Transthyretin (Prealbumin) and the Ambiguous Nature of Malnutrition

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Lacy and colleagues identify an important "Thing We Do For No Reason"—prealbumin testing to diagnose malnutrition in hospitalized patients.[1] They highlight the frequency and costs of ordering prealbumin tests although prealbumin is neither specific nor sensitive as a "marker of nutritional status," shows no response to nutritional interventions, and has not been shown to correlate with clinical outcomes. We strongly support their analysis. A core problem in the process of nutrition assessment underlies this meaningless and costly practice. The term "malnutrition" is perfectly ambiguous. In one common usage, the term means that "markers of nutritional status" are abnormal. This usage allows a circular reasoning process where prealbumin is defined as a marker of nutritional status, and people with low prealbumin are then diagnosed as malnourished.

The term is also used to mean a condition where evidence shows better patient outcomes when improved nutrition is provided. Distinguishing between these two meanings is essential, as numerous patients with inflammatory illness will present abnormal "markers" when good evidence shows that they cannot benefit from nutritional support.

For example, a patient with advanced untreated human immunodeficiency virus (HIV) is likely to be considered malnourished because all of her "markers of nutritional status" are abnormal. She barely eats, has lost weight, and has low anthropometric, immunologic, and serologic measures, poor functional status, extreme vulnerability, and very poor prognosis. In this way she resembles a person in a famine situation. However, the patient is not malnourished in the sense that improved nutrient intake will lead to better patient outcomes. A Cochrane review of "nutritional interventions for reducing morbidity and mortality in people with HIV" found "no evidence that such supplementation translates into reductions in disease progression or HIV-related complications, such as opportunistic infections or death."[2] The patient is dying of an inflammatory, cachectic illness. The same is true in managing patients with advanced cancer or several other serious illnesses.

Low prealbumin measures are associated with poor outcomes, which are then attributed to "malnutrition." However, as Lacy and colleagues argue, prealbumin is a negative acute phase reactant and is thus a marker of the inflammatory effects of sickness/injury; it also responds variably to nutritional support. Citing Koretz, they note that "even when changes in nutritional markers are seen with nutritional support, the 'changes in nutritional markers do not predict clinical outcomes.'"[1,3] We know of no evidence from randomized controlled trials that prealbumin measurements help identify patients who can benefit from nutrition support.

By contrast, we and our colleagues have shown that in people who barely eat but show no inflammatory disease, eg, prison hunger-strikers and patients with anorexia nervosa, prealbumin level remains normal down to a body mass index below 13. The same is generally true for albumin.[4] These measures fail to identify "malnutrition" in people who are starving.

Despite the complete lack of clinical trial evidence of benefit, prealbumin is widely used as an indicator of malnutrition. The National Institutes of Health's Medline Plus website for the general public lists low prealbumin levels as a possible sign of malnutrition, for example, and advises that the prealbumin test may be used to "find out if you are getting enough nutrients, especially protein, in your diet" and to "check to see if you are getting enough nutrition if you are in the hospital."[5] Unjustified assertions such as these contribute to the dramatic overuse of nutritional interventions.

However, as a rule, things do occur for a reason. Using the term "prealbumin" conjures a certain relationship, perhaps as a precursor, to albumin, a venerable (but valueless) "marker of nutrition status." In fact, the term refers only to a difference in electrophoretic mobility (prealbumin migrates faster). If prealbumin were called it by its proper name, transthyretin, it would probably have languished in obscurity among serum proteins until, in recent years, drug suppression of transthyretin synthesis has been shown to benefit patients with hereditary transthyretin amyloidosis.[6] Using a name that references albumin, this protein has found the limelight as a marker of nutritional status.

The close similarity in appearance between starvation and wasting illness enables the strong, largely evidence-free[7] emphasis on nutrition support. Many families and individuals suffer when a loved one loses weight. As a prominent reminder of serious illness, this wasted appearance can be painful to bear. Several caregivers may fear that they will be judged as neglectful by outside observers. Other individuals also wish to maintain their body weight for social reasons (as weight loss may be interpreted as a sign of illness, especially HIV). Nutrition maintains a special status in various contexts during the care of

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sick patients, and the drive to provide food to individuals who appear undernourished seems fundamental in humans.

A third reason for the frivolous, widespread overdiagnosis of "malnutrition" is that it leads directly to favorable consequences for the multibillion-dollar nutritional support industry. A consistent rational approach to the use of nutritional support products for sick people would lead to multibillion-dollar harm for that industry. For now, however, no self-respecting clinician could fail to provide nutritional support to a patient diagnosed as "malnourished" regardless of evidence.

The consistent rational approach in caring for patients is to search for good evidence of benefit before initiating a treatment course. Although sending blood tests for "nutritional markers" to diagnose nutritional needs may be easier and more popular, we caution against such over-simplification. Using prealbumin as a marker for malnutrition could lead to overlooking potentially treatable inflammatory or infectious illness. On the other hand, the use of prealbumin could also lead to unnecessary and potentially dangerous treatments, such as feeding tube placement and/or total parental nutrition. Thus, with one small amendment, we fully support Lacy and colleagues' conclusion that prealbumin testing to identify malnutrition in hospitalized patients is a "Thing We Do For No (good) Reason."

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References

1. Lacy M, Roesch J, Langsjoen J. Things we do for no reason: prealbumin testing to diagnose malnutrition in the hospitalized patient. *J Hosp Med.* 2019;14(4):239-241. doi: 10.12788/jhm.3088.
2. Grobler L, Siegfried N, Visser ME, Mahlungulu SSN, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. *Cochrane Database Syst Rev.* 2013;28(2):CD004536. doi: 10.1002/14651858.CD004536.pub3
3. Koretz RL. Death, morbidity and economics are the only end points for trials. *Proc Nutr Soc.* 2005;64(3):277-284. doi:10.1079/PNS20054332015.
4. Lee JL, Oh ES, Lee RW, Finucane TE. Serum albumin and prealbumin in calorically restricted, nondiseased individuals: a systematic review. *Am J Med.* 2015;128(9):1023.e1-e22. doi: 10.1016/j.amjmed.2015.03.032.
5. Prealbumin Blood Test. https://medlineplus.gov/lab-tests/prealbumin-blood-test/, updated June 14, 2018. Accessed November 12, 2018.
6. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med.* 2018;379(1):22-31. doi: 10.1056/NEJMoa1716793.
7. U.S. dietary guidelines: an evidence-free zone. *Ann Intern Med.* 2016;164(8):558-559. doi: 10.7326/M16-0035.