Short Communication

Standard values of rapid turnover proteins and zinc in Japanese children

Kei Yamamoto MD[1,2], Norihiko Kitagawa MD, PhD[3], Tetsuya Takamasu MD[4]

[1]*Department of General Pediatrics, Kanagawa Children's Medical Center, Yokohama, Japan*
[2]*Division of Infectious Diseases, National Center for Global Health and Medicine, Tokyo, Japan*
[3]*Department of Pediatric Surgery, Kanagawa Children's Medical Center, Yokohama, Japan*
[4]*Department of Allergy, Kanagawa Children's Medical Center, Yokohama, Japan*

Measurement of rapid-turnover proteins has an established place in nutrition assessment and is partly dependent on the zinc metallo-enzymes involved. We investigated the reference values of rapid turnover proteins and zinc in Japanese children. This cross-sectional study was conducted at a single center. We collected data from children aged 0 to 12 years with inguinal hernia, umbilical hernia, or hydrocele of the spermatic cord, who had body mass index z scores of -2 to 2. The standard references (mean±2 SD) of transthyretin were 11.5-21.5 mg/dL in infants (≤1.5 years), 13.6-21.5 mg/dL in preschool children (1.6-6 years), and 12.3-23.4 mg/dL in preadolescent children (6.1-12 years). The standard references of retinol binding protein were 1.27-2.55 mg/dL, 1.28-2.54 mg/dL, and 1.27-2.44 mg/dL in each age group, respectively. Rapid turnover proteins did not differ significantly in each group. The transthyretin level was weakly correlated with aging (r=0.284, p=0.003) and estimated lean body mass (r=0.274, p=0.004). Retinol-binding protein was not correlated with aging and anthropometric parameters. We established reference values for rapid turnover proteins with known zinc status in Japanese children. These values were not, or only weakly, correlated with anthropometric parameters for assessing protein energy malnutrition.

Key Words: children, retinol binding protein, transthyretin, zinc, Japanese

INTRODUCTION

The standard values of important chemical markers for nutritional assessment, such as rapid turnover protein (RTP) and zinc in children, are not well known. Transthyretin (TTR) and retinol binding protein (RBP) form a complex with retinol and thyroxine, respectively. RBP is a carrier protein of retinol and TTR is a carrier protein of thyroxine.[1] These proteins are used for assessment of protein energy malnutrition, called RTP, because they reflect a low protein state more rapidly than serum albumin, owing to their rapid synthesis and short halflife.[1-3] There are few reports on children's standard values of RTP.[4-7] RTP values in children are lower than those in adults. Therefore, these values may be affected by age, immaturity of metabolism, and other factors. Zinc is also an important minor element in nutritional assessment. Anthropometric values, such as z scores of body weight (BWZ) and body mass index (BMIZ), are usually used to assess children's growth and nutritional status.[8]

The present study investigated the standard values of RTP and zinc according to age in healthy children. We also examined whether some anthropometric values were related to RTP in Japanese children.

MATERIALS AND METHODS

This cross-sectional study was conducted at a single center between June 2010 and February 2011. We selected data from children who had no severe nutritional problem, patients with inguinal hernia, umbilical hernia, or hydrocele of the spermatic cord, aged 0 to 12 years, and whose BMIZ was -2 to 2. Patients with congenital heart disease, respiratory disease with home oxygen therapy, or severe multiple handicaps were excluded. Data of blood sampling from a routine preoperative medical check-up were examined in our clinical laboratory. TTR, RBP and zinc were determined by immunonephelometry (N-assay TIA Prealbumin Nittobo, Fukushima, Japan), latex coagulating nephelometry (N-assay LA RBP Nittobo, Fukushima, Japan), and atomic absorption spectrometry, respectively. We also measured albumin, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, cholinesterase, free thyroxin, and C-reactive protein (CRP) levels. The anthropometric parameters, such as body height and weight, were measured on the same day of blood sampling.

Patients who had elevated hepatic enzyme, creatinine (normal values were based on sex and age), and CRP (≥0.5 mg/dL) levels, and/or other abnormal laboratory

Corresponding Author: Dr Kei Yamamoto, National Center for Global Health and Medicine, Division of Infectious Disease, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
Tel: +81-3-3202-7181; Fax: +81-3-3207-1038
Email: kyamamoto@hosp.ncgm.go.jp; nicepoko@gmail.com
Manuscript received 18 March 2014. Initial review completed 7 July 2014. Revision accepted 21 October 2014.
doi: 10.6133/apjcn.2015.24.4.01

data were excluded. We calculated the BWZ and BMIZ from standard data from Japanese children in 2000. We estimated lean body mass (LBM) by Boer equations.[9] The patients were separated into three groups according to age. Patients aged up to 1 year and 6 months were the infants, those aged >1 year and 6 months to 6 years were the preschool children, and those aged >6 years to 12 years were the preadolescent children, respectively.

All reference ranges are presented as mean±2 SD. We established standard references for TTR, RBP, and zinc in children. Children's background and laboratory data in each age group were compared by multiple comparisons using ANOVA and Tukey's method. We examined correlations between laboratory data for nutritional assessment, such as TTR, RBP, zinc and anthropometric parameters by the Pearson product–moment correlation coefficient. A p value <0.05 was considered to indicate statistical significance. The software program SPSS version 20 (IBM, New York, USA) was used for descriptive and comparative statistical analysis.

Written informed consent was obtained from all participants. This study was certificated by the Ethics Committee in Kanagawa Children's Medical Centre (59-2).

RESULTS

A total of 124 children were enrolled in the study. Among them, six children were excluded because of elevated CRP levels (n=5) and severe iron deficiency anaemia (hemoglobin, 6.7 g/dL, n=1). A total of 118 children (66 male and 52 female) were separated into 32 infants, 48 preschool children, and 38 preadolescent children. There were 29 (22 male; mean age, 0.976±0.366 years), 47 (26 male; mean age, 3.75±1.28 years), and 35 (14 male; mean age, 8.03±1.45 years) children, whose BMIZ was −2 to 2, in each group, respectively. Z score of height and weight were not significantly different in each age group. BMIZ in preadolescent children was significantly lower than in preschool children (p=0.036) (Table 1). The mean±SD of LBM was 6.16±0.99 kg in infants, 11.2±2.45 kg in preschool children, and 18.5±3.53 kg in preadolescent children.

The standard range of TTR was 11.5-21.5 mg/dL in infants, 13.6-21.5 mg/dL in preschool children, and 12.3-23.4 mg/dL in preadolescent children. The values were weakly correlated with age (r=0.284, p=0.003). However, the mean values of TTR in each age group did not differ significantly (Table 1). The mean values of RBP and zinc were not significantly different among the groups (Table 1).

TTR was significantly correlated with LBM (r=0.274, p=0.004), but not with BWZ (r=0.0209, p=0.828) or BMIZ (r=-0.0105, p=0.913). RBP was not correlated with LBM (r=-0.00880, p=0.660), BWZ (r=-0.00626, p=0.948), and BMIZ (r=0.0422, p=0.927). BWZ was weakly correlated with zinc (r=-0.211, p=0.026).

DISCUSSION

RTPs are useful for nutritional assessment in adults[2] and are associated with protein energy malnutrition.[2,3] However, the absolute values useful for children's nutritional assessment are unknown because the normal values in children are age dependent. It had been reported previously that TTR and RBP increased according to age, especially in puberty (Table 2).[6,7] In our study, although only TTR was weakly correlated with age, there were no significant differences in TTR, RBP, and zinc in each age group. This was the reason why adolescents were not included in our study. Lower BMIZ in preadolescent children than in the other age groups may have affected the value of RTPs, because RTPs start increasing in preadolescent children.

To the best of our knowledge, no study has reported a correlation between nutritional chemical markers and other anthropometric values in children. In the present study, TTR was not correlated with BMIZ and BWZ, which are usually used for nutritional assessment for protein energy malnutrition in children. TTR was significantly increased by LBM, as reported in adults.[10] However, the correlation was not so strong, and RBP was not correlated with any anthropometric parameters either. These findings showed that these absolute values of RTPs were independent of anthropometric parameters for nutritional assessment in children.

We established reference values for TTR, RBP and zinc in Japanese children, and these values were not strongly correlated with anthropometric parameters for assessing protein energy malnutrition, such as BWZ, BMIZ and LBM.

Table 1. The z scores of height, weight, and BMI for age, and standard reference of transthyretin, retinol binding protein and zinc in children whose z scores of BMI were between -2 and 2.

Age group	Infants	Preschool children	Preadolescent children	ANOVA p values	Adults
n (male/female)	29 (22/7)	47 (26/21)	35 (14/21)		
Mean z score of height (95% CI)	-0.49 (-0.99 to 0.005)	-0.46 (-0.37 to 0.28)	-0.15 (-0.52 to 0.23)	0.26	-
Mean z score of weight (95% CI)	-0.372 (-0.86 to 0.11)	0.464 (-0.25 to 0.34)	-0.39 (-0.68 to -0.10)	0.10	-
Mean z score of BMI (95% CI)	0.0455 (-0.33 to 0.42)	0.13* (-0.081 to 0.34)	-0.34* (-0.63 to -0.045)	0.039	-
TTR (mg/dL)	11.5-21.5**	13.6-21.5	12.3-23.4**	0.067	15-36
RBP (mg/dL)	1.3-2.6	1.3-2.5	1.3-2.4	0.70	2.6-7.6
Zn (μg/dL)	42.9-89.3	46.1-82.7	48.2-83.1	0.73	70-120

The reference range was calculated from the mean±2 standard deviations.
*p<0.05, **p<0.1: results of post hoc test (multiple comparisons in each age group, Tukey's methods)
CI: confidential interval; TTR: transthyretin; RBP: retinol binding protein; Zn: zinc

Table 2. Literature review on the standard values of RTP in children

Publication year, country	1984, Japan[4]		1988, United States[5]		1988, Canada[6]		2011, United States[7]		
n	99		76		450		1716		
	Age	Ref	Age	Ref	Age	†Ref	Age	Ref: male	Ref: female
TTR (mg/dL)	0-1 mo	7.5-18.3	2-5.9 mo	14.2-33.0	0-5 day	6.0-21.0	6 mo-2 yr	12.2-22.1	11.1-25.2
	1-4 mo	13.0-24.6	6-11.9 mo	12.0-27.4	1-5 yr	14.0-30.0	3-5 yr	13.0-22.9	11.9-22.9
	5 mo-1 yr	9.9-28.7	12-17.9 mo	11.5-25.9	6-9 yr	15.0-33.0	6-8 yr	13.2-31.2	13.6-31.8
	1-2 yr	13.2-26.4	18-23.9 mo	14.3-24.3	10-13 yr	20.0-36.0	9-11 yr	15.3-38.2	13.5-32.9
			2-3 yr	10.8-25.8	14-19 yr	22.0-45.0	12-14 yr	17.6-38.9	18.0-37.4
							15-17 yr	18.2-39.5	19.7-42.3
RBP (mg/dL)	0-1 mo	1.5-3.9			0-5 day	0.8-4.5			
	1-4 mo	1.9-4.3			1-5 yr	1.0-7.6			
	5 mo-1 yr	1.8-4.6			6-9 yr	2.0-7.8			
	1-2 yr	2.2-4.6			10-13 yr	1.3-9.9			
					14-19 yr	3.0-9.2			

The reference range was calculated from the mean±2 standard deviations.
†The reference range of TTR reported by Lockitch et al[6] was described as a range from the 2.5th percentile to the 97.5th percentile.
TTR: transthyretin; RBP: retinol binding protein; Ref: reference range; yr: year, or years; mo: month, or months

ACKNOWLEDGMENTS
We are grateful to the clinical laboratory of Kanagawa Children's Medical Center, which performed tests, and to all staff in the department of pediatric surgery for help with this study.

SOURCES OF FUNDING
KY is supported by a Kanagawa Prefectural Hospitals Child Health Care and Research Fund.

AUTHOR DISCLOSURES
The authors declare no conflicts of interest.

REFERENCES
1. Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. Annu Rev Nutr. 1994;14:495-533. doi: 10.1146/annurev.nu.14.070194.002431.
2. Beck FK, Rosenthal TC. Prealbumin: a marker for nutritional evaluation. Am Fam Physician. 2002;65:1575-8.
3. Bernstein L, Pleban W. Prealbumin in nutrition evaluation. Nutrition. 1996;12:255-9.
4. Kanaya S, Nose O, Harada T, Ogawa M, Maki I, Tajiri H et al. Research of nutritional assessment in children-part 1-; Normal value of prealbumin, retinol binding protein and transferrin. Nihon Shounika Gakkai Zasshi. 1984;88:591-8. (In Japanese)
5. Sherry B, Jack RM, Weber A, Smith AL. Reference interval for prealbumin for children two to 36 months old. Clin Chem. 1988;34:1878-80.
6. Lockitch G, Halstead AC, Quigley G, MacCallum C. Age- and sex-specific pediatric reference intervals: study design and methods illustrated by measurement of serum proteins with the Behring LN Nephlometer. Clin Chem. 1988;34:1618-21.
7. Clifford SM, Bunker AM, Jacobsen JR, Roberts WL. Age and gender specific pediatric reference intervals for aldolase, amylase, ceruloplasmin, creatine kinase, pancreatic amylase, prealbumin, and uric acid. Clinica Chimica Acta. 2011;412:788-90. doi: 10.1016/j.cca.2011.01.011.
8. Report of a WHO Expert Committee. Physical status: the use and interpretation of anthropometry. Geneva: WHO Technical Report Series No. 854. 1995. [cited 2013/10/2]; Available from: http://whqlibdoc.who.int/trs/WHO_TRS_854.pdf.
9. Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. Br J Anaesth. 2011;106:719-23. doi: 10.1093/bja/aer057.
10. Ingenbleek Y. Plasma transthyretin reflects the fluctuations of lean body mass in health and disease. In: Richardson SJ, Cody V, editors. Recent Advances in Transthyretin Evolution, Structure and Biological Functions. Berlin: Springer-Verlag; 2009. pp. 329-57.

Short Communication

Standard values of rapid turnover proteins and zinc in Japanese children

Kei Yamamoto MD[1,2], Norihiko Kitagawa MD, PhD[3], Tetsuya Takamasu MD[4]

[1]*Department of General Pediatrics, Kanagawa Children's Medical Center, Yokohama, Japan*
[2]*Division of Infectious Diseases, National Center for Global Health and Medicine, Tokyo, Japan*
[3]*Department of Pediatric Surgery, Kanagawa Children's Medical Center, Yokohama, Japan*
[4]*Department of Allergy, Kanagawa Children's Medical Center, Yokohama, Japan*

日本兒童微量蛋白質與鋅的標準值

微量蛋白質的測量是營養評估的一環，它的營養狀況部分取決於鋅金屬酶。本研究探討日本兒童微量蛋白質與鋅的參考值。這個橫斷性研究在單一中心進行。我們收集腹股溝疝氣、臍疝氣或是精索鞘膜積液（水疝），且身體質量指數 z 分數界於-2 至 2 的 0-12 歲兒童的數據。甲狀腺素運載蛋白的標準參考值（平均值±2 標準差）嬰兒（≤1.5 歲）為 11.5-21.5 mg/dL、學齡前兒童（1.6-6 歲）為 13.6-21.5 mg/dL、青春期前兒童（6.1-12 歲）為 12.3-23.4 mg/dL。各年齡層的視網醇結合蛋白的標準參考值分別為 1.27-2.55 mg/dL、1.28-2.54 mg/dL 及 1.27-2.44 mg/dL。微量蛋白質在各組並沒有顯著差異。甲狀腺素運載蛋白濃度與年齡（r=0.284，p=0.003）及推估的瘦體組織（r=0.274，p=0.004）有弱相關。視網醇結合蛋白與年齡及體位測量值沒有相關性。我們建立日本兒童的微量蛋白質的參考值並確認鋅的狀況。這些數值與評估蛋白質能量營養不良的體位測量值沒有或僅是弱相關。

關鍵字：兒童、視網醇結合蛋白、甲狀腺素運載蛋白、鋅、日本人