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The Use of Visceral Proteins as Nutrition Markers: An ASPEN Position Paper

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Serum albumin and prealbumin, well-known visceral proteins, have traditionally been considered useful biochemical laboratory values in a nutrition assessment. However, recent literature disputes this contention. The aim of this document is to clarify that these proteins characterize inflammation rather than describe nutrition status or protein-energy malnutrition. Both critical illness and chronic illness are characterized by inflammation and, as such, hepatic reprioritization of protein synthesis occurs, resulting in lower serum concentrations of albumin and prealbumin. In addition, the redistribution of serum proteins occurs because of an increase in capillary permeability. There is an association between inflammation and malnutrition, however, not between malnutrition and visceral-protein levels. These proteins correlate well with patients' risk for adverse outcomes rather than with protein-energy malnutrition. Therefore, serum albumin and prealbumin should not serve as proxy measures of total body protein or total muscle mass and should not be used as nutrition markers. This paper has been approved by the American Society for Parenteral and Enteral Nutrition Board of Directors. (*Nutr Clin Pract.* 2021;36:22–28)

Keywords
adverse outcomes; albumin; critical care; inflammation; nutrition assessment; prealbumin; risk; visceral proteins

Introduction

Serum albumin and prealbumin (historically known as transthyretin) have traditionally been used as nutrition laboratory values (markers) to quantify the amount of plasma-circulating proteins and, thereby, thought to reflect nutrition status. The aim of this document is to correct the misconception that these proteins reflect nutrition status; rather, they are associated with inflammation and, thereby, are a component of nutrition risk assessment. Nutrition risk assessment may identify patients who do not yet demonstrate signs and symptoms of malnutrition but are at risk for its subsequent development if nutrition support is not provided in a timely manner.[1] For example, low visceral-protein levels may be

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Executive Summary

- Serum albumin and prealbumin are not components of currently accepted definitions of malnutrition.
- Serum albumin and prealbumin do not serve as valid proxy measures of total body protein or total muscle mass and should not be used as nutrition markers.
- The serum concentrations of albumin and prealbumin decline in the presence of inflammation, regardless of underlying nutrition status.
- Serum albumin and prealbumin declines must be recognized as inflammatory markers associated with "nutrition risk" in the context of nutrition assessment rather than with malnutrition per se. Nutrition risk is broadly defined as the risk of developing malnutrition and/or poor clinical outcomes if nutrition support is not provided.
- The role of serum albumin and prealbumin in monitoring delivery and efficacy of nutrition support remains undefined. Their normalization may indicate the resolution of inflammation, the reduction of nutrition risk, a transition to anabolism, or potentially lower calorie and protein requirements.

seen in a well-nourished individual admitted to an intensive care unit (ICU) after traumatic injury. This patient is not malnourished but is hypermetabolic and hypercatabolic and will become malnourished if he/she does not receive adequate early enteral and/or parenteral nutrition. Malnutrition (actual, diagnosed malnutrition) and nutrition risk (at risk for malnutrition as previously described) include either inadequate intake or risk of inadequate intake of nutrients "caused by one or more of the following factors: insufficient intake, impaired absorption, increased nutrient requirements, and altered nutrient transport and/or utilization."[2]

Illness, infection, and inflammation have long been associated with the loss of lean body mass, and recent studies have confirmed significant loss of muscle size, cellularity, and leg muscle protein in critical illness.[3] Identifying the presence and severity of inflammation is crucial to characterizing and assessing malnutrition.[2] Cytokines, produced during inflammation, often result in anorexia, in large part by impairing the ability to digest or absorb nutrients.[4] Hospitalized patients with severe inflammatory responses (defined as C-reactive protein [CRP] > 100 mg/L) did not demonstrate a strong, measurable response to nutrition support in a large randomized controlled trial.[5] See Figure 1 below.

With the vast majority of nutrition screening and assessment tools, characterization of disease burden or inflammation is considered a foundational criterion to appropriately assess and diagnose malnutrition.[6] Of the 3 etiologic types of malnutrition proposed by The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN) consensus characteristics for the identification of adult malnutrition,[2] malnutrition related to both acute and chronic disease is characterized by the presence of inflammation, whereas starvation-related malnutrition is not.[2] Inflammation is also recognized as a key component in the definition of illness-related pediatric malnutrition.[7] Inflammation is often associated with a negative nitrogen balance and an increased resting energy expenditure, resulting in increased protein and energy requirements.[4] This, coupled with illnesses leading to poor appetite, anorexia, inanition, dysphagia, or other clinical aspects, limit adequate nutrient intake and represent significant nutrition risk faced by critically ill patients.

Any recommendations in this paper do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, this is the result of the sole professional judgment of the attending healthcare professional whose judgment is the primary component of quality medical care. The information presented here is not a substitute for the exercise of such judgment by the healthcare professional. Circumstances in clinical settings and patient indications may require actions different from those recommended in this document, and in those cases, the judgment of the treating professional should prevail. This paper was approved by the ASPEN Board of Directors.

Historical Use in Nutrition Assessment

Use of serum albumin in nutrition assessment was first described by Blackburn et al in the classic 1977 publication, "Nutritional and Metabolic Assessment of the Hospitalized Patient,"[8] as an important parameter in completing a nutrition assessment. Serum proteins described for use with this metabolic nutrition assessment included serum albumin and serum transferrin or its derived marker, total iron-binding capacity. The authors suggested that this nutrition assessment process could be used to identify malnutrition, which could influence morbidity and mortality. Subsequently, serum albumin and transferrin became highly utilized

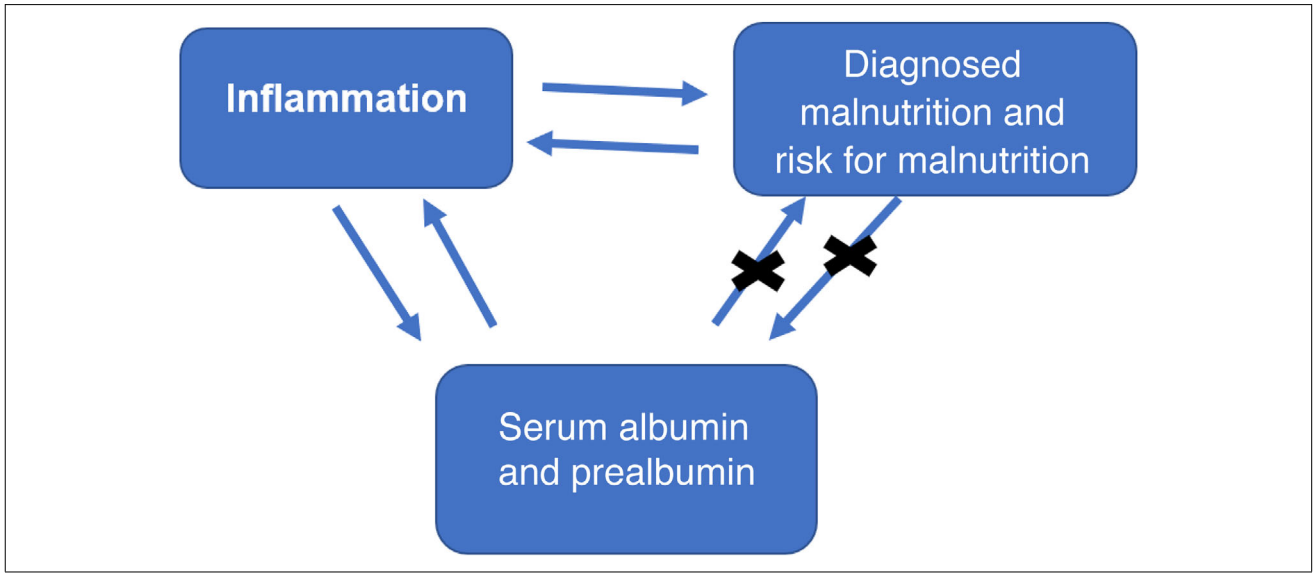

Figure 1. Relationship between malnutrition, inflammation, and visceral proteins.

markers to assess for malnutrition in hospitalized patients. In 1979, researchers recommended the use of serum albumin as 1 of 2 biochemical parameters for an "instant nutrition assessment" to identify those patients requiring aggressive nutrition support.[9,10] Serum albumin and/or transferrin became standard components of nutrition assessment to diagnose malnutrition by those involved in clinical nutrition support.[11,12]

Subsequently, serum transthyretin, or prealbumin, emerged as a more sensitive nutrition marker because of its shorter half-life of <2 days, as compared with albumin (20 days) and transferrin (8 days). In 1996, Mears reported finding that serum prealbumin was a more sensitive measure of nutrition status compared with serum albumin.[13] In the proceedings of a 1995 roundtable on measuring protein status, serum prealbumin was emphasized to be the preferred laboratory measurement to assess nutrition status, as well as to monitor the response to nutrition therapy.[14] At that time, advancements in clinical laboratories allowed ready availability of serum prealbumin measurements, which facilitated clinical nutrition use.

Relationship With Inflammation

Critical illness is characterized by severe acute inflammation, whereas chronic illness is characterized by a relatively lower but more prolonged, or intermittent, inflammatory state. The acute-phase response may occur in both acute and chronic illness and is evidenced by changes in concentrations of various proteins mediated by smaller molecules known as cytokines. Traditionally, the affected proteins have been divided into 2 categories on the basis of whether their serum concentrations increase or decrease during the response. Those whose concentrations increase are known as positive acute-phase proteins; these include complement factors, various proteins involved in coagulation and fibrinolysis, and CRP. Proteins whose concentrations decrease include visceral proteins, such as serum albumin, serum prealbumin (transthyretin), α_2-macroglobulin, and transferrin.[15] Several early studies of critically ill trauma and sepsis patients demonstrated rises in positive acute-phase proteins and declines in negative acute-phase proteins.[16,17]

The explanation posited for the decrease in visceral proteins during the acute-phase response has generally been that there is a hepatic reprioritization of protein synthesis, resulting in redirected synthesis of the negative acute-phase proteins toward synthesis of positive acute-phase reactants. One of the most studied of the positive acute-phase proteins, CRP, has been shown to have pleiotropic roles in both proinflammation and anti-inflammation.[15]

This hepatic reprioritization of protein synthesis has been theorized to be an indication that visceral proteins may not be an essential component for host defense during the acute-phase response, and their synthesis is a lesser priority to the stressed host.[18] However, this explanation may be overly simplistic, as some evidence suggests that the fractional albumin synthesis rate in the plasma (although not necessarily in the whole body) may actually be increased during the acute-phase response.[19]

Another important reason exists for the observed decrease in serum albumin plasma concentrations during the acute-phase response. Albumin is the most abundant protein in human plasma. An increase in capillary permeability,

as it occurs in inflammatory states, leads to albumin leaving the intravascular space (the compartment where concentrations are most commonly measured in clinical practice) and entering the interstitial space.[19,20] There may be functional advantages to the redistribution of albumin during the acute-phase response. Albumin is a key extracellular antioxidant.[19] As such, it serves as a ligand for pro-oxidative metals, such as copper and iron, as well as free fatty acids. Increased amounts of albumin in the interstitium increase the capacity of the protein to act as an antioxidant in this space.

Yet another proposed mechanism for the decreased concentration of visceral proteins, particularly serum albumin, during the acute-phase response is increased tissue catabolism.[21] This accelerated breakdown may lead to a decreased half-life of serum albumin.[19] Other contributing factors to declines in serum albumin concentrations could include renal and gastrointestinal losses.[19,21]

Albumin is a major contributor to colloid oncotic pressure. As hypoalbuminemia occurs in the intravascular space, edema develops. Interstitial edema associated with low serum albumin could lead to tissue damage, delayed wound healing, impaired gastrointestinal function, impaired respiratory gas exchange, impaired mobility, and resultant longer hospitalization and a reduction in functional outcomes.[22]

In summary, serum concentrations of visceral proteins, such as albumin and prealbumin, are decreased during the acute-phase response associated with acute and chronic illness and inflammation. Many of the clinical situations in which nutrition support is utilized are characterized by acute and/or chronic inflammation, and edema may be present on examination.[23] Clinicians must continue to recognize that decreased serum visceral-protein concentrations do not reflect malnutrition but rather are the result of the underlying inflammatory response.

Visceral Proteins as Markers of Nutrition Status

Serum albumin and prealbumin continue to be incorrectly cited as nutrition markers. Because of the strong associations between inflammation and malnutrition, visceral proteins correlate well with patient risk for adverse outcomes while not specifically reflecting a patient's current nutrition state.[24] Inflammatory markers are useful for determining nutrition risk by identifying those patients likely to be at an increased risk of poor outcomes if adequate nutrition is not delivered. For example, the Nutrition Risk in Critically Ill tool for critically ill patients identifies those who have an elevated risk of poor outcomes when adequate enteral nutrition is not delivered.[25] Malnutrition may be characterized by the type of inflammation present: acute illness/injury or chronic illness. Relatively few patients in developed countries have starvation-associated malnutrition, despite the continuing presence of food insecurity and low-quality diets deficient in protein.[2]

Serum albumin has historically been established as a marker of surgical risk, and some surgical guidelines recommend delaying surgery to allow time for nutrition support.[26] A serum albumin level < 3.5 g/dL is associated with increased postoperative mortality.[27] A serum prealbumin level < 10 mg/dL is associated with more complications after free-flap surgery.[28] Low serum prealbumin is also associated with poor results after skin grafting.[29] A large Veterans Affairs database confirmed that a low serum albumin level was associated with operative morbidity and mortality.[30] Surgical-site infection, in particular, was associated with hypoalbuminemia.[30] Delay of surgery and initiation of protein supplementation (or parenteral nutrition) was associated with improved biomarkers and improved clinical outcomes.[31] The European Society for Clinical Nutrition and Metabolism recommends delay of surgery when the serum albumin level is <3 g/dL.[26] Although nutrition status has historically been the focus, delaying surgery to allow the resolution of inflammation with the use of sufficient nutrition support may be the key factor. It has long been recognized that patient outcomes are improved when any therapy is delayed after an inflammatory event; a well-documented example of this phenomenon is waiting to allow recovery and resolution of inflammation before surgery to reverse a colostomy after Hartmann procedure for diverticulitis.[32,33] However, it must be recognized that sometimes surgery is required to resolve an inflammatory process. This may be true in conditions such as inflammatory bowel disease or chronic infection of prosthetic implants, for example. These patients should receive nutrition support and specific treatments directed at inflammation and infection, when possible, prior to surgery. Should they not improve and require surgery in the setting of active inflammation, their elevated risk of complications must be recognized and mitigated, as possible.

Another common misconception is that serum albumin and prealbumin are markers of protein and muscle mass in body composition. Serum albumin and prealbumin levels in healthy patients do not decline until their body mass index (BMI) is <12 (calculated as weight in kilograms divided by height in meters squared) after ≥ 6 weeks of starvation.[34] The same is reported in elderly patients.[35] Serum albumin and prealbumin levels are known to correlate poorly with nutrition intake—changes in dietary intake correlate poorly with visceral proteins.[36,37]

Serum albumin and prealbumin levels have also been examined in children—in whom growth and development are additional factors—with similar overall findings. Although the visceral proteins retain similar correlations with inflammation as they do in adult patients, there is poor correlation with muscle mass or overall malnutrition assessments. One study evaluating the nutrition status of 45 children at the

Table 1. Potential Nutrition Screening and Assessment Tools.

Nutrition screening		MUST	NRS-2002		MST	PON
Nutrition assessment	SGA			MNA		
Body mass index		X	X	X		X
Weight changes	X	X	X	X	X	X
Disease severity	X	X	X	X	X	
Gastrointestinal symptoms	X					
Physical examination	X					
Mobility				X		
Functional capacity	X					
Cognitive function				X		
Aged > 70 years			X			
Serum albumin						X

Developed by the author. Data are from references.[50–54]
MNA, mini nutritional assessment; MST, malnutrition screening tool; MUST, malnutrition universal screening tool; NRS-2002, nutrition risk screening 2002; PON, perioperative nutrition screening tool; SGA, subjective global assessment.

initial diagnosis of cancer compared anthropometrics with serum albumin/prealbumin levels.[38] Based on anthropometrics, 49% of the patients were malnourished, but there was no relationship with either serum albumin or prealbumin. Another study evaluated critically ill children admitted to a pediatric ICU.[39] Anthropometrics were utilized for the diagnosis of malnutrition and were compared with serum albumin levels. The study included 271 patients, with a 42% malnutrition prevalence. Serum albumin level was significantly associated with survival and duration of mechanical ventilation. Multivariate analysis confirmed an association of serum albumin with malnutrition. A more recent evaluation of children post–liver transplant found significantly lower weight and height *z*-scores in those with confirmed sarcopenia; however, the serum albumin levels were identical regardless of alterations in body composition.[40] Similar findings were noted in preoperative evaluations of children with Crohn's disease. Children with severe malnutrition, as defined by BMI-for-age *z*-scores, despite normal serum albumin levels, had increased odds of complications, similar to those with low serum albumin levels.[41] A recent evaluation of prealbumin in neonates in the neonatal ICU demonstrated a negative correlation of -0.62 ($P < .005$) with CRP, indicating the decrease in serum prealbumin was associated with inflammation.[42]

Serum albumin and prealbumin have been evaluated as nutrition markers in patients with restrictive eating disorders, such as anorexia nervosa. A retrospective study evaluated 75 children with severe weight loss due to restrictive eating disorders.[43] These children were malnourished, with a BMI *z*-score of -3.19. None of the patients had a low serum albumin level and 32% had a low prealbumin level. Despite the anthropometrics demonstrating malnutrition, neither serum albumin or prealbumin level correlated with BMI *z*-score.

Role of Visceral Proteins in Monitoring Nutrition Support Efficacy

Research evaluating the utility of visceral proteins as measures to assess efficacy of nutrition intervention has provided mixed results. Early work in the 1980s by Ota[44] and Winkler[45] in cancer and surgical patients, respectively, demonstrated serum prealbumin to be a more sensitive indicator of adequate nutrition support compared with other assessment parameters, including serum albumin and transferrin. However, these results have not been confirmed in subsequent studies and may have actually been a manifestation of resolving inflammation. In 2012, Davis et al evaluated the use of serum prealbumin in monitoring nutrition support efficacy in a large urban medical center.[36] In their analyses, serum prealbumin levels correlated only with inflammation and did not reflect the delivery of adequate energy and protein.[36] Yeh et al demonstrated similar results in patients receiving enteral nutrition.[37] Despite the early enthusiasm, serum prealbumin and other visceral proteins have not been shown to be sensitive markers of energy and protein intake adequacy and, therefore, should not be a guide for therapeutic changes. The return of serum albumin and prealbumin levels to normal ranges may still have value in the monitoring of recovery. Normalization of visceral proteins may indicate the resolution of inflammation, the reduction of nutrition risk, a transition to anabolism, and potentially lower calorie and protein requirements.

Alternatives for Nutrition Assessment and Monitoring Efficacy

Numerous tools for nutrition assessment have been proposed. A thorough discussion is beyond the scope of this document, but there are various approaches that have been

suggested for outpatients, inpatients, and specific-disease states. Most include a component of impaired oral intake and/or weight loss (Table 1). Most of these tools do not include visceral-protein parameters—the exception is the perioperative nutrition screening tool (PONS) proposed by Wischmeyer et al, in 2018.[46] The PONS tool is unique because it is designed to evaluate preoperative outpatients before surgery. The other measures in Table 1 are designed for the inpatient setting and do not include serum albumin. PONS has not been prospectively validated but relies on the findings of Khuri et al that demonstrated serum albumin levels are an excellent measure of surgical risk.[27]

Imaging represents a new frontier in nutrition assessment. Dual-energy X-ray absorptiometry, bioelectrical impedance, ultrasound, and computed tomography scan are increasingly used for assessment of muscle mass. Each tool has been validated in select populations but are limited either by availability, standardization, or validation in relevant clinical populations.[47] Imaging holds the potential of emerging as a "biomarker" for standardized nutrition assessment in the future as limitations are overcome.[48] In addition, the use of other assessment measures, including creatinine height index, can be considered.[49]

Nutrition efficacy is an even more challenging parameter to measure. While in a state of acute inflammation, adequate nutrition may mitigate weight loss, loss of muscle function, and skin breakdown. Adequate nutrition may be reflected by effective wound healing and resolution of edema. Improvements in muscle strength and endurance may be measured. However, meaningful gains in muscle mass are unlikely in the acutely inflamed state; only after inflammation subsides are such patients typically able to achieve these gains.[20]

Conclusion

The visceral proteins albumin and prealbumin must be correctly recognized as inflammatory markers associated with "nutrition risk" in nutrition assessment. The concepts of malnutrition and nutrition risk are distinct concepts that are often inappropriately interchanged in application. Serum albumin and prealbumin levels do not, however, serve as proxy measures of total body protein or total muscle mass and are not useful monitoring parameters to guide nutrition support therapy. To identify these as markers of malnutrition is an oversimplification that should be avoided.

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