (76 % of SGA and 80 % of AGA) had a weight nadir in the first week of hospitalization. However, approximately 10 % of SGA and AGA preterm infants had lower birth weights during hospitalization (Fig. 2A). The weight gain phase started in the second week for both SGA and AGA preterm infants, where the rate of weight gain was 16 g/kg/day for AGA and 13 g/kg/day for SGA. At week three the AGA preemies (18 g/kg/day) showed a faster rate of weight gain when compared to SGA preemies (11 g/kg/day; $p < 0.05$) (Fig. 2B).

In SGA preterm infants the weight-for-age E-z differed between admission and week 1 means (-0.53 z-score; $p < 0.05$) (Fig. 2C). In the AGA preterm infants, there was a difference between the means at admission and during the entire hospitalization period (week 1, -1.01; week 2, -1.18; week 3, -1.16, and week 4 -1.23) ($p < 0.05$) (Fig. 2D). The mean z-score at admission (-1.84) and at weeks 1 (-1.34), 2 (-0.84), 3 (-1.01) and 4 (-0.98) differed between SGA and AGA preemies ($p < 0.05$) (Fig. 2C and 2D).

The second week of hospitalization marked the beginning of the weight recovery phase. Therefore, linear regression analysis was performed to identify the association between z-score weight in the second week of hospitalization with GA at birth, birth weight, time to start enteral nutrition, and protein and calorie content administered in week 1. Table II shows that the change in weight z-score was explained by GA and birth weight in both SGA ($p = 0.003$; $p = 0.001$) and AGA preterm infants ($p = 0.000$; $p = 0.000$). In addition, in SGA preterm infants, the change in z-score was also explained by time to the start of enteral nutrition ($p = 0.033$).

DISCUSSION

This study showed the distinct trajectory of weight z-score in SGA and AGA preterm infants during a four-week NICU stay. In both groups there was a significant reduction in weight z-score in the first week of hospitalization. In SGA preterm infants, the z-score values in the other periods of hospitalization were similar to those at admission. In AGA preterm infants, the negative

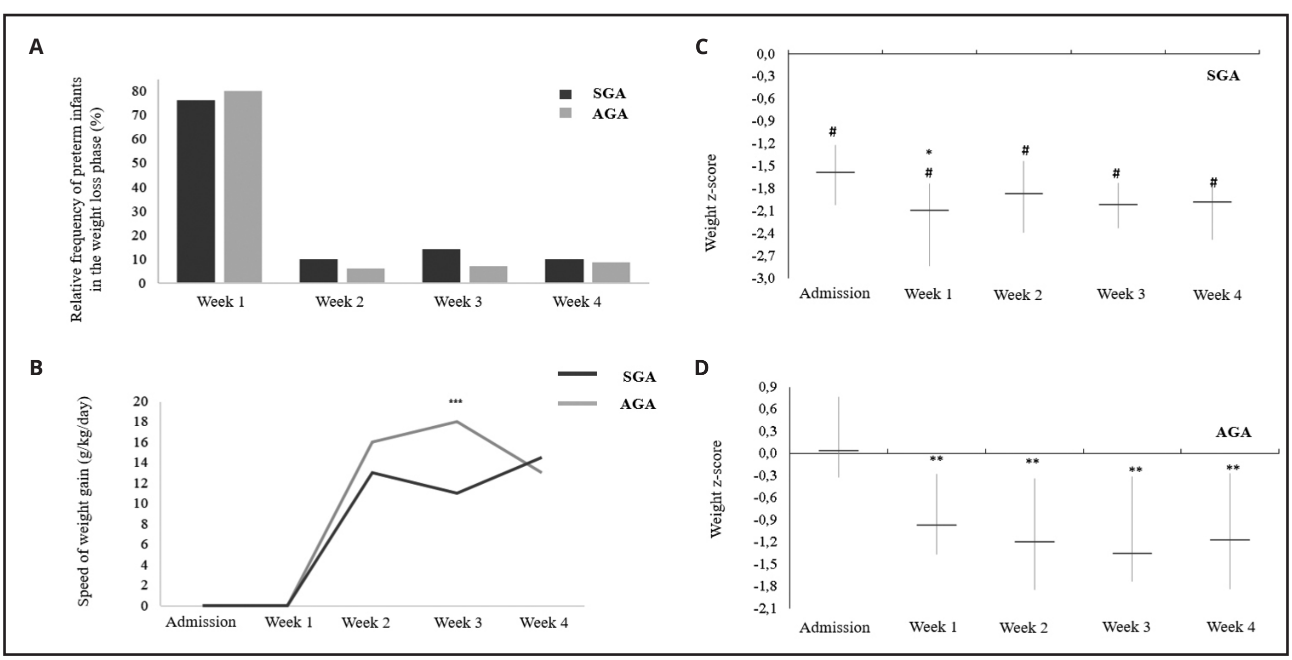

Figure 2.

Relative frequency of preterm infants with weight loss according to nutritional status (A) and rate of weight gain according to nutritional status (B); weight z-score behavior in small-for-gestational-age preterm infants (SGA) (C) and weight z-score behavior in adequate-for-gestational-age preterm infants (AGA) (D) during four weeks of hospitalization. Neonatal intensive care unit. HS-UFPEL/EBSERH, Pelotas, 2017-2019 (n = 155, 93, 59 and 36, weeks 1, 2, 3 and 4, respectively). ***$p < 0.05$ between SGA and AGA at week 3 of hospitalization, ANOVA-MR. *$p < 0.05$ between admission and week 1 in the SGA group; **$p < 0.05$ between admission and 4 weeks of hospitalization in the AGA group; #$p < 0.05$ between weight z-score comparing SGA and AGA, ANOVA-MR.

Table II. Linear regression of weight z-score at week two according to nutritional status in preterm infants. Neonatal intensive care unit. HS-UFPEL/EBSERH, Pelotas, 2017-2019 (n = 88)

	Weight z-score					
	B	β	B (95 % CI)		Adjusted R^2	p-value
SGA						
Constant	6.37	ref	0.773	11.959	36 %	0.028
Birth weight[a]	0.002	1.219	0.001	0.004		0.001
Gestational age[b]	-0.367	-1.050	-0.589	-0.145		0.003
Start EN[c]	0.017	0.422	0.002	0.032		0.033
AGA						
Constant	7.49	ref	3.911	11.062	40 %	0.000
Birth weight[a]	0.002	1.433	0.001	0.003		0.000
Gestational age[b]	-0.374	-1.378	-0.510	-0.237		0.000

SGA: small for gestational age; AGA: adequate for gestational age; β: regression coefficient; CI: confidence interval. [a]Birth weight in grams; [b]Gestational age in weeks; [c]Start of enteral nutrition in hours.

impact observed on z-score was maintained until the fourth week of hospitalization. The resumption of weight gain in the second week of hospitalization, although quantitatively adequate, did not mitigate the impact on the nutritional status of preterm AGA infants. GA and birth weight explained the change in weight z-score for both groups of preemies. In SGA preterm infants the change in z-score was also explained by the time elapsed until the start of enteral nutrition.

The z-score of an anthropometric measure indicates how far and in what direction the observed value deviates from a central value in the reference population (11). An international multicenter cohort study showed that healthy premature infants hospitalized in NICUs with minimal disease influence adapted in the first three weeks of life to a postnatal trajectory that was on average a -0.8 z-score below their birth weight percentile and then grew parallel to their intrauterine curves (18).

In the present study, GA was one of the factors that explained the change in weight z-score. GA at birth is directly related to the postnatal downward growth trajectory, and a study conducted in a NICU with preterm infants born between 22 and 31 weeks identified that those with a GA ≥ 29 weeks took two weeks to interrupt the downward profile, while those with a GA < 29 weeks took longer (19). The relative distance between the z-score varies with GA and is greater at lower GAs (18). Importantly, the lower the GA, the longer it will take to reach final growth recovery and the worse the long-term prognosis will be (1).

Recovery growth is represented by weight or length gain greater than 0.67 z-score, indicating significant percentile crossover (20). Most SGA children complete catch-up by reaching their growth canal between the normal percentiles on their reference curves by the age of 2 years, whereas SGA preterm infants may reach this goal by the age of 4 years (7). Regardless of body size, SGA preterm infants have higher central adiposity and tend to accumulate more intra-abdominal fat throughout their growth, thus allowing the programming of excessive abdominal fat deposition later on (6). Thus, when compared to preterm AGA, the rapid weight gain in SGA preterm infants during the first two years of life is related to obesity, higher visceral and abdominal fat, and lower lean body mass in later life (21). Based on this, early feeding of SGA children requires special attention, providing adequate nutritional intake to avoid excessive weight gain (6).

As seen, the relative frequency of preterm infants in the weight loss phase was highest in the first week of hospitalization. Weight loss in the first days of life is not considered a growth alteration, but rather a short-term adaptive process (2). On the other hand, the intensity and duration of this phase is inversely related to GA, birth weight, and severity of the newborn (3). In the present study the percentage of preemies in weight loss decreased dramatically by the second week of hospitalization, assuming that these patients were clinically stable to begin the next phase. After the loss phase, a delay between the increasing extrauterine growth curve and the fetal growth curve is expected, and the postnatal weight curve will parallel but not exceed the intrauterine one, characterizing a "new" postnatal growth trajectory (22,23).

In the present study, the change in weight z-score could also be explained by the birth weight of the preterm infants. A study that evaluated 23,970 preterm infants identified that the incidence of extrauterine growth restriction was present in 28 % of the individuals for weight, and this growth parameter increased the incidence of restriction along with the decrease in birth weight, that is, the lower the birth weight the greater the difficulty in growing (24).

Finally, SGA preterm infants had the change in weight z-score also justified by the time elapsed until the start of enteral nutrition. A study of 349 preterm infants in a NICU in Africa identified postnatal growth failure in 73 % of the subjects, one of the main reasons being the late initiation of enteral nutrition (> 48 hours) (25). In the present study, the mean in hours from the start of enteral nutrition in SGA was 12.2 (± 16.0). Minimal enteral nutrition has several benefits, such as growth and development of the intestinal mucosa, better feeding tolerance, and improved postnatal growth because it results in earlier achievement of full enteral nutrition and consequent reduction of cumulative protein and energy deficits, promoting greater weight gain (26,25).

It can be suggested that the SGA preterm infants in this study are a sample of clinically stable patients because they had physiological weight loss in the first week of hospitalization, started the recovery phase in the following week, showed appropriate and parallel weight gain velocity to what occurs intrauterine, keeping the weight z-score constant over the four weeks of hospitalization and demonstrating z-score values in the postnatal growth path less than -0.8 z-score. This demonstrates a satisfactory postnatal growth from exposure to satisfactory medical and hospital care.

The main limitations of the study are related to the progressive decrease in the number of preterm infants over the four weeks of hospitalization, and because it is a retrospective analysis of medical records, much information was incomplete or missing. A sample of clinically stable premature patients stands out as a strength.

CONCLUSION

It is concluded that the behavior of the z-score weight curve in preterm infants was downward compared to admission, but stable at the end of a 4-week NICU stay. The z-score weight trajectory proved to be different according to nutritional status at birth, requiring attention to its behavior. In AGA preterm infants, the decline observed in nutritional status at the beginning of hospitalization was not recovered until 4 weeks of extrauterine life. In SGA preterm infants, their unfavorable nutritional status at birth was maintained for up to 4 weeks in the NICU.

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