Efficacy of Corrected Rapid Turnover Protein Increment Index (CRII) for Early Detection of Improvement of Nutrition Status in Patients with Malnutrition

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Summary **Serum prealbumin level is useful for assessment of changes in nutritional status but it is markedly affected by the inflammation. In this study, we examined the efficacy of the corrected rapid turnover protein increment index (CRII) for prealbumin, which is calculated as [prealbumin level/C-reactive protein (CRP) level on the assessment day]/[prealbumin level/ CRP level on the day of starting nutritional care], for prediction of improvement of nutritional status in patients with malnutrition. The subjects were 50 hospitalized patients with low albuminemia, who were receiving nutritional care. Serum concentrations of albumin, pre-albumin and CRP were measured every week for 5 weeks. We defined patients whose serum albumin level was elevated by more than 0.2 g/dl after 5 weeks as those showing improved nutritional status. There was a significant difference in the prealbumin level between improved and unimproved patients at 5 weeks after the start of nutritional support. On the other hand, the prealbumin CRII value showed a significant difference between the groups at 1 and 2 weeks after the start of nutritional support. In conclusion, assessment of prealbumin CRII is useful for early prediction of improved nutritional status in patients with malnutrition.**

Key Words: **prealbumin, nutritional assessment, C-reactive protein, inflammation, rapid turn over protein**

Introduction

The association between poor nutrition and illness has long been recognized. Malnutrition is a well-known problem in hospitals, and highlights the need for education on clinical nutrition [1]. A number of clinical studies have been conducted to determine suitable laboratory markers for evaluation of malnutrition [2–9]. Among laboratory markers of nutritional status, serum hepatic proteins have been used because they are capable of indicating malnutrition and/or nutritional risk in hospitalized patients. Serum albumin has been the most widely used determinant of nutritional status. However, albumin has a relatively large body pool and a half-life of 20 days, and its level typically takes 14 days to return to normal when the pool has been depleted [8]. Therefore, the level of serum albumin is considered to be relatively insensitive to changes in nutritional intake and nutritional risk [6].

In contrast to albumin, the half-life of rapid turnover proteins (RTPs), such as prealbumin (transthyretin), retinol binding protein and transferrin, is relatively short, and the

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levels of serum RTPs are changed by alterations in nutritional intake and nutritional risk [6, 7, 9–14]. Therefore, RTP has been recognized as a more sensitive indicator of nutritional status than albumin. In a 1995 consensus statement, measurement of the serum prealbumin level was recommended for all patients admitted to hospital with malnutrition or nutritional risk factors. In addition, sequential measurement of prealbumin is considered useful for evaluation of changes in nutritional status and risk. However, it was sometimes difficult to correctly evaluate the nutritional condition of patients by using serum prealbumin, since its sequential level changed markedly at each measurement. The levels of hepatic proteins reflect the nutritional status of patients, and several kinds of inflammation may contribute to an increase in net protein loss caused by catabolism [7, 15–17]. Inflammation also induces anorexia, reducing the probability that a patient will consume adequate nutrients for even normal metabolic requirements. Since the half-life of prealbumin is relatively short, its level is dramatically changed not only by alteration of nutritional intake but also by the presence and the degree of inflammation. Recently, we designed the corrected RTP increment index (CRII), which is calculated as [RTP level/C-reactive protein (CRP) level on the assessment day]/[RTP level/CRP level on the day of starting nutritional care]. Theoretically, the level of serum RTP is inversely correlated with the presence of inflammation, and we consider that CRII is a more sensitive marker of the degree of inflammation than the RTP level. We performed the present study to clarify the efficacy of our newly designed parameter, CRII, for early prediction of improved nutritional status in patients with malnutrition being cared for by the nutrition support team (NST) at our hospital.

Subjects and Methods

The study subjects were 50 consecutive hospitalized patients, whose serum albumin levels were under 3.0 g/dl at the start of nutritional support and who received nutritional care by the NST for over 5 weeks (Table 1). Care by the NST was started after recommendation by the physician and/or nurse in charge, and written informed consent was obtained from all of the patients and/or their family members. All patients were nutritionally supported so that they received an adequate volume of water, energy, protein, vitamins, trace elements, etc., which were calculated using the Harris-Benedict formula, activity index, injury index, and other methods. Serum concentrations of albumin, prealbumin and high-sensitive CRP were measured every week while the patients were receiving nutritional support.

Measurements of albumin, prealbumin and CRP were performed by an automatic analyzer (Toshiba 200F, Toshiba Medical Supply Co. Ltd., Tokyo, Japan) using kits for each measurement (N-assay TIA prealbumin, Nittobo Co. Ltd., Tokyo, Japan; Albumin II HA-test, Wako Pure Chemical Industries, Ltd., Osaka, Japan; CRP latex-enhanced TIA, Denka Seiken Co. Ltd., Tokyo, Japan) in accordance with the manufacturers' instructions in the central laboratory of our hospital. We did not measure other RTPs, such as retinol biding protein and tranfferrin, in this study. We defined patients whose serum albumin level was elevated by more than 0.2 g/dl at 5 weeks after the start of nutritional support as those showing improved nutritional status, and the study subjects were divided into improved patients and unimproved (unchanged or worsened) patients, since the mean increases in albumin levels (g/dl) during 5 weeks in the

Table 1. Study subjects

	Improved patients	Unimproved patients	p value
Gender (male/female)	14/13	8/15	0.226
Age (mean ± SD)	77.0 ± 1.8 (54–94)	78.7 ± 2.0 (57–94)	0.408
Main complicating disease			
Malignancy[1]	11	4	
Cardiovascular diseases[2]	4	6	
Cerebral diseases[3]	4	2	
Pneumonia[4]	1	4	
Skin diseases[5]	5	4	
Postoperative state[6]	2	3	
Serum albumin level (g/dl)	2.3 ± 0.1 (1.5–2.9)	2.6 ± 0.1 (2.0–3.0)	0.001
Serum prealbumin level (mg/dl)	11.2 ± 1.2 (4.1–30.3)	13.3 ± 1.9 (4.1–39.4)	0.676
C-reactive protein (mg/dl)	4.8 ± 1.0 (0.2–17.9)	2.7 ± 0.5 (0.2–7.5)	0.243

Data are expressed as the number of patients and mean ± SE (range).
[1] Gastric cancer, pituitary tumor, pancreatic cancer, ovarian cancer, malignant lymphoma and leukemia; [2] acute myocardial infarction and aneurysm; [3] cerebral infarction and hemorrhage; [4] pneumonia and aspiration pneumonia; [5] burn and decubitus; [6] postoperative state in patients with gastric cancer and aneurysm.

improved and unimproved groups were 0.5 and −0.2, respectively. Temporal changes in the serum concentrations of albumin and prealbumin and CRII level were compared between the improved and the unimproved patients.

Data were expressed as mean ± SE. Statistical analyses were performed by the chi-squared test for comparisons between the improved and the unimproved patients, and by the Mann-Whitney *U* test. All calculations were done with Stat View 5.0 software (Abacus Concepts Inc., Berkeley, CA) for Macintosh. Differences at *p*<0.05 were considered statistically significant.

Results

Mean serum albumin and prealbumin concentrations at the start of nutrition support in the study subjects were 2.4 ± 0.1 (1.5–3.0) g/dl and 12.2 ± 1.1 (4.1–39.4) mg/dl, respectively. The numbers of patients showing improvement and no improvement were 27 and 23, respectively (Table 1). There was no significant difference between the two groups in age, gender, or main complicating diseases. Mean serum albumin concentrations at the start of nutritional support in the improved and unimproved groups were 2.3 ± 0.1 and 2.6 ± 0.1 g/dl, respectively, and mean serum prealbumin concentrations were 11.2 ± 1.2 and 13.3 ± 1.9 mg/dl, respectively. Mean serum CRP levels at the start of nutritional support in the improved and unimproved groups were 4.8 ± 1.0 and 2.7 ± 0.5 mg/dl, respectively. The difference in serum albumin level at the start of nutritional support between the two groups was significant. However, the inter-group differences in the levels of prealbumin and CRP were not significant. Temporal changes in albumin, prealbumin and prealbumin CRII are shown in Fig. 1. The mean increases in albumin levels (g/dl) during 5 weeks in the improved and unimproved groups were 0.5 and −0.2, respectively. The serum concentrations of albumin and prealbumin gradually increased in the improved patients, and those in the unimproved patients gradually decreased (Fig. 1-a, b). A significant inter-group difference in prealbumin levels was observed at 5 weeks after the start of nutritional support. On the other hand, the CRII value for prealbumin was markedly different between the groups during the 5 weeks of follow-up, and the CRII value was significantly different between the groups at 1 and 2 weeks after the start of nutritional support (Fig. 1-c).

Discussion

Measurement of hepatic proteins such as prealbumin has been repeatedly demonstrated to be useful for monitoring of malnutrition [2–14]. However, the presence of several kinds of inflammation is recognized to be the most important factor affecting the serum level of hepatic protein, due to
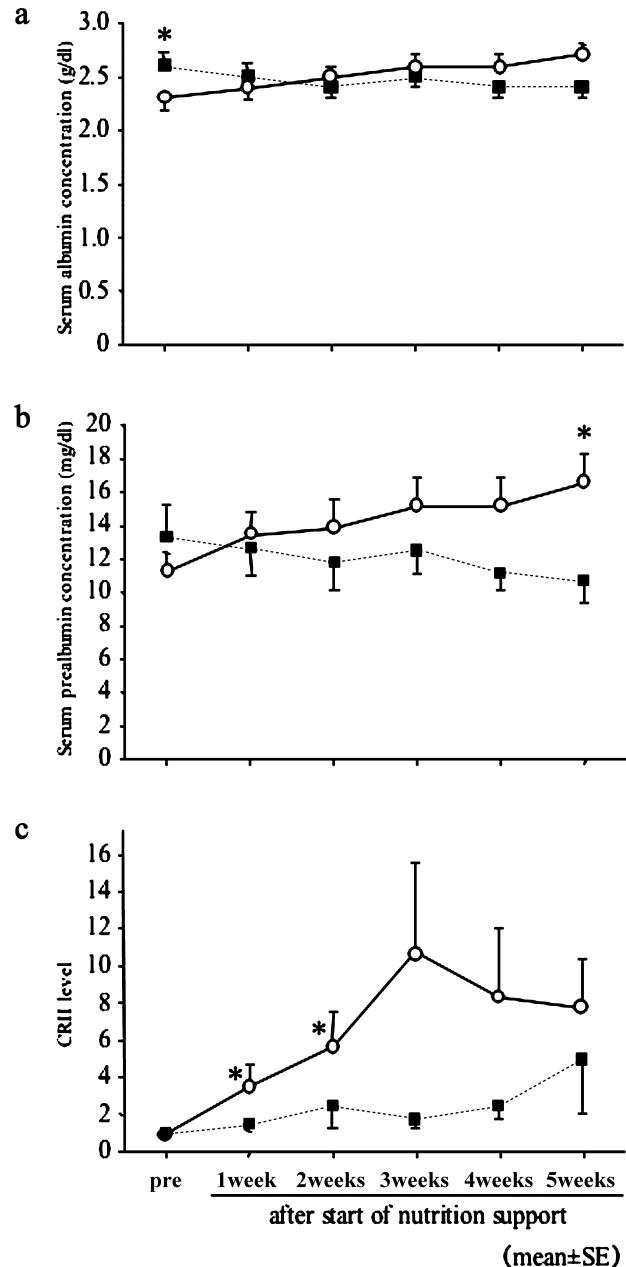

Fig. 1.   Temporal changes in albumin (a), prealbumin (b) and CRII for prealbumin (c). CRII for prealbumin was calculated as [prealbumin level/C-reactive protein (CRP) level on the assessment day]/[prealbumin level/CRP level on the day of starting nutritional care].
Open circle indicates the change in improved patients, and closed square indicates the change in unimproved patients. Data are expressed as mean ± SE.
*: The difference between the improved and unimproved patients was significant.

capillary leakage or alteration of normal hepatic protein metabolism [7, 14–17]. The inflammation-associated cytokines, especially IL-6 and TNF-α, were demonstrated to

play a central role in the acute-phase response, which can include a decline in serum concentration of albumin and prealbumin and an increase in CRP [15]. Therefore, hepatic proteins have been recognized as indicators of inflammatory processes that accelerate nutritional depletion, thus being correlated not with nutritional status, but with morbidity and mortality and recovery from acute and chronic disease [7]. Measurement of serum hepatic protein levels helps the clinician to identify the sickest of patients, i.e. those most likely to develop malnutrition. Patients with low serum concentrations of hepatic proteins are considered to require aggressive and closely monitored nutritional intervention [7]. In addition, failure of serum protein levels to increase with aggressive nutritional support does not indicate that such support is inadequate, but rather that a patient is not recovering from the primary problem underlying inflammatory metabolism or has developed a secondary problem such as infection [7, 15–17].

Serum prealbumin has a short half-life, and its synthesis increases above baseline levels in the short term. Therefore, the level of prealbumin would be expected to change rapidly according to nutritional condition and the degree of inflammation, and determination of its serum level is considered to be a cost-effective and objective method for assessing the severity of illness in patients who are critically ill or have a chronic disease [3, 5–11]. In addition, temporal changes in the level of prealbumin can easily be used to evaluate changes in nutritional condition and the risk to patients. However, assessment of patient status on the basis of sequential changes in the level of prealbumin is sometimes difficult, because this parameter varies markedly with short-term changes in the degree of inflammation [7, 12–14, 16, 17]. Therefore, we designed several parameters that might be potentially useful for early prediction of long-term changes in nutritional status after the start of intensive nutritional support. Among these newly designed parameters, we noticed that CRII, calculated as [RTP level/CRP level on the assessment day]/[RTP level/CRP level on the day of starting nutritional care], is affected more markedly by the degree of inflammation in comparison with RTP level. In this study, we compared the temporal changes in the CRII value for prealbumin with the level of prealbumin, and demonstrated that changes in the former were able to more rapidly predict the increment of serum albumin concentration after nutritional support than the level of prealbumin alone. However, this study was retrospective, and the improvement of nutritional status was evaluated only on the basis of the change in the serum albumin concentration during 5 weeks. Therefore, a further prospective study will be required in order to clarify whether CRII can indeed predict the long-term clinical course of critically ill patients. In addition, it will be necessary to clarify the types of patients who are more suitable for assessment using CRII and to investigate whether other modifications might more clearly reflect patient nutritional status and risk.

In conclusion, this study has demonstrated that changes in the CRII value for prealbumin are more useful than the prealbumin level alone for early prediction of improvement of nutritional status after the start of intensive nutritional support in patients with malnutrition.

Acknowledgments

References

[1] McWhirter, J.P. and Pennington, C.R.: Incidence and recognition of malnutrition in hospital. *BMJ*, **308**, 945–948, 1994.

[2] Dempsey, D.T., Mullen, J.L., and Buzby, G.P.: The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am. J. Clin. Nutr.*, **47**, S352–S356, 1988.

[3] Young, G.A. and Hill, G.L.: Assessment of protein-calorie malnutrition in surgical patients from plasma proteins and anthropometric measurements. *Am. J. Clin. Nutr.*, **31**, 429–435, 1978.

[4] Lahey, M.E., Behar, M., Viteri, F., and Scrimshaw, N.S.: Values for copper, iron and iron-binding capacity in the serum in kwashiorkor. *Pediatrics*, **22**, 72–79, 1958.

[5] Chertow, G.M., Ackert, K., Lew, N.L., Lazarus, J.M., and Lowrie, E.G.: Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. *Kidney Int.*, **58**, 2512–2517, 2000.

[6] Beck, F.K. and Rosenthal, T.C.: Prealbumin: a marker for nutritional evaluation. *Am. Fam. Physician.*, **65**, 1575–1578, 2002.

[7] Fuhrman, M.P., Charney, P., and Mueller, C.M.: Hepatic proteins and nutrition assessment. *J. Am. Diet. Assoc.*, **104**, 1258–1264, 2004.

[8] Spiekerman, A.M.: Nutritional assessment (protein nutriture). *Anal. Chem.*, **67**, R429–R436, 1995.

[9] Mears, E.: Outcomes of continuous process improvement of a nutritional care program incorporating TTR measurement. *Clin. Chem. Lab. Med.*, **40**, 1355–1359, 2002.

[10] Sergi, G., Coin, A., Enzi, G., Volpato, S., Inelmen, E.M., Buttarello, M., Peloso, M., Mulone, S., Marin, S., and Bonometto, P.: Role of visceral proteins in detecting malnutrition in the elderly. *Eur. J. Clin. Nutr.*, **60**, 203–209, 2006.

[11] Prealbumin in Nutritional Care Consensus Group: Measurement of visceral protein status in assessing protein and energy malnutrition: standard of care. *Nutrition*, **11**, 169–171, 1995.

[12] Marshall, W.J.: Nutritional assessment: its role in the provision of nutritional support. *J. Clin. Pathol.*, **61**, 1083–1088, 2008.

[13] Fellah, H., Omar, S., Feki, M., Abderrahim, E., Ben Abdallah, T., Massy, Z.A., Lacour, B., Ben Maiz, H., Kaabachi, N., and Mebazaa, A.: Is serum transthyretin a reliable marker of nutritional status in patients with end-stage renal disease? *Clin. Biochem.*, **41**, 493–497, 2008.

[14] Dennis, R.A., Johnson, L.E., Roberson, P.K., Heif, M., Bopp, M.M., Cook, J., and Sullivan, D.H.: Changes in prealbumin, nutrient intake, and systemic inflammation in elderly recuperative care patients. *J. Am. Geriatr. Soc.*, **56**, 1270–1275, 2008.

[15] Gabay, C. and Kushner, I.: Acute-phase proteins and other systemic responses to inflammation. *N. Engl. J. Med.*, **340**, 448–454, 1999.

[16] American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit. Care Med.*, **20**, 864–874, 1992.

[17] Casati, A., Muttini, S., Leggieri, C., Colombo, S., Giorgi, E., and Torri, G.: Rapid turnover proteins in critically ill ICU patients. Negative acute phase proteins or nutritional indicators? *Minerva. Anestesiol.*, **64**, 345–350, 1998.