

## Perspectives in Practice

## Hepatic Proteins and Nutrition Assessment

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**ABSTRACT**

Serum hepatic protein (albumin, transferrin, and prealbumin) levels have historically been linked in clinical practice to nutritional status. This paradigm can be traced to two conventional categories of malnutrition: kwashiorkor and marasmus. Explanations for both of these conditions evolved before knowledge of the inflammatory processes of acute and chronic illness were known. Substantial literature on the inflammatory process and its effects on hepatic protein metabolism has replaced previous reports suggesting that nutritional status and protein intake are the significant correlates with serum hepatic protein levels. Compelling evidence suggests that serum hepatic protein levels correlate with morbidity and mortality. Thus, serum hepatic protein levels are useful indicators of severity of illness. They help identify those who are the most likely to develop malnutrition, even if well nourished prior to trauma or the onset of illness. Furthermore, hepatic protein levels do not accurately measure nutritional repletion. Low serum levels indicate that a patient is very ill and probably requires aggressive and closely monitored medical nutrition therapy.

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**H**epatic protein is a term commonly used to refer to albumin, prealbumin (transthyretin), or transferrin. These are three among a much larger group of proteins listed in Figure 1 that are synthesized in the liver. Despite published evidence (1-4), review articles (5,6), and editorials (7,8) that serum levels of these proteins are impacted more significantly by factors other than nutritional intake, hepatic proteins continue to be used to evaluate nutritional status, including the presence of malnutrition.

This paradigm can be traced to the two conventional categories of malnutrition: kwashiorkor and marasmus. Kwashiorkor refers to a condition commonly thought to occur when carbohydrate is the major dietary energy

source and protein is relatively absent from the diet for a prolonged period of time. Hypoalbuminemia is a feature of kwashiorkor and is part of the clinical symptomatology that includes edema, ascites, dermatitis, thin brittle hair, hepatomegaly, and muscle wasting (9). In contrast, marasmus refers to chronic deprivation of adequate dietary energy to maintain body weight (10). Severe marasmus is characterized by extreme weight loss and cachexia. A classic example of severe marasmus in affluent Western societies is anorexia nervosa.

A more recent and controversial category of "malnutrition" is stress-induced hypoalbuminemia (3,11). Stress-induced hypoalbuminemia occurs following a traumatic event or acute illness. The patient quickly and dramatically develops decreased serum hepatic protein levels despite adequate intake of nutrients prior to the illness or injury. Herein is the crux of the misunderstanding of the relationship of hepatic proteins to nutritional status. Malnutrition has been defined as "a state induced by nutrient deficiency that may be improved solely by administration of nutrients" (11). Stress-induced hypoalbuminemia does not reflect a state of malnutrition per se; it reflects the body's physiologic response to injury and infection. Serum levels of albumin, prealbumin, and transferrin decrease in response to infection, injury, or trauma and increase with recovery from the same conditions. The serum levels do not increase in response to the provision of protein and energy. However, the degree of injury or illness can impact appetite, gastrointestinal motility, and hemodynamic stability, which can, in turn, negatively affect the patient's nutritional status.

Publication of "The Skeleton in the Hospital Closet" (12) in 1974 alerted the health care community to the alarming number of patients who were malnourished because of, in part, significantly decreased oral intake while hospitalized (12,13). Compromised nutritional status was associated with clinical deterioration, causing longer hospitalization and increased mortality (14). Serum hepatic protein levels were thought to be indicators of nutritional status based on what was known about hepatic protein metabolism at the time (15-21). Essentially, clinicians associated low serum hepatic protein levels with malnutrition, (22) and a number of clinical studies were conducted making an a priori assumption that albumin and prealbumin levels accurately reflected nutritional status and, as such, could be used to identify a patient's nutritional risk (23,24).

In addition, low serum hepatic protein levels were linked to the amount of dietary protein consumed. Supplementary dietary protein was thought to improve nutritional status in the critically ill patient, which was verifiable by increased serum hepatic protein levels (22,25,26). In truth, the mechanisms mediating responses to disease and trauma were obscure, and, therefore, there was a failure to distinguish the differences between mal-

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<p><b>Positive acute-phase proteins</b></p> <ul style="list-style-type: none"> <li>Complement system</li> <li>C3</li> <li>C4</li> <li>C9</li> <li>Factor B</li> <li>C1 inhibitor</li> <li>C4b-binding protein</li> <li>Mannose-binding lectin</li> <li>Coagulation and fibrinolytic system</li> <li>Fibrinogen</li> <li>Plasminogen</li> <li>Tissue plasminogen activator</li> <li>Urokinase</li> <li>Protein S</li> <li>Vitronectin</li> <li>Plasminogen-activator inhibitor</li> <li>Antiproteases</li> <li><math>\alpha_1</math>-Protease inhibitor</li> <li><math>\alpha_1</math>-Antichymotrypsin</li> <li>Pancreatic secretory trypsin inhibitor</li> <li>Inter-<math>\alpha</math>-trypsin inhibitors</li> <li>Transport proteins</li> <li>Ceruloplasmin</li> <li>Haptoglobin</li> <li>Hemopexin</li> <li>Participants in inflammatory responses</li> <li>Secreted phospholipase A<sub>2</sub></li> <li>Lipopolysaccharide-binding protein</li> <li>Interleukin-1-receptor antagonist</li> <li>Granulocyte colony-stimulating factor</li> <li>Others</li> <li>C-reactive protein</li> <li>Serum amyloid A</li> <li><math>\alpha_1</math>-Acid glycoprotein</li> <li>Fibronectin</li> <li>Ferritin</li> <li>Angiotensinogen</li> <li><b>Negative acute-phase proteins</b></li> <li>Albumin</li> <li>Transferrin</li> <li>Transthyretin (prealbumin)</li> <li><math>\alpha_2</math>-HS glycoprotein</li> <li>Alpha-fetoprotein</li> <li>Thyroxin-binding globulin</li> <li>Insulin-like growth factor I</li> <li>Factor XII</li> </ul>
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**Figure 1.** Human acute-phase proteins. (Reprinted with permission from reference 1: Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med.* 1999;340:448-454. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

nutrition caused by nutrient deficiency and physiologic changes caused by disease and trauma.

The purposes of this article are threefold. The first is to discuss kwashiorkor, marasmus, and hepatic protein metabolism in both normal health and inflammation associated with disease or trauma. The second is to review critically the literature that suggests serum hepatic protein levels correlate with nutritional status and, more significantly, acuity of illness or trauma. The last purpose

is to propose the most appropriate role for hepatic proteins in the nutrition assessment process.

**KWASHIORKOR AND MARASMUS**

The term *kwashiorkor* was first used to describe what was thought to be a form of malnutrition observed in young children from underdeveloped areas of the world. Health care experts associated early weaning from human milk to a protein-deficient oral diet, consisting mainly of grain-based foods, with kwashiorkor. Children presented with hypoalbuminemia; edema of the extremities, lower back, and face; fatty liver; and anorexia (9,27). To date, this condition has not been observed in adults or children in industrialized areas of the world.

Kwashiorkor has been theoretically ascribed to diets composed almost exclusively of carbohydrate, causing high insulin levels, which diminish the rate of protein and fat oxidation. The relative absence of protein in the diet leads to inadequate amounts and altered ratios of amino acid substrate for protein synthesis. Hypoalbuminemia causes a reduction in colloid oncotic pressure in the vascular space and subsequent extravascular fluid accumulation, which presents as edema and ascites (28). However, the impact of a severely protein-deficient diet on serum albumin is neither immediate nor dramatic. Two weeks of a severely protein-deficient diet is necessary to demonstrate a 10% reduction in serum albumin levels (29,30).

In fact, protein deficiency may not be the causative factor of kwashiorkor. Studies using a low-protein diet in healthy volunteers and animals have failed consistently to produce kwashiorkor (31). Furthermore, kwashiorkor in breastfed infants who received adequate protein from maternal milk despite poor maternal diet failed to support conventional causation theory (32).

Alternative etiologies include infections, aflatoxin poisoning (33), and oxidative stress (34). The relationship between pediatric infectious diarrhea and kwashiorkor-like malnutrition is fairly well known (35). Chronic ingestion of aflatoxin, a toxin produced by mold growing on grain products in hot and humid climates, may have

Increase	Decrease
Intravascular volume deficit	Intravascular volume excess
Exogenous albumin infusion	Recumbent posture
Renal failure	Extraneous loss of albumin
Iron deficiency <sup>a</sup>	Liver disease
	Pregnancy
	Hypothyroid
	Alcohol abuse
	Nephrotic syndrome
	Uremia
	Corticosteroids
	Malignancy
	Trauma (including surgery)
	Inflammation

<sup>a</sup>Transferrin only.

**Figure 2.** Factors that impact serum levels of albumin, prealbumin, and transferrin. (Developed from references 26, 40, 41, and 43.)

Author	Design/method	Population sample size	Results	Comments
Seltzer and colleagues (50)	Case control/Associations between serum albumin and diagnosis, complications, mortality, and surgical procedures.	N=500, consecutive hospital admissions.	Hypoalbuminemia significantly associated with fourfold increase in morbidity and a sixfold increase in mortality.	Albumin is a prognostic indicator.
Weinsier and colleagues (14)	Cohort/Nutritional and clinical status using eight nutrition-related parameters including serum albumin were evaluated at admission and after 2 weeks' hospitalization.	N=134, consecutive hospital admissions.	Hypoalbuminemia and decreased hematocrit correlated with increased LOS <sup>a</sup> . Serum albumin decreased with longer hospitalization.	Subjects with decreased serum albumin levels had longer LOS.
Forse and Shizgal (48)	Descriptive, population-based point in time/Body composition was compared with serum albumin levels on or before starting PN <sup>b</sup> .	N=102, hospitalized patients.	Significant correlation between albumin and body composition, but serum albumin neither specific nor sensitive: 44% of normally nourished patients were hypoalbuminemic; 11.2% of malnourished patients had normal serum albumin levels. No correlation between body cell mass and albumin.	Serum protein levels have poor specificity and sensitivity. Serum albumin did not correlate with body cell mass.
Anderson and Wocho (51)	Cohort/Albumin, anthropometrics and %IBW <sup>c</sup> correlated with LOS.	N=47, hospitalized nephrology patients.	Hypoalbuminemia associated with longer LOS. Low albumin-associated infections.	Hypoalbuminemia associated with morbidity.
Sganga and colleagues (2)	Cohort/Serum hepatic protein levels monitored postinjury during sepsis.	N=26, severely injured patients.	C-reactive protein, fibrinogen, ceruloplasmin, and $\alpha_1$ -antitrypsin levels increased and albumin, transferrin, and $\alpha_2$ -macroglobulin levels decreased with injury and sepsis.	Effects of injury and sepsis on hepatic protein metabolism.
Boosalis and colleagues (52)	Cohort/Relationships of hepatic proteins and mortality and morbidity.	N=78, critically ill patients.	Admission albumin and prealbumin decreased in all patients. Albumin and prealbumin significantly lower in nonsurvivors. Prealbumin levels recovered sooner than albumin. C-reactive protein elevated in injured patients.	Albumin and prealbumin as prognostic indicators.
McClave and colleagues (3)	Case control/Costs, morbidity and mortality were compared with either marasmic or hypoalbuminemic protein calorie malnutrition.	N=180, PN patients for 12-month period.	Hypoalbuminemic protein calorie malnutrition (defined by the presence of abnormal levels of three of the following: albumin, transferrin, prealbumin, and TLC <sup>d</sup> ) resulted in increased LOS, cost, morbidity, and mortality.	Decreased albumin, transferrin, prealbumin, and TLC associated with increased cost, morbidity, and mortality.
Ballmer and colleagues (53)	Quasi-experimental/Albumin synthesis and nitrogen balance before and during two levels of induced metabolic acidosis.	N=8, healthy adult males.	Both groups lost weight despite 2,800 kcal/d. Significantly decreased albumin in the high-dose group. Nitrogen loss greater in the high-dose group.	Morbidity rather than nutrition affects albumin levels.
Sreedhara and colleagues (54)	Cohort/Baseline prealbumin and albumin levels were compared with mortality at 5 years.	N=111, chronic hemodialysis and 78, peritoneal dialysis outpatients.	Low prealbumin (<30 g/L) correlated with mortality in both patient groups. Albumin <35 g/L associated with increased mortality in peritoneal dialysis patients.	Relationships between hepatic proteins and mortality.

Clark and colleagues (45)	Case series/Hepatic proteins and insulin-like growth factor-1 were measured at 5, 10, 15, and 21 days after patients were hemodynamically stable. Magnitude and direction of hepatic protein metabolism compared with total body protein metabolism.	N=24, critically ill patients admitted during a 12-month period.	Insulin-like growth factor-1, prealbumin, and transferrin decreased and C-reactive protein and $\alpha_1$ -antitrypsin levels increased early postdisease/injury. During recovery, hepatic protein levels returned to normal despite continued proteolysis and increased energy expenditure.	Normalization of hepatic protein metabolism is independent of normal total body protein metabolism in the postinjury phase.
Phang and Aeberhardt (49)	Cohort/Relationships between energy balance and fluid status, weight, serum albumin, prealbumin, TLC, body cell mass, extracellular fluid, body fat, and mortality.	N=45, critically ill patients.	At 7 days, significant changes in weight, serum albumin and prealbumin, and extracellular mass did not correlate with energy or fluid balance. At 3 weeks, significant changes in weight, prealbumin, and extracellular mass did not correlate with energy balance. Albumin did not correlate with fluid balance. Significant correlation between weight and extracellular mass and fluid balance. No significant change in TLC, body cell mass, or body fat.	Albumin, prealbumin TLC, and body composition are not responsive to energy balance in critical illness.

<sup>a</sup>LOS=length of hospital stay.  
<sup>b</sup>PN=parenteral nutrition.  
<sup>c</sup>IBW=ideal body weight.  
<sup>d</sup>TLC=total lymphocyte count.

**Figure 3.** Hepatic proteins in acute, chronic, and critical illness.

adverse effects on hepatic metabolism (36). Oxidative stress may contribute to kwashiorkor symptoms by virtue of oxidative damage to proteins (37). Thus, very low-protein diets may not be the cause of hypoalbuminemia in pediatric populations in underdeveloped countries.

In contrast, marasmus is caused by long-term inadequate intake of all macronutrients. During short-term starvation, homeostatic mechanisms maintain glucose supply to glucose-requiring tissues by utilizing muscle-derived amino acid substrate for gluconeogenesis. Continuous muscle protein catabolism for gluconeogenic substrate can cause death. The process is abated by increased utilization of fatty acids for oxidative substrate and from oxidation of ketones derived from fatty acid oxidation. In this manner, muscle protein is “spared.” Protein catabolism continues, albeit at a slow rate, to provide obligatory glucose requirements. Death from marasmus is usually caused by loss of respiratory muscle function and subsequent respiratory failure. In the case of marasmus, serum hepatic protein levels are not affected by inadequate nutrient intake in that synthesis of hepatic proteins is maintained until very late in the process (38).

### HEPATIC PROTEINS

The approximate distribution of body protein is 40% in muscle, 10% in organs, 30% in skin and blood, and 20% in various other tissues and protein-containing components (39). Circulating hepatic proteins are part of the blood compartment. Hepatic proteins are not stored to any extent in the hepatocytes; rather, they are synthesized by hepatocytes and released into the circulation. Body protein is in a constant state of anabolism (synthesis) and catabolism (breakdown). The flux of amino acids moving through this process of turnover is referred to as the amino acid pool. Amino acids derived from muscle catabolism and dietary intake supply the pool for subsequent structural (muscle) and functional (hepatic) protein synthesis. When the body’s requirement for protein exceeds availability, muscle protein is catabolized in deference to maintaining functional proteins, which include hepatic proteins (39).

We have adopted the categorization of hepatic proteins described by Gabay and Kushner (1) outlined in Figure 1 based on their property of plasma concentrations increasing or decreasing by at least 25% during physiologic stress. Positive acute-phase proteins comprise those proteins that are elevated during illness or trauma and negative acute-phase proteins are those that decrease during the same conditions. The latter includes albumin, transferrin, and prealbumin. The most commonly monitored hepatic protein in clinical care is albumin. Twelve to 25 g albumin are synthesized daily by the liver, which represents approximately 40% of total hepatic protein synthesis (40). Albumin synthesis responds to colloid oncotic pressure variations. Albumin, transferrin, and prealbumin function as carrier proteins for minerals, fatty acids, bilirubin, vitamins, and hormones (6,40-42). A number of conditions that affect serum hepatic protein levels are listed in Figure 2 (26,40,41,43). Among these, inflammation is the most important.

## INFLAMMATION

Inflammation, or, more accurately, the mediators of inflammation, exerts the most significant effects on serum hepatic protein levels by altering normal hepatic protein metabolism and inducing capillary leak. Inflammation has been defined as the aggregate of clinical, hematologic, metabolic, and organ function abnormalities associated with sepsis, trauma, and a variety of other conditions such as pancreatitis (44). These symptoms are systemic and, indeed, represent systemic inflammation. They are caused by overproduction and circulation of a number of humeral and cellular mediators such as cytokines, hematopoietic factors, prostaglandins, thromboxanes, and complement. The mediators also activate neuroendocrine mechanisms that change physiologic and metabolic homeostasis. Evidence suggests that inflammation initiates and sustains immune and healing responses to ensure survival from a traumatic event or infection (44).

In the last 15 years, cytokines have been the most extensively studied inflammatory mediators. Cytokines are polypeptide proteins that function as both paracrine (cell to cell) and autocrine (cell to self) signals. They have multiple cellular targets and multiple effects, among them the metabolism of hepatic proteins. In general, cytokines act as a cascade and as a network, both stimulating and regulating each other. The cytokine interleukin 6 is the most potent known stimulator of positive acute-phase protein synthesis in hepatocytes. Changes in the concentration of positive and negative acute phase proteins are assumed to assist inflammatory processes. For example, C-reactive protein, which increases as much as 1,000-fold during inflammation, plays an important role in the recognition of foreign pathogens and phospholipid components of damaged cells. Alterations in hepatic metabolism vary somewhat, depending on the inflammatory stimulus. Acute-phase protein metabolism during inflammation has been reviewed in detail elsewhere (1).

Serum-negative acute-phase protein levels decrease acutely during inflammation by another cytokine-mediated mechanism as well. The cytokine tumor necrosis factor and secondary eicosenoid metabolites cause capillary membrane leak, which, in turn, causes serum (including hepatic proteins) to move into the extravascular body compartment. Treatment of this phenomenon includes fluid resuscitation, which dilutes residual intervascular hepatic protein concentrations.

The net effect of reduced synthesis and dilution of albumin, prealbumin, and transferrin is lower serum levels, independent of nutritional status. Resolution of inflammation, not exogenous substrate (protein, carbohydrate, and fat) from nutrition support, restores normal hepatic protein metabolism and, eventually, serum levels.

A number of studies published in the 1990s have investigated serum hepatic protein status during critical illness. In 1996, Clark and colleagues found that insulin-like growth factor-1 (IGF-1), transferrin, and prealbumin levels did not correlate with total body protein loss in critically ill patients (45). In 1998, Manelli and colleagues reported that albumin, prealbumin, and retinol-binding protein, after an initial decrease postburn, increased steadily, whereas positive acute-phase protein levels, especially C-reactive protein, after an initial increase postburn, decreased (46). These changes are consistent with

recovery from inflammation. In the same year, Casati and colleagues found that prealbumin and retinol-binding protein decreased and then rose in stressed critically ill patients receiving parenteral nutrition, whereas C-reactive protein was elevated and remained so (47). The increase in prealbumin and retinol-binding protein correlated positively with nitrogen balance. The authors concluded that prealbumin and retinol-binding protein might be useful for evaluating nutritional therapy in the critically ill patients.

Herein lies a commonly repeated assumption; increased negative acute-phase protein synthesis is linked to exogenous substrate, such as nutrition support, rather than a specific mediator of metabolism, such as a cytokine. In this assumption, improvement in nitrogen balance is seen as further proof of a cause and effect relationship. However, a correlation between nitrogen balance and protein synthesis during inflammation does not establish a causative link between nutritional adequacy and synthesis (4,48,49). Improved nitrogen balance reflects recovery from inflammation, subsequent normalization of inflammatory mediators, and decrease in net protein catabolism. Hepatic proteins are more appropriately viewed as indicators of morbidity and possibly predictors of mortality (50-54). Figure 3 reviews a number of studies, in addition to those cited above, that investigated these associations.

## HEPATIC PROTEINS AND NUTRITIONAL STATUS

A number of studies have investigated associations between nutritional status and serum hepatic protein levels (13,15-21,23-26). Most of this literature was published prior to the current understanding of the physiology of inflammation. As such, none of the studies addressed the relationship between inflammation and hepatic protein status. Investigators did not measure inflammation, thus missing the most important variable impacting hepatic protein metabolism. Studies in children (55) and adults (56) indicate that the serum albumin level remains essentially unchanged by virtue of decreased turnover (reduced synthesis and catabolism) during protein and energy deprivation. The same is probably true for other hepatically synthesized proteins (57).

Therefore, serum hepatic protein levels are not directly linked to nutritional deprivation. However, there is an indirect relationship with nutritional status that is important for clinicians to appreciate. Inflammation contributes to an increase in net protein loss caused by catabolism. Inflammation also induces anorexia, reducing the probability that a patient will consume adequate nutrients for even normal metabolic requirements (58,59). Albumin, transferrin, and prealbumin can be viewed as indicators of inflammatory processes that will accelerate nutritional depletion. This is not to say that nutritional interventions will correct aberrations of serum hepatic proteins and the signs and symptoms of severe illness.

## NUTRITION ASSESSMENT IMPLICATIONS

Serum hepatic protein status can help identify patients who are likely to become malnourished even if they are

adequately nourished at the point of hospital admission. This has been referred to as the “inextricable relationship between nutritional status and severity of illness” (11). When properly evaluated, serum hepatic protein levels assist the clinician in identifying patients who are the most morbid and, thus, those at risk for developing serious nutritional deficits. A patient with a decreased albumin, prealbumin, or transferrin level is less likely to meet energy and nutrient requirements volitionally and therefore will probably require aggressive medical nutrition therapies. Such patients are also likely to be clinically unstable and therefore require frequent monitoring for adjustments in nutritional interventions.

## CONCLUSIONS

Hepatic proteins are not indicators of nutritional status but rather indicators of morbidity and mortality and recovery from acute and chronic disease. Serum hepatic protein levels help the clinician to identify the sickest of patients—those who are the most likely to develop malnutrition even if well nourished prior to trauma or the onset of illness. These patients usually require aggressive and closely monitored nutritional interventions. Failure of serum levels to increase with aggressive nutrition support does not indicate inadequate nutrition support, rather that a patient is not recovering from the primary problem that caused inflammatory metabolism or has developed a secondary problem such as infection.

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