Malnutrition is common in hospitalized patients and is associated with increased morbidity and mortality. However, a single, effective laboratory indicator identifying malnutrition is lacking, although serum proteins, particularly albumin, have often been used. Many variables, including inflammation, are known to affect serum protein markers, decreasing their effectiveness. As a result, many practitioners have replaced albumin with prealbumin as the marker of choice. Although prealbumin is also affected by inflammation, it is now common practice for prealbumin levels to be checked along with a marker of inflammation, in most cases, C-reactive protein. Appealing as it may be, there is little outcome data to support this practice. The purpose of this review is to evaluate the most commonly used protein markers of malnutrition in clinical practice, and by doing so, perhaps discourage their widespread, and often inappropriate, use.

“After All, For the Well-Ordered Mind, Serum Proteins Tell Us Nothing We Do Not Already Know” adapted from my co-worker who reads too much Harry Potter

IDENTIFYING MALNUTRITION

The high incidence of malnutrition in the hospital setting was first described in the 1974 publication, “The Skeleton in the Hospital Closet” (1). Over time, the presence of malnutrition has been consistently correlated with increased length of stay, clinical deterioration, increased use of hospital resources, and increased risk of complications (2). Because of the deleterious effects of malnutrition on morbidity and mortality, identifying patients at nutritional risk early should improve outcomes and decrease costs. However, malnutrition is sometimes difficult to define. Is malnutrition a deficiency in caloric intake, protein intake, or a deficiency in both? Could a deficiency in micronutrients such as vitamins and minerals be defined as malnutrition? Is malnutrition defined by a specific clinical condition, or is it the presence of multiple conditions? Although there is no clear consensus among health care professionals on these issues, clinicians have a responsibility to identify and address nutritional deficiencies in their patients.

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professionals as to what the ideal parameters of malnutrition are, the use of serum albumin (Alb) and prealbumin (PAB) remains prevalent today.

An ideal marker would be one that is sensitive and specific to nutrition intake. Alb, transferrin, PAB, and retinol-binding protein (RBP) have been suggested as indicators, or markers of, nutrition status. The most common, and likely the most flawed marker that has been used historically has been the hepatic protein, Alb. Despite the multitude of reviews and studies on this subject that have refuted Alb’s utility as a nutritional indicator, health practitioners continue to be taught, and to use, Alb as a marker of malnutrition (2–4). The majority of the literature on the subject of serum proteins as it relates to nutritional status has been conducted using Alb, although many of these studies also include PAB, transferrin, and RBP. This review will discuss all of these proteins, with an emphasis on Alb.

A TALE OF TWO CASES . . .

Before a discussion on “markers of malnutrition” begins, a review of two case studies involving how malnutrition is evaluated in the hospital setting may be helpful.

Case 1
AP is a well-nourished 70-year-old female with community-acquired pneumonia that is intubated in the medical ICU, on tube feedings. Nursing flow sheets reveal that the patient has received at least three-quarters of her ordered tube feedings the past 3 days. The patient’s albumin level is 2.1 g/dL. The physician orders weekly albumin and prealbumin monitoring and a re-assessment of nutrition needs.

Case 2
SA is a 70-year-old female nursing home resident that is admitted to the general medicine service with altered mental status, a urinary tract infection and a recent 10 lb weight loss. She is cleared by the speech pathologist for a “dysphagia 2” diet. Only one meal/day of a 3-day caloric count is recorded and the nurse reports that the patient is eating very little. SA’s albumin level is 4.2 g/dL. The physician orders further caloric counts.

Which patient is more malnourished?
These case studies demonstrate inconsistencies that sometimes take place in the nutritional assessment in hospitalized patients. There is a tendency to consider the stressed patient, or those receiving specialized nutrition support, as the patient at increased nutrition risk and in need of additional lab monitoring. In contrast, those patients tolerating food by mouth are often perceived as less of a nutrition risk, especially if they do not currently look cachectic. Distinguishing the difference in these two situations is important in cases where a medical intervention or surgical procedure is based on the patient’s nutritional state. In the ICU case, it is not uncommon for an Alb or PAB to be checked serially until levels are normal in order for an invasive intervention to occur, while in the latter situation, this is generally not deemed necessary as they are “eating.” However, it is generally accepted that inadequate intake or weight loss are clear indicators of compromised nutrition status regardless of serum protein level or percentage of “ideal” weight. Conversely, if a stressed patient was previously well nourished, and has been receiving adequate nutrition support, it is unclear what additional information will be gained by monitoring serum proteins.

SERUM PROTEINS

Alb is a serum protein with a relatively large body pool size, only 5% of which is synthesized by the liver daily. The majority of the body’s Alb pool is distributed between the vascular and interstitial spaces, with more than 50% located extravascularly. Because very little of the Alb pool is comprised of newly synthesized Alb, protein intake has very little effect on the total Alb pool on a daily basis. Redistribution between the extravascular and intravascular space occurs frequently; this distribution is affected by the infusion of large amounts of fluid (as in the case of critically ill patients who require fluid resuscitation). The majority of the changes in Alb are likely due to this redistribution in response to the many factors outlined in Table 1 (5–7).

Serum proteins are affected by capillary permeability, drugs, impaired liver function, and inflammation and a host of other factors (Tables 1–3). Alb levels may be falsely high in dehydration due to decreased plasma
volume. It is also a negative acute phase reactant: levels decrease during the acute phase response.

Alb has a relatively long half-life, approximately 14–20 days, and because of this, has been touted as a marker of chronic nutritional status. Albumin’s function is primarily as a carrier protein and helps to maintain oncotic pressure. Because of this latter role, Alb has been given to hospitalized patients to this effect, although this practice is controversial (8).

Synthesis and catabolism of serum proteins are affected by multiple factors, including whether or not hypoalbuminemia is already present. Synthesis in hypoalbuminemic hemodialysis (HD) patients has been shown to be lower compared to normoalbuminemic HD patients (9). Catabolism of Alb has been shown to correlate directly with an increase in positive acute-phase reactants, ceruloplasmin and alpha-1 acid glycoprotein, but surprisingly, not by the more commonly employed CRP (10).

PAB, also known as transthyretin or transthyretin-bound prealbumin, like Alb, is a visceral protein and a negative acute phase reactant. Visceral proteins are a small part of the total body protein pool and include serum proteins, erythrocytes, granulocytes, lymphocytes, and other solid tissue organs (6). Consequently, it is also affected by many of the same factors that affect Alb. PAB’s advantage over Alb is its shorter half-life (2–3 days), and the belief that it is expected to change more rapidly with changes in nutrient intake. Its body pool size is significantly smaller than Alb’s, at about 0.01 g/kg body weight. It acts as a transport protein for thyroxine and as a carrier for retinol binding protein (RBP). PAB may be elevated in acute renal failure as it is degraded by the kidney (5, 6).

Transferrin (half-life: 8–10 days; <0.1 g/kg body weight) and RBP (half-life: 12 hours; 0.002 g/kg body weight) have also been identified as markers of nutrition status. However, because transferrin is involved with iron transport, its levels are influenced by iron status. Iron deficiency can cause increased transferrin levels due to increased iron absorption and is often used as an indirect method of determining total iron binding capacity. The majority of RBP presents as retinol-circulating complex that includes PAB, retinol,
and RBP. It is catabolized in the kidneys and is elevated with renal failure. RBP is dependent on normal levels of Vitamin A and zinc, as low levels of these nutrients inhibit mobilization of RBP in the liver (5,6).

**ACUTE PHASE REACTANTS AND THE INFLAMMATORY RESPONSE**

It would be impossible to have a discussion on Alb, PAB, RBP, and transferrin without discussing the acute phase response. The acute phase response is the systemic response that is elicited with the advent of inflammatory processes including infection, trauma, surgery, cancer autoimmune processes, burn injuries, Crohn’s disease, and even psychiatric disease (11). This response occurs in both acute and chronic inflammation, and is due to an increase in cytokines (in particular, interleukin-6 which is responsible for the production of most acute-phase proteins); different conditions produce diverse patterns of cytokine release. Cytokine release has also been responsible for fever, inflammation of chronic disease, and loss of appetite or cachexia (11).

Serum levels of certain proteins change during the acute-phase response; those that increase are called positive acute phase proteins; those that decline are called the negative acute-phase proteins (Tables 4 and 5, respectively). By definition, an acute-phase protein changes by at least 25% during inflammation. Alb, PAB, transferrin, and RBP are expected to return to normal as the inflammatory response resolves. It is clear that these negative acute-phase reactants are affected by factors other than intake. The reasons for this alteration in protein concentration are complex, but likely due to the need to increase synthesis of immune mediators during times of stress and the decreased need for other proteins that are not essential for immune function. The most widely used indicator for the presence of inflammation is CRP because of its ability to change rapidly with changing conditions, its wide availability, and its sensitivity as a marker of inflammation. Cytokines are not generally tested because of limited availability, lack of standardization for serum levels, and high cost. A more detailed review of the acute-phase response can be found elsewhere (11–13).

**TABLE 3**

<table>
<thead>
<tr>
<th>Factors Affecting Serum Transferrin Levels (73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased in</strong></td>
</tr>
<tr>
<td>Iron deficiency</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
<tr>
<td>Pregnancy (third trimester)</td>
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<tr>
<td>Oral contraception/</td>
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<tr>
<td>Estrogens</td>
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<tr>
<td>Chronic blood loss</td>
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<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Hypoxia</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
</tbody>
</table>

| **Decreased in**                              |
| Pernicious anemia (B12 deficiency)            |
| Anemia of chronic disease                     |
| Folate deficiency anemia                      |
| Overhydration                                  |
| Chronic infection                              |
| Iron overload/iron dextran therapy            |
| Acute catabolic states                         |
| Uremia                                        |
| Nephrotic syndrome (permeability of glomerulus)|
| Severe liver disease/hepatic congestion       |
| Kwashiorkor                                   |
| Age                                           |
| Zinc deficiency                               |
| Corticosteroids                               |
| Cancer                                        |
| Protein                                       |

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**ALBUMIN, PREALBUMIN, TRANSFERRIN, AND RETINOL-BINDING PROTEIN STUDIES**

Many studies, and recently published reviews, have established Alb as an indicator of morbidity and mortality (2,4,14). Although this is true, the assumption, until recently, has been that a change in nutritional intake would have a positive and dramatic effect on Alb concentration. However, the literature available on adults comparing intake and Alb levels has shown inconsistent results. (continued on page 53)
As noted earlier, Alb is affected by factors other than nutrition intake (Table 1). Despite this, and because of its strong correlation with morbidity and mortality, Alb has been studied extensively to determine whether it is an effective nutrition marker. In order for Alb to be an effective nutrition marker, it should not only be sensitive to changes in nutrition intake, but should not be altered by other factors. Additionally, this change should happen over a short period of time (not 3 weeks), and finally, an increase in protein and calorie intake should cause an increase in Alb, that is, unless calorie intake is insufficient, then protein would be degraded for energy. Therefore, increasing nutrition intake should consistently cause a rise in Alb, and conversely, decreasing intake should consistently cause a fall in Alb.

Studies in healthy volunteers involving restriction of energy and protein intake have not shown consistent decreases in serum protein levels (15,16). Furthermore, extreme cases of starvation have not precipitated a decrease in Alb and PAB levels. In a fascinating case study of a medical student missing in the Himalayan mountains in the early 1990’s, over 40 days of starvation did not cause a decrease in Alb, even after rehydration (17). Anorexia nervosa patients, in whom malnutrition is clear, overt, and indisputable, have normal levels of serum proteins. Alb and PAB in the setting of anorexia nervosa were normal and similar to controls and did not differ after nutritional intervention (18,19). In a study...
involving patients with known anorexia and bulimia, only four of 37 patients had low albumin levels (20). It is clear from this data that decreased intake does not necessarily result in a decrease in Alb and PAB levels.

Interventional Studies
If Alb is an indicator of nutritional intake, it would logically follow that increasing calories and protein intake would cause a rise in the setting of hypoalbuminemia. A number of interventional studies have looked at the effect of different calorie and/or protein amounts on Alb, transferrin, RBP, or PAB levels. Unfortunately, the populations studied, route (in a few studies, PO vs enteral (EN) vs parenteral nutrition (PN) showed differences in alb and PAB levels) type of feeding, as well as the protein and calorie level of nutrition used were widely variable. In addition, the majority of the studies did not account for the acute phase response to the inflammation or stressed patient.

The interventional studies that involved an increasing intake (both caloric and/or protein) and its effects on serum protein status have had varied results (21–30). Patients with emphysema were studied for two weeks on oral diets that were above their basal metabolic rates (25). Of Alb, total protein, transferrin, and total lymphocyte count, only transferrin had significantly increased. In another study, patients who received PN were less likely to have depleted PAB and Alb levels (30); however, the actual protein and calorie intakes were unknown in the PN group; in addition, the results were not stratified into severely malnourished versus normal malnourished patients.

Observational Studies
Several observational studies have been conducted to ascertain the role of serum proteins as markers of nutrition (31–41). Alb increased in 3 of the studies (31,35,38), but did not change in 4 (33,36,37,39). PAB increased in 5 studies (36–39,41), with no change in 1 study (40). Transferrin levels increased in 2 studies (34,37), with no significant change in 5 studies (31,33,39–41). In one of the studies, Alb and transferrin actually decreased (32). In a study of 48 critically ill patients receiving hypocaloric nutrition support in a surgical intensive care unit, PAB and Alb did not correlate with intake, but was inversely proportional to inflammatory status as evidenced by CRP levels (42). Finally, Clark et al studied severely septic and multiple-injury patients, PAB, IGF-1, and transferrin did not correlate with total body protein changes (43).

NITROGEN BALANCE
Nitrogen balance has long been accepted as the “gold standard” for assessment of adequate protein intake. Correlations between nitrogen balance and serum proteins have also been inconsistent (21,24). Nitrogen balance correlated better with PAB as compared to RBP, transferrin, and Alb in one study (33), while in another, transferrin correlated better with nitrogen balance than PAB (34).

C-REACTIVE PROTEIN
CRP is a positive acute-phase reactant whose levels are elevated with both acute and chronic inflammation (Table 4). It has a short half-life of 19 hours (44). Approximately one-third of Americans have minimally elevated CRP levels at baseline (45). Low grade inflammatory processes, dietary and behavioral factors, as well as cardiovascular and non-cardiovascular medical conditions, just to name a few, are associated with an increase in CRP levels (see reference 45 for a complete list). However, in certain conditions that are associated with severe inflammation, CRP does not increase. These conditions include, but are not limited to, ulcerative colitis, systemic lupus erythematosus and leukemia (44).

Albumin and Prealbumin and the Inflammatory Response
Although the effect of inflammation on serum proteins has been known for some time (11), only recently has it become appreciated in the world of nutrition assessment. Few studies have examined CRP and other indicators of stress and/or inflammation on “nutrition indicators” (21,28). One of the largest interventional studies was conducted on 120 medical and surgical ICU (continued on page 57)
patients to determine whether early concomitant EN with PN would increase levels of PAB and RBP (23). In this prospective, double-blind trial in which two groups of 60 patients each were randomized to receive either EN and placebo (control), or EN and PN concurrently (experimental). PAB and RBP levels were checked on day 0, 4, 7, and 14; patients were followed after treatment up to 2 years. There were no differences in number of days on the ventilator, nosocomial infections, ICU length of stay, mortality, or organ system failure score. The control group received significantly fewer calories than the treatment group (14 kcals/kg versus 25 kcals/kg), with the difference in calories being contributed by the PN. PAB and RBP were significantly higher in the treatment group at day 7, but this significance did not continue throughout the study. There were no significant differences in Alb or CRP after 21 days. Hospital length of stay was significantly shorter in the treatment group but direct costs were higher. CRP, although not statistically different at day 7, did show the greatest change throughout the study period. Because differences were seen in RBP and PAB on that day, this may have been attributed to whatever was influencing the CRP levels. This large, well-designed study did not show any clinically significant change in protein levels (23).

In a randomized study, Lo, et al evaluated the effects of the stress response on nitrogen balance, Alb, PAB, and RBP and carbon dioxide production in 28 stable, mechanically ventilated patients fed hypercaloric (1.8 × REE) versus eucaloric (1.2 × REE) EN (21). Alb increased in both groups with time, but there were no differences between the groups; absolute intake above 1.2 times the REE increased total protein concentration in these patients, but it did not appear that levels above this had any effect on albumin. PAB and transferrin had increased significantly in the high calorie group, but this was not significantly different from the control group. CRP did not significantly change with time or calorie level; inflammation did not appear to be playing a role in the differences between the two groups (21).

Another randomized study looked at the effect of the stress response on changes in cortisol, glucose, and CRP in surgical patients randomized to differing levels of protein and calorie intake (28). The results demonstrated a gradation of both the stress and nutritional effect on the so-called nutrition indicators. Nitrogen balance and IGF-1 were strongly affected by nutrition, but not by the stress response (28). This finding is in contrast to what has previously been documented about the role of stress on IGF-1 (46). RBP and PAB both showed a strong response to nutrition; however, the latter was more affected by stress (28). In total, these relatively well-designed randomized studies have failed to consistently show an increase in hepatic proteins despite ruling out (or in the last study, ruling in) the effect of stress on the patient. One must also consider that the increase in levels of these proteins may mirror improving clinical status despite whatever nutrition was provided.

CRP levels have been shown to be negatively associated with PAB and Alb in a number of studies (47–64). Nakamura and colleagues showed that among those receiving PN, the rapid turnover proteins (transferrin, RBP, PAB), were inversely correlated with CRP, although those receiving PN had higher levels of these rapid turnover proteins than those who did not. Surprisingly, patients on PN had higher CRP levels; the malnourished group having even higher CRP levels than those who were not malnourished (61). This suggests that although PN increases rapid turnover proteins, it is independent of the level of inflammation. Patients, who had prolonged elevations of CRP, along with consistently low serum PAB and Alb, appeared sicker and more resistant to treatment (56,58).

In spite of the numerous data that shows that CRP is negatively associated with Alb and PAB, CRP has actually been shown to decrease with weight loss in otherwise healthy, obese volunteers (65–68). In those patients who lost weight, Alb also decreased. Here, CRP and Alb were positively correlated (65). It is clear from these studies that the relationship between the negative and positive acute phase reactants is very complex and varies with differing disease states (critical illness versus obesity).

The ratio of CRP to PAB has been correlated with multiple organ dysfunction (49) and has been useful in the diagnosis of post-operative infection even before clinical symptoms developed (50). Because of these findings, many individuals have extrapolated this data to suggest that Alb/PAB and CRP level should be used on a routine basis to determine nutrition status. In a
study by Manelli, et al that reviewed the level of negative and positive acute phase reactants in burn patients, the authors concluded that because Alb and PAB are widely affected by CRP levels, these 3 markers should be performed twice weekly (in burn patients in particular), and should be interpreted as follows: if low serum protein levels are accompanied with high CRP levels, inflammation most likely caused the depression; however, if these low serum protein levels are accompanied with a low or normal CRP, then these levels are due to poor nutrition (54). However, Kaysen and his colleagues demonstrated that a normal Alb level was not affected by CRP values greater than 13 mg/L (53). That is, normal Alb levels do not exclude inflammation. Also, not all people will elicit an acute phase response after an injury. In the majority of the patients studied after an open fracture of the lower limb, serum alpha-1 acid glycoprotein (AAP), another positive acute phase reactant, did increase, with a decrease in PAB. However, in two patients, injury did not alter CRP, AAP, or PAB levels (69).

Another danger with checking concurrent CRP and PAB is that the rates at which they indirectly rise and fall are not consistent, greatly hindering their reliability in the clinical setting. In a study by Deodhar, CRP started to rise 4–6 hours post-injury, peaked after 48–72 hours, and returned to baseline within 4–5 days (70); patients after an acute myocardial infarction had peak CRP levels at 3–4 days, with the lowest PAB levels 7 days post-injury (48). Men and women seem to have different responses to injury as evidenced by the study of Louw, et al, where CRP returned back to baseline 7 days post-injury in women, while CRP was still significantly elevated from baseline in the same period in men. Both men and women in this study, did however, reach peak values at 48 hours (71).

It is clear from these studies that, depending on the condition present CRP and PAB may or may not be elevated. Whether an acute phase response is seen also varies from person to person and gender to gender; if CRP levels are elevated, duration and peak of the rise and fall for PAB and CRP are not standard. Also, an elevated CRP does not exclude the possibility of normal levels of serum proteins. Given these variables, compounded by the problems with PAB and Alb mentioned earlier, there is little reason to believe that checking CRP and Alb together, or at all, is of any value as a marker of nutritional status.

STUDIES THAT ATTEMPT TO CORRELATE INCREASING INTAKE WITH AN INCREASE IN ALBUMIN AND PREALBUMIN ALONG WITH AN IMPROVEMENT IN OUTCOME

To date, there have been no prospective, randomized studies that have shown an increase in Alb and PAB in response to changes in protein and calorie intake that have also translated into improved outcomes. Three studies have looked at the effect of different intakes on serum proteins and clinical outcomes, but not one was able to show this linear correlation. Hu, et al (30) attempted to look at 35 post-operative spinal cord patients, randomized to receive PN versus IVF. Although there were correlations between PAB and Alb levels and infectious complications, there were no significant differences in infectious complications when comparing the PN group versus the IVF group. In a study by Bauer and colleagues (23) examining 120 ICU patients receiving EN and placebo versus EN and PN, there were no differences in ICU morbidity, length of stay in the ICU, ventilator days, mortality after 90 days, and infectious complications. There was, however, a decrease in hospital length of stay, but there were no significant changes in PAB, Alb, and transferrin by the end of the study in response to nutrition. This study is of limited benefit in demonstrating whether a change in nutrition intake, with a corresponding change in “nutrition parameters,” results in a change in outcomes. The most recent study published to date provided oral nutritional supplements versus placebo to elderly patients with CRP levels of different ranges (72). Those participants with elevated CRP, regardless of what treatment they were given, had longer lengths of stay and increased risk of mortality. When the effect of supplementation was examined, the authors concluded that those with an acute-phase response (as shown by an increased CRP) benefited most from supplementation, with an increase in albumin and transferrin. Survival and length of stay data was not analyzed between the treatment and placebo group; no conclusion could be made regarding whether

(continued on page 60)
increased calories and protein intake, with a subsequent increase in protein levels, improved outcomes.

**OTHER TOOLS USED FOR NUTRITION ASSESSMENT**

Besides levels of serum protein levels, other laboratory values, techniques and equations have been proposed for use in assessing nutrition status. Many of these tools include both positive and negative acute phase reactants, so caution should be taken when using these formulas, as the problems with using these proteins as nutrition markers alone will still exist within these formulas (unless a PRCT demonstrates otherwise), with the effects either diluted or amplified (Table 6).

**CONCLUSION**

It is clear from many randomized, interventional, and prospective cohort studies that there is a very poor relationship between serum protein levels and nutrition status. Decreasing intake does not consistently correlate with a decrease in Alb, PAB, transferrin, and RBP; nor does increasing intake necessarily increase these levels. In light of these disparate results, it would be safe to conclude that serum proteins are neither specific, nor sensitive indicators of nutrition status. As negative acute-phase reactants, the concentrations of these proteins are affected by the acute phase response and have been shown to be inversely associated with...

(continued on page 63)
CRP. Many other factors also affect the levels of these proteins. The concurrent use of CRP and PAB values as nutritional indicators has also not been substantiated. When these values go in the direction we want, we are confident in our nutrition prescription. In contrast, if these values decline, we feel compelled to change our recommendations. Until better data is available, perhaps we should focus on other aspects of their nutrition care, such as ensuring that the patient actually receives what is prescribed, and whether or not the patient is clinically improving based on parameters such as ventilator weaning, wound healing, or participation in physical, occupational, or speech therapy. It is important to realize that an increase in PAB or Alb level may be the result of improvement in overall clinical status, and not necessarily due to improved nutritional status.

References


Serum Proteins as Markers of Nutrition
Serum Proteins as Markers of Nutrition


