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Effectiveness of prealbumin as an indicator of growth in neonates

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Abstract

We designed this study to assess the effectiveness of prealbumin as an indicator of growth as well as a nutritional marker in neonates.

Between March 2017 and June 2019, we measured serum prealbumin concentrations of 80 neonates in neonatal intensive care unit at birth, postnatal day 14 and 28, and classified them into 3 groups (early preterm, late preterm, and term infants). And we examined correlation among prealbumin levels, nutritional intake, and anthropometric measurements (weight, length, and head circumference) in neonates.

Prealbumin measured on the 14th postnatal day in early preterm infants showed significant correlations with the length, weight, and head circumference z-scores. Prealbumin levels increased with time in the late preterm and term groups. At birth, prealbumin levels were the lowest in late preterm babies, implying that they are nutritionally deficient and need nutritional support. At postnatal day 28, the prealbumin levels of many preterm infants did not reach those seen in term babies at birth, suggesting the presence of extrauterine growth restriction.

Prealbumin can be considered as an indicator of sufficient growth in early preterm infants.

Abbreviations: BUN = blood urea nitrogen, CRP = C-reactive protein, EUGR = extrauterine growth restriction, GA = gestational age, NICU = neonatal intensive care unit, RDS = respiratory distress syndrome, TPN = total parenteral nutrition.

Keywords: anthropometrics, extrauterine growth restriction, prealbumin, preterm, protein-calory status

1. Introduction

In neonatal intensive care units (NICUs), it is important to assess the nutritional state and growth of neonates.[1–3] Generally, anthropometric measurements are considered the easiest method to assess neonatal growth, but some clinicians prefer objective or laboratory markers: hemoglobin and red blood cell indices, electrolytes, blood urea nitrogen (BUN), vitamins, minerals, albumin, and prealbumin.[2,4]

Prealbumin is an unglycosylated plasma protein synthesized in the liver, which transports thyroxine and vitamin A.[5] Prealbumin levels decrease in cases of acute phase response, malnutrition, liver disease, thyroid disease, and protein-losing diseases of the kidneys and intestine[5–7]; they increase with the administration of exogenous corticosteroids and non-steroidal anti-inflammatory agents and in the presence of chronic renal failure.[5] The half-life of prealbumin is about 2 days, so it reflects changes in protein synthesis and catabolism.[5] Poor dietary intake decreases the serum prealbumin concentration, and proper nutritional management normalizes it. For these reasons, prealbumin is used to assess the nutritional status of patients with protein depletion and the effectiveness of nutritional support. To investigate the possible uses of prealbumin as a biomarker of conditions other than nutrition, we focused on growth in neonates. Therefore, we designed this study to assess the effectiveness of prealbumin as an indicator of growth as well as a nutritional marker in neonates. We conducted correlation analysis between anthropometric parameters and prealbumin and between protein, calorie intakes and prealbumin.

2. Methods

We retrospectively studied neonates admitted to the NICU of Chung-Ang University Hospital, Seoul, Korea between March 2017 and June 2019. We measured serum prealbumin concentrations when the neonate's chronological age was 0, 14, and 28 days.[8] The reference value (mean ± standard deviation) for the prealbumin level in preterm infants is 7.0 ± 1.7 mg/dL at birth, 9.5 ± 3.3 mg/dL at the 14th postnatal day, and 8.7 ± 2.3 mg/dL at the 28th postnatal day.[3,9] Serum prealbumin concentration in term infants was 10.2 ± 2.6 mg/dL in appropriate for gestational age, 12.1 ± 3.3 mg/dL in large for gestational age, and 8.31 ± 1.2 mg/dL in the birth date.[10] We measured body weight, body length, and head circumference. Measurements were made regularly by 1 doctor and 1 nurse. The body weight of the naked neonate was measured every day with an electronic scale.

Length and head circumference were measured with a measuring tape weekly. The percentile values corresponding to these measurements were derived from the Fenton growth chart.[11,12]

The data recorded included those of gestational age (GA); birth weight; sex; type of delivery; serum concentrations of prealbumin, BUN, creatinine, and C-reactive protein (CRP); and anthropometric measurements of weight, length, and head circumference when the chronological age was 0, 14, and 28 days. The protein-calorie status 2 to 3 days before measurement of the prealbumin level and its average protein and calorie intakes were also assessed. And morbidities until discharge were investigated. Respiratory distress syndrome (RDS) was diagnosed based on characteristic clinical symptoms and chest X-ray. Criteria for the classification of RDS was obtained from European Consensus Guidelines on the Management of Respiratory Distress Syndrome.[13,14] Patent ductus arteriosus was diagnosed by clinical symptoms and echocardiography performed by the same cardiologist at 24 to 96 postnatal hours of life and during the first 2 weeks of life, as needed. Bronchopulmonary dysplasia was defined based on National Institutes of Health consensus definition of bronchopulmonary dysplasia.[15] Intraventricular hemorrhage was diagnosed based on the Papile staging of the transfontanelle ultrasonographic assessments.[16,17] Necrotizing enterocolitis was diagnosed based on systemic symptoms and radiographic findings, with severity based on Modified Bell clinical criteria.[18] Retinopathy of prematurity was diagnosed by an ophthalmologist following a schedule of the American Academy of Ophthalmology. Findings were classified according to the Revisited International Classification of Retinopathy of Prematurity.[19,20]

Through retrospective chart review, we thoroughly checked the composition of the administered parenteral nutritional fluid; we also checked the quantity of milk fed to the babies, the type of milk (e.g., breast milk, formula milk), and whether fortifiers or supplements were mixed with the milk. Total parenteral nutrition (TPN) was started in for infants in any group who needed it. In general, IV amino acids and dextrose were started immediately after birth. A minimum of 2 g/kg of amino acids were given in the first 24 hour after birth, with the goal of supplying at least 3.5 g/kg within 48 hours after birth while monitoring BUN. Four to 5 of glucose infusion rate were given in the first 24 hour after birth. And glucose infusion rate was increased as necessary while monitoring blood glucose test. IV lipids were also required to meet total energy requirements. A minimum of 1 g/kg of lipids were given in the first 24 hour after birth, with the goal of supplying at least 3.0 g/kg within 48 hours after birth while monitoring triglyceride. Subsequently, TPN was adjusted according to each patient's condition. In early preterm group, enteral feeding was started as soon as possible with trophic feeding monitoring gastrointestinal condition. When they reached 34 weeks of postmenstrual age, we tried oral feeding. In late preterm group, enteral feeding were started after birth and we could try oral feeding and tube feeding together. In term group, oral feeding were initially applied. Duocal and Promax were used as supplements to supply more energy and protein, respectively. Enfamil Human Milk Fortifier was used as fortifier to supply more energy and protein. Vitamin was mixed with TPN and we supplied Alvityl I Syrup as vitamin multiplex in patients who did not need TPN.

We excluded neonates who died within 14 days of birth and neonates with conditions that could alter serum prealbumin concentration; culture-proven sepsis, hepatic disease, thyroid disease, protein-losing disease and whose CRP level is upper than 15 mg/L at each time points.[21]

Based on GA, we classified neonates into 3 groups: GA less than 34 weeks (early preterm infants), GA 34 to 36 weeks and 6 days (late preterm infants), and GA 37 to 41 weeks and 6 days (term infants). Considering the 3 time points and the 3 groups, we performed analyses to identify the correlations between prealbumin levels and (a) protein and calorie intakes and (b) anthropometric measurements.

2.1. Statistical analysis

For statistical analyses, the mean ± standard deviation was calculated for the anthropometrics and biochemical variables of each neonate at the 3 time points of the study. The Pearson correlation coefficient was used to test for associations between variables. Analysis of variance and the chi-square test were used to test for differences among groups. P values <.05 were considered statistically significant. The data analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

2.2. Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted after obtaining approval from the Institutional Review Board of Chung-Ang University Hospital (IRB no. 2012-033-19346) and informed consent was waived owing to the retrospective nature of the study.

3. Results

Between March 2017 and June 2019, we evaluated the results of 205 serum prealbumin tests performed in 91 neonates. Culture-proven sepsis was identified in 6 neonates; CRP is elevated upper than 15 mg/L in 5 neonates; these neonates were excluded from the statistical analysis. A total of 80 neonates were analyzed.

We described morbidities until discharge in the study population and there were RDS, patent ductus arteriosus, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, and bronchopulmonary dysplasia (Table 1).

In the study population, the mean GA was 33.3 ± 2.9 weeks, and the mean birth weight was 1854.6 ± 686.6 g. The male: female ratio was 38:42 and 16 neonates had been delivered via

Table 1				
Morbidities in the study population until discharge.				
	Total	**Early preterm**	**Late preterm**	**Term**
	N = 80	**n = 54**	**n = 17**	**n = 9**
Sex, male	38 (47.5)	29 (53.7)	6 (35.3)	3 (33.3)
RDS	28 (35.0)	24 (44.4)	2 (11.8)	2 (22.2)
PDA	25 (31.3)	18 (33.3)	4 (23.5)	3 (33.3)
BPD	19 (23.8)	16 (29.6)	2 (11.8)	1 (11.1)
IVH	3 (3.8)	2 (3.7)	1 (5.9)	0 (0)
NEC	1 (1.3)	1 (1.9)	0 (0)	0 (0)
ROP	3 (3.8)	3 (5.6)	0 (0)	0 (0)

Results are described as N(%).
BPD = bronchopulmonary dysplasia, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, RDS = respiratory distress syndrome, ROP = retinopathy of prematurity.

Table 2

Patient characteristics and anthropometric parameters at 3 time points.

1st time point	Total N = 80	Early preterm n = 54	Late preterm n = 17	Term n = 9	P value
Sex (M:F)	0.90	1.16	0.54	0.50	.28
Delivery type (N:C)	0.25	0.08	0.70	1.25	<.001[**]
GA (wks)	33.3 ± 2.9	31.8 ± 1.9	35.0 ± 0.7	39.0 ± 1.0	<.001[**]
Height (cm)	41.9 ± 4.6	40.1 ± 4.1	43.9 ± 2.6	48.5 ± 2.7	<.001[**]
Height (Z-score)	−0.5 ± 1.21	−0.47 ± 1.32	−0.59 ± 0.98	−0.5 ± 0.98	.64
Weight (g)	1854.6 ± 686.6	1587.2 ± 491	2101.2 ± 473	2992.7 ± 735.6	<.001[**]
Weight (Z-score)	−0.48 ± 1.18	−0.36 ± 1.18	−0.74 ± 1.03	−0.72 ± 1.46	.49
Head circumference (cm)	29.7 ± 3.3	28.7 ± 3.2	30.8 ± 1.9	33.4 ± 2.8	<.001[**]
Head circumference (Z-score)	−0.29 ± 1.67	−0.16 ± 1.77	−0.53 ± 1.25	−0.56 ± 1.78	.55

2nd time point	Total N = 55	Early preterm n = 35	Late preterm n = 13	Term n = 7	P value
Height (cm)	44 ± 4.2	42.2 ± 3.5	45.5 ± 2.9	50.2 ± 2.1	<.001[**]
Height (Z-score)	−0.94 ± 1.11	−0.98 ± 1.2	−0.99 ± 1.12	−0.66 ± 0.64	.86
Weight (g)	2055.9 ± 703.4	1735.4 ± 463.3	2299.2 ± 520.5	3206.4 ± 650.5	<.001[**]
Weight (Z-score)	−1.33 ± 0.99	−1.34 ± 0.93	−1.41 ± 1.16	−1.11 ± 1.11	.76
Head circumference (cm)	30.8 ± 2.7	29.6 ± 2.3	31.8 ± 1.7	34.6 ± 2.1	<.001[**]
Head circumference (Z-score)	−0.93 ± 1.16	−1.02 ± 1.15	−0.91 ± 1.16	−0.52 ± 1.3	.59

3rd time point	Total N = 45	Early preterm n = 35	Late preterm n = 7	Term n = 3	P value
Height (cm)	43.7 ± 4.7	42.5 ± 4.5	47.8 ± 2.5	49 ± 1.7	<.001[**]
Height (Z-score)	−1.54 ± 1.44	−1.68 ± 1.51	−0.71 ± 0.96	−1.77 ± 1.14	.23
Weight (g)	2151.5 ± 650.1	1988.2 ± 583.9	2722.3 ± 476	2725.3 ± 850.3	.005[*]
Weight (Z-score)	−1.62 ± 1.24	−1.61 ± 1.19	−1.17 ± 1.03	−2.79 ± 1.95	.36
Head circumference (cm)	30.9 ± 2.8	30.2 ± 2.7	32.9 ± 1.1	33.7 ± 4.1	<.001[**]
Head circumference (Z-score)	−1.34 ± 1.29	−1.4 ± 1.24	−0.86 ± 0.68	−1.73 ± 2.88	.50

GA = gestational age, M:F = male:female, N:C = natural delivery:cesarean section.

[*] P < .01.

[**] P < .001.

vaginal delivery (20%). Out of 80 neonates, 54 were early preterm neonates, 17 were late preterm neonates, and 9 were term neonates. Anthropometric measurements at birth showed significant differences among the groups, but there were no differences in terms of anthropometric z-scores (Table 2). CRP, BUN, and creatinine levels at birth were not significantly different among the groups.

At the 1st and 3rd time points, prealbumin levels showed significant differences among the groups (Table 3).

We also conducted Pearson correlation analysis for protein intake, calorie intake, and anthropometric measurements with respect to prealbumin levels. At the 2nd time point, there was a significant correlation between prealbumin levels and calorie intake in total neonates. In particular, subgroup analysis showed that prealbumin levels were significantly correlated with calorie intake in the early preterm group (Table 5).

At the 1st time point, subgroup analysis showed a significant correlation of prealbumin levels with the weight z-score in term

Table 3

Calorie and protein intakes and prealbumin levels in the 3 groups at 3 time points.

1st time point	Total N = 80	Early preterm n = 54	Late preterm n = 17	Term n = 9	P value
Prealbumin	8.29 ± 0.27	8.08 ± 0.30	7.51 ± 0.35	10.97 ± 0.98	.005[**]

2nd time point	Total N = 55	Early preterm n = 35	Late preterm n = 13	Term n = 7	P value
Total calorie intake (kcal/kg)	109.2 ± 3.4	100.3 ± 2.5	112.8 ± 4.9	126.3 ± 8.7	.001[**]
Total protein intake (g/kg)	3.1 ± 0.1	2.9 ± 0.1	3.1 ± 0.1	2.7 ± 0.2	.33
Prealbumin	11.45 ± 0.73	12.56 ± 0.51	11.59 ± 0.93	16.31 ± 1.6	.01[*]

3rd time point	Total N = 45	Early preterm n = 35	Late preterm n = 7	Term n = 3	P value
Total calorie intake (kcal/kg)	109.2 ± 3.4	110.5 ± 4.1	99.5 ± 5.6	115.6 ± 10.4	.26
Total protein intake (g/kg)	3.1 ± 0.1	3.2 ± 0.1	3 ± 0.2	2.7 ± 0.6	.44
Prealbumin	11.45 ± 0.73	10.26 ± 0.43	13.56 ± 2.44	20.4 ± 6.49	.02[*]

[*] P < .05.

[**] P < .01.

Table 4

Pearson correlations between anthropometric parameters and prealbumin levels in each group at 3 time points.

1st time point	Total N=80		Early preterm n=54		Late preterm n=17		Term n=9	
	Pearson r	P value	Pearson r	P value	Pearson r	P value	Pearson r	P value
Height (Z-score)	0.02	.84	0.06	.66	−0.01	.97	−0.22	.56
Weight (Z-score)	−0.05	.66	0.11	.42	0.03	.91	−0.69	.04*
Head circumference (Z-score)	0.11	.31	0.25	.07	0.20	.44	−0.44	.24

2nd time point	Total N=55		Early preterm n=35		Late preterm n=13		Term n=7	
	Pearson r	P value	Pearson r	P value	Pearson r	P value	Pearson r	P value
Height (Z-score)	0.28	.04*	0.41	.01*	−0.05	.88	0.10	.83
Weight (Z-score)	0.21	.13	0.42	.01*	0.09	.78	−0.41	.36
Head circumference (Z-score)	0.31	.02*	0.50	.002**	−0.10	.74	0.10	.84

3rd time point	Total N=45		Early preterm n=35		Late preterm n=7		Term n=3	
	Pearson r	P value	Pearson r	P value	Pearson r	P value	Pearson r	P value
Height (Z-score)	0.24	.12	0.34	.05*	0.31	.49	0.19	.88
Weight (Z-score)	−0.10	.52	0.37	.03*	0.04	.93	−0.93	.25
Head circumference (Z-score)	−0.11	.49	0.25	.15	−0.28	.54	−0.73	.48

* P < .05.
** P < .01.

neonates. At the 2nd time point, prealbumin levels showed significant correlations with the length and head circumference z-scores in total neonates. Subgroup analysis showed significant correlations of prealbumin levels with the length, weight, and head circumference z-scores in early preterm neonates. At the 3rd time point, subgroup analysis showed that prealbumin levels were significantly correlated with the length and weight z-score in early preterm neonates (Table 4).

4. Discussion

In this study, we aimed to evaluate the usefulness of prealbumin as a biomarker of growth in neonates based on its correlations with protein intake, calorie intake, and anthropometric parameters. Prealbumin showed a significant correlation with calorie intake, rather than protein intake, at the 2nd study time point. Moreover, it showed a significant correlation with anthropometric measurements, especially in early preterm infants.

At the 1st study time point, prealbumin levels were the lowest in late preterm babies among the 3 groups, implying that late preterm infants are nutritionally deficient and need nutritional support. In the presence of term babies and less severe patients in the NICU, these infants are often nutritionally neglected, even though they require proper nutritional management.

At the 3rd study time point, the prealbumin levels of many preterm infants did not reach those seen in term babies at the 1st

study time point. Regardless of how much effort is put into the nutritional management of preterm infants, it is difficult to reach the prealbumin levels and anthropometric z-scores observed in term babies at the 1st time point. These results suggest the presence of extrauterine growth restriction (EUGR), which should be managed more aggressively through nutritional support.[22–25]

In NICUs, nutritional assessment is necessary to devise therapeutic plans.[26,27] Most patients are preterm infants born before sufficient maturation of organs and sufficient nutrient accumulation[28] who need nutritional support because TPN is no better than transplacental nutritional supply.[23,29–32] After birth, the lack of protein and lipid accumulation cause EUGR; consequently, EUGR usually results in poor neurodevelopmental outcomes.[24,33–37]

Anthropometric parameters can be easily and inexpensively measured to assess intrauterine growth.[4] In addition, objective laboratory markers are also used to make proper decisions in terms of nutritional support.[38] Prealbumin is often evaluated as a representative biomarker.[39]

There are few previous studies on the serum prealbumin levels of preterm infants. Moskowitz et al[40] reported that prealbumin levels were significantly correlated with protein and calorie intakes. In the study by Nadeau et al[38] a higher prealbumin concentration was found in infants with higher nutritional intakes. Helms et al[25] reported that a higher protein intake, rather than a higher calorie intake, resulted in significantly higher prealbumin levels.

Table 5

Pearson correlations between protein, calorie, and prealbumin levels in each group at 3 time points.

2nd time point	Total N=55		Early preterm n=35		Late preterm n=13		Term n=7	
	Pearson r	P value	Pearson r	P value	Pearson r	P value	Pearson r	P value
Total calorie intake (kcal/kg)	0.33	.01*	0.36	.03*	0.41	.17	−0.18	.70
Total protein intake (g/kg)	−0.2	.15	0.01	.94	−0.49	.09	−0.12	.80

3rd time point	Total N=45		Early preterm n=35		Late preterm n=7		Term n=3	
	Pearson r	P value	Pearson r	P value	Pearson r	P value	Pearson r	P value
Total calorie intake (kcal/kg)	0.11	.49	0.17	.34	0.68	.09	−0.49	.67
Total protein intake (g/kg)	−0.07	.63	0.16	.37	0.32	.48	−0.53	.65

* P < .05.

This study has some limitations that should be considered when interpreting the results. This is single-center study that generalization is limited. As babies grow older than 34 weeks of postmenstrual age, sucking and swallowing reflexes develop; but some of them have difficulty digesting milk. There may be inaccuracies in calculating calories and protein amounts due to gastric residual milk. Moreover, NICU hospitalization lasting 4 weeks implies that the baby is in a critical condition or was born before 34 weeks of GA. Therefore, the correlations showed by prealbumin levels at the 3rd study time point in late preterm and term infants could be affected by morbidities.

Further studies with larger study populations and a thorough investigation of morbidities will be needed to confirm these results.

In conclusion, prealbumin levels in NICU patients were significantly correlated with several nutritional and anthropometric parameters. In particular, prealbumin levels measured on the 14th postnatal day in early preterm infants showed significant correlations with the length, weight, and head circumference z-scores. These results imply that prealbumin can be used as biomarker of growth in neonates.

Author contributions

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