

New thinking about postoperative hypoalbuminemia: a hypothesis of occult protein-losing enteropathy

DONALD A REDELMEIER

Donald A Redelmeier is with the Department of Medicine, University of Toronto; the Clinical Epidemiology and Health Care Research Program, Sunnybrook Health Sciences Centre; the Institute for Clinical Evaluative Sciences in Ontario; and the Patient Safety Service of the Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada.

Correspondence: Donald A. Redelmeier, Sunnybrook Health Sciences Centre, G-151 Bayview Ave., Toronto ON Canada M4N 3M5 (416) 480-6999; fax (416) 480-6048; dar@ices.on.ca

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HYPOALBUMINEMIA IS A COMMON AND VEXING postoperative complication. In some case series, about 20% to 40% of patients sustained an acute, prolonged, and profound drop in serum albumin after elective surgery.¹⁻³ Acute hypoalbuminemia is sufficiently common in critical care as to be an established risk factor in the APACHE index.⁴ Hypoalbuminemia can lead to delayed mobilization, inadequate vascular access and unnecessary doses of diuretics. Where does the albumin go?

The laws of physiology suggest that hypoalbuminemia reflects some combination of decreased albumin production, increased losses, acute dilution or shifts from the vascular space.⁵ Low production is easy to hypothesize in a patient with anorexia. However, the half-life of albumin is about 3 weeks.⁶ Hence, total starvation with

zero production would not explain rapid-onset hypoalbuminemia. Acute dilution could be rapid, yet it seems implausible in patients who have a normal hemoglobin and uric acid level after surgery.

One popular explanation relates to displacement into an extravascular space; however, three points indicate that this might not be the entire story. First, such a space should eventually become fully saturated, whereas endless albumin transfusions generally fail to increase a patient's serum albumin.⁷ Second, an inert space should also give back the sequestered albumin; however, it can take months before a patient's serum albumin is fully normalized. Third, data from animal studies do not support the hypothesis of major redistribution.⁸

Classical textbooks also mention that albumin can be lost through epidermal, renal or gastrointestinal sources.⁹ Excess epidermal losses are generally implausible in the absence of burns, dermatitis or open wounds. Excess renal losses are easily excluded if a urinalysis shows no proteinuria. The case for gastrointestinal losses is not compelling, since most patients manifest no vomiting, diarrhea, or abdominal pain. Such patients with postoperative hypoalbuminemia have the markings of an enigma.

Many other sick patients also develop unexplained hypoalbuminemia. Septic patients in intensive care are notorious for albumin levels as low as 10 g/L.¹⁰ Patients with acute trauma seen in the emergency department are also classic for developing hypoalbuminemia soon after injury—a scenario that does not reflect dilution.¹¹ In all cases, the hypoalbuminemia is an ominous prognostic factor and correlates with generally increased hospital mortality.¹²

Concept

Here's a new theory based on the small intestine. This internal organ has a length of about 7 m and a surface area of about 0.25 m² if opened longitudinally. However, folds, villi and microvilli make the absorptive surface much larger than this. Indeed, calculations from histology and fractal geometry estimate the true surface area at about 250 m².¹³ This substantial surface area, similar to the size of a tennis court, is a thousand times larger than is apparent by simple inspection.

The large surface area makes the small intestine an effective structure for absorbing diverse types of food. No surprise, therefore, that healthy people can assimilate massive quantities of meat, vegetables, fruit and other exotica in a single day. No surprise, as well, that malabsorption diseases are rare even among older adults. From an evolutionary perspective, an organism with fallible

absorption would face harsh selective disadvantages in a competitive environment that had limited food.

This situation changes during surgery or other acute stresses. At such times, eating is dispensable and the maintenance of the vital organs becomes the priority of physiological responses. The autonomic nervous system sacrifices perfusion to the small intestine (along with the skin, hair follicles and other less critical organs) in favour of the brain and heart (which have little reserve capacity). Furthermore, the diversion is regulated such that the small intestine still receives some blood and becomes hypoperfused but not infarcted.

A compromised small intestine may eventually return fully to normal function, but this takes time (especially if stresses are ongoing). In the interim, the small intestine might malfunction and switch from being a remarkable absorptive surface to becoming a counterproductive excretory surface. That is, blood continues to flow through the splanchnic circulation, but with capillary exchange occurring in the wrong direction: nutrients leak from the plasma down their concentration gradient into the lumen of the intestine.¹⁴

Evidence

Capillary leak is defined as an excessive loss of fluid and protein into the interstitial space as a result of endothelial cell dysfunction. This is one of the most widely studied and clinically apparent consequences of ischemia-reperfusion vessel injury and other acute inflammatory reactions.¹⁵ Both apoptosis and necrosis of endothelial cells may contribute to capillary leak, as well as the inflammatory mediators released from activated neutrophils such as tumour necrosis factor alpha and interleukin beta.^{16–18}

It would not take much capillary leak in the splanchnic circulation to cause a profound drop in albumin. Total body albumin synthesis is believed to be about 13 g per day.¹⁹ Under completely normal circumstances, an intact small intestine accounts for about 10% of daily losses (stemming from endothelial gaps and other imperfections). If the entire 250 m² of intestinal lining were to become permeable, therefore, the patient could have a rapid, large and ongoing decrease in albumin (Fig. 1).

The wasting might also be widespread. A patient could leak IgG along with other immunoglobulins and become prone to pneumonia. A patient could leak antithrombin III along with other anticoagulants and become prone to thromboembolism. A patient could leak thyroglobulin along with other carrier proteins and become prone to adverse drug reactions. Meanwhile, and in silence, bowel microbes might consume plentiful substrate, proliferate to high numbers, and predispose the patient to sepsis.

Of course, because simple molecules can be reabsorbed, the wasting is not universal. That is, reabsorption of sodium is relatively non-competitive, so that the patient does not develop salt depletion.²⁰ Similarly, water reabsorption might be preserved in the large intestine, particularly if a concurrent ileus prolongs contact time. The net effect from intestinal capillary leak, therefore, might be loss of complex plasma constituents but no major diarrhea (akin to the protein loss from inflammatory bowel disease).^{21–23}

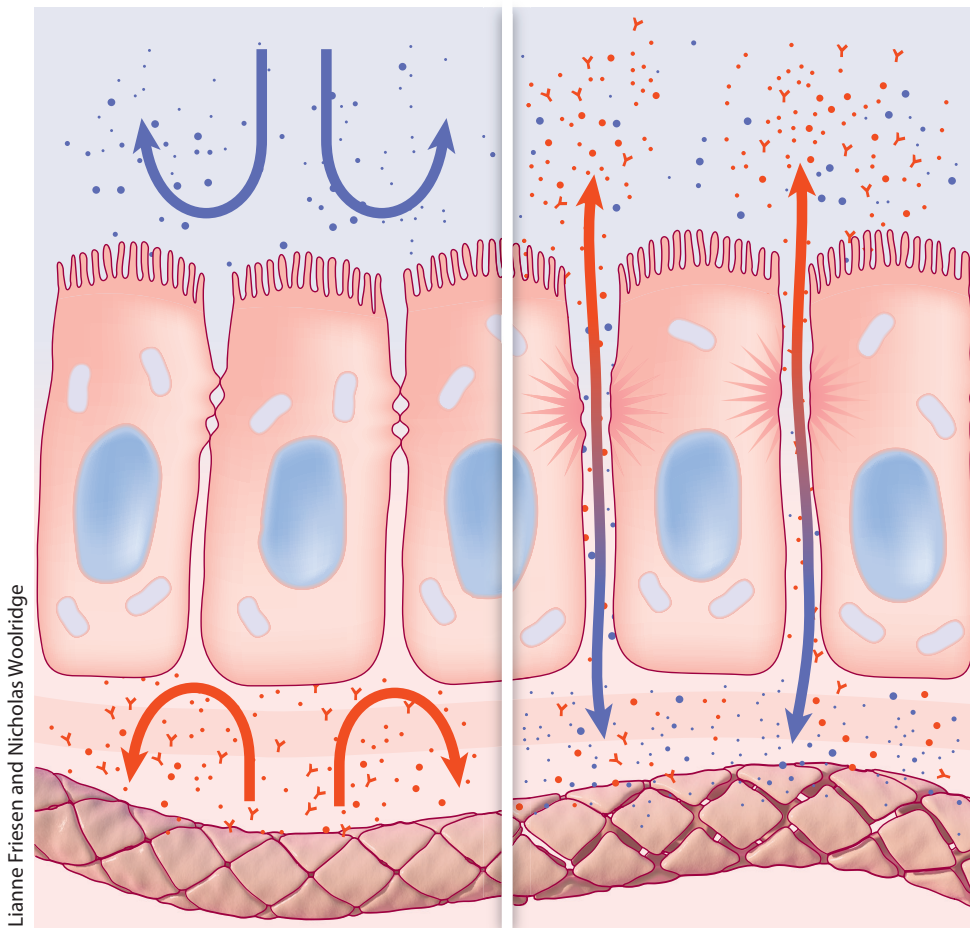
Animal models of protein-losing enteropathy typically induce intestinal mucosa failure by the injection of inflammatory cytokines (or interferon-gamma) into syndecan-1-deficient mice. The result is a rapid leak of serum proteins into the stool, causing profound hypoalbuminemia.²⁴ Microscopically, the lesions appear as defective intercellular junctions between epithelial cells at the lamina propria.²⁵ Interestingly, some agents show promise in reversing the intestinal barrier dysfunction in mice.²⁶

Controversies

The irony of protein-losing enteropathy is that many physicians think they have never seen a case. House staff spend months on hospital wards continually treating patients with an unexplained low serum albumin, yet rarely list this diagnosis. Clinicians read clinical trials and meta-analyses about albumin transfusions being relatively unsuccessful and expensive, yet still remain tempted to order such replacements.^{7,27,28} Trainees repeatedly check the normality of liver or kidney function and still miss the diagnosis.

Physiologic stress responses are familiar to most clinicians, such as when a patient manifests tachycardia, diaphoresis or pallor. This classic appearance is often described as “the patient looked acutely ill.” However, another element of the stress response is almost universal yet is not visible to clinicians: namely, the 50% (or greater) reduction in splanchnic blood flow that accompanies even small stresses.²⁹ Such large reductions in intestinal blood flow typically go unnoticed except in the most blatant clinical cases.³⁰

The reality may be that surgeons, intensivists, traumatologists and other physicians have seen hundreds of cases of protein-losing enteropathy but failed to recognize this potential contributor to hypoalbuminemia. They have also seen patients die from pneumonia, thromboembolism and sepsis that may reflect complications of other unmeasured lost plasma proteins.³¹ This idea can also explain why parenteral nutrition rarely normalizes the serum albumin (although it can stop a bad situation from becoming worse).



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Figure 1: Protein loss in intact and leaky small intestine. The left panel shows intact mucosal lining cells of the small intestine with ongoing submucosal vascular perfusion and minimal loss of plasma constituents in the lumen of the gastrointestinal tract. The right panel shows leaky mucosal lining cells of the small intestine with ongoing submucosal vascular endothelial gaps and ongoing loss of plasma constituents into the lumen of the gastrointestinal tract. Note that the increased losses of plasma constituents also provide a substrate for aerobic and anaerobic bacterial proliferation in the lumen. The red particles depict plasma constituents such as proteins, immunoglobulins and other middle molecules; the blue particles depict luminal contents such as bacteria, fungi and other potential toxins.

This idea also relates to interstitial sequestration whereby blood constituents escape to inert extravascular locations during shock.³² The main difference is to shift some attention away from the skin (with a surface $< 2 \text{ m}^2$ and a somewhat inelastic capacity) to the intestines (with a surface $> 200 \text{ m}^2$ and a potentially endless capacity). This idea can also explain why albumin infusions can be ineffective and give pause to pharmacies that spend more than a quarter of their budget on such infusions.³³

The idea also helps solve an anomaly revealed by past research. Namely, major surgery leads to a roughly 100% increase in the transcapillary escape rate of albumin from the vascular space into the skin.³⁴ This increased egress of albumin should lead to increased lymphatic return to the intravascular compartment. However, studies of albumin kinetics during major surgery have shown a drop in lymphatic flow and lymphatic albumin concentration.³⁵ Apparently, albumin is not just shifted into the skin.

As a mechanism that would explain hypoalbuminemia, occult protein-losing also differs from the speculation that direct protein catabolism by vascular endothelium or other body organs is the cause.³⁶ Such speculations have some basis, since normal skin and muscle account for about 7 g of albumin degradation per day.³⁷ Yet catabolic states tend to down-regulate, not increase, skin and muscle metabolism. The liver, brain, heart and other major organs have a much lower ability to metabolize albumin.³⁸

Capillary leak with intestinal loss also explains the mathematics of the situation. Consider a patient with a drop in albumin from 40 g/L to 20 g/L, a plasma volume of 3 L, and an extravascular space of 6 L. Hence, about 180 g of albumin appears lost $([40 - 20] \times [3 + 6])$. Doubling the extravascular space to 12 L (an extreme assumption that exceeds the conditions of animal studies) would not account for a reduction of this magnitude.⁸ Moreover, clinical studies have found that the infusion of similar quantities of albumin failed to normalize a patient's albumin level.³⁹⁻⁴¹

Intestinal capillary leak also explains why MEDLINE has not once described a survivor with reabsorptive hyperalbuminemia. Many patients recover from catastrophic illnesses and reabsorb factors from inert spaces. Survivors, for example, may develop unwanted adverse effects when they mobilize subcutaneous insulin or morphine. Reabsorption of sequestered saline can also lead to dramatic fluid overload. Yet patients do not seem to develop rebound hyperalbuminemia, suggesting that the albumin is gone.

Application

One way to test this idea would be to collect stool after surgery and correlate decreases in serum albumin with increases in fecal albumin. Such research has not been conducted, because degradation by coliforms prevents albumin from surviving transit in the colon. This destruction of evidence explains why dictionaries offer a term for

stool mixed with blood but not for stool mixed with protein (unlike the kidneys, which can manifest both hematuria and proteinuria). Perhaps the term “proteinocchezia” could be coined to denote increased fecal protein.

An indirect approach for detecting fecal albumin could involve stool studies for alpha-1-antitrypsin. This protein is another plasma constituent that resists coliform catabolism, but it might also leak into the intestinal lumen. The main disadvantages of stool tests for alpha-1-antitrypsin are of a practical nature. First, postoperative ileus can create problems in interpreting the results observed.⁴² Second, specimen collection and handling is unappealing to clinical and laboratory staff. Third, most institutions are not equipped with the necessary analytic technology.

Medical imaging tests might also help increase our understanding of patients with postoperative hypoalbuminemia. Specifically, scanning individuals 24 h after an infusion of technetium 99m-labelled human serum albumin can be a reliable method for detecting tracer exudation in the gut for those with overt protein-losing enteropathy.⁴³ In some cases the sites of protein loss can be demonstrated. The main drawbacks with such scanning are cost, availability, resolution and potential adverse reactions.

Many avenues are also available for refutation. For example, perhaps the lack of efficacy of albumin replacement therapy stems from unwanted storage lesions. If so, better replacement therapy might exonerate the role of intestinal lumen leakage (however, modern colloids have not been more effective than albumin infusions to date).⁴⁴ Alternatively, perhaps albumin degradation reflects oxidation in the body rather than catabolism by intestinal microbes. If so, perhaps a systemic antioxidant might prevent postoperative hypoalbuminemia.⁴⁵

A more radical way to test the idea might be to discover a new intervention that maintains capillary integrity throughout the intestinal mucosa. However, such a revolutionary agent might cause widespread changes to the inflammatory cascade and unwanted effects elsewhere. An impaired intestine can eventually heal perfectly, whereas a compromised brain or heart can cause permanent disability. A temporary interval of intestinal capillary leak may be an unfortunate but necessary compromise in preserving the critical organs.

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