PROTEIN ENERGY MALNUTRITION
AND THE NON-HEALING CUTANEOUS WOUND

Robert H. Demling, M.D.
Burn Center
Brigham and Women’s Hospital
Boston, MA
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Section I. INTRODUCTION

The focus of this educational program will be the pathogenesis and treatment of wounds where healing is impaired by the systemic process of protein energy malnutrition and involuntary weight loss.

I. Introduction

The focus of this educational program will be the pathogenesis, diagnosis and treatment of wounds where healing is impaired by the systemic process of protein energy malnutrition and involuntary weight loss.

The objectives of this program are:

1. Describe the function of skin and the normal cutaneous wound healing process with specific focus on the requirements for adequate energy, protein intake and anabolic activity.
2. Describe the negative effect of involuntary weight loss, lost lean mass and protein-energy malnutrition (PEM) on healing of both the acute and chronic wound.
3. Describe the populations at high risk for PEM and impaired healing.
4. Describe the correction of the problem using nutritional support and the adjuvant use of anabolic agents, to restore the wound healing process.

Section II. CUTANEOUS WOUND HEALING PROCESS

Wound healing may be defined as the process whereby an injured tissue is repaired, resulting in regeneration of the cell lining of the tissue with the reorganization of the deep tissue components into scar. This process occurs in all organ systems in the body. Cutaneous wound healing can be categorized, in clinical terms, into first, second, and third intention.

HEALING PROCESSES:

First Intention: (Primary Healing)
- The process whereby an incision or open wound is immediately closed (usually elective surgery incision)

Second Intention: (Secondary Healing)
- The process whereby an open wound closes by new tissue formation with subsequent wound contraction and re-epithelialization

Third Intention (Delayed Primary Closure)
- The process whereby a wound is temporarily left open to be closed at a later day (4-7 days) using a primary closure technique
The focus will be wound healing by secondary intent or delayed primary closure, as most traumatic infection induced or disease induced wounds are not are not closed by primary intention. Since local new tissue synthesis is required, increased energy demands and increased protein synthesis is required. In addition, the wound itself activates a systemic hypermetabolic and catabolic state further increasing nutritional demands. This latter concept will be discussed in a later section.

Although the type of wound, timing of wound closure, and wound care techniques used may vary, the process of healing and the factors affecting the healing process are basically the same for all wounds. There are five major interrelated and overlapping components to the healing process.

### Phases of Wound Healing

- Inflammation
- Cellular proliferation
- Connective tissue formation
- Wound contracture
- Wound remodeling

All phases require energy, protein and an anabolic stimulus.

### Acute Wound Healing

#### Inflammatory Phase (Immediate Onset)

**Components**

The initial phase of healing requires the onset of wound inflammation. This process consists of an initial activation of clotting to seal bleeding vessels, increased vessel permeability to allow for antibodies and fibrin to enter the tissues. Increased blood flow, through vasodilatation then occurs, as does an accumulation of neutrophils in the wound within minutes of injury to help prevent invasive infection. Neutrophils require oxygen to kill bacteria so early defenses are depended on blood flow, delivering oxygen to the wound. Activation of inflammation sends out chemical messages, which also attract macrophages to the wound. These long lived cells (weeks) orchestrate the remaining states of wound healing through the release of a variety of polypeptides known as growth factors which produce the various wound healing messages.

#### Inflammatory Phase (immediate onset)

**Components:**

- clotting of bleeders (1-5 min)
- increased blood flow (20-30 min)
- increase oxygen O$_2$ in wound
- antibodies released in wound
- increased neutrophils (bacterial killing)
- increased macrophages
Abnormalities:

- Process suppressed
  - Inadequate O₂ for host defenses
  - Corticosteroids stopping the process
- Process accentuated; tissue damage
  - Excessive inflammation

**Cellular Proliferation Phase (Components)**

Cellular proliferation involves three key processes, angiogenesis, fibroblast, and epithelial proliferation. (all require energy, protein synthesis and anabolism)

**Angiogenesis.** The wound surface or edge is relatively ischemic and healing cannot effectively proceed until sufficient blood flow is restored to allow delivery of nutrients. Macrophages secrete a substance known as angiogenesis factor, which is felt to be a chemo-attractant for mesothelial and vascular endothelial cells. The remarkable process of neovascularization or angiogenesis begins in the first several days although the process is delayed if a thick layer of surface necrosis is present. Endothelial cells proliferate and form capillary buds at the wound surface. The buds form a network of loops which fuse with other buds forming a new capillary bed. If the wound edges are approximated, the capillaries can bridge the wound.

**Fibroblast Proliferation.** The fibroblast begins to appear in the wound about 2 days after injury. The initial cells on the scene appear to migrate from nearby connective tissue. The stimulus for subsequent fibroblast proliferation as well as subsequent collagen synthesis appears to be growth factors from platelets and macrophages. The fibroblasts migrate into the wound along local fibrin strands from the initial wound coagulation as well as any remaining collagen strands. The fibroblasts, being metabolically active, depend on the adequacy of local O₂ supply and the adequacy of neurovascularization for continued proliferation.

**Epithelialization.** The epidermal lining of skin is in a continual state of proliferation and desquamation as opposed to the more dormant mesenchymal tissues. With loss of the epidermis, adjacent cells become reprogrammed. They appear detached from their basement membrane, divide, and migrate toward and across the wound, first forming a single cell layer. Various epidermal growth factors released from the macrophage and platelet, initiate the response. This process, however, is quite limited and any dead tissue on the surface will retard epithelialization. Also the cell distance traveled is limited to about 3 cm from the wound edge. The re-epithelialization process can be rapid, i.e., 3 to 5 days in a superficial injury or several months, depending on the size of the defect, the nutrient supply, the number of remaining basal cells, and the wound environment. Once a single layer develops, additional layers form from mitotic division.
**Cell Proliferation Phase (Begins day 2)**

**Components:**

1. **Angiogenesis (new vessel formation at wound surface)**
   a. Requires growth factor: access to wound surface
2. **Fibroblast migration to wound and proliferation**
   a. Oxygen and energy requiring process
   b. Requires protein synthesis (protein intake)
   c. Requires growth factors
3. **Re-epithelialization: epithelial migration**
   a. Requires O₂, energy, protein synthesis
   b. Requires moisture layer for migration
   c. Requires growth factors

**Impairment:** The new layer is also very vulnerable to desiccation or destruction by release of neutrophil protease as a result of a surface infection and/or a new focus of inflammation.

**Impairment of Process:**

- Decreased perfusion
- Inadequate nutrients
- Decreased anabolic activity
- Corticosteroids
- Excess inflammation
Epithelial Migration

New vessel formation, increased fibroblasts, epithelial cell migration, macrophages, $O_2$ in wounds.

Angiogenesis - new capillaries on wound surface.

Fibroblast Proliferation - numerous fibroblasts now present.
Connective Tissue Production Phase

**Collagen Production.** The stimulus for the fibroblast to begin producing collagen appears to be fibroblast stimulating growth factors released from macrophages and platelets. The rate of production of collagen is dependent on a number of factors, the most important being the adequacy of perfusion and nutrients for energy and protein synthesis. Adequate molecular O$_2$ is essential for a number of key steps in collagen metabolism.

In the presence of adequate blood flow, the rate of collagen production appears to be directly proportional to the wound O$_2$ tension and adequate nutrients especially amino acids and in anabolic stimulus to protein synthesis. Ferrous iron, ascorbic acid, pyridoxal, and copper are also specifically required for collagen synthesis.

The rate of collagen synthesis is maximal in the first 1 to 2 weeks and collagen deposition is maximal at 3 to 4 weeks.

Two other factors, well known to modulate this phase, are vitamin A and zinc.

Vitamin A maintains and restores (in the case of corticosteroids) the inflammatory stimulus required to generate the healing factors. Zinc is a cofactor in a number of enzyme systems including new protein production.

**Interstitial Matrix Synthesis.** The interstitial matrix, also produced by fibroblasts and other mesenchymal cells, appears to have an extremely important influence over the architectural structure and strength of the collagen fibers. Proteoglycans, which are composed of a protein core enclosed by glycosaminoglycans, are a major component. The end result is a firm, non-pliable wound as the collagen fibers become bound into the more rigid matrix. With gradual scar maturation and remodeling, the proteoglycan content decreases.
Connective Tissue Formation (Begins 5-7 days)

- **Collagen subunit production in fibroblast**
  - (Oxygen, protein) substrate required plus growth factors
- **Collagen excretion as fibers in wound**
  - (Oxygen, protein, ascorbic acid, iron, zinc, copper, required)
- **Collagen cross-linking**
  - (O2, vitamin C, required)
- **Ground substance (interstitial cement) from fibroblasts**
  a. Production of proteoglycans
  b. Production chondroitin sulfates
  c. Cementing of collagen in place

Connective Tissue Formation Abnormalities

- **Decreased collagen formation**
  a. Malnutrition
  b. Inadequate anabolic stimulus
  c. Lack of required factors

Impairment

**Wound Contraction Phase**
Wound contraction is the process whereby open wounds close by movement of the wound edges (not just epithelium) toward the center. The mechanism of the contraction, which shrinks the wound, is the generation of forces in the contractile elements of the fibroblasts towards the center of the wound. With fibroblast contraction, collagen and proteoglycan is secreted essentially locking the new tissue in place.
Wound Contraction (begins about day 10)

Movement of wound edges toward each other

- Contraction of fibroblasts toward edge
- Collagen deposition
- Cementing in place
- Requires energy, oxygen, necessary amino acids

Abnormalities:
Impediment to wound closing by contracture

- Dead tissue between edges
- Lack of nutrition, anabolic stimulus
- Lack of O₂ for energy
Wound Remodeling (Scar Maturation) Phase

The remodeling process officially begins about 3 weeks after injury and persists for months to years.

**Wound remodeling is the result of:**

a. Increasing collagen cross-linking, resulting in increased strength;
b. Action of collagenase to begin breaking down excess collagen accumulation;
c. Regression of the lush network of surface capillaries as metabolic demands diminish, and
d. Decrease in the proteoglycan and, in turn, the wound water content.

The loss of wound blood flow or addition of infection, however, can lead to a net increase in collagen loss, resulting in a weakened wound. In general, wound strength continues to increase even beyond a year. Skin and fascia never do regain full strength.

**Abnormalities.** The excessive deposition of scar can occur, leading to hypertrophic or excessive scar formation which will impede movements of the tissue and usually result in a friable wound with pain on movement. Keloid is excess in connective tissue formation.

Wound Remodeling Phase (3 weeks-1 year)

**Components:**

- Increasing collagen crosslinking increasing strength
- Breaking down excess collagen by collagenase
- Regression of granulation tissue and return to normal blood flow
- Decrease in interstitial cement making wound more supple
**Abnormalities:**

- Excess scarring (hypertrophic scar)
- Wound Weakening:
  - Dead tissue between edges
  - Lack of nutrition, anabolic stimulus
  - Lack of O₂ for energy

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**Local factors impeding healing**

**Local Factors**

- Inadequate Nutrients
  - Inadequate energy
  - Inadequate protein
  - Inadequate anabolic stimulus
- Tissue hypoxia
  - Low blood flow
  - Eschar on exudates
- Tissue desiccation
  - Occurs with open wound
  - Impedes epithelial migration
- - Risk of wound conversion
- Wound exudates
  - Released proteases
  - Injures new tissue
  - Uses wound oxygen
- Wound infection
  - Due to impaired local defense
  - Exposure to microbes in the environment
  - Increases inflammation induced injury
- Wound trauma
  - Environmental insult
  - Use of toxic chemicals
  - Traumatic dressing changes
II. PROTEIN ENERGY MALNUTRITION AND IMPAIRED WOUND HEALING

Combination of Catabolism and Cachexia

The result is a non-healing wound

Effect of Malnutrition

A. Defining The Terminology

**Involuntary weight loss:** A involuntary loss of 10% or more of body weight in 6 months or 5% in 30 days

**Protein-energy malnutrition (PEM):** is the most common form of malnutrition in the wound population. This pathological state results when the intake of energy and protein is inadequate to meet the bodys’ needs. It is frequently associated with significant involuntary weight loss. Losses of body weight, muscle wasting, poor healing and the development of chronic wounds along with chronic infections, are all results of PEM.
Catabolism – tissue breakdown

Anabolism -- tissue synthesis

**Involuntary weight loss and PEM** can develop rapidly in days or weeks, especially after severe injury. PEM can lead to a rapid depletion of lean body mass especially in the presence of a wound, impairing the healing process.

**Cutaneous Wound** is a wound which involves the skin and potentially the underlying soft tissue

**Cutaneous wound healing:** a dynamic interactive process whereby a tissue injury is repaired.

**Acute wound:**
- Wounds that heal rapidly and uneventfully
- Wounds that heal by the normal healing process
- Wounds that are traumatic or accidental in origin or electively produced such as the acute surgical wound

**Chronic wound:**
- Failure of the normal healing process
- Lack of any significant healing for a 3 month period despite appropriate local care
- Chronic inflammation
- Bacterial colonization

**B. The Problem of PEM Induced Altered Body Composition**

**Importance Of Maintaining Lean Body Mass**

In order to better understand the impact of erosion of lean mass and the normal or abnormal utilization of protein and fat for fuel, a general understanding of normal body composition is required.

The body composition can be divided into fat and fat-free components. Body protein is present in the fat free or lean body mass (LBM) compartment. Fat mass is usually about 20-30% of total.

Lean mass contains the body’s protein content. Every protein molecule has a role in maintaining body homeostasis. Loss of any body protein is deleterious. The majority of the protein in the lean body mass is in the skeletal muscle mass. Lean body mass is 50-60% muscle mass by weight, the rest is bone and tendon. It is the loss of body protein, not fat loss, that produces the complications of malnutrition. Protein makes up the critical cell structure in muscle, viscera, red cells, and a connective tissue. Enzymes which direct metabolism and antibodies which maintain immune functions are also proteins. Skin is composed primarily of the protein Collagen. Protein synthesis is essential for any tissue repair, any loss of body protein is detrimental.
What is Lean Mass and Its Importance?

**Fat Mass**

The stored body fat is used mainly as a reservoir for energy. The size of the fat depot is controlled by both genetic and environmental stimuli. Components of lipids not stored, are critical for body functions and specific forms of fat products are required. The size of the fat depot is also strongly influenced by environmental or eating habits. Excess nutrients, especially carbohydrates, will expand the depot while inadequate intake will decrease depot size.

**Lipids**

- Free fatty acids – fat
- Phospholipids
- Lecithin
- Cholesterol
- Lipo-proteins

Stored fat is metabolically inactive. There is no metabolic activity outside of converting fat to fatty acids for use for energy and fatty acids to fat for storage. However, there is a component of body fat which is considered essential and is maintained by hormonal activity.

**Concept of Essential vs Storage Fat**

- Some essential fat is needed for normal physiological function
- This essential storage is greater in women than in men, likely due to a biologically range to provide energy for childbearing
- Storage fat makes up the majority of fat in the average individual
Maintaining Lean Mass
There are a number of body adaptations which attempt to maintain lean body mass or body protein as any net loss of body protein or lean mass is deleterious

<table>
<thead>
<tr>
<th>What maintains Lean Mass?</th>
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</thead>
<tbody>
<tr>
<td>• Intense genetic drive to maintain essential protein stores</td>
</tr>
<tr>
<td>• Anabolic hormones which stimulate protein synthesis to preserve protein stores</td>
</tr>
<tr>
<td>• Resistance exercise</td>
</tr>
<tr>
<td>• Adequate protein intake to meet the demands</td>
</tr>
</tbody>
</table>

There is an ongoing metabolic drive to preserve lean mass as a self protective process since lost protein is deleterious. However, activation of the “stress response” from physical or psychological stress will block these adaptive responses and protein stores will diminish, leading to further illness.

Body Compositional Changes

There is a major difference between involuntary weight loss and voluntary weight loss. The former can be dangerous if not controlled as the problem of weight loss is lean mass loss. Loss of lean mass instead of fat is sure to lead to significant complications. The complications, therefore, are those of lost lean mass.

Complications Relative to Loss of Lean Body Mass (Body Protein Loss)

<table>
<thead>
<tr>
<th>Lean Body Mass (% loss of total)</th>
<th>Complications (related to lost lean mass)</th>
<th>Associated Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Impaired immunity, increased infection</td>
<td>10</td>
</tr>
<tr>
<td>15-20</td>
<td>Decreased healing, weakness, infection</td>
<td>30</td>
</tr>
<tr>
<td>25-30</td>
<td>Too weak to sit, pressure ulcers, pneumonia, no healing</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>Death, usually from pneumonia</td>
<td>100</td>
</tr>
</tbody>
</table>

*Assuming no previous loss
Complications correlate with the percent of total lean mass lost assuming normal body composition prior to the loss. Pre-existing losses are added to the loss from a body insult. A 40% loss of total lean mass is fatal. Relationship of loss of lean mass and degree of morbidity and mortality is shown.

**Effect of Lean Mass Loss on Protein to the Wound**

**Priority for Use of Protein; Lean mass vs Wound Healing**

As lean mass is decreased, more consumed protein is used to restore LBM with less being available to the wound. With a loss of lean mass exceeding 20% of total, spontaneous wounds can develop due to the thinning of skin from lost collagen and healing can cease. Wound healing rate decreases until lean mass is restored.

The impairment of cutaneous wound healing is also proportional to the amount of lost lean mass. Although the wound likely has initial priority for protein substrate for healing, but with a LBM loss of up to 10% of total. With progressive losses, the lean mass compartment increasingly competes with available protein substrate to restore itself. This self-preservation process is aimed at avoiding further morbidity with lost lean mass, which become a higher risk than the wound itself. As the skin protein decreases throughout the body, new wounds will develop as well as the reopening of old wounds.

Wounds, mainly pressure sores, begin to develop as a result of involuntary weight and lean mass losses exceeding 20% of total (moderate-severe PEM). As collagen and other proteins in skin decrease with lean mass and muscle weakness decreases mobility, wounds begin to develop.

These wounds by definition will be non-healing until sufficient lean mass is regained. As weight gain increases, more energy and protein substrate becomes available to the wound.

**The following wounds are good examples of the interrelationship of wound healing and PEM.**
Involuntary wt loss exceeding 15% of total has lead to a decrease in healing rate. Since much of the weight loss was lean mass, there is competition for nutrients for the wound and for restoring the lean mass compartment.

<table>
<thead>
<tr>
<th>Involuntary Weight Loss % of Total</th>
<th>Spontaneous Skin Breakdown in Presence of PEM and Progressive Loss of Lean Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
<td>Decrease in skin collagen, a component of lean mass with decrease in LBM approaching 20%, results in skin breakdown, a precursor to pressure ulcers</td>
</tr>
</tbody>
</table>
Involuntary Weight Loss

% of Total

10%

20%

30%

Progressive loss of lean mass exceeding 20% of total in the presence of a wound leads to an enlarging wound, further tissue breakdown and infection

C. Conditions Associated With PEM, Weight Loss And Impaired Healing

The incidence of involuntary weight loss is very high in the severely injured patient population as catabolism is a characteristic of the stress response to injury or infection.

The spinal cord injured patient is at high risk for loss of weight mainly lean mass caused by the stress response as well as decreased muscle mobility. During the chronic stage of management these patients remain hypermetabolic and catabolic as well as having a decrease in endogenous anabolic activity. Weight may be regained as fat if sufficient protein (1.5g/kg/day) is not provided.

The chronic care population is at high risk due to the fact that many patients need chronic care because of a persistent PEM and weight loss which is never corrected. The nutritional needs, especially protein intake, is higher than the younger population (> 1.2g/kg/day compared to 0.8g/kg/day) and is often not met, accentuating the problem.

This population has comorbid factors like increasing age, disability, impaired cognition, which can rapidly lead to PEM.

The aging population, especially after a “stress” or bodily insult, are at high risk for ongoing loss of lean mass. Protein needs are also increased to 1.2g/kg/day compared to the younger population.

Patients with wounds, especially chronic wounds, have increased energy and protein needs which will lead to further weight loss and often develop wounds because of existing PEM, especially in the presence of co-morbid factors.
### Causes of Protein Energy Malnutrition

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td>Severe trauma, infection</td>
<td>-catabolic response to the insult is characteristic of this degree of insult</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>-acute losses caused by response to injury and immobility</td>
</tr>
<tr>
<td></td>
<td>-chronic losses caused by ongoing catabolism and decreased anabolism</td>
</tr>
<tr>
<td>Chronic Care</td>
<td>-often have weight loss as the reason for lost function and hour, non-treated PEM</td>
</tr>
<tr>
<td></td>
<td>-have co-morbid factors which increase risk of PEM</td>
</tr>
<tr>
<td></td>
<td>-often have a wound which further increases the risk factor</td>
</tr>
<tr>
<td>Wounds</td>
<td>Wound will increase catabolic activity and increase the degree of PEM</td>
</tr>
<tr>
<td></td>
<td>-have ongoing needs for increased energy, protein</td>
</tr>
<tr>
<td></td>
<td>-often have chronic wound due to PEM</td>
</tr>
</tbody>
</table>

### Conditions Associated with Development of Protein-Energy Malnutrition:

- **Catabolic illness**: the stress response  
  e.g., trauma, surgery, wounds, infection, corticosteroids  
- **Involuntary weight loss from any cause** (exceeding 10% of ideal body weight)  
- **Chronic illness**:  
  e.g. diabetes, cancer, renal failure
D) High Risk Population For PEM and Impaired Healing

1) Catabolic Illness Induced PEM: The “Stress Response”

The most common precipitating cause of protein energy malnutrition is an acute injury or illness leading to a “stress response” with resulting hypermetabolism and increased catabolism.

The range of increased metabolic demands varies with the degree of insult or injury. An entire spectrum of abnormalities can be seen after injury, infection and inflammation due to degrees of the manifestation of the host “stress response.” This abnormal metabolic response is initiated by factors from a wound or infection and perpetuated by an increase in catechols, cortisol and glucagons) and decrease in anabolic hormones testosterones and growth hormone. The magnitude of the systemic inflammation is dependent not only on the degree and persistence of the initial insult, but also the patient’s preprogrammed genetic response to a bodily insult.[92-99]

Increased local metabolic activity and cellular work is required at the site of injury. Damaged and devitalized tissue must be reabsorbed by the host and then the tissues must be repaired. The wound consumes large quantities of energy during the healing process both by the large population of inflammatory cells and by the fibroblasts production of collagen and matrix. The metabolic and catabolic response is both prolonged in degree and also in time course, lasting weeks to months as opposed to days to weeks with most other insults.

Of major concern is the adaptive response to preserve lean mass as seen with starvation is overridden by the maladaptive hormonal environment leading to a rapid loss of protein.

Under these circumstances both increased energy and protein production are required. However, the energy production is pathologically altered such that nutrient utilization to make energy become very inefficient. Substrate mainly pyruvate and fatty acids recycle back to glucose and fat formation instead of being metabolized totally to CO₂ and H₂O. This results in less ATP, and a wasted increased of energy in the form of heat production.

More calories in the form of nutrients are needed to keep up with needs, or an energy deficit results. The protein synthesis pathway decreased anabolic activity such at 20-30% of amino acids escape the protein synthesis pathway and are used instead for energy production. In addition, a significant portion of the amino acid intake is not captured at all for use with and is instead excreted in urine. Decreased endogenous anabolic activity is also responsible for the increased losses.
Stress Response Injury

The maladaptive response from a wound is characterized by severe catabolism with use of amino acids for excess glucose production (gluconeogenesis) and a rapid erosion of lean mass. Despite increased energy demands, the fat stores are not effectively utilized. Depletions of micronutrients, especially glutamines, and antioxidants. The maladaptive hormonal response persists until the wound is eliminated.

Therefore, a prominent characteristic of a severe wound or of a systemic insult including a wound is the rapid loss of lean body mass or body protein as a result of the “stress response to injury”. In addition, the restoration of lean mass, especially muscle, is very difficult in the recovery phase due to persistent metabolic abnormalities.

All aspects of wound healing are dependent on energy and on protein synthesis. In addition, an anabolic stimulus thru anabolic hormones or local growth factors is also required.
2) Persistent PEM and Lost Lean Mass Into the Recovery Phase

The problem often initiated by a catabolic insult (e.g. a hip fracture) results in the “stress response” being activated. The rate of lean mass loss can reach 1-2 pounds a day, depending on the degree of catabolism and nutritional support. The recovery phase is entered when the catabolic insult is resolving and metabolic rate is returning to normal. However it is well recognized that the stress response persists well into the rehabilitation period.

The high net catabolism during the acute phase is not matched by an excess endogenous anabolic stimulus during recovery. In fact, endogenous anabolic hormonal activity may remain low.

The rate of recovery of lean mass and therefore wound healing, if a wound remains, is 5-10 times slower than the rate of loss in spite of optimum nutritional support.

Of interest is the fact that the addition of an exogenous anabolic agent will markedly accelerate protein synthesis as the metabolic machinery of the cells is activated and activity is dependent on protein substrate and an anabolic stimulus.

Rate of Recovery

The rate of gain of lost lean mass is much slower than the rate of loss, despite optimum nutrition and exercise. Adding further anabolic stimulus will accelerate the lean mass gain.
3) Relationships between Weight Restoration and Wound Healing

A series of non-healing wounds with severe PEM in 10 patients are shown. The rate of healing does not increase until about 50% of lost weight and lost lean mass is restored.

This finding demonstrates that restoration of good nutrition will not be sufficient to immediately be effective in restoring healing in the presence of significant lean mass loss. Restoration of lost lean mass will be the first priority for protein substrate.
### 4) Summary of High Risk Patients for Poor Healing and Treatment Modalities

#### Acutely Injured or Infected Patient

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked hypermetabolism with energy deficit: stress-induced metabolism leading to rapid lean mass loss; or micronutrient depletion.</td>
<td>Early aggressive initiation nutrition support (preferably oral) of high-protein, high-energy, micronutrient-rich diet. Nutrient supplements may be required</td>
</tr>
<tr>
<td>Inactivity leading to muscle loss</td>
<td>Early initiation of physical rehabilitation and appropriate nitrogen and caloric intake</td>
</tr>
<tr>
<td>Decreased endogenous anabolic activity</td>
<td>Use of anabolic agents to decrease lean mass loss and more rapidly restore lean mass.</td>
</tr>
</tbody>
</table>

#### Age Related Frailty

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor nutrition due to disability, chewing and swallowing problems, and significant psychosocial issues.</td>
<td>Aggressive restoration of high-protein, high-energy, micronutrient-rich diet. Early use of ancillary support services.</td>
</tr>
<tr>
<td>Inactivity leading to muscle loss and further inactivity (“cycle of inactivity”).</td>
<td>Resistance exercise program.</td>
</tr>
<tr>
<td>Decreased endogenous anabolic activity</td>
<td>Use of anabolic agents to restore lost weight and lean mass.</td>
</tr>
</tbody>
</table>

#### Immobility (bedridden or wheelchair-bound individuals)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor nutrition due to disability, chewing and swallowing difficulties, and significant psychosocial issues.</td>
<td>Aggressive restoration of high-protein, high-energy, micronutrient-rich diet.</td>
</tr>
<tr>
<td>Inactivity leading to muscle loss and further inactivity (“cycle of inactivity”).</td>
<td>Appropriate physical rehabilitation.</td>
</tr>
<tr>
<td>Decreased endogenous anabolic activity</td>
<td>Use of anabolic agents to restore lost weight and lean mass, as indicated.</td>
</tr>
</tbody>
</table>

#### Diabetes Mellitus

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased capillary blood flow from elevated glucose.</td>
<td>Careful monitoring and control of glucose. Education.</td>
</tr>
<tr>
<td>Protein malnutrition and decreased muscle mass.</td>
<td>Increase protein intake to 1.5 g/kg/d.</td>
</tr>
<tr>
<td>Decreased Insulin and anabolic hormones.</td>
<td>Increase exercise. Provide adequate Insulin. Use anabolic Agents.</td>
</tr>
</tbody>
</table>
E) Diagnosis of PEM and Involuntary Weight Loss (Protein Energy Malnutrition)

Protein energy malnutrition is defined as inadequate intake of energy and protein to meet bodily needs.

The prevalence of protein energy malnutrition in hospitals and chronic care facilities ranges from 20 to 50% with an even higher incidence in the population who also has a chronic non-healing wound. Therefore, a nutritional assessment is essential to determine which patients have or are at risk for or have protein-energy malnutrition. All care providers must play a key role in determining which patients are malnourished or have potential nutrient deficiencies.

Because PEM is a metabolic disorder, diagnosis depends on a combination of findings on history and physical exam as well as biochemical markers. The latter are often more sensitive. Because this assessment is not an exact science there are a variety of different scales used for defining the degree of malnutrition.

Physical Examination

The routine physical examination should note signs suggesting nutritional deficiencies, including muscle wasting or weakness, dermatitis, ulceration of mucous membranes, delayed wound healing, central nervous system depression, glossitis and congestive heart failure. However, impaired wound healing is often the first and best diagnostic finding.

Because each phase of the healing process requires adequate nutritional intake, there is a clear correlation between malnutrition and wound healing failure.

Physical Findings of PEM

- Unintentional loss of body weight
- Loss of subcutaneous fat, evidenced by loose skin, especially on extremities
- Muscle wasting, usually first Evidenced by quadriceps wasting
- Poor healing of chronic wounds or pressure sores
- Chronic infections
- Listlessness, apathy

Biochemical Data

These data are useful, objective and usually readily available. They are, however, affected by the stress response to injury of infection or other medical conditions.

**Serum albumin** is a common indicator of the patient’s protein stores. But because albumin has a half-life of about 20 days, and large amounts are stored in the body, a patient may already be malnourished before serum albumin levels drop. Serum albumin below 3.5 grams/dl is considered low and a level below 2.5 grams/dl indicates a seriously deficient protein store.

**Serum pre-albumin** is a more accurate indicator of protein stores. It responds more readily than serum albumin to acute changes in protein status. Serum pre-albumin has a shorter half-life (2 to 3 days) and smaller body stores than albumin. A serum transferring level below 15mg/dl is considered to reflect mild PEM and below 5mg/dl is considered severe depletion of protein stores.
Total lymphocyte cell count is decreased with PEM, as revealed by loss of cutaneous anergy or the ability to respond to skin testing.

**Biochemical Markers of PEM Defining Severity**

<table>
<thead>
<tr>
<th>Index</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)*</td>
<td>2.8-3.5</td>
<td>2.1-2.7</td>
<td>&lt; 2.1</td>
</tr>
<tr>
<td>Pre-albumin+ (mg/dL)</td>
<td>&lt;15</td>
<td>&lt;10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Total lymphocyte count (per mm³)</td>
<td>1200-1500</td>
<td>800-1199</td>
<td>&lt; 800</td>
</tr>
<tr>
<td>+normal is 20mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*Not an early marker of PEM

**Involuntary Weight Loss**

One of the most common markers for PEM is unintentional weight loss. Defined as 5% loss of body weight in 30 days, 7% loss in 3 months, or 10% loss in 6 months, this amount of weight loss may produce a significant health risk.

Assessment should be based on patients “normal” weight, not weight just prior to being a wound patient as weight loss could and likely already occurred.

<table>
<thead>
<tr>
<th>Unintentional Weight Loss (&gt; 10% in 6 months)</th>
<th>Patient Population</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major burns and trauma</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Chronic care</td>
<td>25% plus</td>
<td></td>
</tr>
<tr>
<td>Chronic wounds</td>
<td>50% plus</td>
<td></td>
</tr>
</tbody>
</table>