Clin Chem Lab Med 2002; 40(12):1344–1348 © 2002 by Walter de Gruyter · Berlin · New York

Transthyretin: Its Response to Malnutrition and Stress Injury. Clinical Usefulness and Economic Implications

Larry H. Bernstein[1]* and Yves Ingenbleek[2]

[1] Department of Pathology, Bridgeport Hospital Yale New Haven Health, Bridgeport, CT, USA
[2] Laboratoire de Nutrition, Faculte de Pharmacie, Universite Louis Pasteur de Strasbourg, France

Serum transthyretin is an ideal marker for monitoring patients who are malnourished or have metabolic consequences of acute stress injury because it has a short half-life, it measures the level of metabolic deficit, the response to nutritional metabolic support, and because it is a prognostic indicator. Mounting clinical evidence indicates that the use of transthyretin to assess and monitor a patient's nutritional status results in improved treatment outcomes and lower overall healthcare costs. Clin Chem Lab Med 2002; 40(12):1344–1348

Key words: Transthyretin; Malnutrition; Stress injury; Economic implications.

Abbreviations: APR, acute phase reactant; CBG, corticosteroid-binding globulin; GI, gastrointestinal; ICU, intensive care unit; IGF-I-BP, insulin-like growth factor I-binding proteins; IL, interleukin; LOS, length of stay; NDAD, nutritionally dependent adaptive dichotomy; PEM, protein-energy malnutrition; RBP, retinol-binding protein; RQ, Respiratory Quotient; T3, triiodothyronine; T4, thyroxine; TBG, T4-binding globulin; TNFα, tumor necrosis factor α; TTR, transthyretin.

Introduction

Transthyretin (TTR), a 55 kDa plasma protein, carries both thyroid hormones and retinol (1) by forming a trimolecular complex. TTR was originally named prealbumin by its electrophoretic migration in front of albumin by alkaline electrophoresis but was renamed TTR based on a physiological denomination (2). TTR and retinol-binding protein (RBP) both manifest rapid turnover rates, and their concentrations quickly decline in response to any change of protein nutritional status and/or under stressful conditions. The decrease in TTR is accompanied by concerted decreases in other binding proteins (Table 1). Associated with its half-life of 1.9 days, TTR responds more quickly to a change in nutritional status than albumin (3).

*E-mail of the corresponding author:
larryberns@earthlink.net

Measurement

TTR can be measured by nephelometric or by turbidimetric assays. In either assay, the reaction of TTR with a specific antibody forms a complex, and the rate or the amount of reflected light is proportional to the concentration of the protein. The method can be performed on routine automated chemistry instruments, such as the Array protein system, Immage immunochemistry system, or Synchron clinical analyzer (Beckman Coulter, Fullerton, CA, USA), Dimension (Dade Behring, Deerfield, IL, USA), Integra or Hitachi (Roche Diagnostics, Indianapolis, IN, USA), Advia (Bayer, Tarrytown, NY, USA), Vitros or ECI (Ortho [J&J] Diagnostics, New Brunswick, NJ, USA), and Olympus (Long Island, NY, USA) using Kamiya or Diasorin reagents.

Stress Hypermetabolism – the Metabolism of Injury

Injury of any cause mediated by cytokines, mainly interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor α (TNFα), triggers a cascade of effects evolving in three successive steps (4): the hemodynamic or ebb phase is dominated by fever, anorexia, tachycardia and circulatory changes in the first 12 hours; the flow phase occurs over three or more days associated with catabolic processes with massive urinary nitrogen loss; the anabolic phase ensues as the starting point of repair activities coinciding with a decreased loss and retention of nitrogen as the stressed body restores its organic and functional integrity. The evolution towards healing implies the compartmentalization of adaptive responses (3). The hypermetabolism as it affects protein metabolism is measured by the breakdown of skeletal muscle

Table 1 Reciprocal alterations of the plasma concentrations of the main visceral proteins and their transported ligands in the course of any acute stressful condition. The distortion from normal is proportionate to the magnitude and severity of the causal factor. This adaptive pattern is blunted in the case of preexisting malnutrition, impairing the hormonally mediated defence and repair processes.

Binding protein		Hormonal change	
Albumin	▽		
TBG	▽	Free T4	△
CBG	▽	Free cortisol	△
Transthyretin	▽	Free T4	△
RBP	▽	Free retinol	△
IGF1-BP3	▽	Free IGF1	△

associated with nitrogen losses, proportional to the severity and extent of trauma, and the amount of this metabolic loss declines after 7–14 days. The loss is obligatory and cytokine-driven, but the shortening of the catabolic phase and more rapid reversion to anabolism is a subject of ongoing investigation.

Downregulation of Healthy Tissues

These metabolic events, proportionate to the amount of the injury, are characterized by the cytokine-induced release of glucagon and catecholamines, and cortisol, which result in plasma hyperglycemia, increased catabolic rate, release of fatty acids and ketones – and negative nitrogen balance. The systemic effects of fever, tachycardia, increased energy expenditure, muscle weakness and wasting are associated with the elevations of acute phase reactants (APRs). The energy requirements of healthy tissues rely upon lipolysis, aerobic oxidation of fatty acids and the release of ketone bodies (Respiratory Quotient, RQ ~0.7). TNFα and hypercortisolemia drive loss of muscle mass to provide amino acids, partly used as gluconeogenic precursors through alanine conversion, accounting for muscle weakness and wasting associated with severe stress. The counter-regulatory hormones override the action of insulin, reinforced by a tissue insulin resistance. Thyroid function is concomitantly altered as decreased conversion of thyroxine (T4) to triiodothyronine (T3), and the production of T3 declines to the minimal levels compatible with euthyroidism. Taken together, both insulin resistance and low T3 syndrome work in concert to create an overall down-regulation of energy expenditure and anabolic pathways in healthy tissues (3).

Upregulation of Inflamed Territories

The liver is central to these adaptive changes, a salient feature involving IL-6 mediated reprioritization of syntheses. While the production of APRs is strongly enhanced by the provision of amino acids derived from muscle breakdown, that of most visceral proteins (albumin, transferrin, TTR, RBP, T4-binding globulin (TBG), corticosteroid-binding globulin (CBG) and insulin-like growth factor I-binding proteins (mainly IGF-I-BP3)) is suppressed. Following the law of mass action, any abrupt decline in the concentration of these carrier-proteins entails the spontaneous dissociation of the protein-ligand complex and increases the intracellular disposal rate of the free mediators. As a result of this free hormonal concept, all T4-, retinol-, and cortisol-dependent processes are amplified during a transient hypermetabolic flow phase. This endocrine tone is reinforced by the fact that TBG and CBG are degraded by activated neutrophils at the site of inflammation, allowing the local deposit of their ligand. In addition, mediators involved in immune responses and tissue repair, as well as cell lines contributing to tissue rebuilding are stimulated in this reactive state (3), and the cleavage of BP3 releases significantly augmented fractions of IGF-I in free form. Anabolic processes are therefore strongly promoted in the inflamed tissue. The energy requirements of diseased tissues are fulfilled by anaerobic glycolysis (RQ ~1). The site of injury is supported by the breakdown of whole body protein to enhance the immune response.

Interpretation of Laboratory Criteria

Healthy and inflamed tissues manifest metabolic partitioning with distinct energy requirements and adaptive responses. This metabolic adjustment is referred to as the nutritionally dependent adaptive dichotomy (NDAD; 3, 5). One has to consider the implications of this relationship, which is affected by protein malnutrition prior to the injured state. A reasonable explanation for this is that because the basal level of TTR and RBP is set low, the flux of ligands released in free form is reduced and the adaptive response is blunted.

Consequences from Failure to Manage Protein Loss

Protein-energy malnutrition (PEM) affects between 30 and 50% of hospitalized patients at the time of or soon after admission due to the stress response to disease and trauma, prior to inadequate nutritional intake, or a combination of both. Identified late, these cases can have severe medical and financial consequences. Considering the implications of the obligatory breakdown of lean body tissue described above, the body autocannabilizes its lean body mass to heal the wound, and runs a deficit in the absence of provision of protein substrate and the hormonal milieu to sustain it. The net accretion of body protein in the reparative process is slow in the post-injury phase. Anabolism with refeeding occurs at a constant rate of 3 g of nitrogen (20 g of protein) per 70 kg body weight per day. Net accretion of lean body mass is slower than initial degradation, and if a loss of 10 g nitrogen per day persists unabated, the result leads to nitrogen death at an unreplaced loss rate of 70 g (466 g protein) per week.

PEM provides a poor setting in a context of stress injury for wound healing, wound site infection, pressure sores, pneumonia, urinary infection, and septicemia. The stressed patients can take 40% longer to recover from illnesses, have 2 to 3 times more complications, and require hospital stays that are 90% longer, according to surveys conducted by the U.S. Nutritional Screening Initiative (NSI) in 1993 and 1996.

The cost of failure to identify PEM and to provide timely support is largely in managing the unintended complications. Programmatic use of TTR reduces the risk of failure (6). The effective identification of elderly high-risk patients is a measure of quality assigned by the Joint Commission for Accreditation of Healthcare Organizations for hospitals and nursing homes. Using TTR to assess and monitor a patient's nutritional status

can help hospitals reduce costs and improve patient outcomes. At Bridgeport Hospital, 245 relevant cases of gastrointestinal (GI) surgery were reviewed. The total hospital cost for elective GI surgery is $4,534 without complications and without a program of nutrition intervention. But if there are complications as a result of PEM, the cost can increase to as much as $19,334. These unexpected costs are accounted for mainly by antibiotics ($1,500), total parenteral nutrition ($800), reoperation ($4,000), intensive care unit (ICU) costs ($4,500) and non-ICU length of stay (LOS) costs ($4,000). Extended LOS without complications may add a few days ($2,000) and extended LOS resulting from infection or poor wound healing may add as much as 5 days ($4,000). Assuming the minimal case occurs 10 times more often than the major complication, the weighted average increased cost per 100 cases with 11 failures is at least $34,800 ($14,800 + (10 × $2,000)).

If we were to select 200 of the 245 cases studied, then the added failure costs to do nothing is $69,600 over a base expected cost of $906,800. One third of the group were found to be malnourished. Consequently, the increased cost of malnutrition for the 200 cases is potentially 23% greater than – or $208,800 – over the base cost.

Perioperative total parenteral nutrition (TPN) and laboratory monitoring would add $944 per case. The cost of testing is only 0.33% of the base cost (even less than including failures). The cost of providing TPN perioperatively in only 6 of 11 cases is 1% of the added costs. The cost-savings that result from using TTR to screen for PCM and stress injury are very clear.

Identifying Patients at PCM Risk

TTR is the ideal screening method for PCM (Table 2). Today, Bridgeport Hospital conducts routine TTR testing using the following scaled intervals for degree of malnutrition risk (Table 3) on all patients at high risk for PCM who are placed in three categories:

Table 2 Characteristics of ideal nutritional markers.

- Short half-life allowing for changes with improved nutrition status
- Ability to detect non-critical and near-critical changes
- Reflection of clinically significant functional changes
- Reflects metabolic pathway function (whether protein, lipids, micronutrients)

Table 3 Prealbumin levels for nutritional assessment.

<5 mg/dl	Critical
5–10 mg/dl	High risk
11–19 mg/dl	Mild
20–40 mg/dl	Normal

- Level 1 – Patients who are over 70 years age, regardless of ability to take food orally
- Level 2 – Patients who need oral supplements and are at risk of decline in nutritional status
- Level 3 – Patients who are severely stressed or malnourished and require special nutritional support

The ability to identify PEM patients and to implement early intervention has implications for continuous quality improvement. Using laboratory as well as clinical indicators of PEM should allow identification of all patients at risk within 24 hours of admission. Laboratory tests can be triggered by admission criteria, such as weight loss, decreased food intake, or medical condition, or they can be added to a standard admission profile. Advanced age over 65 years or serum albumin concentration below 3.2 g/dl can be used as automatic criteria for obtaining TTR.

The greatest value of TTR is its measure of current nutritional status. Thereby, it allows determination of adequacy of feeding, and it should reduce the discharge of wasted patients who are at risk of readmission. Its physiological range is 20–40 mg/dl. Serious PEM is reflected by a serum concentration <11 mg/dl, severe at <5 mg/dl. It increases at a rate of 1 mg/dl per day with adequate nutritional support. Serum TTR concentration is also a prognostic indicator. Failure to increase TTR is an indication of the inability to provide adequate nutrients by the method of feeding. Systematic identification of patients at risk, appropriate timing and mode of feeding, and monitoring effectiveness are essential elements for such a guideline.

Systematic Identification of PEM Risk and Improvement in Practice

In an environment of increased accountability, there is an increased need for the standardization of processes used in patient care, and the program requires individual commitment, teamwork, and learning. Standardization of processes is achieved by using evidence-based protocols developed from review of the literature, and from the recommendations of professional societies. The guideline, however, is only the first step in developing a workable and effective program. There have to be benchmarks that define the best practice, and an alignment of staff and resources to accomplish the goals.

In this case of malnutrition, the weight of evidence is that a delay in providing nutritional support for more than 3–5 days for acutely or chronically ill, hospitalized patients, is associated with impaired healing, increased infection rates, risk of pressure ulcers, and extended LOS. A requirement for timely identification of geriatric patients at high risk for malnutrition has been developed by the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) with advise from the American Dietetic Association and the American Society for Parenteral and Enteral Nutrition. These are not the only patients at high risk, but they are particu-

larly vulnerable and not easily managed. They may live in isolation, have depression, take multiple drugs and have limited activities of daily living. If they have an acute illness superimposed on a chronic illness, overly aggressive nutritional support carries a risk of refeeding without the ability to fully utilize the nutrients and serious metabolic consequences. We are concerned with issues of the type of nutritional support as well as timeliness, and the need to monitor effectiveness of the care provided. The laboratory has to be actively involved in the care process. All of this is needed to improve clinical outcomes by eliminating unexplained variation in clinical practice. The implementation of a nutrition care guideline for identifying patients at risk and assuring that the care is adequate is not as simple as it may seem. The most easily identified barriers are physicians and nurses. Physicians present problems by not being aligned to "best practice" recommendations of the team, and nurses may pose a problem because they have too little time or commitment to the nutritional needs of the patient.

The implementation of a nutrition clinical effectiveness improvement program has to be an organizational commitment, with the systematic recording of quality performance indicators to the quality council. We now have: guidelines, definition of acceptable performance, and the recording of variation, review of data, profiling, and sharing the data for improvement (Table 4). One could argue that in order to do this well there has to be an information system to support the process. In the absence of that, there has to be a simple audit trail and reporting mechanism. The steps of the care process have to be identified, and the process is profiled for improvement. There can be delays or variation in process flow due to failure to identify patients, failure in notification of a nutritionist, failure to develop a care plan in timely manner, or failure to effectively monitor. Each step can be measured.

Table 4 Continuous improvement cycle for a nutrition programm that goes from a guideline and benchmarking for target goals, implementation, measurement and reassessment.

Guideline
– Benchmarks (percent of patients to risk identified in 24 hours, time to notification, time to intervention)
– Protocols (criteria for action, forms)
– Assignment of responsibility (nursing, nutritionist)
– Tracking of steps in patient care process
– Review of data
– Changes
– Cycle for improvement

Table 5 Implement TTR in nutrition support program.

How to implement a nutritional assessment program
Form a nutritional support team or Nutrition Committee. This nutritional support team determines criteria for acceptable nutritional support and meets regularly to ensure that the criteria are met.
Establish testing criteria. Criteria could include: – All newly-admitted patients deemed to be at high risk for PEM or with stress associated hypermetabolism – Patients >65 years old – Patients with an inability to swallow or ingest food for five days prior to admission – Patients with a history of loss of >20% of their weight – Patients with specific diseases, such as AIDS – Patients whose serum albumin level is <2.8–3.2 mg/dl – Patients who are placed on TPN, PPN or enteral support
Develop a nutritional plan. A plan based on the estimated nutrient requirements of the patients identified as being malnourished needs to be developed in 24–48 hours.
Monitor nutrition. TTR should be measured 2 to 3 times per week
Measure impact of implementation. The actual effect on complications, hospital costs and hospital length of stay can be measured.

Nutrition Support Monitoring

We have seen how the use of a short half-life protein, such as TTR, can be used alone, or in combination with serum albumin and clinical indicators for identifying serious risk (7, 8) (Table 5). TTR is a measure of the NDAD. A TTR concentration of less than 11 mg/dl after 1 week of nutrition support or a daily increase of less than 0.5 mg/dl is a reasonable indication that the feeding is inadequate or that the patient is unresponsive. In some patients who have received high dose corticosteroids, TTR is elevated. In these patients, urinary nitrogen excretion may be done weekly. Adequate treatment of the severely PEM patient requires adequate nutritional support with careful monitoring.

Quality management has to focus on medical outcomes of alternative strategies, *i.e.* feeding, not feeding, delayed intervention, and the costs of interventions (7, 8). Policy considerations are the organizational purview of a Nutrition Committee and the Nutrition Support Team. The cost of data collection can be significant. The cost of prevention, with an effect on under- and over-utilization, can be less than the cost of failure to develop a system. The use of the laboratory has a low cost in supporting a system of quality management.

Use of TTR as a method to assess nutritional status and stress injury has broad implications for hospitals. Timely provision of nutrition support leads to higher quality of care, improved treatment outcomes and lower overall costs for the hospital. But to effectively implement such a program, laboratories need to involve all areas of the hospital, including administration, dieticians, pharmacists, nurses and physicians. While TTR is the right tool, only through a multi-disciplinary support team can a hospital achieve its goals of lower overall healthcare costs and better patient care.

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Corresponding author: Larry Bernstein, M.D., Department of Pathology, New York Methodist Hospital, 506 Sixth Street, Brooklyn, New York 11215-9008, USA
Fax +1 203-384-3237, E-mail: larryberns@earthlink.net