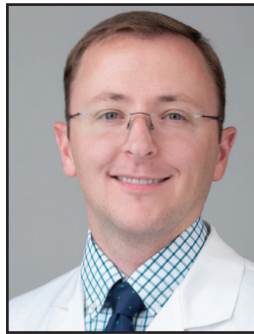


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More than Just Weight Loss: Understanding the Toll of Malnutrition on the Body



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Protein-calorie malnutrition is associated with a variety of adverse clinical outcomes including delayed wound healing, nosocomial infections, hospital readmissions, and increased hospital length of stay. Identifying malnutrition is vital to prevent these adverse outcomes and to hasten recovery. Starvation and inflammation affect muscle mass and adipose tissue as well as the body's ability to utilize nutrition and hydration. Changes to body cell mass alone do not explain the profound impact that malnutrition has on clinical outcomes. This paper will explore the impact that malnutrition has on different organ systems and how treatment may need to be modified for the malnourished patient.

INTRODUCTION

Malnutrition in the hospitalized patient is associated with a variety of adverse clinical outcomes, including increases in infectious complications, hospital length of stay, hospital readmissions, and mortality.¹⁻³ “Malnutrition” is an umbrella term that has been used to refer to the following: excessive or insufficient energy intake, inadequate intake of vitamins and minerals, or protein-calorie malnutrition, which is defined by inadequate energy intake required for proper tissue growth and maintenance.⁴ For the purposes

of this article, the term “malnutrition” shall be synonymous with adult undernutrition or, more specifically, protein-calorie malnutrition.

In order to prevent the deleterious effects of malnutrition, one must first be able to identify it. A variety of assessments exist for diagnosing malnutrition, most of which focus on both the etiology of malnutrition and its phenotypic presentation. Examples of these assessments include the Subjective Global Assessment (SGA), the Malnutrition Clinical Characteristics (MCC), and the Global Leadership Initiative on Malnutrition (GLIM) criteria (see Table 1).⁴⁻⁶ All three assessment tools recognize that inflammation can expedite the loss of muscle, fat, and body cell mass beyond what one would expect from

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starvation alone. As the degree of inflammation increases, protein-calorie malnutrition accelerates. The SGA breaks down the metabolic demand of illness into four simple categories: no stress (starvation without illness), low stress, moderate stress, and high stress. The GLIM criteria present four similar categories: starvation, chronic disease with minimal or no inflammation, chronic disease with inflammation, and acute disease or injury with severe inflammation. The MCC also follows this theme, but with three categories instead of four: starvation, chronic disease-related, and acute disease or injury-related. In addition to the disease burden of inflammation, these assessments describe criteria related to the etiology of malnutrition, which include reduced food intake and/or gastrointestinal symptoms (nausea, vomiting, diarrhea, anorexia) persisting greater than 2 weeks. These assessments also describe criteria related to phenotypic presentations of malnutrition, including involuntary weight loss, loss of subcutaneous fat, loss of muscle mass, fluid accumulation, and diminished functional capacity. Table 1 highlights the differences between SGA, MCC, and GLIM criteria along with questions and observations clinicians should consider when determining if malnutrition is present.

The fact that malnutrition and illness often appear in concert complicates the clinical picture of an individual with malnutrition. Inflammatory responses induced by illness or injury can alter metabolism in such a way that shorter durations of limited intake can result in a profound decrease in weight and protein stores. Systemic inflammation also induces anorexia, meaning that these individuals often avoid nutrition at a time when the body would benefit most from consistent ingestion of nutrients, particularly protein. Given that modern medicine can keep people alive much longer than naturally anticipated, it is not uncommon to encounter individuals with malnutrition as a result of prolonged illness and inflammation. This clinical picture can result in a variety of deleterious effects on many different organ systems.

Malnutrition and the Musculoskeletal System

The most apparent changes seen in the setting of malnutrition are often related to the loss of skeletal muscle and protein stores. Protein is integral to

survival due to its involvement in cell structure, red blood cells, enzymes, antibodies, and collagen.⁷ In addition to being the body's major source of amino acids, skeletal muscle also plays a key role in metabolic regulation.^{8,9} In homeostasis, and even during starvation in the absence of illness, the body works to preserve protein. During illness or after injury, however, the body adapts to fight infection and heal wounds at the expense of protein storage.⁷

Sarcopenia is the progressive loss of skeletal mass and function due to a combination of factors including a reduction in anabolic hormones, decreased physical activity, and low protein intake.^{9,10} Cachexia is the presence of weight loss and rapid muscle atrophy in the absence of simple starvation.¹¹ Patients with underlying sarcopenia or cachexia are at a significant disadvantage if they also develop malnutrition. Weight loss and skeletal muscle loss as a result of malnutrition will likely respond to adequate nutrition. However, muscle atrophy due to decreased mobility, hormonal changes, or illness-induced inflammation will not improve with nutrition alone. As such, treatment of sarcopenia and cachexia requires not only adequate nutrition, but also physical therapy, weight bearing exercise, treatment of illness or infection, and potentially medication management to offset hormonal changes.¹¹

Malnutrition and the Immune System

During systemic inflammation, metabolism is altered due to an increased secretion of cytokines, catecholamines, glucocorticoids, and cortisol, among other substances. These changes increase resting energy expenditure and change how the body utilizes fat and protein stores (Table 2). Triglycerides from adipose tissue provide the dominant energy source and protein is catabolized for gluconeogenesis and for the synthesis of acute phase proteins.¹² These acute phase proteins are involved in regulating the immunoinflammatory response.¹³

Inadequate intake of protein and calories, while simultaneously catabolizing protein and mobilizing lipid, results in a rapid loss of lean body mass and subcutaneous fat. The reliance on adipose tissue to provide energy and skeletal protein as the source of amino acids to mount an immune response places the malnourished patient

Table 1. Criteria for Diagnosing Malnutrition⁴⁻⁶

	Phenotype or Etiology	MCC	SGA	GLIM
Disease Burden/Inflammation	E	X	X	X
Unintentional Weight Loss	P	X	X	X
Reduced Food Intake	E	X	X	X
Muscle Loss	P	X	X	X
Reduced Functional Capacity	P	X	X	
Fat Loss	P	X	X	
GI Symptoms (>2 weeks)	E		X	
Edema*	P	X		
Low BMI	P			X

- First four characteristics are consistent for all three criteria
- Need at least 2 characteristics to diagnose moderate or severe malnutrition

Questions and clinical observations to consider when evaluating for malnutrition:

- Have you lost weight? Over what period of time?
- Have you been eating less than usual?
- Do you have nausea, vomiting, or diarrhea persisting longer than 2 weeks?
- Do you have reduced functional capacity or low energy level?
- Does the patient have a loss of subcutaneous fat? (triceps, face, ribs)
- Does the patient have muscle wasting (temporal, pectoralis, deltoid, quadriceps, gastrocnemius)

E = etiology of malnutrition, P = phenotypic presentation of malnutrition, MCC = Malnutrition Clinical Characteristics, SGA = Subjective Global Assessment, GLIM = Global Leadership Initiative on Malnutrition

*Edema that cannot be explained by disease process such as heart failure, cirrhosis, or kidney disease

at a disadvantage. The malnourished obese patient with ample adipose tissue but limited lean body stores may have the energy stores to stay alive, but the inability to fight infections or heal wounds. The severely underweight patient, with limited stores of both protein and fat, would be even further disadvantaged.

Advances in critical care allow patients to survive previously deadly injuries or infections, leading to patients who now suffer from chronic critical illness. The term Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) has been proposed as a new phenotype to define this subset of patients.¹⁴ There is ongoing investigation into the mechanism of PICS with some evidence suggesting that these patients

experience an innate and adaptive suppression of their immune system which causes persistent low grade inflammation, immunosuppression, and chronic protein catabolism. Those suffering from PICS need a combination of physical therapy and nutrition support to improve clinically.¹⁴

Malnutrition and the Endocrine System

A wide range of hormonal changes have been described in the setting of malnutrition. Insulin-like growth factor (IGF), one of the major anabolic hormones responsible for tissue growth, has been demonstrated to be low in severe forms of malnutrition.¹⁵ Serum cortisol levels are elevated, in part related to the presence of infections and the stress of the malnourished state. In the absence of a

Table 2. Malnutrition with and without Inflammation^{7,61}

Marker	Malnutrition with Inflammation	Malnutrition without Inflammation
Catecholamines	↑	↑
Cytokines	↑	↔
REE*	↑	↓
Positive Acute Phase Proteins	↑	↔
Negative Acute Phase Proteins	↓	↔
Albumin	↓	↓↑
Edema	+	-
Body Cell Mass	↓	↓
Amino Acids for Fuel	↑	↓
Catabolism	↑	↓

*REE = Resting Energy Expenditure

need to metabolize carbohydrates during prolonged fasting, insulin levels are decreased.¹⁵

These alterations in hormone levels function to defend the body against malnutrition.¹⁵ Lipolysis is stimulated by elevated cortisol levels and lipogenesis is inhibited by low insulin-like growth factor, resulting in an increased supply of fatty acids to provide fuel to the brain and peripheral organs. The low insulin/glucagon ratio results in decreased glucose uptake by muscle and adipose tissue as well as increased muscle protein catabolism and increased lipolysis. Similarly, the reduction in anabolic activity (in part related to reduced insulin-like growth factor) and the increase in protein catabolism (mediated in part by the elevated cortisol level) ensure that an adequate supply of amino acids to the liver and protein synthesis continues.

When nutrition is reintroduced, especially carbohydrate, the body responds by secreting insulin. The secretion of insulin drives carbohydrate into the previously starved cells, along with potassium, phosphorus, and magnesium, causing serum levels to drop (refeeding syndrome).¹⁶ As such, nutrition should be delivered cautiously in individuals at risk for refeeding syndrome, with careful monitoring and repletion of electrolytes and vitamins.

Malnutrition and the Heart

Specific micronutrient deficiencies are well known to cause direct deleterious effects on the heart.

Severe thiamine deficiency can cause a dilated cardiomyopathy that leads to a high-output heart failure.¹⁷ Electrolyte deficiencies, especially in the setting of refeeding syndrome, can result in reduced cardiac contractility, severe arrhythmias, and rapid cardiac decompensation.¹⁷⁻²¹ The effects of protein-calorie malnutrition and starvation on the heart, however, is also notable and profound.

In the 1940s, large autopsy studies performed on individuals with starvation showed a proportional decrease in cardiac muscle mass to the degree of muscle wasting in the rest of the body.^{22,23} A separate study of healthy conscientious objectors during World War II who lost an average of 25% of their body weight on a low-energy and low-protein diet for 6 months were found to have markedly decreased heart sizes on radiographs.²⁴ Similar studies have shown reduced heart size in individuals with anorexia nervosa and kwashiorkor.^{25,26} Despite this reduced mass, however, a variety of compensatory mechanisms usually maintains the needs of circulation. While cardiac output and stroke volume fall with reduced myocardial mass, a reduction in body size often preserves the cardiac index and a reduction in blood volume and blood pressure also occurs.^{27,28} Although these compensatory mechanisms make heart failure rare in simple starvation-related malnutrition, they may not be adequate in the setting of systemic inflammation and malnutrition.

As previously stated, refeeding syndrome can cause electrolyte imbalances that lead to

Table 3. Consequences of Malnutrition by System

Organ System	Malnutrition Consequences	Considerations
Musculoskeletal	<ul style="list-style-type: none"> • Loss of lean body mass 	<ul style="list-style-type: none"> • Provide adequate calories and protein to spare lean body mass • Early physical therapy and mobilization
Immune	<ul style="list-style-type: none"> • Increased REE¹ • Increased protein catabolism • Increased risk for infection • PICS² 	<ul style="list-style-type: none"> • Early nutrition support • Provide adequate calories and protein • Maintain a low threshold to screen for infection
Endocrine	<ul style="list-style-type: none"> • Reduced IGF³ • Increased cortisol • Decreased insulin • Refeeding syndrome 	<ul style="list-style-type: none"> • Early nutrition support • Slow and careful introduction of any source of carbohydrate: IVF⁴, food/drinks, tube feeding, parenteral nutrition • Monitor potassium, magnesium, and phosphorus levels and promptly correct deficiencies • Give thiamine if deficiency suspected
Cardiovascular	<ul style="list-style-type: none"> • Thiamine deficiency: vasodilation and high output heart failure • Electrolyte deficiencies: reduced cardiac contractility • Decreased cardiac tissue and heart size 	<ul style="list-style-type: none"> • Correct micronutrient deficiencies • Slow initiation of IVF⁴ and nutrition • Monitor for arrhythmias or evidence of heart failure
Gastrointestinal	<ul style="list-style-type: none"> • Gut barrier dysfunction 	<ul style="list-style-type: none"> • Early enteral feeding when feasible
Respiratory	<ul style="list-style-type: none"> • Reduced exercise capacity • Loss of respiratory muscle function • Weakened cough • Increased risk of pneumonia 	<ul style="list-style-type: none"> • Early nutrition support • Early physical therapy and mobilization
Neurological	<ul style="list-style-type: none"> • Decreased brain volume • Cognitive decline • Increased risk of post-operative delirium 	<ul style="list-style-type: none"> • Early nutrition support • Delirium mitigations
Skin	<ul style="list-style-type: none"> • Pressure ulcer development • Delayed wound healing • Wound infections 	<ul style="list-style-type: none"> • Provide adequate calories and protein • Give adequate vitamins and minerals to treat deficiencies or to provide the RDA⁵ in the absence of deficiencies

REE: Resting Energy Expenditure, PICS: Persistent Inflammation, Immunosuppression, and Catabolism, IGF: Insulin-Like Growth Factor, IVF: Intravenous Fluids, RDA: Recommended Dietary Allowances

rapid cardiac decompensation via arrhythmia. Moreover, carbohydrate and fat intake can lead to the release of catecholamines and activation of the renin-angiotensin-aldosterone axis which increase blood pressure and blood volume and augment

the shifts of electrolytes into cells, resulting in cardiac dysfunction and dysrhythmias.²⁹ The increase in energy consumption also corresponds to an increase in oxygen demand driving cardiac

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output at a much faster pace than the atrophied cardiac muscle can accommodate. As such, cardiac failure and refeeding must remain a consideration in severely malnourished individuals. In this setting, care should be taken to slowly increase caloric intake with careful attention to electrolyte deficiencies that can rapidly develop; intravascular fluids, if needed, should be provided with caution and close monitoring.

Malnutrition and the Gut

The gastrointestinal mucosa plays a major role in preventing bacterial translocation into the systemic circulation, and failure of this intestinal barrier is increasingly recognized to play a role in the development of organ failure and infectious complications. A range of evidence argues that the intestinal barrier function is compromised in malnourished individuals.^{30–32}

Poor dietary intake and environmental exposures in children can lead to a vicious cycle in which an alteration in gut microbiota triggers gut barrier dysfunction, pathogen translocation, and impaired absorption.³⁰ In malnourished adults, gut barrier dysfunction is also present. One study indirectly suggested altered mucosal immunity in malnutrition, after reporting higher levels of systemic antibodies to food proteins (gliadin and B-lactoglobulin) in malnourished individuals.³¹ A follow up study assessing gastrointestinal permeability using the lactulose mannitol test and endoscopic biopsies showed that intestinal barrier function was severely impaired in malnourished patients compared to healthy controls.³²

Malnutrition and the Lungs

Malnutrition has several potential deleterious effects on the respiratory system, including reduced exercise capacity, loss of respiratory muscle function, and reduced lung defense mechanisms.^{33,34} The loss of muscle mass that occurs with sarcopenia and malnutrition has important implications for the respiratory system as inspiration and expiration rely on the diaphragm, external intercostal muscles, and abdominal muscles. In this setting, malnutrition can clearly impair respiratory function through reduced respiratory muscle mass and contractile force.

Additionally, malnutrition can also depress

lung defense mechanisms. Respiratory muscles described above are important to generate effective coughing.^{33,34} Recent weight loss, reduced respiratory muscle strength, and a clinical diagnosis of malnutrition have all been associated with an increased risk of pneumonia.^{35–38} Higher rates of post-operative pneumonia and atelectasis have been noted in protein-depleted patients.³⁹ Furthermore, the prevalence of malnutrition has been prospectively shown to be associated with expiratory muscle weakness and decreased chest wall expansion after upper abdominal surgery, with an associated higher chance of postoperative pulmonary complications.⁴⁰

Malnutrition and the Brain

The energy demands of the brain are high relative to the size of the organ, accounting for at least 20% of the body's energy consumption.⁴¹ Imaging studies have demonstrated that individuals with anorexia nervosa can have smaller brain volumes and less grey matter.⁴² After treatment and weight gain, some studies report full recovery of this brain atrophy,^{42–45} while other studies report partial recovery.^{46,47}

In adult patients, the association between malnutrition and cognitive function is largely studied in the context of cognitive decline and post-operative delirium. In the geriatric population, malnutrition has been associated with cognitive decline,^{48–50} early stage Alzheimer's disease, and behavioral psychiatric symptoms of dementia.⁴⁹ Rosted et al. found that for patients admitted to a geriatric department, delirium is associated with malnutrition and individuals with both had four times the mortality risk in one month follow-up, a seven fold risk of discharge to a nursing home, and a longer length of hospital stay by 3 days.⁵¹ Due to the nature of these studies, it is not possible to conclude if decreased nutritional status is an early result of cognitive decline or if malnutrition exacerbates cognitive decline.

Post-operative delirium is associated with increased hospital length of stay, decreased health related quality of life, lower functional abilities, increased post-operative resources, higher readmission rates, and increased mortality.^{52–54} Developing delirium after hip fracture repair was found to be independently associated with being at

risk of malnutrition or being frankly malnourished.⁵⁵ The same was found to be true for post-operative coronary artery bypass graft patients, where those with severe malnutrition were nearly three times more likely to develop post-operative delirium.⁵²

Malnutrition and the Skin

Malnutrition is associated with an increased risk of pressure ulcer development^{56–58} and delayed wound healing.⁵⁹ This is partly because nutrition is necessary to support cell metabolism and collagen formation. Collagen, the most abundant protein in the human body, is the main structural protein found in the extracellular matrix.⁶⁰ In order for a wound to heal, the body needs protein either from an exogenous source or from the breakdown of lean body mass. Providing adequate carbohydrate and fat for energy can spare protein for cell structure and collagen synthesis. Insufficient energy intake will force the body to turn to muscle as a source of amino acids for gluconeogenesis.⁶⁰

The patient presenting with malnutrition will struggle to heal wounds until their nutritional status is improved. Furthermore, the presence of a wound increases energy and protein needs, so that established malnutrition, if not properly attended to, worsens. The malnourished obese patient may be the most at risk for wound healing complications. In a state of low LBM, there is competition between using protein to heal wounds and using protein to rebuild LBM.^{7,58} In addition, adipose tissue is hypo-perfused and skin folds provide moist areas for bacterial growth.⁵⁸ This combination means wounds are ripe for infection, dehiscence, and ischemia.

Lastly, vitamin, mineral, and trace element deficiencies often coincide with malnutrition and these deficiencies may impair wound healing. Vitamin C is necessary for synthesizing collagen, improving activation of leukocytes and macrophages, and increasing wound tensile strength.^{7,58} Vitamin A is involved in protein synthesis, epithelization, and fibroblast deposition of collagen.^{7,58} Zinc is a cofactor for collagen formation that liberates vitamin A from the liver and serves as a potent antioxidant.^{7,58} Vitamin E, copper, and iron also have roles in collagen formation.⁵⁸ Current guidelines do not recommend routinely supplementing these micronutrients for

wound healing, but do recommend checking for and correcting deficiencies if clinical signs and symptoms warrant.⁵⁸ It is also important to ensure patients receive adequate vitamins and minerals throughout their hospital course.

CONCLUSION

While malnutrition alone can be detrimental to the body, it can be especially costly when combined with acute and chronic illness. The interplay between malnutrition and inflammation can create a cascade of physiological changes that hasten the loss of lean body mass, increase nutritional requirements, and affect the function of vital organ systems. These changes require careful consideration during treatment. Nutrition and hydration should be introduced early, but cautiously; electrolytes and vitamin levels should be monitored and corrected as appropriate, and physical therapy should be incorporated to preserve lean body mass. Identifying and treating malnutrition in cooperation with medical management reduces the risk of complications and improves patient outcomes. ■

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