

Serum Prealbumin: Is It a Marker of Nutritional Status or of Risk of Malnutrition?

Hospitalized patients who are undernourished are more likely to develop clinical complications and have relatively poor outcomes, with increased length of stay (LOS)¹ and higher mortality compared with well-nourished patients. Provision of adequate nutritional support reduces the complication rate and improves outcome (1). Considerable efforts have therefore been made to identify patients at risk of malnutrition, with a view to early provision of nutritional support. A full nutritional assessment is a complex process, involving detailed assessment of nutritional intake, changes in body composition, signs or symptoms of nutritional deficiency or excess, and laboratory tests, and it should include not only protein-energy status but also vitamins and essential trace elements. Because of this complexity, rapid screening tests have been sought to identify patients who may already be malnourished or are at risk of malnutrition, who can then undergo a more detailed nutritional assessment. The screening tools with the most validation for protein-energy malnutrition include body mass index (weight/height²) in conjunction with recent changes in weight and a simple assessment of illness severity (2). In many patients, however, obtaining an accurate measurement of current and previous weight to allow calculation of rate of weight loss may not be possible, so clinicians have sought a rapid, reliable laboratory method, usually involving plasma proteins, to obtain comparable information.

Serum albumin is of virtually no value in assessment or monitoring of nutritional status (3) but is mentioned here because, surprisingly, there still remain some clinicians who use it as part of their nutritional assessment. The main factor affecting plasma albumin concentration in patients is the rate of transcapillary escape into the interstitial fluid. This transcapillary escape of albumin is markedly increased in disease [as part of the systemic inflammatory response syndrome (SIRS)], leading to decreased plasma albumin concentrations (4). It is inevitable that postoperative patients and patients with severe infection will have low plasma albumin concentrations. The more severe the disease, the lower the albumin, and therefore the lower the albumin, the worse the prognosis.

Prealbumin, also known as transthyretin, has a half-life in plasma of ~2 days, much shorter than that of albumin. Prealbumin is therefore more sensitive to changes in protein-energy status than albumin, and its concentration closely reflects recent dietary intake rather than overall nutritional status (5). Because of this short half-life, however, the concentration of prealbumin falls rapidly as a result of the fall in its synthetic rate when there is a reprioritization of synthesis toward acute-phase proteins

such as C-reactive protein (CRP), fibrinogen, or α_1 -acid glycoprotein. Moreover, prealbumin concentration in plasma, like that of albumin, is affected by changes in transcapillary escape. Hence, interpretation of plasma prealbumin is difficult in patients with infections, inflammation, or recent trauma (4). Despite this difficulty, interest in prealbumin as a potential marker of nutritional status in certain groups of patients led to the First International Congress on Transthyretin in Health and Disease in 2002 (6).

Some studies have screened patients on the basis of their prealbumin on admission, with values <100 mg/L being regarded as indicating severe risk of protein-energy malnutrition, 100–170 mg/L moderate risk, and >170 mg/L no risk. This type of classification, however, may often reflect severity of illness and the magnitude of the SIRS rather than nutritional status. When screening protocols that use prealbumin have been compared with a 2-stage process involving a screening questionnaire followed by an assessment by a professional dietitian, the prealbumin protocols identified many more patients considered to be malnourished (7,8). The authors have tended to interpret this finding as showing the increased sensitivity of prealbumin in detecting malnutrition, rather than the lack of specificity of this test.

Nonetheless, these results do suggest a place for prealbumin measurement soon after admission. In this issue of *Clinical Chemistry*, Devoto et al. (9) report their investigation of the concordance of prealbumin measurement, made on day 3 after admission, with a Detailed Nutritional Assessment (DNA) as a reference method to detect protein-energy malnutrition. Intriguingly, they found excellent correlation of prealbumin with the DNA, in patients with and without increased CRP (>5 mg/L). Devoto et al. (9) interpret this correlation as indicating that prealbumin is a good screening tool for malnutrition, in both the presence and absence of SIRS. Closer examination raises some concerns, however. First, the DNA score is not affected only by nutritional status—it contains variables affected both by nutritional status and by inflammation. Low albumin and low cholesterol, both of which are influenced by SIRS, may account for up to 50% of DNA scores classified as “malnourished”. Thus, in the group with increased CRP, it is not surprising that there is good concordance between prealbumin and DNA. Similarly, because the DNA does contain true nutritional indicators such as low nutritional intake or weight loss that lead to low prealbumin, it can be expected that in patients without increased CRP, there would also be good concordance between DNA and prealbumin concentration. Moreover, nearly half the patients in their study either had undergone trauma or had an infection, so their CRP was probably stabilizing or decreasing on treatment during the 3 days before prealbumin was measured. As noted below, an intake of as little as 66% of the nutritional

¹ Nonstandard abbreviations: LOS, length of stay; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; DNA, Detailed Nutritional Assessment; ICU, intensive care unit.

requirement could be associated with an increase in prealbumin in such patients, and hence for many patients with an inadequate intake, the prealbumin was already rising.

So, one-off measurements of prealbumin are of limited use in screening for malnutrition. A better interpretation of the nutritional component could probably be achieved from 2 measurements, 3 to 5 days apart, to assess the trend both in prealbumin and in CRP.

What about prealbumin in monitoring adequacy of nutritional intake? In seriously ill patients, very low prealbumin concentrations are typical and are inversely related to CRP (10). Therefore, an increase in prealbumin in response to feeding might reasonably be interpreted as a sign of either improvement of metabolic status or improvement of nutritional status. In some studies, changes in prealbumin concentration have correlated with changes in nitrogen balance (11). It has been suggested, but without experimental proof, that a weekly increase of >40 mg/L in prealbumin concentrations reflects a switch to anabolism (12). An important observation was that patients in intensive care units (ICUs) receiving an approximately adequate nutritional intake showed a rise in prealbumin concentrations of ~40 mg/L during 1 week, whereas a control group receiving an inadequate intake still showed an increase, but it was somewhat smaller, at 20 mg/L, while CRP concentrations were decreasing substantially (13). In one ICU study, a loss of total body protein was observed along with an increase in prealbumin and a decrease in CRP (10). Although it is possible that a patient with a daily deficit of 200–400 kcal will still show improvement in visceral protein concentrations associated with a reduction in SIRS, nutritional intake with a deficit of this magnitude would not support muscle protein anabolism, which is a key objective of adequate nutritional support (14).

Interpretation of nutritional status data may differ for patients in ICUs compared with more typical patients requiring nutritional support. Nonetheless, Raguso et al. (14) reached the interesting conclusion that in the early acute phase, an increase in prealbumin indicates that at least 65% of protein-energy needs have been met. More importantly, they also concluded that there had been a reprioritization of hepatic protein synthesis away from acute-phase proteins. At a later stage, the prealbumin concentration may be a more accurate measure to assess the adequacy of nutritional intake.

Given the complexity of this issue, it is not surprising that there are conflicting reports in the literature regarding whether increasing prealbumin concentrations are associated with a reduced hospital LOS. For example, in one study, ICU LOS was not affected by nutritional therapy that led to a rise in prealbumin (13), whereas in a small study of medical and surgical patients, Mears (15) found that when patients were classified as malnourished based on a local protocol, those patients who were randomized to receive nutritional supplementation had greater improvement in prealbumin, along with a significant reduction of 1–3 days in LOS compared with those

receiving standard care. Moreover, in a landmark study performed more than 20 years ago, Bastow et al. (16) showed that overnight enteral tube feeding in severely malnourished patients with femoral neck fracture led to a highly significant reduction of rehabilitation time in hospital, associated with an increase in prealbumin. These studies therefore confirm that in non-ICU patients, increasing prealbumin concentrations are likely to be associated with an improvement in outcome, but the key question as to how any change in prealbumin (taken together with CRP) can be used to inform changes in nutritional therapy in an individual patient will require careful further studies.

Although prealbumin has been considered a potential nutritional marker for some time, it is only in recent years, with improvement in analytical methods and recognition of the importance of nutrition in patient outcome, that inclusion of prealbumin as part of inpatient screening or monitoring profiles has been considered. As for all laboratory tests, an understanding of the reasons for a low result will allow more appropriate action to be taken. An important concept is the difference between patients who are classified as “malnourished” and those “at risk of malnutrition”. Patients who are malnourished are already in a situation in which they are likely to develop the complications of malnutrition and therefore require active nutritional support without further delay, whereas patients at risk of malnutrition may become malnourished over the next few days unless their disease process improves so that metabolic demand decreases and oral nutritional intake increases, or active steps are taken to ensure that their nutritional intake meets their ongoing metabolic demands.

A low prealbumin concentration can therefore be regarded primarily as a signal identifying the at-risk patient who requires careful assessment and monitoring and for whom nutritional support may be needed as part of the treatment plan. Nutritional assessment and monitoring protocols should be developed in all hospitals treating patients with acute or chronic illness, and these protocols should include assessment of adequacy of nutritional intake and possibly serial measurements of plasma prealbumin and CRP concentrations.

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Alan Shenkin

*Division of Clinical Chemistry
University of Liverpool
Liverpool, United Kingdom
Fax 44-151-7065813
E-mail shenkin@liv.ac.uk*

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